

ASSESSING FACTORS AFFECTING PARTICIPATION IN HIV CURE-RELATED RESEARCH:  
IMPLICATIONS FOR EFFECTIVE AND ETHICAL IMPLEMENTATION

Karine Dubé

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Approved by:

Sandra B. Greene

Asheley C. Skinner

Bryan J. Weiner

Stuart M. Rennie

Harsha Thirumurthy

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## **ABSTRACT**

Karine Dubé: Assessing Factors Affecting Participation in HIV Cure-Related Research: Implications for Effective and Ethical Implementation  
(Under the direction of Sandra B. Greene)

The data collected and analyzed within the context of this dissertation project contribute to the emerging body of knowledge about factors affecting entry of people living with HIV in HIV cure-related research.

This DrPH dissertation project:

- 1) Examines whether perceived risks and benefits of studies act as deterrents and motivators of participation using a semi-structured survey;
- 2) Explores how various stakeholders perceive risks and benefits of HIV cure-related studies using qualitative methods;
- 3) Seeks to understand some of the pragmatic issues affecting participation in and implementation of HIV cure-related studies using qualitative methods.

Key survey findings include:

- Willingness to participate in HIV cure-related research is high, but may not translate into actual research participation.
- Although HIV cure studies confer no expectation of direct benefit, potential volunteers may still perceive the likelihood of benefits when deciding to join studies. Psychosocial factors, such as feeling good about contributing to the biomedical HIV cure-related research agenda, should not be under-estimated when planning studies.
- More education is needed around risks and benefits of HIV cure research.

Key qualitative findings include:

- Factors affecting participation in HIV cure-related research are multi-faceted. Main motivators related to the desire to contribute to HIV cure science. Altruism also plays a significant role.
- It is possible to derive factors that facilitate recruitment and retention of study participants in HIV cure-related studies, as well as effective and ethical implementation of research.

#### Plan for Change

Drawing from principles of research ethics, implementation science and leadership theories, the plan for change focuses on the need to avoid unintended consequences during HIV cure-related research implementation. There are five main elements of the plan for change: summation of research findings in usable format, community engagement and coalition building, considerations and tools to facilitate the implementation of HIV cure research, development and implementation of an HIV cure research training curriculum (the “CUREiculum”) and possible avenues for future research.

I dedicate this DrPH dissertation to all those we lost to HIV/AIDS and Ebola

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## TABLE OF CONTENTS

LIST OF TABLES .....	xiv
LIST OF FIGURES .....	xvi
LIST OF ABBREVIATIONS .....	xviii
CHAPTER 1   BACKGROUND .....	1
HIV Cure-Related Research.....	3
HIV Cure-Related Research Modalities.....	3
Participation in HIV Cure-Related Studies and Willingness to Participate .....	5
Conceptual Framework: Participation in HIV Cure-Related Research and Willingness to “Participate” .....	6
Significance .....	7
Effective Implementation .....	8
Ethical Implementation .....	9
Risks and Benefits .....	13
Therapeutic (or Curative) Misconception.....	13
CHAPTER 2   METHODS.....	17
Overview.....	17
Rationale for Mixed Design .....	20
Data Collection Methods: Quantitative Inquiry .....	21
Semi-Structured Survey (Potential Participants of HIV Cure-Related Studies).....	21
Data Collection Methods: Qualitative Inquiry .....	23
Document Review .....	25
Key Informant Interviews .....	26



Inclusion/Exclusion of Study Participants and Delimitations .....	28
Study Participation Duration .....	29
Reliability and Validity .....	29
Strengths and Limitations.....	31
Confidentiality and Protection of Study Participants .....	31
Informed Consent.....	33
Institutional Review Board Approval.....	34
Compensation for Study Participation .....	34
Study Management .....	35
CHAPTER 3   DATA MANAGEMENT AND ANALYSIS.....	36
Document Review.....	38
Quantitative Data Management and Analysis: Survey Data .....	38
Quantitative Data Management.....	38
Quantitative Data Analysis .....	40
Survey Variables .....	40
Survey Data Inclusion and Cleaning .....	40
Baseline (Descriptive) Quantitative Data Analysis .....	49
Presentation of Quantitative Results .....	68
Qualitative Data Management and Analysis: Key Informant Interviews .....	70
Qualitative Data Management .....	70
Qualitative Data Analysis.....	72
Presentation of Qualitative Data and Interpretation of Results .....	74
Reliability and Validity .....	74
Comparison between Quantitative and Qualitative Study Results.....	74
CHAPTER 4   QUANTITATIVE SURVEY RESULTS .....	76

Descriptive Statistics.....	77
Bivariate Association Analyses .....	95
Multivariate Regression Analyses.....	111
CHAPTER 5   QUALITATIVE STUDY RESULTS .....	129
Factors to Consider during Decision-Making.....	130
Motivators to HIV Cure-Related Research Participation .....	133
Deterrents to HIV Cure-Related Research Participation .....	137
Perceived Risks of HIV Cure-Related Research Participation .....	140
Clinical or Medical Risks .....	140
Social Risks.....	145
Financial Risks.....	146
No Perceived Risks .....	146
Riskiest HIV Cure-Related Research Modalities .....	147
Stem Cell Transplants/Gene Therapy.....	147
Latency-Reversing Agents .....	148
Combination Approaches.....	149
“Too Much” or Unacceptable Risks of HIV Cure Research Participation .....	149
Regulations and Clinical Holds .....	150
Patient-Participant Perspectives .....	151
Unacceptable Strategies.....	152
Treatment Interruptions and Associated Risks .....	153
“Healthy Subjects” .....	154
Beyond Clinical Risks: Social and Financial Risks.....	157
Concerns, Burdens and Barriers around HIV Cure-Related Research Participation .....	161
Perceived Burdens of HIV Cure-Related Research Participation .....	165

Perceived Barriers to HIV Cure Research Participation.....	166
Safest HIV Cure-Related Research Strategies.....	170
General Considerations.....	170
Perceived Safe HIV Cure Research Strategies .....	171
Perceived Benefits of HIV Cure Research Participation .....	172
No Expectation of Direct Benefits .....	173
Societal Benefits .....	173
Personal Benefits.....	174
“Risk-Benefit Ratios” and Equipoise in HIV Cure Research .....	177
Equipoise .....	180
Perceptions of Treatment Interruptions .....	185
General Attitudes around Treatment Interruptions .....	186
Motivations for Treatment Interruptions .....	188
Concerns around Treatment Interruptions.....	190
Considerations for Treatment Interruptions.....	191
Factors Facilitating Recruitment in, Retention in and Implementation of HIV Cure Studies.....	193
Expectations and Hopes in HIV Cure Research.....	200
Factors Facilitating Ethical Implementation of HIV Cure Research .....	203
General Considerations in HIV Cure Research .....	205
Justification for HIV Cure Research .....	205
Meanings of HIV Cure.....	206
Language of HIV Cure Research .....	208
CHAPTER 6   DISCUSSION OF STUDY RESULTS.....	212
Discussion of Quantitative Findings .....	213
Discussion of Bivariate Study Results .....	216

Discussion of Multivariate Study Results.....	217
Discussion of Qualitative Findings .....	219
Reflections on the Ethical Implementation of HIV Cure Studies .....	223
Principle of Respect for Persons.....	224
Therapeutic Misconception or Fallacy .....	229
Revisiting the Principle of Respect for Persons .....	233
Principles of Nonmaleficence and Beneficence .....	235
Risks in HIV Cure Research .....	236
Benefits in HIV Cure Research .....	239
Risk-Benefit Ratios.....	240
Equipoise .....	241
“Healthy Subjects” .....	243
Standard of Care and Treatment Interruptions .....	244
Scientific Uncertainty .....	244
Gaining Medical Knowledge and Returning Study Results .....	247
Principle of Justice .....	247
Reflections on the Effective Implementation of HIV Cure Studies.....	252
The Role of Implementation Research.....	256
Towards a Possible Implementation Ethics Framework in HIV Cure Research .....	259
Strengths and Limitations of Research .....	266
CHAPTER 7   PLAN FOR CHANGE/LEADERSHIP/IMPLEMENTATION .....	271
Plan for Change Overview .....	271
Principles of Leading Change and Inspired Actions.....	274
Participative Processes .....	275
Guiding Leadership Theory: Team Leadership [128].....	276

Guiding Leadership Theory: Servant Leadership [128] .....	277
Effective Implementation .....	277
Guiding Leadership Theory: Authentic Leadership [128] .....	279
Ethical Implementation, Moral Courage and Professional Issues .....	280
Guiding Leadership Theory: Ethical Leadership [128] .....	281
Plan for Change/Leadership/Implementation Deliverables .....	282
Dissemination of Research Findings .....	282
Journal Articles and Abstracts (Formal Channels) .....	282
Blog Posts (Informal Channels) .....	286
Community Engagement and Coalition Building/Strengthening .....	286
Engagement in and Contribution to Research and Policy and Implementation Dialogues and Development of Tools to Facilitate Research Implementation .....	287
Development and Implementation of HIV Cure Research Training Curriculum: The CUREiculum .....	293
Possible Avenues for Future Research .....	299
CHAPTER 8   CONCLUDING REMARKS .....	302
APPENDIX 1: List of Recruitment Channels and/or Key Informants .....	306
APPENDIX 2: Sample Recruitment Emails/Scripts for Listservs (Approved by UNC IRB) .....	307
APPENDIX 3: Project Fact Sheet (Approved by UNC IRB) .....	309
APPENDIX 4: Informed Consent Forms (Approved by UNC IRB) .....	310
APPENDIX 5: Patient/Participant Questionnaire (Approved by UNC IRB) .....	316
APPENDIX 6: Key Informant Interview Guides (Approved by UNC IRB) .....	331
APPENDIX 7: grey literature reviewed and key informant interviews .....	336
REFERENCES .....	340

## LIST OF TABLES

Table 1. Requirements for Ethical Implementation of Clinical Research that Affect Participants' Recruitment and Participation .....	10
Table 2. Summary Statistics of the Dependent Variable.....	47
Table 3. Survey Sample Size .....	77
Table 4. Bivariate Association between Perceptions of Potential Benefits as Very Important Motivators and Willingness to Participate (WTP) in all Types of HIV Cure-Related Studies .....	97
Table 5. Bivariate Association between Perceptions of Potential Risks as Very Likely to Discourage Participation and Willingness to Participate (WTP) in all Types of HIV Cure-Related Studies .....	101
Table 6. Bivariate Association between Socio-Demographic Characteristics and Willingness to Participate in All Types of HIV Cure-Related Studies.....	106
Table 7. Multivariate Logistic Regression of Willingness to Participate in All Types of HIV Cure-Related Studies on Individual-Level Socio-Demographic Characteristics (Model 1) .....	112
Table 8. Odds Ratios of Willingness to Participate in All Types of HIV Cure-Related Studies and Perception of Potential Benefits as Very Important Motivating Factors for Considering Participation, Controlling for Socio-Demographic Characteristics in 21 Individual Logistic Models (Models 2 – 22) .....	117
Table 9. Odds Ratios of Willingness to Participate in All Types of HIV Cure-Related Studies and Perception of Potential Risks as Very Likely to Discourage Participation, Controlling for Socio-Demographic Characteristics in 35 Individual Logistic Models (Models 23 – 57).....	120
Table 10. Multivariate Logistic Regression of Willingness to Participate in All Types of HIV Cure-Related Studies and the Number of Potential Benefits Deemed Very Important Motivators and Number of Potential Risks Deemed Very Likely to Discourage Motivation, Controlling for Socio-Demographic Characteristics (Model 58).....	125
Table 11. Key Informant Interviews by Type of Informants.....	130
Table 12. Perceived Clinical – Medical Risks by Clinician-Researchers .....	142
Table 13. Perceived Clinical – Medical Risks by Policy-Makers/Regulators .....	144
Table 14. Concerns around Treatment Interruption.....	191
Table 15. Considerations for Implementation of Treatment Interruptions.....	192

Table 16. Possible Recommendations to Facilitate Recruitment in HIV Cure Studies .....	194
Table 17. Possible Recommendations to Facilitate Retention in HIV Cure Studies .....	196
Table 18. Recommendations to Help Execute HIV Cure Studies Effectively .....	197
Table 19. Main Expectations from the Study Participation Experience .....	200
Table 20. Recommendations to Facilitate Ethical Implementation of HIV Cure Studies .....	204
Table 21. Recommendations for Informed Consent Forms in Early Phase Clinical Studies .....	232
Table 22. Types of Risks in HIV Cure Research and Ways to Tackle.....	237
Table 23. Ways to Tackle Benefits in HIV Cure Research .....	240
Table 24. Steps to Evaluate Risks and Benefits in Biomedical Research.....	241
Table 25. Alternatives to Equipoise Relevant to HIV Cure Research.....	242
Table 26. Four Steps to Facilitate Decision-Making in Situations of Uncertainty .....	246
Table 27. Factors Relevant in the Effective Implementation of HIV Cure Research – Perspectives and Opportunities from the Implementation Science Literature .....	257
Table 28. Strengths and Limitations of Methods .....	267
Table 29. Ethical Principles under Conditions of Clinical Uncertainty.....	281
Table 30. Possible Considerations for Stakeholders to Facilitate Effective and Ethical Implementation of HIV Cure Research .....	291
Table 31. Ethical Considerations for Various HIV Cure Research Modalities – The CUREiculum .....	298
Table 32. Future Possible Social Sciences Questions around HIV Cure Research .....	300

## LIST OF FIGURES

Figure 1. Conceptual Framework for Assessing Factors Affecting Participation in HIV Cure-Related Research: Implications for Effective and Ethical Implementation .....	6
Figure 2. Logic Flow for Methods and Derivation of Samples.....	19
Figure 3. Logic Flow for Data Collection and Analysis .....	37
Figure 4. Distribution of Values of the Dependent Variable .....	47
Figure 5. Flow of Qualitative Data Analysis (Adapted from Creswell, Chapter 9, Qualitative Methods, p. 197) .....	71
Figure 6. Gender of Respondents (n=400) .....	78
Figure 7. Age Group of Respondents (n=400) .....	78
Figure 8. Ethnicity of Respondents (n=400) .....	79
Figure 9. Highest Level of Education Completed (n=399) .....	79
Figure 10. Yearly Household Income (U.S. Dollars) of Respondents (n=399) .....	80
Figure 11. Residence of Survey Respondents (n=394) .....	80
Figure 12. Self-Reported Health Status of Respondents (n=400) .....	81
Figure 13. Respondents' Feeling of Control over Health Care (n=400).....	81
Figure 14. Percentage of Respondents' Lifetime Living with HIV Diagnosis (n=394) .....	82
Figure 15. Respondents have Ever Been in or Volunteered for an HIV Cure Study (n=400) .....	83
Figure 16. Willingness to Consider Participating in HIV Cure-Related Studies .....	84
Figure 17. Total Number of Types of HIV Cure-Related Studies respondents are Willing to Consider Participating in (n=361).....	85
Figure 18. Willingness to Consider Participating in HIV Cure-Related Studies after Having Previously Participated in Similar (HIV or non-HIV) Health Study in the Past.....	87
Figure 19. Importance of Factors to Motivate Considering Participating in HIV Cure-Related Studies .....	88
Figure 20. Likelihood of Factors to Discourage Considering Participation in HIV Cure-Related Studies .....	90



Figure 21. Willingness to Stop HIV Treatment as Part of an HIV Cure-Related Study (n=359) .....	91
Figure 22. Importance of Factors in Making a Decision about Considering Participation in an HIV Cure-Related Study.....	92
Figure 23. How would Participants Most Likely Describe Themselves in they were to Participate in an HIV Cure-Related Study (n=348) .....	93
Figure 24. Personal Beliefs about an HIV Cure.....	93
Figure 25. How Many Years Do Participants Think it will take to Find a Cure for HIV (n=350).....	94
Figure 26. What does a Cure Mean to Participants? (n=350) .....	94
Figure 27. Building Blocks for Proposed Plan for Change/Leadership/ Implementation.....	273
Figure 28. Principles of Leading Change and Inspired Actions.....	274
Figure 29. The CUREiculum .....	297
Figure 30. Critical Questions to Address in the Integration of Social Science in the HIV Cure Research Agenda[41] .....	301
Figure 31. Research with Ebola Survivors .....	302

## LIST OF ABBREVIATIONS

ACTG	AIDS Clinical Trials Group
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ATI	Analytical Treatment Interruption
AVAC	Formerly the AIDS Vaccine Advocacy Coalition
CAB	Community Advisory Board
CAR	Chimeric Antigen Receptor
CARE	Collaboratory of AIDS Researchers for Eradication
CCR5	C-C Chemokine Receptor Type 5
CD4+	Cluster of Differentiation 4 (T Helper Lymphocytes)
CFAR	Center for AIDS Research
CFR	Code of Federal Regulations
CUREiculum	HIV Cure Research Training Curriculum
CXCR4	C-X-C Chemokine Receptor Type 4
DAIDS	Division of AIDS
DHHS	Department of Health and Human Services
DNA	Deoxyribonucleic Acid
DrPH	Doctor of Public Health
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPP	Good Participatory Practice

H <sub>0</sub>	Null Hypothesis
HAART	Highly Active Antiretroviral Therapy
HDACi	Histone Deacetylase Inhibitor
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPM	Health Policy and Management
HPTN	HIV Prevention Trials Network
HSV	Herpes Simplex Virus
IAS	International AIDS Society
IC	Informed Consent
ICH	International Conference on Harmonization
IPDAS	International Patient Decision Aids Standards
IMAP	Intensively Monitored Antiretroviral Pause
IND	Investigational New Drug
IOM	Institute of Medicine
IRB	Institutional Review Board
IT	Information Technology
LRA	Latency-Reversing Agent
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
PD-1	Programmed Cell Death Protein 1
PrEP	Pre-Exposure Prophylaxis
QVOA	Quantitative Viral Outgrowth Assay
RAC	Recombinant Advisory Committee

RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAHA	Suberanolhydroxamic Acid
SCT	Stem Cell Transplant(ation)
START	Strategic Timing of AntiRetroviral Treatment
TLR	Toll-Like Receptors
UNC-CH	University of North Carolina at Chapel Hill
USD	United States Dollars
VSOT	Virological Suppression Off Treatment
WTP	Willingness to Participate

## CHAPTER 1 | BACKGROUND

The long-held assumption that HIV/AIDS is incurable is being challenged. There is one person who has been cured from HIV – Timothy Ray Brown, also known as the “Berlin patient” [1]. The Mississippi child – an infant who was seemingly cured of HIV in 2013 – was reported to have detectable levels of HIV in July 2014, after more than two years off treatment without evidence of the virus [2][3]. Timothy Brown inspired cautious optimism that it may be possible to cure HIV infection, but the relapse of the Mississippi child along with other case reports, such as the Boston patients [4], raised new questions and challenges for the field. While the advent of highly potent and well-tolerated antiretroviral therapy (ART) for HIV infection has substantially decreased AIDS-related morbidity and mortality worldwide, ART alone does not eliminate HIV infection. Patients must continue therapy throughout life at all stages of HIV disease. Millions of HIV-positive individuals are now currently taking ART to remain alive. While HIV is no longer a fatal disease, the virus persists in the human body by establishing latent proviral reservoirs [5]. Furthermore, the highly innovative nature of HIV cure research and the prospect of ART interruption indicated in some study designs create unique implementation challenges and raise critical technical, regulatory and ethical questions for HIV clinical research scientists. These challenges are heightened because people living with HIV have access to highly effective antiretroviral therapy and most are able to lead normal lives.

It is unclear what would motivate or deter people living with HIV to participate in HIV cure research in the United States. This study seeks to fill this information gap by attempting to answer the following question: What factors affect participation in HIV cure-related research in order to facilitate the effective and ethical implementation of studies in the United States?

In early 2016, there were more than 120 ongoing or completed HIV cure-related clinical studies conducted worldwide (<http://www.treatmentactiongroup.org/cure/trials>). This number is expected to grow in the coming year as HIV cure research progresses and novel compounds move through the drug development pathway [6]. On December 2, 2013, President Obama announced that \$USD 100 million were redirected towards HIV cure research in the next three years. HIV cure research is a top scientific priority of the United States government and the United States National Institutes of Health (NIH). Furthermore, HIV cure research is a strategic priority of the International AIDS Society (IAS), which launched the “Towards an HIV Cure” initiative to promote multi-disciplinary research for a safe and scalable HIV cure [7].

Despite major advances in HIV prevention and HIV drug development, including the development of five distinct classes of antiretroviral drugs, there is now a strong rationale to pursue a cure for HIV infection. The costs of delivering ART are overwhelming, not to mention the potential for ART resistance and the stigma associated with HIV disease [7][8][9]. Furthermore, in order to test a new scientific intervention, it is vital that a sufficient number of participants join the study in order to test the intervention adequately. The sample size usually depends on the phase of the study, with latter phase trials requiring larger sample sizes. Reduced study participant rates are problematic because they can slow down research progress, increase research costs and threaten the validity and generalizability of research results [10]. HIV cure studies are no different. HIV cure research is highly complex, multi-faceted and remains in the early phases of investigation, but efforts will be scaled up in the coming years requiring more participants to join studies. Currently, almost all of the proposed HIV cure research modalities remain at the proof-of-concept stage and involve high risks to study participants with little prospect of individual benefit [11]. Moving forward, we will need to gain a deep and meaningful understanding of HIV-positive patients’

expectations and perceptions of HIV cure research, and understand the factors that affect their willingness to participate in HIV cure-related studies.

The literature on decision-making reveals that decisions to join clinical studies have two main elements: 1) a technical component, which requires knowledge of the risks, benefits and possible side effects associated with a study, and 2) a value component which requires input from patients about their values and preferences [12]. Besides evaluating technical aspects and perceptions of participants, it is necessary to bridge these perceptions with the scientific and clinical realities of HIV cure research study implementation. As with other fields or diseases, such as cancer, several factors affect participation in clinical studies ranging from patients' perceptions of studies to the practical and scientific aspects of specific interventions, inclusion/exclusion criteria for entry into clinical research as well as the physicians/researchers' preferences for specific modalities. The perspectives of policy-makers and regulators – such as those working for Institutional Review Boards (IRBs) or Ethics Committee (ECs), are also important to take into consideration.

### **HIV Cure-Related Research**

The Food and Drug Administration (FDA) defines HIV cure research as an investigation evaluating therapeutic interventions that would control or eliminate HIV infection to the point where no more HIV treatment would be needed to maintain health [13]. Two main approaches are being investigated: 1) a sterilizing cure, which would clear all latent viral reservoirs in the body (eradication); and 2) a functional cure, which would allow a person's immune response to control HIV without medication [14]. A functional cure, or post-treatment control, may be much easier to achieve than a completely sterilizing cure.

### **HIV Cure-Related Research Modalities**

Researchers contend that it will be unlikely that we will find the “one cure” – or the single magic bullet that will lead to HIV eradication or a functional cure [14]. Rather, scientists will likely

explore several research pathways that will intersect. There are different types of HIV-cure research modalities being explored, as well as scientific and practical challenges and realities associated with each approach. Essentially, finding a cure for HIV will be a daunting task [15] and a long arduous journey [9]. Initial investigations towards an HIV cure should be framed as clinical experiments [11]. Early experiments will be used to direct future scientific and drug development efforts and pave the way for future HIV cure-related research efforts [13]. Very unlikely will these studies lead directly to a cure for HIV or even to substantial benefits for people living with HIV. Initial HIV cure research efforts will carry great risks, some of which remain unknown at this time [13].

**Several approaches are being investigated in HIV cure research, including:**

1. Reactivation of latent HIV from resting CD4+ T lymphocyte cells and other cellular and tissue compartments;
2. Early therapy as seen with pediatric HIV cure research (i.e. Mississippi child) or using HAART and megaHAART in acutely infected patients;
3. Intensification of ART;
4. Immune-based therapies to boost HIV specific immune responses (such as therapeutic vaccinations);
5. Gene therapy;
6. Autologous and allogeneic stem cell transplant (as seen with Timothy Brown); and
7. Combinatorial approaches.

The significance of HIV cure research rests in finding the right approach or combination of approaches that will be safe and effective at managing acute or chronic HIV infections without ART (functional cure) or at clearing HIV infection (sterilizing cure).

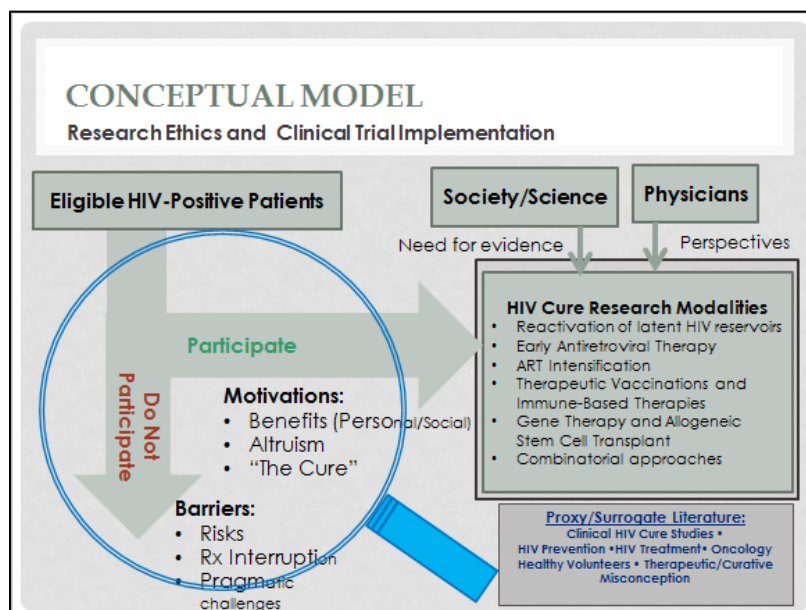


## **Participation in HIV Cure-Related Studies and Willingness to Participate**

Willingness to participate (WTP) refers to the state of readiness to participate in a clinical study. The study of WTP is usually divided between the consideration of the motivators and the barriers to participation [16]. In the context of clinical study implementation, motivators/facilitators to participation are any factors that would increase likelihood of eligible individuals to participate in studies. Barriers/inhibitors/deterrents to participation are any factor that would decrease likelihood of eligible individuals to participate in studies. The main criticism related to the WTP concept is that it relies on hypotheticals (or stated preferences). The WTP concept has predictive value nonetheless [16], especially in the initial exploratory phase. Some authors have studied the determinants of actual participation (or revealed preferences) in clinical studies [17] or conversely, determinants associated with refusal to participate [18].

In the context of HIV cure research, social scientists are considering broadening the theme of “willingness to participate” due to the complexity of the research (personal communication with J. Sugarman). We should consider exploring “willingness to take risks” and/or “willingness to donate” in the context of early HIV cure studies.

## Conceptual Framework: Participation in HIV Cure-Related Research and Willingness to “Participate”



**Figure 1. Conceptual Framework for Assessing Factors Affecting Participation in HIV Cure-Related Research: Implications for Effective and Ethical Implementation**

The above conceptual framework provided the initial foundation to help identify motivators and barriers to participation in HIV studies. Broad sets of variables and their linkages were identified, including involvement of clinical researchers in study implementation and the need for scientific evidence in order to move closer towards a cure for HIV infection. Individuals living with the disease need to make decisions about whether or not to participate in HIV cure-related research. The decisional element is accentuated by the magnifying glass and represents the topic under investigation. For my literature review, I relied extensively on the proxy fields to determine potential factors that influence participation in HIV cure-related research, due to the transient shortage of social science publications on HIV cure research. My literature review informed the development of interview questions and survey instruments.

## Significance

Moving forward, it is essential that we pursue HIV cure-related research in a way that places the needs and perspectives of people living with HIV at the center of the process. In June 2013, the FDA launched an initiative on patient-focused drug development and HIV cure research.<sup>1</sup> To ensure successful implementation of HIV cure studies, it is necessary to engage people living with HIV in a significant and sustained dialogue to address the factors that affect their participation in HIV cure-related studies. People living with HIV should in turn help co-create the research implementation, regulatory and policy agendas about these studies. The research enterprise is thus an exchange of knowledge between the participants and the clinical researchers and an act of active collaborative knowledge building [19].

The topic of participation in HIV cure-related research is evidently ripe for future research. Social sciences related to HIV cure research should also keep pace with the exponentially growing translational and clinical sciences. Social scientists are in fact calling for “[A] proactive and multidisciplinary exploration of social dimensions of an HIV cure (...) [to] inform the conduct of clinical research studies and perhaps help ensure that an HIV cure is accurately perceived and appropriately implemented” [7]. Human studies in HIV cure are part of a nascent field that raises several complex implementation challenges as well as ethical issues related to participation. HIV cure studies will increase in scale and scope in the coming years concurrently with increased research funding. Understanding perceptions of risks and benefits of HIV cure research participation and factors that affect decisions to participate can thus help inform study design and the development of ethical informed consent procedures, not to mention help determine the community acceptability of various methodologies.

---

<sup>1</sup><http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm348598.htm>

Factors affecting willingness to participate in clinical studies have been extensively examined in the context of HIV prevention, particularly HIV vaccine trials. Willingness to participate has also been described for HIV treatment trial participation, although to a much lesser extent. One could wonder whether the HIV prevention literature could help inform the HIV curative field since there are fundamental differences between HIV prevention interventions (aimed at higher-risk HIV-negative individuals) and HIV curative interventions (aimed at HIV-infected patients). Similarly, there can be similarities and differences between HIV treatment interventions and HIV cure interventions. The definitive test for a cure, however, will be the interruption of antiretroviral treatment [6].

Alternatively, in the absence of a robust ‘willingness to participate’ literature on HIV cure research, a proxy or surrogate literature can help inform the debate and provide helpful frames of reference. For example, oncology research is older than HIV cure research, but involves early-phase studies, risky interventions and overlapping themes. In fact, some of the compounds being tested in clinical studies to reactivate latent HIV, such as Vorinostat or SAHA (suberanilohydroxamic acid), Romidepsin and Panobinostat, are used as anti-cancer drugs, notably in the treatment of Hodgkin’s lymphoma [20]. Participation in HIV cure research is hitherto not emerging in a vacuum and may gain from a thorough assessment of applicable concepts found in the proxy medical research literature.

### **Effective Implementation**

Clinical research implementation – including HIV cure-related research – would fit well within an implementation science framework. In fact, translational research and implementation science are akin to each other, with their attempts at closing the gap between the creation of evidence and translation into practice [21]. Implementation science has been widely described in the context of HIV prevention and treatment [22][23] and seeks to identify success factors [21], as well as possible obstacles [24], to implementation. In the context of translational research, Khoury

and colleagues developed a classification framework for translational researchers involving four categories: 1) T1 – development of applications and interventions; 2) T2 – development of evidence-based guidelines; 3) T3 – transition to practice; and 4) T4 – transition to improve population health [25]. Implementation of HIV cure research in human populations would thus correspond to the transition between T1 and T2. With its focus on collecting any vital information about any factor affecting successful implementation (including risks/benefits or deterrents/motivators), the attention to practical issues and the onus on planning proactively for change, implementation science can provide helpful considerations for the effective and detailed planning of HIV cure research execution. Aim 3 of this dissertation project seeks to explore some of these issues in more detail. We will revisit the topic of effective implementation in the discussion and plan for change sections.

### **Ethical Implementation**

Since medical research is oftentimes viewed as conferring access to first class novel therapies and since patient-participants expect clinician-researchers to act in their best interest (under the Hippocratic Oath), it is not surprising that people living with HIV may enroll in studies with the hope that they will be “cured.” The aims of the research – to obtain generalizable knowledge and identify new paradigms to cure the disease – may not coincide with the personal interests of people living with HIV. In an attempt to determine what factors affect HIV-positive patients’ decisions to participate in HIV cure studies, it is therefore important to acknowledge the underlying applicable ethical considerations. At this time, most HIV cure studies represent proof-of-concept activities with no expectation of positive clinical outcomes [11]. In fact, HIV cure studies face many of the same ethical dilemmas surrounding early-phase trials, such as the need to carefully assess risks and benefits, the scientific validity of the study and the voluntary aspect of the informed consent process [26].

In their seminal article on “What makes clinical research ethical?” [27], Emanuel and colleagues outlined seven requirements that provide an ethical framework for clinical studies. Their ethical framework was drawn by synthesizing the literature on the ethics of research with human participants, including the Nuremberg Core (1947), the Declaration of Helsinki (1964, 1975, 1983, 1989, 1996), the Belmont Report (1979) and the International Ethical Guidelines for Biomedical Research Involving Human Subjects (1982, 1993), among others. The seven requirements include: 1) social and scientific value; 2) scientific validity; 3) fair selection of research participants; 4) favorable risk-benefit ratio; 5) independent review; 6) informed consent and 7) respect for potential or enrolled study participants.

Of the seven principles, four pertain specifically to the topic of recruitment/participation of people living with HIV in HIV cure-related studies:

**Table 1. Requirements for Ethical Implementation of Clinical Research that Affect Participants’ Recruitment and Participation**

<b>1. Fair selection of research participants</b>	Selection of participants so that stigmatized and vulnerable individuals are not targeted for risky research	Justice	Scientific knowledge Ethical and legal knowledge
<b>2. Favorable risk-benefit ratio</b>	Minimization of risks; enhancement of potential benefits, risks to the participant are proportionate to the benefits to the participant and society	Nonmaleficence, beneficence, and nonexploitation	Scientific knowledge Citizen’s understanding of social values
<b>3. Informed consent</b>	Provision of information to participants about the purpose of the research, its procedures, potential risks, benefits and alternatives, so that the individual understands this information and can make a voluntary decision whether to enroll and continue to participate	Respect for participant Autonomy	Scientific knowledge Ethical and legal knowledge
<b>4. Respect for potential and enrolled study</b>	Respect for participants by: 1) Permitting withdrawal from the research	Respect for participant Autonomy and welfare	Scientific knowledge Ethical and legal knowledge

<b>participants (and respect for community)*</b>	2)	Protecting privacy through confidentiality	Knowledge of particular participant population
	3)	Informing participants of newly discovered risks and benefits	
	4)	Informing participants of results of clinical research	
	5)	Maintaining welfare of participants	

\*Participation in clinical studies is not isolated from societal influences

Adapted from Emanuel Ej, Wendley D, Grady C. What Makes Clinical Research Ethical? *Jama* 2000; 283(20): 2701 – 11.[27]

Furthermore, in their article on the “Ethical Considerations for HIV Cure Research: Points to Consider [28]”, Lo and Grady argued that while established guidelines provide an ethical foundation for HIV cure research, the cutting-edge nature of the research presents novel ethical dilemmas. For example, while ethical guidelines postulate that participants must be selected fairly and equitably, most HIV cure-related studies usually include participants on long-term, stable antiretroviral therapy. There are difficulties in enrolling women [29][30][31] and special considerations for HIV cure-related studies with newborns [32]. The risk-benefit ratio may not be favorable in these early-phase studies that do not have a direct therapeutic or curative intent. Finally, the desire for a cure may distort the informed consent and decision-making process, and special efforts should be made to ensure that participants understand the potential risks as well as lack of direct clinical benefits. To discuss the ethical implementation of HIV cure-related studies, we must thus rely on the established ethical guidelines as well as special ethical considerations for HIV cure-related studies [28][33]. The three principles of the Belmont Report [34] – 1) respect for autonomy, 2) beneficence and 3) justice – remain at the cornerstone of an ethical implementation framework and provide a convenient way to analyze several issues pertaining to participation of people living with in cure-related studies. Justice refers to “fairness in distribution” of the risks and benefits of research [34] and access to HIV cure research on the part of minority populations. Furthermore, the standard of

care debate falls under the principles of respect or justice, because removal of the standard of care, as in the case of antiretroviral treatment interruption or intensively monitored antiretroviral pause (IMAP), may unfairly raise the burden of risks on study participants relative to those in the future who may benefit [35]. The principle of beneficence –or the converse, nonmaleficence – highlights the importance of maximizing possible benefits while minimizing possible harms (doing absolutely no harm being practically impossible) [34]. Finally, the principle of respect for autonomy demands that individuals should have the opportunity to act as “autonomous agents” [34]. Participants should evaluate the pros and cons and arrive at a considered decision about whether or not participate in research. It is important to note that these important considerations can also come into conflict and need to be managed. For instance, respecting autonomy can conflict with concerns about the risks participants take and the disproportional burdens they may bear.

The application of these principles for ethical implementation of research leads to considerations for informed consent, assessments of risks/benefits and the selection of study participants [34]. In the case of HIV cure research, the informed consent document should clearly state the lack of therapeutic – or curative – intent, as well as the unique requirements for the research (i.e. invasive procedures) and the associated risks and benefits (or lack thereof). Possible harms can include physical, psychosocial, legal, social as well as economic harms [34]. Finally, the principle of justice brings up moral requirements about what constitute fair procedures in the selection of study participants [34]. These principles must all be operationalized in the design, protocol development and implementation of HIV cure studies. Aims 2 and 3 of this dissertation research seek to explore some of these issues in more detail, such as perceptions of risks and benefits. A qualitative design and interview approach confers a great way to begin exploring some of these elements in the formative stage of the research. We also revisit the topic of ethical implementation in the discussion and plan for change sections.



## **Risks and Benefits**

Each clinical study or experiment has its own risks and benefits – some of which are known or unknown. Risks of clinical study participation include possibilities for harm or injury or negative consequences, such as a decrease in CD4+ count or increase in HIV viral load when taken off antiretroviral treatment. In turn, benefits are possible advantages gained from taking part in a clinical study – some of which are collateral benefits – such as access to state-of-the art medical “care.” There remains a controversy about whether these collateral benefits ought to be counted as weighing against the risks of the research. While IRBs tend to say that they ought not to count, participants may think that they do count and these may affect their decision to participate in studies. Risks and benefits provide an organizing framework for the entire dissertation research.

## **Therapeutic (or Curative) Misconception**

The topic of therapeutic misconception provides a valuable framework to conclude the background section. Appelbaum and colleagues first described therapeutic misconception in 1982 in the context of psychiatry [36]. One definition of therapeutic misconception, from the National Bioethics Advisory Commission, is “the belief that the purpose of a clinical trial is to benefit the individual patient rather than to gather data for the purpose of contributing to scientific knowledge” [37]. Therapeutic misconception occurs when a study participant does not fully understand the boundaries between standard clinical care and experimental or clinical research [37]. For example, a research participant can misestimate the likelihood of direct medical benefits, misconstrue the purpose of a study or join a study in order to obtain therapeutic benefit, when none should be expected [37]. Most of the therapeutic misconception literature draws from discussion in early-phase cancer experiments (i.e. gene therapy transfer, when no therapy should in fact be expected).

Therapeutic – or curative – misconception is enlightening and can definitely be transposed to the context of HIV cure research. Possible future benefits of the science accruing to society or

future people living with HIV should be separated from possible benefits to individual participants [38]. As stated before, most clinical experiments in HIV cure research at this juncture represent proof-of-concept activities with no direct expectation of positive clinical outcomes [11]. They remain a critical step in the translational research process, and allow us to transfer interventions into initial human testing [11]. Furthermore, the occurrence of concomitant clinical care and treatment should not be confounded with the scientific objectives of HIV cure studies [37]. It is thus imperative to understand the motivations, expectations and understandings of people living with HIV who would be eligible, willing or unwilling to participate in HIV cure-related research. Clinician-researchers and IRB members may also be subject to the therapeutic misconception [37]. It is also important to understand the extent HIV cure-related research participants will be prey to these misconceptions. Hopes to be cured could be a strong motivator, but one considered ethically dubious from the standpoint of having genuine informed consent.

### **Project Aims**

Therefore, the main objective of this study is to help inform the planning of HIV cure-related research in the United States by exploring the factors that may affect participation in HIV cure-related studies. The study isolates, articulates and communicates opinions of people living with HIV, clinician-researchers and policy-makers (i.e. regulators), broadly defined, about participation in HIV cure-related studies, and derive possible considerations to propel the field forward. Knowledge emanating from biomedical and social science research is a valuable social good, and such research should live up to the highest ethical, scientific and implementation standards [39].

My three specific research aims include:

Aim 1: Do the perceived risks/benefits from HIV cure-related research act as deterrents/motivators to participation?

I developed a semi-structured quantitative survey instrument based on my literature review of the reported risks and benefits (or surrogate clinical markers) of 14 different types of HIV cure-related research. For this aim, I surveyed adults living with HIV in the United States. The quantitative portion sought to provide descriptive statistics, distribution of responses and strengths of association and derive respondent profiles. This component also allowed to derive a sample of volunteers willing to be interviewed in more depth (aims 2 and 3).

Aim 2: Explore how various stakeholders perceive risks and benefits of HIV cure-related research using qualitative methods.

This aim was closely linked to aim 1, but was purely qualitative and exploratory in nature. I performed 12 key informant interviews with people living with HIV in order to gain more meaning and depth regarding perceived risks and benefits from HIV cure-related studies (convergent parallel mixed methods). I also interviewed key informants such as 11 clinician-researchers and 13 policy-makers (broadly defined – such as bioethicists, members of IRBs and FDA representatives) in order to obtain their perspectives as well. This aim sought to derive meanings and deeper understandings about how/whether risks and benefits acted as deterrents/motivators to participation in HIV cure-related studies. Attention was placed on actual perceptions of risks and benefits of participating in HIV cure-related research. For example, I probed about what constituted “too much” risk or “too little” benefit. The perceptions of risks and benefits, even if they did not represent actual experiences, are important because they can influence individuals’ decisions to participate in studies and shape public perceptions around the various HIV cure-related research modalities.

Aim 3: What are some of the practical or pragmatic issues affecting participation in HIV cure-related studies?

I conducted key informant interviews with people living with HIV and clinician-researchers in order to better understand the practical and pragmatic issues affecting participation in and implementation of HIV cure-related studies. This portion was fact-finding and informed possible considerations for the effective implementation of HIV cure-related research.

## CHAPTER 2 | METHODS

The literature review revealed the dearth of information regarding the factors that would influence people living with HIV to join cure-related studies – thus the need to borrow from the proxy fields of literature until more social sciences data are available. The purpose of this mixed-methods study is to obtain the perspectives of patient-participants, clinician-researchers and other stakeholders about factors influencing participation in HIV cure-related research. The study used a non-experimental, descriptive, mixed methods and exploratory sequential design. The schema below (Figure 3) illustrates the logical flow of the aims and methods.

### Overview

Aim 1: Based on the literature review, I implemented a cross-sectional, internet-based, semi-structured survey of people living with HIV to assess whether potential benefits and risks (or surrogate clinical endpoints) of HIV cure-related research would act as motivators or deterrents of participation. Most questions were closed-ended. Targeted respondents were potential HIV cure-related research participants who were openly HIV-positive (to prevent stigma and discrimination), living in the United States or its territories, relatively knowledgeable about the state of HIV cure-related research and who served as advocates for other people living with HIV for the most part. This convenience, purposive national sample represented patient-participants who were as diverse as possible with respect to age, gender, race/ethnicity, educational attainment, income, time since diagnosis, health status and history of participation in HIV-related studies. The target survey sample was least 100 ( $n \geq 100$ ) due to time constraints to complete this study; however, participation rate during the data collection phase of the research was higher than anticipated and the survey sample size reached  $n = 400$ . This increased the precision of the survey results.

Aim 2: Based on a sample of HIV-positive respondents derived from Aim 1, I interviewed key informants in order to better explore perceptions of risks and benefits of HIV cure-related research. I also interviewed people living with HIV, clinician-researchers and other stakeholders to derive meanings and deep understandings about perceived risks and benefits of HIV cure-related studies. Targeted respondents included 12 – 15 people living with HIV (n = 12 actual); 6 clinician-researchers (n = 11 actual) and 6 policy-makers/regulators (broadly defined) (n = 13 actual).<sup>2</sup>

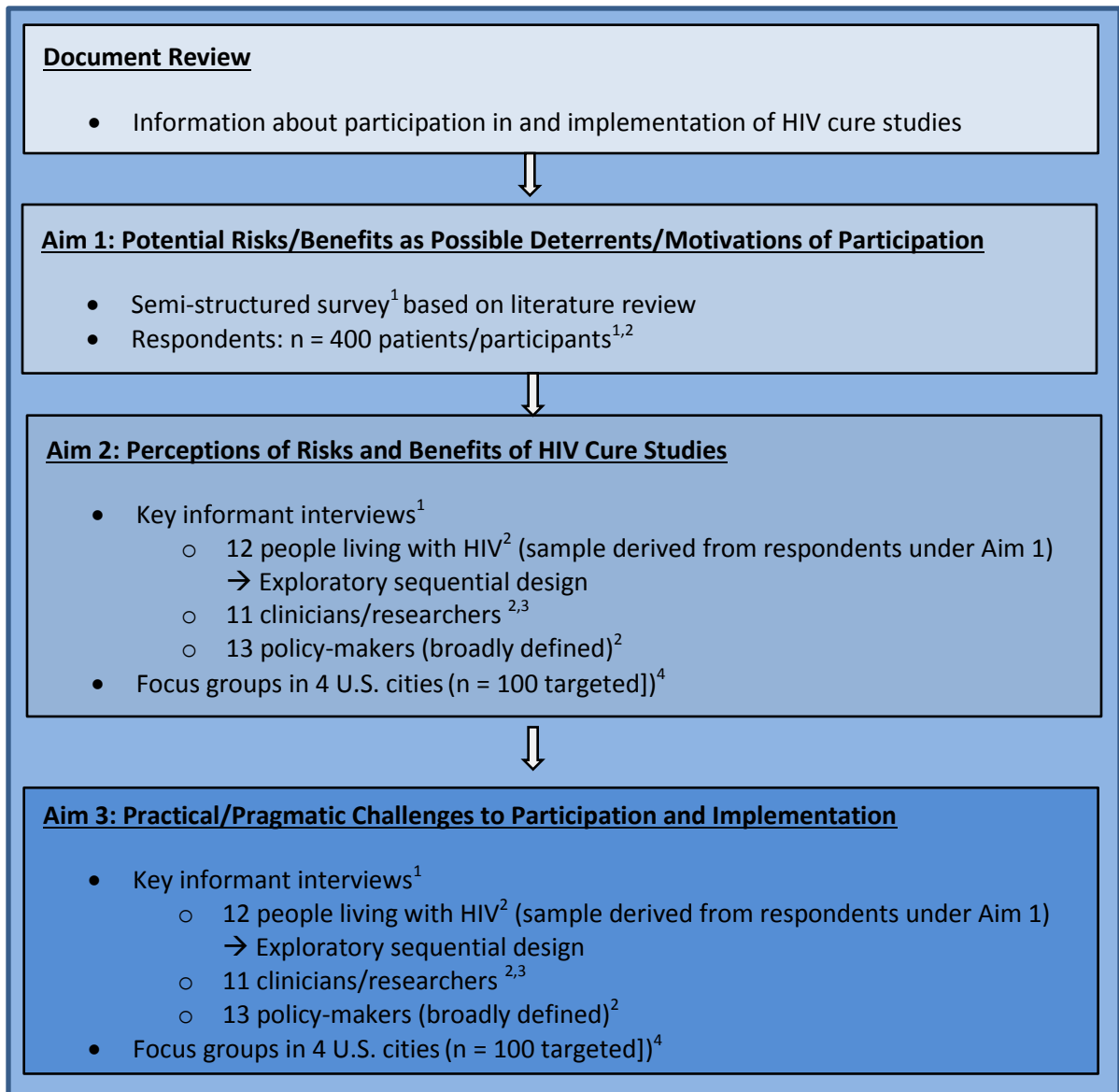
Aim 3: During the key informant interviews, I also sought to better understand the practical and pragmatic issues affecting participation in HIV cure studies. The targeted respondents interviewed in Aim 2 were also asked questions related to this aim.<sup>3</sup>

Since aims 2 and 3 are more qualitative in nature and involved the same key informants, they are connected with one another. I attempted to make the information flow between the topics covered in aims 2 and 3 in the data analysis section, as themes were closely interconnected. While HIV-positive key informants were recruited via the survey instrument based on specific responses, I recruited clinician-researchers and policy-makers/regulators via individual formal requests for their time. Policy-makers were defined broadly to include regulators of HIV cure-related studies such as IRB representatives as well as known advocates and policy-makers in the field. I supplemented these primary data collection methods with a document review including peer-reviewed journal articles and documents from the grey literature on HIV cure-related research.

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<sup>2</sup>Beyond the scope of this dissertation, I am conducting focus group discussions in 4 U.S. locales (Seattle, San Francisco/Los Angeles, San Diego/Palm Springs and Chapel Hill). The plan for the focus group discussions was approved by the UNC IRB in January 2016 via an amendment to the main protocol and is part of my research but not my dissertation.

<sup>3</sup>Similarly, the focus group discussions that are taking place in four U.S. locales will be used to further investigate the practical and pragmatic issues, but the focus groups are not included as part of my dissertation findings.



**Figure 2. Logic Flow for Methods and Derivation of Samples**

<sup>1</sup>Original, primary data

<sup>2</sup>Actual sample size

<sup>3</sup>Representing various HIV cure research modalities

<sup>4</sup>Part of research protocol but not DrPH dissertation; analysis deferred until completion

## **Rationale for Mixed Design**

This section provides a rationale for the use of a mixed methods approach. Since the social sciences in HIV cure-related research remains relatively nascent [7][41], there is a strong justification for combining and capitalizing on the strengths of both quantitative and qualitative methods within a single study. This design permitted both breadth and depth of understanding to occur [42]. The use of multiple methods and specifically the use of a quantitative method (survey) with qualitative methods (document review and key informant interviews<sup>4</sup>) provided better traction and insight into the topic of participation in HIV cure-related research than the use of a single method alone. This approach also helped compensate for the constraints of each method. In fact, the key to strong mixed methods research rests in the effective integration of the methods used. The explanatory sequential design allowed quantitative data to be collected first, followed by the collection of qualitative data that helped explain (or refute) the quantitative data.

Since my topic of inquiry involved participation in HIV cure-related research, it was important to understand contextual factors that would facilitate implementation, including the barriers and facilitators of entry into research. The use of mixed methods added validity to my inquiry, as multiple strategies for validation can be necessary to obtain accurate information [42]. Tensions between the results obtained from quantitative versus qualitative inquiry may themselves be revealing and lead to new insights. I analyzed results from the survey separately from the qualitative results, and then attempted comparisons to determine whether the findings confirmed or contradicted each other. Additionally, I attempted to compare, whenever possible, the perspectives between patient-participants, clinician-researchers and policy-makers/regulators. This juxtaposition proved enlightening in some cases, especially where gaps, contrasts and contradictions were revealed (see Qualitative Analysis Section for details).

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<sup>4</sup>Focus group discussed deferred



### **Data Collection Methods: Quantitative Inquiry**

Quantitative methods emphasize the use of an objective, deductive and generalizing approach. Researchers use them to help prove or disprove a hypothesis based on a conceptual model. Quantitative methods also help obtain breadth, rather than depth, of understanding of the predictors of successful implementation, and yield numeric descriptions of opinions or attitudes of a study sample [42]. Survey instruments are efficient data collection tools and offer a uniform modality to administer simple questions. They are also cost-effective and can be standardized. In my study design, the survey implementation further helped derive a study sample for later qualitative inquiry.

#### **Semi-Structured Survey (Potential Participants of HIV Cure-Related Studies)**

I implemented a semi-structured survey with potential HIV-positive participants (aim 1) developed to determine whether reported potential risks and benefits (or surrogate clinical endpoints) of HIV cure-related studies acted as deterrents and/or motivators for considering participation in HIV cure-related studies. The sample size reached was  $n = 400$  (four times the initial target of  $n = 100$  respondents), which, at a 95% confidence level, produced an interval of approximately  $\pm 5\%$ . The sample size was still limited due to time constraints to complete the study in the allotted time, and because of the difficulty of recruiting people living with HIV who were at least partly aware of HIV cure-related research. Nonetheless, the sample size obtained was satisfactory given the extensive length of the survey.

I tested the hypothesis of whether potential risks acted as deterrents and potential benefits (or positive surrogate clinical endpoints) acted as motivators of participation in HIV cure-related research. Most of the questions were closed-ended, with few open-ended questions. I constructed the survey instrument/questionnaire based on my literature review[40] of the possible deterrents and motivators of participation in clinical research. Most of the closed-ended questions were either

dichotomous (Yes/No), ordinal (i.e. on a Likert scale), categorical (i.e. groupings) or continuous (i.e. spectrum such as age). Most of the socio-demographic variables were categorical and/or continuous, whereas the questions related to potential study participation (dependent variable) were dichotomous, and the questions related to perceptions of risks and benefits (key independent variables) were ordinal, on a Likert scale. Some of the variables were aggregated into newly structured constructs (see Data Management and Analysis for details).

A quantitative analysis of the variables provided preliminary empirical evidence about which potential risks or benefits (or surrogate clinical endpoints) of HIV cure studies may act as deterrents or motivators to participation in HIV cure-related research. The results may lead to greater discussion among researchers and policy-makers and a prioritization of which risks and/or benefits HIV cure research implementers must pay attention to during study design and implementation.

I administered the semi-structured survey online only, via the UNC-CH Qualtrics portal. The online survey was designed to use skip logic between questions and required responses to certain questions where necessary. Target respondents were adults living with HIV in the United States who were willing to answer questions around perceptions of HIV cure-related research. The sample was purposively derived using various HIV cure research listservs, such as the immune-based therapy (IBT) listserv, the Martin Delaney Collaboratories Community Advisory Board (MDC CAB) listservs, and other listservs of patient advocates (such as the AIDS Clinical Trials Group (ACTG)). We administered the survey from September – October 2015. To encourage participation in the survey, we did a random drawing of 1 for every 25 survey respondents who completed the survey and awarded each a \$25 gift card. Funds for the gift cards were provided from my own money and not funded by an external agency. The random drawing was conducted after the last day of the survey, on October 31, 2015, and 13 gift cards were awarded to 13 random-draw prize winners from the 345 survey respondents who completed the full survey and provided their contact information for

the prize drawing. Please see Appendix II for the IRB-approved recruitment script that was disseminated via listservs and/or emails. I also provided a copy of the IRB-approved dissertation project fact sheet to prospective respondents (see Appendix III).

In order to establish content and construct validity, I asked members of the CARE Community Advisory Board to review the survey instrument. Main categories of questions comprising the survey instrument related to demographic characteristics, health perceptions, history with and willingness to participate in HIV cure-related research, perceptions around different HIV cure-related research modalities, personal benefits, personal risks, social benefits and social risks. The survey instrument also asked questions related to the risk of therapeutic/curative misconception and barriers and facilitators of HIV cure-related research implementation. The survey was extensively reviewed with people living with HIV who provided feedback on the validity of constructs and terms used in the survey. One person suggested using the survey as a teaching opportunity and we therefore embedded basic definitions of difficult terms (e.g. allogeneic vs. autologous stem cell transplant) directly in the survey. The questionnaire was amended and IRB-approved in August 2015 in order to allow for community input and better validity of constructs (after initial IRB approval in May 2015). A copy of the final questionnaire can be found in Appendix V.

#### **Data Collection Methods: Qualitative Inquiry**

Qualitative research emphasizes breadth of knowledge and can be helpful in the formative stage. The design is emergent and the inquiry is interpretive and iterative, involving a sustained and intensive experience with a small group of participants [42]. Qualitative inquiry involves a subjective, contextual and inductive approach, and is helpful when one needs to examine the intentions, motivations, perspectives, values and opinions of individuals, as well as to generate hypotheses from the information gained. Due to the exploratory nature of this study and the relative novelty of

the topic of HIV cure-related research participation, I found it appropriate to integrate qualitative methods in order to obtain new knowledge and contribute to the body of research in a meaningful way.

In this dissertation, the emphasis on the voice of the patients and on participative and servant leadership as well community engagement created an intrinsic need for the utilization of qualitative methods. Additionally, qualitative inquiry proved helpful to understand the reasons behind deterrents and motivators to participation in HIV cure-related research, and behind successes or challenges of implementation. Qualitative research further helped inform the ethical and effective implementation of research.

The qualitative approach in aims 2 and 3 gave voice to and explored the lived experiences and perceptions of people living with HIV (as well as clinician-researchers and policy-makers/regulators). The qualitative orientation in aims 2 and 3 allowed a submersion into the complexity of the lived experiences of people living with HIV who may have participated in, currently participate in or are candidates for future HIV cure-related studies. This exploration informed ethical HIV cure study design, development and implementation. In fact, the emergent and innovative nature of the field of participation in HIV cure-related research calls for an approach that permits a more meaningful engagement of people living with HIV during the research design process. This co-agency allows patients and their advocates to become active co-creators of the HIV cure-related research agenda and a better integration of the biomedical and the social sciences [41]. The qualitative inquiry also included a review of key documents and key informant interviews. The combination of methods permitted gaining a deep understanding around perceptions of risks and/or benefits of HIV cure-related research and pragmatic challenges of study implementation. Data sources included adults living with HIV in the United States, clinician-researchers and policy-makers (broadly defined), as described above. I attempted to triangulate these multiple data

sources, including data from the potential volunteer survey implemented in aim 1. For example, I selected key informants from survey respondents who were the most and least willing to participate in HIV cure-related studies, stratified by gender, in order to determine differences in perceptions and attitudes between these different groups.

### **Document Review**

The document review included *systematically* written notes from conferences and meetings on the topic of participation in HIV cure-related research. I took notes methodically from conferences and meetings as part of my work with the Collaboratory of AIDS Researchers for Eradication (CARE) from 2013 – 2015 in order to provide an unbiased way of capturing information. This included conference reports, meeting proceedings and working documents from subject matter experts relating to the topic of participation in HIV cure-related research, as available. For example, I reviewed notes from NIH meetings on the topic of the social sciences in HIV cure-related research and notes from conference calls with the Forum for Collaborative HIV Research – subgroup 3 on patient recruitment, education and informed consent. The reference section contains the list of documents reviewed. I also scouted for and reviewed policy documents related to HIV cure-related research, including meeting reports from FDA, such as *The Voice of the Patient* report [43]. I did not need to request permission to use these documents, as there was no custodian of the data or they were publicly available.

The document review served two purposes. First, it provided a secondary data source for possible deterrents and/or motivators of participation in HIV cure-related research as well as possible implementation realities, challenges and opportunities. Secondly, it identified organizations and/or key informants to tap into for interviews. I conducted the document review in a systematic fashion. The main goal was to extract information on the possible barriers and facilitators of participation and implementation of HIV cure-related research. In conjunction with primary data

collection and analysis, the summary informed possible considerations to ensure the effective and ethical implementation of HIV cure studies. Document review considerations are included in the discussion section instead of the qualitative results section. Further, as peer-reviewed articles became available on the topic of participation in HIV cure-related research during the study period, I incorporated them as well, to the extent possible.

### **Key Informant Interviews**

I conducted key informant interviews with patient-participants, clinician-researchers and policy-makers/regulators to obtain their expert opinions and to better understand perceptions of risks and benefits (or surrogate clinical endpoints) of HIV cure-related studies. I also gained insights into the pragmatic challenges affecting implementation of these studies. Key informant interviews permitted the collection of information from knowledgeable individuals as well as the flexibility to explore emerging themes. I developed the key informant interview guides based my review of the literature. I refined them further as needed based on the semi-structured survey responses, on the document review and following discussions with seasoned community advisory board members who were willing to provide feedback. In order to establish content validity, I asked members of the CARE Community Advisory Board to review the interview guides prior to implementation. See Appendix VI for the IRB-approved interview guides with patient-participants, clinician-researchers and policy-makers, respectively.

For feasibility reasons, I conducted around  $n = 12$  interviews with people living with HIV,  $n = 11$  clinician-researchers and  $n = 13$  policy-makers/regulators. I found that I reached saturation of key themes and exhausted study questions for all three groups of key informants. In fact, qualitative data analysis guidelines suggest that purposive samples should be determined on the basis of theoretical saturation – or “the point in data analysis when new incoming data produce little or no change to the existing code network” [44]. I reached saturation and data redundancy in the

qualitative inquiry. I derived the sample of patient-participant key informants from the survey. These selected patient-participants had indicated that they would be willing to be contacted to answer additional questions around the topic of participation in HIV cure-related research. Based on the results from the survey, the categories of key informants who were purposively interviewed corresponded to the following 4 groups: 1) male more willing to participate in HIV cure research; 2) male less willing, 3) female more willing and 4) female less willing. This selection was based on: 1) a separation of respondents between males and females; 2) an assessment of the number of types of HIV cure-related studies potential volunteers would be willing to participate in; 3) diversity of respondents by age, education and geography/location across the United States; 4) willingness to participate in the interviews. Further, I identified clinician-researchers and regulators/policy-makers using my experience working in the field of HIV cure-related research, from meeting lists and/or the relationships that I had built with colleague organizations. I selected these respondents purposefully and used recommendations from experts and a snowballing approach to identify additional key informants. I also strived to interview clinical research coordinators and study nurses who were in direct contact with people living with HIV and who were actual implementers of HIV cure research. The analysis section provides a summary of key informants.

I contacted all potential key informants by email and/or phone and explained the purpose of the study and the reasons for requesting their participation and assistance. I provided a copy of the IRB-approved dissertation project fact sheet (see Appendix III). I tracked all efforts to reach key informants in a contact log. During initial contacts, I emphasized that I was interested in their personal opinion – not the official position of their organization – due to their experience with HIV cure-related research. If individuals were willing to be interviewed, I deferred to their preferences as to the best modality for interview (e.g. telephone or face-to-face) as well as time for the interview. Most interviews were conducted by phone and a few interviews were done in person, as expected.

I provided a copy of the informed consent form and interview guide in advance of the scheduled interview to give informants the time to think about their participation in the study and about each question. I also asked for their permission to record the interview – if not granted, I took notes systematically. I assigned a unique identifier code for each key informant interview (patient-participants: 101 and above; clinician-researchers: 201 and above; policy/makers/regulators: 301 and above). I transcribed all key informant interviews in order to have a deeper experience with the data (see Data Management and Analysis for details).

### **Inclusion/Exclusion of Study Participants and Delimitations**

Inclusion criteria for participation in this study<sup>5</sup> were: 1) persons living with HIV; 2) willingness to answer survey questions and/or participate in key informant interviews; 3) being at least 18 years of age; 4) living in the United States or its territories; and 5) willingness to provide informed consent. The survey was conducted amongst self-disclosed HIV-positive individuals. Interviews with people living with HIV were conducted with those who were willing to disclose their status to me.<sup>6</sup> I also attempted to select study participants who were representative of the various HIV cure research modalities and who were diverse in gender, age, education, income and geography/location, and had different degrees of willingness to participate in HIV cure-related studies. ART status did not affect participation in the study, meaning that those who were HIV-positive on ART or not on ART could be in the study. There was no exclusion criterion. In order to gain entry into the reality of people living with HIV and to secure permission to ask them sensitive research questions, I worked closely with the leader of the CARE Community Advisory Board and other Community Advisory Boards (i.e. DARE and defeatHIV) as they were important gatekeepers.

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<sup>5</sup>We added two inclusion criteria for the focus group discussions during the amendment in January 2016: 6) comfortable discussing HIV cure-related research with other people living with HIV and 7) willingness to keep information shared in the focus groups confidential.

<sup>6</sup>Focus group discussions will be conducted with openly HIV-positive individuals in order to reduce the risk for harm, stigma and discrimination.



Delimitations refer to the boundaries of the research. This dissertation project was delimited to HIV cure-related studies implemented in the United States and focused on the Martin Delaney Collaboratories. The main reason was that the United States provided a research-rich environment to conduct HIV cure-related studies. There are much deeper ethical concerns with implementing HIV cure-related studies in resource-limited settings that are beyond the scope of this dissertation. Furthermore, I have focused most of my recent work with advocates located in the United States.

### **Study Participation Duration**

The survey/questionnaire took most respondents between 15 minutes and 30 minutes to complete. Key informant interview lasted between 30 minutes to 1 hour for the most part. All key informant interviews were scheduled a few days in advance. As expected during study planning, the discussion of the perceptions of risks and benefits bled into topics related to the pragmatic challenges of implementing HIV cure studies. I derived considerations related to the ethical implementation of HIV cure-related studies and explicitly asked about them during the interviews.

### **Reliability and Validity**

Aim 1 of this dissertation intended to test the hypothesis of whether potential risks and benefits of HIV cure research acted as deterrents/motivators of participation in HIV cure-related studies. Aims 2 and 3 intended to generate knowledge and they were more descriptive and exploratory in nature. Aim 2 explored how various stakeholders perceived risks and benefits of HIV cure-related studies. Aim 3 probed about the pragmatic issues affecting participation in and implementation of HIV cure studies, both using qualitative methods. As described earlier, I attempted to reach validity by matching the aims of the study with the appropriate study methods. This allowed for the best approximation to the “truth” although most of the research was centered on *hypothetical* willingness to participate in HIV cure-related research, since we were not recruiting

for actual HIV cure-related studies. I tried to augment internal validity by minimizing bias in the selection of study participants and by the careful inference of conclusions related to the study findings. I tried to maximize external validity by obtaining a diverse, yet purposeful sample of people living with HIV. The discussion section explores the extent to which the results of the study can be generalizable to a wider sample. For qualitative study findings, I was reminded that particularity, rather than generalizability, was the hallmark of robust qualitative research and therefore attempted to avoid the generalizability fallacy [42].

I tried to reach construct validity by carefully selecting key themes and concepts, such as risks, benefits, deterrents and motivators. I developed the survey instrument and interview guides with the understanding and assumption that the potential burdens/risks and benefits of participation in HIV cure-related studies extended beyond those inherent to specific studies, such as clinical endpoints. Taken together, I attempted to capture the complexity of factors that may influence decision-making and found out that factors extend way beyond considerations of risks and benefits. Furthermore, I designed the survey instrument and key informant interview guides in a stepwise process, using a comprehensive literature review, discussion with experts and community leaders in the field, drafting and re-drafting, review, pilot testing and revising. Furthermore, I attempted to reach reliability by attempting to make the research findings consistent and replicable as much as possible. I kept a log of notes after each key informant interview, and wrote the transcripts as close as possible to the end of each interview. I used an Olympus digital voice recorder (VN-7200) that provided outstanding sound quality for the recordings. Finally, I debriefed with the study community co-investigator regularly in order to enhance the accuracy of each account.

## **Strengths and Limitations**

The strengths and limitations of this dissertation project can be found in the Discussion section.

## **Confidentiality and Protection of Study Participants**

This study was classified as “minimal risk.” No HIV testing or biomedical procedure was conducted with anyone involved in this research. HIV-seropositive status was self-disclosed. I followed the utmost confidentiality and data security guidelines. Most potential participants were actively involved in HIV treatment and cure activism, had openly disclosed their seropositive status and were fairly knowledgeable about the topic of HIV cure-related research. Several HIV-positive patient advocates were also known and respected community leaders and spoke on behalf of other patients about HIV treatment and cure research issues.

In order to minimize the risk of harm, study participants self-selected. Vulnerability of patient-participants was minimized and protected via the informed consent process. For the survey and key informant interviews, risks to participants were minimal. Furthermore, some participants divulged private information, such as health insurance status, health and health care information and past study participation and special attention was taken to keep this information confidential. All key informant interviews were conducted in private. Participants were free to join and/or stop the study at any time. If participants felt uncomfortable or vulnerable in the study, they had the option to continue in the study or not. As there are rather limited opportunities to provide a voice to the experiences of people living with HIV, this study presented an opportunity for patient advocates to articulate their concerns about participation in HIV cure-related research. Some participants actually found the interview to be quite cathartic. Because of the research methods applied in this project, the research provided rich insights into the possible factors affecting participation in HIV cure-related studies and can guide the implementation of future studies. The benefits of the study

extended to the broader scientific community, although no immediate benefits could be anticipated from the survey or key informant interview participation.

Every attempt was made to maintain the confidentiality of study participants.<sup>7</sup> No study data were linked with personal identifiers under any circumstances. Where participant name was provided (e.g. in order to participate in the survey prize drawing or to volunteer for follow-up interviews), the names and contact information were extracted into a separate file (with no survey data) and deleted from the survey data files in order to anonymize the survey data. All semi-structured survey data were kept on the password-protected UNC-CH Qualtrics system, which could only be accessed by myself using my UNC-CH Onyen and password. After my DrPH dissertation defense, the survey data downloaded into Excel and STATA (all of which do not include participant names or identifying numbers) and analyzed will be removed from the UNC-CH Qualtrics system to minimize any risk of data interception. I did not store any audio file electronically since my recording device did not permit downloading of audio files. My recording device is being kept under lock and key. After I successfully defend my DrPH dissertation, I will destroy the audio recordings. This will minimize the risks of linking any study data to an individual respondent.

Study results are presented as aggregate data, with no personal information. All names of study participants and key informants are kept confidential and private. Broad descriptors of study participants and key informants are included in the narrative; however, no unique personal identifier is included. I further stored all paper copies of the informed consent forms in a locked cabinet for written consents given. Access to electronic and hard copies of notes and study documents is restricted to myself and my dissertation committee only. The only inadvertent disclosure of information may include HIV status. To minimize risks, the online survey could be

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<sup>7</sup>For the focus group discussions, participants will be told that confidentiality could not be guaranteed but we will ask them not to talk about anything shared in the focus group with third parties.

completed anonymously (amongst self-disclosed adults living with HIV) without the need to share name or contact information. I only interviewed people living with HIV who were willing to disclosure their status to me.<sup>8</sup> I transcribed all interview data *verbatim*. Please see Data Management and Analysis for further details regarding qualitative data analysis.

### **Informed Consent**

I requested informed consent from all study participants. For the online semi-structured survey, participants were prompted to read the informed consent form and to give their online consent before proceeding to the survey. For the key informant interview, informed consent was requested in writing if the interview was conducted face-to-face and was requested verbally if the interview was done by phone.<sup>9</sup> Some informants interviewed by phone sent a signed, scanned consent form to be prior to the interview. All others provided verbal consent. Due to the minimal risk involved with this study, I sought to waive the requirement for written informed consent for the key informant interviews and this was granted by the UNC-CH non-biomedical IRB. All key informants were sent a copy of the IRB-approved informed consent form together with a fact sheet describing the research project electronically ahead the time.

Prior to giving consent, participants were given the opportunity to ask any questions about the study. All study participants were consented and interviewed in English. All the study procedures were explained in detail so that participants were fully informed about their requirements for the study. All potential study participants were reminded that they were free to choose to participate in the study or not. For people living with HIV, decisions of whether or not to participate in this study did not affect the health care they normally received as well as their employment status or

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<sup>8</sup>Focus groups will be conducted with HIV-positive individuals who are willing to discuss their status within the focus group setting.

<sup>9</sup>For focus group discussions, informed consent will be requested in writing since all the focus group discussions will be conducted face-to-face.

relationship with the Community Advisory Boards. Only those who consented to take part in the study were enrolled. Copies of the IRB-approved informed consent forms for the patient-participants, clinician-researchers, policy-makers/regulators and focus group participants are included in Appendix IV.

### **Institutional Review Board Approval**

The non-biomedical Institutional Review Board (IRB) and Human Research Ethics Committee of the University of North Carolina at Chapel Hill is the primary and sole IRB for this study. I filed the initial IRB application and obtained initial approval on May 18, 2015, before beginning any of the proposed research. In August 2015, I amended the survey prior to implementation and based on feedback received from patient advocates and obtained IRB approval on September 3, 2015. Survey implementation and key informant interviews were initiated thereafter in September 2015.<sup>10</sup>

### **Compensation for Study Participation**

To reward participants who completed the survey, there was a random reward of \$25 for each 25 completed survey respondents, in the form of a VISA gift card, Target™ gift card or Starbucks™ gift card. To participate in the drawing, respondents needed to complete the survey and specifically indicate they wanted to be included in the draw, providing a name and email address or phone number to be contacted upon winning a gift card.

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<sup>10</sup>I amended the focus group discussion guide and procedures in December 2015 and obtained IRB approval on January 4, 2016. Focus group discussions will be implemented from January – June 2016.

There were 345 respondents who completed the necessary information, and thus 13 gift cards were awarded at random. There was no explicit compensation or non-monetary inducements for key informant interviews.<sup>11</sup>

### **Study Management**

I, the Principal Investigator, managed the study, under the supervision of my DrPH dissertation chair, Dr. Sandra Greene, and the guidance of the dissertation committee.

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<sup>11</sup>Focus group participants will receive compensation for their time and effort of \$15 each and this amount was IRB-approved.

### CHAPTER 3 | DATA MANAGEMENT AND ANALYSIS

This section describes the scope of the data management and analysis for this dissertation project. First, I conducted a review of available documents (mostly grey literature) on the topic of participation in HIV cure-related research. Second, I implemented the semi-structured survey and analyzed the *quantitative* data in order to achieve the objectives stated in aim 1. Third, I conducted the key informant interviews and analyzed the key informant *qualitative* data to fulfill the objectives stated in aims 2 and 3. Finally, I attempted to compare the quantitative data (from the semi-structured survey) with the qualitative data (from the key informant interviews) in the discussion section to highlight concordances, discordances and implications of the research to inform the implementation of HIV cure studies and participant recruitment.

Figure 4 represents the logic flow of the data management and analysis for this DrPH dissertation project.



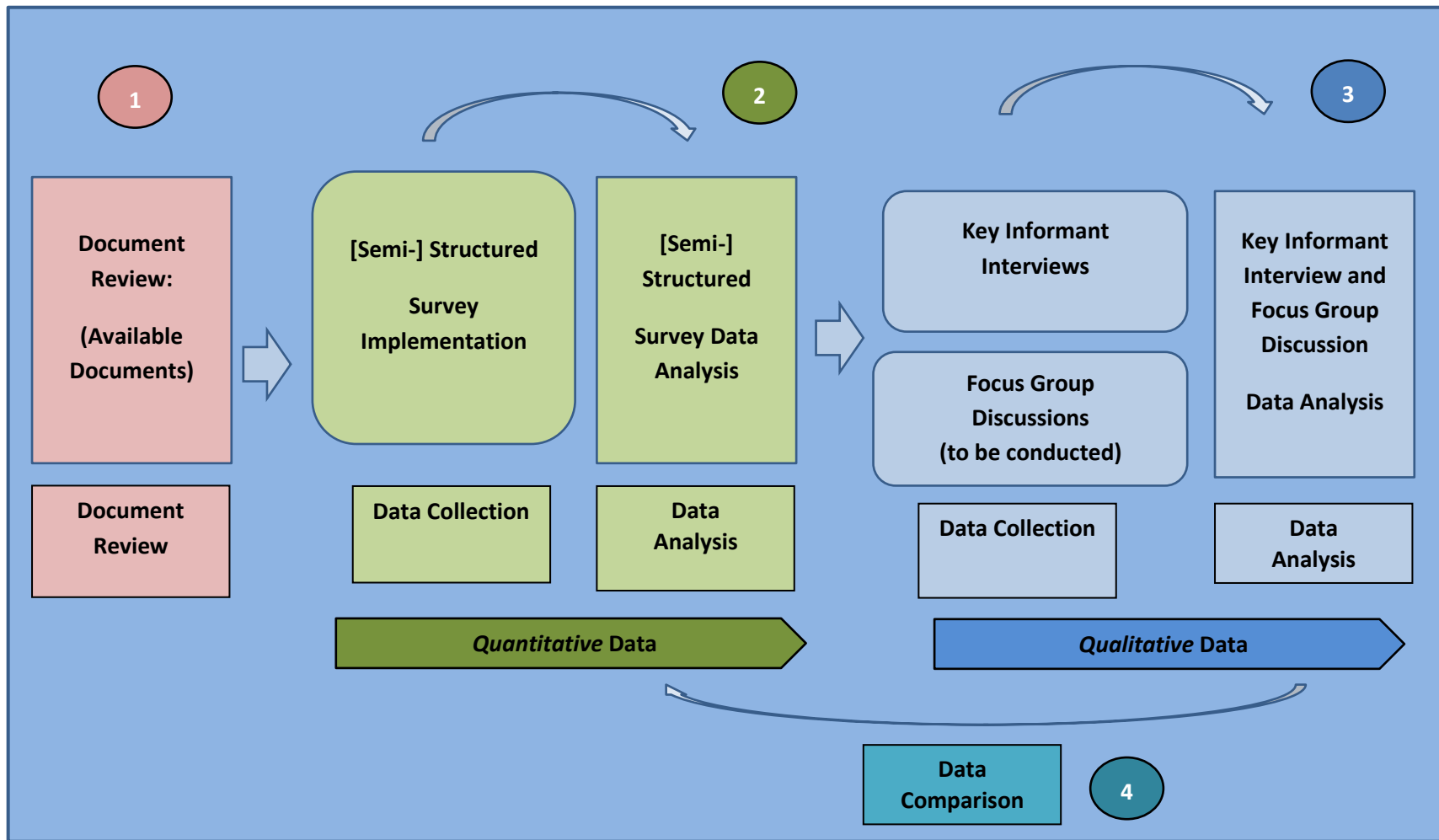


Figure 3. Logic Flow for Data Collection and Analysis

## **Document Review**

As described in the methods section, the document review included systematically written notes from meetings on the topic of participation in HIV cure-related research. The grey literature also included conference reports, published meeting proceedings and working documents from subject matter experts relating to the topic of participation in HIV cure-related studies. The information derived from the document review is included in the discussion section and the list of documents reviewed is can be found in references section.

## **Quantitative Data Management and Analysis: Survey Data**

For the quantitative section, the unit of analysis was survey respondents who were self-disclosed HIV-positive. The primary objective was to determine whether perceived risks of HIV cure-related studies acted as deterrents to participation in HIV cure-related studies and whether perceived (anticipated) benefits (or surrogate clinical endpoints) served as motivators for participation in HIV cure-related research. Survey respondents were asked to respond to questions regarding their willingness to participate in HIV cure-related studies and their perceptions on potential risks and benefits.

## **Quantitative Data Management**

I administered the semi-structured survey using the UNC-CH Qualtrics system from September 8 – October 31, 2015. By then, 409 respondents had at least partially completed the survey, with 9 identifying themselves as ineligible to participate in the survey (they did not meet the eligibility criteria), thus leaving a final sample size of 400 qualified respondents. The survey was the primary data collection capture and management tool for the quantitative data. One advantage of using participant-driven data capture was that participants could key in the data directly, without a second transcription or data entry step, thus minimizing data entry errors. Furthermore, the anonymity of the data collection process allowed answers that were more faithful. Prior to

launching the online questionnaire, I pilot tested the survey in beta mode with the help of community advisory board members to ensure that all necessary skip logics had been incorporated and that all possible kinks have been worked out. After survey administration, I downloaded the data into Excel spreadsheets and converted them into STATA files at the end of the data collection period. I kept the data on my computer dedicated to the DrPH program, which was password-protected. In order to maintain confidentiality, I removed all data containing information that may identify a participant by name, such as text fields requesting participants who may be willing to take part in key informant interviews. These data were kept separately from the main database, and never stored with the survey responses saved in Excel or STATA files. I only used data that had been delinked of all personal identifiers for the analysis.

During the data collection phase, I periodically monitored the dataset to address any issue that arose. I monitored the data using a master Excel spreadsheet downloaded from the UNC-CH Qualtrics system approximately every two weeks. I checked data for out-of-range values, missing text fields and for reasonableness of answers. During the monitoring phase, I performed preliminary descriptive data analyses to determine possible sampling biases (such as a disproportionate percentage of men vs. women). To ensure completion of the survey by most respondents, I did not make text fields mandatory as this would have affected survey completion. I decided instead to report missing data in the final analysis. In the results, I show the number of study respondents who completed each question (out of  $n = 400$ ).

Observations that were not applicable, ineligible, incomplete, or for which participants answered with “Don’t know/Not sure” for specific questions were discarded and treated as missing (see Quantitative Results section for details). Inapplicable and ineligible observations were those coming from survey respondents who were not HIV-positive or *only* answered “I don’t know” or “Not sure” to questions pertaining to their willingness to participate in HIV cure-related studies or

questions regarding benefits or risks of HIV cure-related studies. Incomplete observations were those coming from survey respondents who did not answer questions on their willingness (or unwillingness) to participate in any kind of HIV cure study, which formed the key dependent variable for the analysis. After the exclusion of the inapplicable, ineligible and incomplete survey responses, I prepared a final cleaned data set in Excel for data analysis.

## **Quantitative Data Analysis**

### **Survey Variables**

The survey instrument included questions that captured the respondents' characteristics and attitudes towards HIV cure-related studies, as shown in the IRB-approved questionnaire in Appendix V. The questions were designed specifically to quantitatively assess the correlations between perceived risks and benefits of HIV cure-related research and respondents' willingness to participate in HIV cure studies, fulfilling aim 1.

### **Survey Data Inclusion and Cleaning**

After October 31, 2015, the cutoff date for survey responses, I compiled all of the raw survey data into one spreadsheet using the UNC-CH Qualtrics' built-in software capabilities. Before analyzing the survey results, I checked the quality and completeness of the raw survey data and made corrections and exclusions where necessary to prepare the survey data for analysis. The first step was to exclude incomplete responses, defined as responses by respondents who did not answer any of the questions regarding willingness to participate in types of HIV cure-related studies (the dependent variable), perceptions on potential benefits and potential risks (key independent variables), or more detailed questions regarding global attitudes towards HIV cure research. In other words, these are respondents who may have answered a few demographic questions and nothing else, which provides no significant value to the quantitative or qualitative analyses. As a result, five survey responses were dropped from the raw survey data.

Next, I searched for duplicative responses. One respondent completed the survey twice, providing nearly identical responses, and voluntarily including his or her name on both survey responses. The first (older) response was dropped and the second (latter) response kept, after filling in null responses to specific questions in the second survey response using the answers provided to those questions in the first response, if available. Because the survey was only conducted through the internet, and the UNC-CH Qualtrics software platform was set up to require individual responses for certain questions, skip logic were employed to navigate from one section of the survey to the next. Most of the questions were close-ended questions and transcription errors were virtually null. However, in some multiple choice questions, respondents were given the opportunity to type in text to describe an “Other” multiple choice selection. I reviewed the typed-in text to these questions individually. Where I determined the typed-in text and “Other” selection could be changed to another multiple choice answer, I modified the response.

Finally, names and contact information, which were voluntarily provided by respondents to participate in the survey prize drawing and to volunteer for follow-up interviews, were separated and removed from the survey results. Similarly, all of the answers to open-ended questions were separated and removed from the survey results, and were analyzed independently from the quantitative survey results as part of the qualitative data analysis. This was necessary in order to de-identify the quantitative survey results. The final, cleaned quantitative survey dataset did not include any names, contact information or answers to open-ended questions that may reveal the identity of the respondents. This dataset was imported into Stata statistical software for quantitative analysis.

a) Dependent Variable

The dependent variable for this analysis was the respondent’s relative willingness to participate in HIV cure-related studies. It is formulated from Question 21 in the survey that asked

respondents whether they would consider participating in HIV cure-related studies. The question listed and asked about willingness to participate in the following 14 different types of HIV cure-related studies:

1. Survey/questionnaire research
2. Interviews
3. Focus group discussions
4. Basic blood draw studies
5. Laboratory procedure where selected immune cells are separated out from the participant's blood and the rest of his/her blood is returned to his/her veins (leukapheresis or apheresis)
6. Studies that involve agents that could reactivate HIV that has become dormant inside the cells (latency reversing agents)
7. Studies that would involve the modification of some of the genes in the immune cells
8. Studies that would involve a transplantation of ("autologous") stem cells
9. Studies that would involve a transplantation of someone else's ("allogeneic") stem cells
10. Studies that would involve therapeutic vaccines (vaccines that control disease in people already infected rather than vaccines that prevent infection)
11. Studies that would involve the intensification of treatment or taking more than 3 different classes of drugs at the same time
12. Studies that would involve the use of unique antibodies, proteins or molecules (for example, antibodies that have dual functions)

13. Studies that would involve totally new treatments or approaches (“first-in-human” studies)

14. Studies about safety and efficacy (or phase II or III studies)

The survey respondents answered the question for each type with a categorical “Yes”, “No”, “Don’t know/Not sure”, or could skip any (or all) of the 14 types of HIV cure-related studies. Beyond descriptive statistics, all “Don’t know/Not sure” responses were treated as null responses, similar to a respondent skipping a particular type from the list of 14 types of HIV cure-related studies.

In all, 361 respondents (90%) answered “Yes” or “No” regarding their willingness to participate in at least one of the 14 types of studies, constituting the full sample size for the dependent variable. The distribution of the number of types of HIV cure-related studies (out of 14) that the respondents indicated they were willing to participate in is shown in the results section.

The dependent variable throughout this analysis is the respondent’s willingness to participate in HIV cure-related studies, which can be constructed in different ways from these results. By asking survey respondents whether they would be willing to consider participating in 14 different types of HIV cure studies that span a wide range of intervention and risk (i.e. from responding to questionnaires all the way to intensification of treatment and transplanting stem cells), it was hypothesized that respondents would reveal a variety of willingness to participate in HIV cure-related studies. Surprisingly, nearly everyone indicated they would be willing to participate in at least one type of study. Only 5 out of the 361 people who responded to this question indicated they would not be willing to participate in any of the study types, or at least were not sure that they would. Thus, the dependent variable could not be measured by willingness to participate in *any* type of HIV cure-related study, due to lack of variability.

However, there was variation to the degree of willingness to participate, based on the number of types of studies respondents specifically indicated they would be willing to participate in.

In fact, 26% of the respondents were willing to participate in all 14 types of studies, and nearly half of the respondents were willing to participate in 12 or more types of studies, while 13% were only interested in participating in 4 or fewer types of HIV cure-related studies. For the latter respondents, they were either not sure if they would participate in the other types of studies, or specifically indicated that they would not be willing to participate in those types of studies.

The above results are described in the data analysis section because the number of types of studies the respondents indicated they were willing to participate in were not normally distributed. A skewness/Kurtosis test for normality rejected the null hypothesis that this variable was normally distributed, statistically significant at the 0.1% level. The proportion of respondents generally increased with greater numbers of types of studies the respondents were willing to participate in. The distribution looks similar to a reversed negative binomial distribution. There is also a significant spike at the maximum number of types of studies considered (14).

Attempting to use the number of types of studies a respondent was willing to participate in as the measure of his or her willingness to participate in HIV cure research (and thus as the dependent variable) would create difficulties when fitting a regression model. Since this variable was not continuous (it is a count variable), and has a lower and upper bound, an ordinary least squares (OLS) regression model would poorly fit the data, and particularly when the dependent variable was not normally distributed and was skewed. The result of fitting an OLS model using a count dependent variable with non-normal distribution was that the model residuals may also not be normally distributed and heteroscedastic. In fact, I verified this hypothesis by estimating OLS regression models using the sum of types of studies as the measure of willingness to participate in the dependent variable, and the residuals were clearly not normally distributed and exhibited strong signs of heteroscedasticity. Heteroscedasticity and not normally distributed residuals violated the best linear unbiased estimator assumptions of OLS models (originally proposed in my DrPH



proposal), and the estimated standard errors would not have been inaccurate. As a consequence, statistical tests of significance for the model coefficients would have been flawed. Because the purpose of the statistical analysis was to make inferences on the larger population living with HIV in the United States and their willingness to participate in HIV cure-related studies (and not simply assess willingness to participate among the survey sample), it was important to estimate accurate standard errors. There were different regression model types that were better fitted for count dependent variables, including two-stage models that account for spikes in responses at the boundaries, but the residuals continued to show heteroscedasticity. Thus, I did not use the number of types of HIV cure-related studies respondents were willing to participate in as the dependent variable measuring willingness to participate.

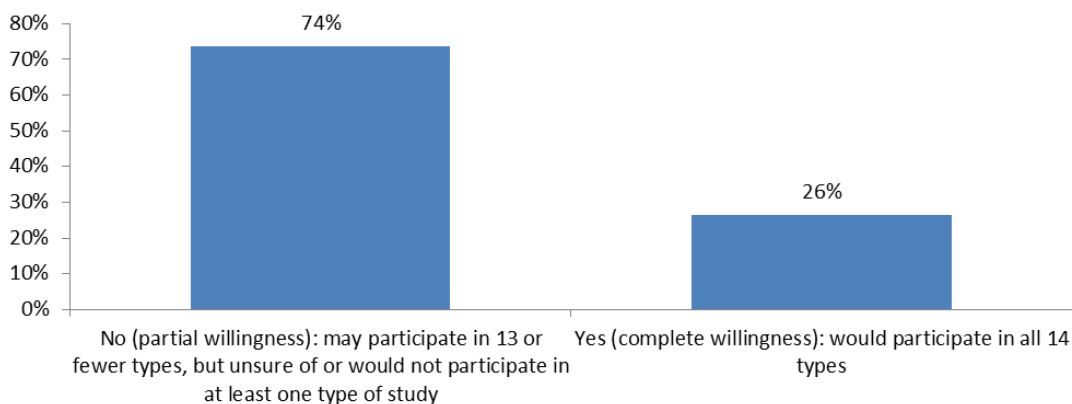
Instead, the dependent variable for my analysis was whether respondents indicated that they would be willing to participate in all 14 types of HIV cure-related studies, versus those who indicated they are willing to participate in 13 or fewer types, but not all types of studies. A respondent who answered “Yes” to all 14 HIV cure study types was assumed to be very willing to participate in HIV cure-related studies, compared to a respondent who answered “No,” “Don’t know/Not sure” or did not answer for one or more types of studies after answering “Yes” to another type of study. The latter respondent was classified as a participant who would be relatively less willing to participate in HIV-cure related studies. This dichotomous dependent variable was true (had a value of 1) if the respondent answered “Yes” to all 14 listed types of HIV cure-related studies, and was false (had a value of 0) if the respondent answered “Yes” to 0 to 13 listed types of HIV cure-related studies, but not to all 14. This particular construct of willingness to participate in HIV cure-related studies had sufficient variation in values to be used to test several correlations with key independent variables to test hypotheses.

The dependent variable split the respondents into two groups: those who were “very willing to participate” in HIV cure-related studies, and those who were “relatively less willing to participate” in HIV cure-related studies. The participants who were very willing to participate indicated in the survey that they would consider participating in all kinds of HIV cure-related studies, including types of studies that have strong interventions such as intensification of treatment, transplanting stem cells, use of latency-reversing agents, modification of genes in immune cells, and first-in-human studies. If a respondent was willing to consider participating in all of these types of studies, they revealed a very strong willingness to participate in HIV cure-related research in the future. Conversely, the participants who were relatively less willing to participate indicated in the survey that while they might consider participating in some, or even many (up to 13), types of studies, they are specifically not willing to participate in, or at the very least are hesitant or do not know if they would consider participating in, at least one type of study. Hence, they were relatively less willing to participate in HIV cure research compared to their counterparts who are “very willing to participate.” Some of the relatively less willing to participate respondents were actually still willing to participate in 11, 12 or even 13 out of 14 types of studies, exhibiting a high degree of willingness to participate in HIV cure research. However, relative to those who are willing to participate in all 14 types of studies, they were relatively less willing. This distinction is important to bear in mind when interpreting the results presented in this dissertation. Among the 361 respondents, 95 (26%) were willing to consider participating in all 14 types of HIV cure-related studies, and are thus classified as “very willing to participate” in HIV cure-related studies, with a value of 1 in the dependent variable. The other 266 (74%) of respondents are classified as “relatively less willing to participate” in HIV cure-related studies, with a value of 0 in the dependent variable, as shown in. By comparison to the 95 respondents who answered “Yes” to all 14 types of studies, these 266 respondents were less willing to participate in HIV cure-related studies.

**Table 2. Summary Statistics of the Dependent Variable**

Dependent variable: willingness to consider participating in all 14 types of HIV cure related studies	Value of the dichotomous dependent variable	n	Percent
No (relatively less willing to participate): may participate in 13 or fewer types, but unsure of or would not participate in at least one type of study	0	266	74%
Yes (very willing to participate): would participate in all 14 types	1	95	26%
Total		361	

**Indicated willingness to consider participating in all 14 types of HIV cure-related studies (as opposed to 13 or fewer types)**  
(n=361)

**Figure 4. Distribution of Values of the Dependent Variable**

Among the 266 respondents who were relatively less willing to participate in HIV cure-related studies, 141 (slightly more than half) specifically answered "No" on considering participating in at least one of the 14 types of HIV cure-related studies. The other half either answered "Don't know/Not sure" and/or did not answer the question for all 14 types of studies. Nevertheless, even respondents who answered "Yes" to some types of HIV cure-related studies and skipped over other types of studies or did not know whether they would participate in other types of studies revealed a

lower level of willingness to participate in "any kind of HIV cure-related study" than the respondents who specifically answered "Yes" to all 14 types. Again, these results are presented in the data analysis section as they drove the selection of key dependent variables.

#### b) Key Independent Variables

In the survey, respondents were asked about their perceptions of the importance of 21 different potential benefits (11 potential personal benefits, 6 potential personal clinical benefits and 4 potential social benefits) as motivating factors to considering participating in HIV cure-related studies. Answers were provided on a Likert scale: very important, somewhat important, barely important, not important, don't know/not applicable. Likewise, respondents were asked about their perceptions of the likelihood of 35 different potential risks (23 potential personal risks, 7 potential personal clinical risks and 6 potential social risks) to discourage them from considering participation in HIV cure-related studies. Answers were provided on a Likert scale: very likely to discourage, somewhat likely to discourage, barely likely to discourage, not likely to discourage (does not affect decision to participate), and don't know/not sure. Beyond summarizing the descriptive statistics, all "Don't know/Not applicable" or "Don't know/Not sure" answers were treated as null responses.

The key independent variables were formulated from the questions about whether different types of potential benefits were perceived by the respondent to be, specifically, "very important" motivators to consider participation in HIV cure-related studies (as opposed to "somewhat important", "barely important" or "not important"). The key independent variables were also formulated from questions about whether potential risks were perceived by the respondent to, specifically, "very likely to discourage" them from considering participation in HIV cure-related studies (as opposed to "somewhat likely to discourage", "barely likely to discourage" or "not likely to discourage"). Thus, the Likert scale responses were reconstructed into dichotomous variables for

the 21 potential benefits and 35 potential risks key independent variables. Collapsing these categories allowed controlling for potential social desirability bias.

### c) Control Variables

Control variables provided socio-demographic characteristics of the respondents as well as their global attitudes towards HIV cure research. The variables were formulated from survey questions about the respondent's gender, age, ethnicity, education, income, location, self-assessment of health status, self-assessment of whether the respondents believed they were in control over their own health care, duration of HIV status as a percent of their life, whether the respondents ever volunteered for HIV treatment or HIV cure studies, and whether the respondents were generally interested in HIV cure research. Age and duration of HIV status as a percent of the respondent's life were continuous variables. All other variables were categorical. Education, income, and self-assessment of health status were ordinal categorical variables. For this analysis, the location variable was constructed as a categorical variable describing four regions in the United States: West, Midwest, Northeast, and South (including two respondents from Puerto Rico). The four regions followed the U.S. Census Bureau's four region categorization that were based on state boundaries that equally divide the geographic land mass of the United States.<sup>12</sup>

### **Baseline (Descriptive) Quantitative Data Analysis**

I started by quantitatively summarizing the responses to all closed-ended survey questions in descriptive statistics tables (see Results section). I displayed the number of responses to each question and summarized the responses for continuous variables by the mean, median, minimum and maximum values. I summarized the responses for dichotomous variables, such as a question regarding whether the respondent were currently participating in a health study, by the number and

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<sup>12</sup>[http://www2.census.gov/geo/pdfs/maps-data/maps/reference/us\\_regdiv.pdf](http://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf). The four regions included the following states: 1) West: CA, NV, AZ, NM, UT, CO, WY, MT, ID, OR, WA, HI, AK; 2) Midwest: KS, MO, IL, IN, OH, MI, WI, IA, NE, SD, ND, MN; 3) Northeast: PA, NJ, NY, RI, CT, MA, VT, NH, ME and 4) South: TX, OK, AR, LA, MS, AL, GA, FL, SC, NC, TN, KY, VA, WV, DC, MD, DE, Puerto Rico.

percentage of responses that answered in the affirmative (i.e.: “% Yes”) and negative (i.e. “% No”). I also summarized the responses for discrete categorical or ordinal variables by the percentage of answers in each mutually exclusive and exhaustive category, including “I don’t know/Not sure,” where applicable. All of the discrete questions on the survey asked the respondents to select only one answer per question.

I displayed the descriptive statistics for all questions using data tables and graphs (see Results section). The questions regarding the respondents’ perceptions about the motivating/detering factors of potential benefits and risks were asked using a Likert scale. For the analysis, these ordinal variables were restructured into dichotomous variables, where the most extreme answer (i.e. benefit is a “very important” motivator, and risk is “very likely to discourage” participation) is given a value of 1 and all other answers except “I don’t know” given a value of 0. Because of the reclassification of these key independent variables, the graphical visualization of the descriptive survey responses were centered around the breakpoint in the Likert scale that corresponded to the dichotomous construct of the variables.

I next regrouped answers to questions and summarized responses to broader grouped questions. For example, I calculated and revealed the percentage of respondents based on the total number of HIV cure-related studies they indicated they would be willing to participate in, and how many respondents indicated they would be willing to participate in all 14 types of studies (i.e. very willing to participate) versus willing to participate in some but not all types of studies (i.e. less willing to participate).

The primary research question in aim 1 was whether potential benefits would motivate participation in HIV cure-related studies and whether potential risks would deter participation. In answering this question, the focus of the baseline (descriptive) analysis was to report on the respondents’ assessments of whether individually named risks would deter their participation, and

whether individually named benefits would motivate their participation in HIV cure-related studies. The greater the proportion of respondents indicating that a specific benefit would motivate them or a risk would deter them, the stronger the likelihood that the specific benefit or risk applied to potential HIV cure study participants with similar characteristics to the sample population. Comparison between the different types of benefits and risks revealed that potential HIV cure study participants more greatly valued certain types of benefits or disliked or feared certain types of risks. The results of these comparisons can inform Principal Investigators and/or implementers of HIV cure-related studies on the types of benefits and risks they should focus their attention on in order to maximize the willingness of eligible potential HIV-positive volunteers to participate in HIV cure-related studies.

Because primary data from potential HIV cure studies are rare, the descriptive statistics obtained from this survey provide a rare glimpse at their attitudes and perceptions, and can be very informative to researchers and policy-makers in designing and recruiting for HIV cure studies in the future. I summarized the key results from the descriptive statistics, drawing attention to particular results that revealed important findings.

### **Bivariate and Multivariate Quantitative Analysis**

To more fully understand HIV-positive patients' willingness to participate in HIV cure-related studies and their attitude towards potential benefits and potential risks of participation, I conducted bivariate and multivariate analyses on the survey responses to test a series of hypotheses. The hypotheses were formulated to identify associations between respondents' perceptions of specific benefits and risks and their willingness to participate in HIV cure-related studies, helping to fulfill the primary research question in aim 1. Another set of hypotheses was tested to answer secondary research questions in aim 1: specifically, how do certain socio-demographic characteristics and

global attitudes of HIV-positive patients correlate with their willingness to participate in these studies?

First, bivariate association analysis was conducted to test whether people who were very willing to participate in HIV cure studies (as measured by their indication that they would participate in any and all of the 14 types of studies listed) have certain perceptions regarding potential benefits and potential risks, and have specific socio-demographic characteristics. The bivariate association analysis illuminated possible strong and weak correlations and helped inform the structure of the multivariate models. Second, multivariate regression models were used to estimate the effects of perceptions regarding benefits, risks and characteristics of people on their willingness to participate in HIV cure-related studies, controlling for extraneous factors.

To prepare the survey data for the bivariate and multivariate analyses, I generated new variables by combining responses from different variables, which allowed me to include important variables in my models that could otherwise be discarded. For instance, I created a continuous variable that approximated the percent of the person's lifetime in which s/he was diagnosed as HIV-positive. This was created by calculating the number of years since their HIV-positive diagnosis (by subtracting the year of diagnosis from 2015) and dividing by the age of the respondent. The higher the percentage, the more of that person's lifetime was spent with an HIV-positive status. This composite variable was strongly correlated with willingness to participate in HIV cure-related studies, as described in the Results section.

I also restructured some variables by aggregating their categorical or ordinal answers into fewer options based on their response rates and the variability within each question. For example, several people chose "Other" in responding to the question of educational attainment, and wrote in that they completed a few years of college but did not complete a degree. I recharacterized those responses as "Some college" and aggregated the results with "Associate degree" to indicate that the



respondent attended college but did not complete a Bachelor's degree. In the multivariate regression analysis, the education variable was restructured in multiple ways and, based on the variability of the responses and the best fit to the model, ultimately ended with three mutually exclusive variables indicating whether the respondent completed a graduate degree (Master's or higher), an undergraduate degree (Bachelor's), or neither (Associate's, G.E.D., high school, or lower).

The response rate for all of the key questions were relatively high; at least 350 people answered questions about their perceptions of perceived risks, and even more answered questions on perceptions of perceived benefits (around 380) and on their characteristics (nearly all 400 respondents). Because the response rate was high for the dependent variables and key independent variables, none of the variables were dropped because of a lack of response.

For a few categorical and ordinal variables, the responses were not sufficiently variable, with more than 90% of the respondents selecting the same answer. However, there were at least 5 individuals who responded differently than the majority, and thus there were always some variation in the responses, even if the variation was small. I tested the bivariate correlations between these variables and the dependent variable (willingness to participate in HIV cure-related studies) to determine whether the small minorities had significantly different levels of willingness to participate in HIV cure-related studies. If the correlation was statistically significant at the 95% level, I included the variable in the multivariate models. However, if the bivariate correlation between the variable with low variation and willingness to participate was not statistically significant, I excluded that variable from the multivariate models because of lack of variability and in order to improve the efficiency of my models. I used robust standard errors in all bivariate and multivariate analyses.

a) Bivariate Association Analysis

Bivariate association analysis was used to test correlations between specific sets of perceptions of potential benefits and risks, and socio-demographic characteristics and global attitudes of potential HIV-positive volunteers on their willingness to participate in HIV cure-related studies. The dependent variable was whether the respondent was willing to participate in all 14 types of HIV cure-related studies that were listed in the survey (very willing to participate) or was willing to participate in none/some but not all of the types of studies listed (relatively less willing to participate). The dependent variable was dichotomous, with 26% of the survey respondents in the very willing category (value of 1) and the remainder in the relatively less willing to participate category (value of 0).

The independent variables were either interval (continuous), ordinal or categorical. Each of the 21 potential personal, personal clinical and social benefits variables were reclassified as binary variables. The binary variables indicated whether the respondent claimed the potential benefit was a “very important” factor to his/her motivation in considering to participate in HIV cure studies (value of 1), versus “somewhat important”, “barely important” or “not important” (all value of 0). All “Don’t know/Not applicable” answers were treated as null. Likewise, each of the 35 potential personal, personal clinical and social risk variables were reclassified as binary variables. The binary variables indicated whether the respondent claimed the risk is a “very likely to discourage” them from considering to participate in HIV cure studies (value of 1), versus “somewhat likely”, “barely likely” or “not likely” (all value of 0). All “Don’t know/Not sure” answers were treated as null responses.

I tested for independence between the dependent variable on willingness to participate and each of the independent variables, one at a time, using univariate logistic regression analysis. Univariate logistic regressions were used to test the bivariate associations instead of using chi-

squared tests, even for paired categorical variables, because univariate logistic regressions quantifies the odds ratio for each category in the independent variable. The odds ratio indicates the direction and magnitude of the association of the independent variable with the dependent variable (willingness to participate), whereas chi-squared tests would only reveal whether the variables are independent. The odds ratios for the different categorical values for each of the variables is summarized in the Results section, along with the p-value for the test of independence of each independent variable and the dependent variable. Data were analyzed using Stata 11.2.

In these tests, the null hypothesis was that the perception of benefit, perception of risk, socio-demographic characteristic or global attitude of the respondent was independent of the respondent's willingness to participate in HIV cure-related studies. The alternative hypotheses were that the two variables were associated. If the resulting univariate logistic regression test statistic was small and produced a p-value less than or equal to 0.05, given the degrees of freedom for the paired variables, the null hypothesis was rejected and an association between the two variables was established.

In particular, the following series of null hypotheses were tested. All of the following null hypotheses took on the form of testing whether potential HIV-positive volunteers who were "very willing to participate" in HIV cure-related studies had certain perceptions or characteristics that were statistically different from potential HIV-positive volunteers who were "relatively less willing" to participate in HIV cure-related studies:

1.  $H_0$ : Willingness to participate in all types of HIV cure-related studies (very willing to participate) is independent of whether the respondent believes that a specific potential benefit would be "very important" in motivating them to consider participating in HIV cure studies.

- ⇒ This null hypothesis was repeated for every individual potential benefit asked about in the survey. Rejecting the null hypothesis and having a positive association (i.e. an odds ratio greater than 1.0) would indicate that the respondents who are very willing to participate in HIV cure-related studies find that particular potential benefit to be a strong motivator for participation; more so than respondents who were relatively less willing to participate in HIV cure-related studies.
2.  $H_0$ : Willingness to participate in all types of HIV cure-related studies (very willing to participate) is independent of whether the respondent believes that a specific potential risk would “very likely discourage” them from considering participating in HIV cure studies.
- ⇒ This null hypothesis was repeated for every individual potential risk asked about in the survey. Rejecting the null hypothesis and having a negative association (i.e. an odds ratio less than 1.0) would indicate that the respondents who are relatively less willing to participate in HIV cure-related studies find that particular potential risk to be a strong deterrent for participation; more so than respondents who are very willing to participate in all HIV cure-related studies.
  - ⇒ Results from the tests of independence listed above could inform Principal Investigators or implementors of HIV cure-related studies about which benefits the potential HIV-positive volunteers that are more willing to participate in HIV cure-related studies cared about. Focusing on the needs of the potential volunteers who are very willing to participate could possibly narrow the scope of variables the Principal Investigators or implementers should pay attention to in preparing their HIV cure-related studies for patient recruitment.
  - ⇒ Additionally, the results would reveal which risks are more strongly associated with a reduced willingness to participate in HIV cure-related studies. If Principal Investigators

or implementers are seeking to increase study enrollment by enlisting volunteers who are less willing to participate in studies, they should focus their attention in mitigating these specific potential risks from their studies.

⇒ Following these analyses, univariate logistic regressions were used to determine whether certain socio-demographic characteristics and attitudes of respondents were associated with their willingness to participate in HIV cure-related studies, answering secondary research questions in aim 1. In particular, the following null hypotheses were tested, with the alternative hypotheses being that the two variables were associated:

3.  $H_0$ : Willingness to participate in all types of HIV cure-related studies (very willing to participate) is independent of each socio-demographic characteristic and global attitude of the respondent towards HIV cure-related research.

⇒ This null hypothesis was repeated for every socio-demographic variable and global attitude question asked about in the survey, including: gender, age, ethnicity, education, income, location, self-assessments of health status and whether respondent is in control of their own health, duration of HIV status, history of participation or volunteering for HIV treatment or HIV cure studies, and whether the respondent is generally interested in HIV cure research. Rejecting the null hypothesis would indicate that there was an association between the respondent characteristic variable and their willingness to participate in HIV cure-related studies. An odds ratio greater than 1.0 would reveal that there is a positive association between the characteristic variable and strong willingness to participate in HIV cure-related studies, while an odds ratio less than 1.0 would reveal that respondents with this characteristic are less willing to participate in HIV cure-related studies. This information might help Principal Investigators or implementers target who to recruit for HIV cure-related studies, all else being equal.

## b) Multivariate Regression Analysis

Bivariate association analyses established which potential benefits and potential risks were associated with respondents' willingness to participate in HIV cure-related studies. These associations, however, may have been indirect and bivariate analyses did not control for simultaneous effects on the relationship between socio-demographic characteristics, potential benefit and potential risk factors, and willingness to participate in HIV cure-related studies. Due to the convenient sampling of survey respondents, it is unlikely that the survey responses were statistically representative of the universe of potential HIV cure research volunteers, which would go beyond people who are aware of HIV cure-related studies and connected to HIV cure listservs and networks to include all people living with HIV in the United states who would meet inclusion/exclusion criteria of studies and actually enter studies. Thus, it is important to control for respondents' socio-demographic characteristics and attitudes in multivariate regression analyses in order to test the correlation between potential benefit and potential risk factors and willingness to participate in studies independent of extraneous factors.

Cross-sectional multivariate logistic regression models were used to answer the primary research question in aim 1, which was whether potential benefits motivates participation in HIV cure-related studies and whether potential risks deters participation, controlling for extraneous factors. Multiple regression models are run to test each key independent variables' association with willingness to participate. I used STATA statistical software to estimate the logistic regression models. All of the logistic models take on the general form of:

$$\ln(WTP_i / (1 - WTP_i)) = \alpha + \beta_b \text{Benefit}_{bi} + \beta_r \text{Risk}_{ri} + \sum \beta_c \text{Control}_{ci}$$
$$i = 1, \dots, n; \quad b = 1, \dots, 21; \quad r = 1, \dots, 35; \quad c = 1, \dots, C \quad [1]$$

where  $\ln(WTP_i / (1 - WTP_i))$  is the expected log of the odds that individual  $i$  is very willing to participate in HIV cure-related studies (versus relatively less willing to participate);  $\text{Benefit}_{bi}$  is a

binary variable indicating whether individual  $i$  considers a potential benefit,  $b$ , to be “very important” to their motivation in considering participating in HIV cure-related studies (versus “somewhat important”, “barely important”, or “not important”);  $Risk_{ri}$  is a binary variable indicating whether individual  $i$  considers a potential risk,  $r$ , to be “very likely” to discourage them from considering participating in HIV cure-related studies (versus “somewhat likely”, “barely likely”, or “not likely”);  $Control_i$  is a vector of control variables that include individual-specific characteristics on gender, age, ethnicity, education, income, location, self-assessments of health status and whether respondent is in control of their own health, duration of HIV status, history of participation or volunteering for HIV treatment or HIV cure studies, and whether the respondent is generally interested in HIV cure research; and  $\alpha$  is the model’s baseline constant. Robust standard errors are estimated in all of the models, to control for potential heteroskedasticity.

The multivariate models were estimated in the following three stages:

1) Multivariate logistic model involving only the control variables

As a first step, the participant’s willingness to participate in HIV cure-related research was regressed on only the individual-level socio-demographic characteristics and global attitudes towards HIV cure research, which were used as control variables in Equation 1. Benefits and risks were excluded from this model. By including only the control variables, this model revealed which individual-level characteristics were more strongly associated with willingness to participate in HIV cure-related studies.

The control variables used in Model 1 included:

- Gender
- Age
- Ethnicity
- Education

- Household income
- Region of the country
- Whether the participant considered themselves to be “not at all healthy” or “not very healthy”
- Whether the participant believed they could control their own health care
- Whether the participant was taking medications for HIV
- Percent of life living with an HIV-positive status
- Whether the participant ever volunteered for an HIV treatment or an HIV cure study and
- The participant’s general interest level in HIV cure-related research.

Several models were iteratively fitted to test the association between willingness to participate and various combinations and constructs of the control variables listed above, in order to determine the best possible combination and construct of control variables that best fit the data. At first, a full model involving all of the variables listed above was estimated (unrestricted model). Then, a second model was estimated by dropping one or more of the control variables, or aggregating dummy variables to reduce the number of categories in a categorical variable (restricted model), using the exact same sample that was used in estimating the unrestricted model. A Likelihood-Ratio test was conducted to test the statistical significance of the difference in the model fits. The null hypothesis is that the model fit of the restricted model is the same as the model fit of the unrestricted model. If the p-value of the Likelihood-Ratio test was 0.05 or lower, the null hypothesis is rejected, and the unrestricted model is preferred over the restricted model, because variables that were dropped or transformed in the restricted model were significant and better predicted willingness to participate than by being omitted or reduced. On the other hand, if the p-value was 0.06 or higher, the null hypothesis is not rejected and the restricted model is preferred over the unrestricted model, in order to produce the most efficient number and constructs of



control variables possible. In models in which variables were transformed, some of the variables (e.g. education, self-assessment on their health status) were tested in ordinal forms as well as dichotomous forms, while some categorical variables (e.g. education, gender) were transformed into various combinations of aggregated dummy variables in some models. The process of estimating and testing nested models was repeated until each of the control variables is tested. Finally, alternative constructs for some control variables were also tested and the version of the construct that produced a better fit (lower p-value) was judged to be superior and used in subsequent models. For example, age produced a better fit as a continuous variable (p-value = 0.018) than as a categorical variable that divides age into five age groups (p-value of the F-test for all age group categories = 0.322).

At the conclusion of these iterative model estimations and tests, a final set of control variables and their constructs was determined as the superior combination of control variables that best fit the data with willingness to participate as the dependent variable. These specific control variables are described in Equation 2 below, and are used in all subsequent models that introduce key independent variables.

Model 1:

$$\begin{aligned} \ln(WTP_i / (1 - WTP_i)) = & \alpha + \beta_{c1} \text{ male}_i + \beta_{c2} \text{ age}_i + \beta_{c3} \text{ africanamerican}_i + \beta_{c4} \text{ hispanic}_i + \beta_{c5} \\ & \text{otherethnicity}_i + \\ & \beta_{c6} \text{ bachelors}_i + \beta_{c7} \text{ graduatedegree}_i + \beta_{c8} \text{ income25-50k}_i + \beta_{c9} \text{ income51-75k}_i + \beta_{c10} \\ & \text{income76-100k}_i + \beta_{c11} \text{ income101-125k}_i + \beta_{c12} \text{ income126-150k}_i + \beta_{c13} \text{ income151-k}_i + \beta_{c14} \\ & \text{northeast}_i + \beta_{c15} \text{ midwest}_i + \beta_{c16} \text{ south}_i + \beta_{c17} \text{ nothealthy}_i + \beta_{c18} \text{ controlhealthcare}_i + \beta_{c19} \\ & \text{percentlifewithHIV}_i + \beta_{c20} \text{ volunteeredcurestudy}_i \quad [2] \end{aligned}$$

where:

- $\text{male}_i$  is whether the respondent is male (versus female or transgender)

- $age_i$  is the age of the respondent as a continuous variable
- $africanamerican_i$ ,  $hispanic_i$ , and  $otherethnicity_i$  are mutually exclusive dummy variables describing the ethnicity of the respondent (versus caucasian)
- $bachelors_i$  and  $graduatedegree_i$  are mutually exclusive dummy variables that describe the maximum education level attainment of the respondent, either completing a Bachelor's degree or a graduate degree (versus Associate's degree or some years in college or lower)
- $income25-50ki$ ,  $income51-75ki$ ,  $income76-100ki$ ,  $income101-125ki$ ,  $income126-150ki$ , and  $income151-ki$  are mutually exclusive dummy variables that describe the annual household income of the respondent in \$25,000 intervals, i.e. between \$25,001 and \$50,000, between \$50,001 and \$75,000, etc. (versus \$0 - \$25,000)
- $northeast_i$ ,  $midwest_i$ , and  $south_i$  are mutually exclusive dummy variables that describe the location of the respondent (versus west)
- $nothealthy_i$  is a dummy variable indicating whether the respondent self-assessed their health status as "not at all healthy" or "not very healthy" (versus "very healthy", "healthy" or "somewhat healthy")
- $controlhealthcare_i$  is a dummy variable indicating whether the respondent felt they have control over their own health care
- $percentlifewithHIV_i$  is the percent of the respondent's life that was lived with an HIV-positive diagnosis, as a continuous variable ranging from 1 to 100
- $volunteeredcurestudy_i$  is a dummy variable indicating whether the respondent had ever been in or volunteered for an HIV cure study

The variables measuring whether the respondent is currently taking HIV medication, whether the respondent ever volunteered for an HIV treatment study, and whether the respondent was generally interested in HIV cure research were omitted because of lack of variation within

responses, poor explanatory power of the variable, and/or perfect correlation with willingness to participate in HIV cure studies. There were only two respondents who were not currently taking HIV medication who were part of the “very willing to participate” group, limiting the variation within responses. All five respondents who indicated they were not generally interested in HIV cure research were part of the “less willing to participate” group of respondents. Whether a respondent volunteered for an HIV treatment study and HIV cure study in the past was perfectly correlated (all who volunteered for HIV cure studies in the past had also volunteered for HIV treatment studies, and all who never volunteered for HIV treatment studies also never volunteered for HIV cure studies). Thus, only one of the two variables should be included as a control variable in Model 1, to prevent multicollinearity, and the variable `volunteeredcurestudy` was selected on the basis of a stronger correlation with willingness to participate in HIV cure-related studies as determined by the bivariate association analysis.

By estimating Model 1 using a logistic regression model, the coefficients estimated the odds ratios of willingness to participate for each socio-demographic variable, controlling for all other variables. Whether the odds ratio estimates were greater than or less than 1 indicated whether participants with those characteristics were more likely or less likely, respectively, to be very willing to participate (in all types of HIV cure-related studies). I tested the statistical significance of the odds ratio of each socio-demographic variable against the null hypothesis that the odds ratio was equal to 1.0 and the alternative hypothesis that it was not equal to 1.0. If the p-value was 0.05 or lower, statistical association was established, revealing the socio-demographic characteristics that were statistically associated with willingness to participate in HIV cure-related studies. This information reveals to Principal Investigators or implementers whether people living with HIV who have specific characteristics (e.g. gender, age, lifetime living with HIV diagnosis, etc.) are more or less willing, on average, to participate in HIV cure-related studies, which is vital information for improving

recruitment for studies. The odds ratio for the control variables listed in Model 1 is reported in the Results section, alongside its 95% confidence interval and p-value.

- 2) Multivariate logistic models involving a single potential benefit or single potential risk as the key independent variable

Although the general form of the model shown in Equation 1 lists both benefit and risk variables in the same equation, only one potential benefit or potential risk is included in the model at a time. The logistic regression model is fitted multiple times, each time using a different potential benefit or potential risk variable in the model as the sole key independent variable. Thus, none of the regression models included multiple potential benefit variables or multiple potential risk variables, or mixed potential benefit and potential risk variables in the same model. This was necessary for two reasons:

- 1) Many potential benefit variables and potential risk variables were very strongly correlated with one another. Including multiple variables that were strongly correlated in a regression model introduced multicollinearity to the model, making it difficult to assess the effect of the key independent variables of interest on willingness to participate. Additionally, because of a lack of variation across different benefit and risk variables (due to the strong correlations between pairs and groups of benefit and risk variables), adding multiple benefit and risk variables in the same model creates perfect collinearity with the dependent variable, eliminating the use of the independent variables that created perfect predictions. For example, when all 35 potential risk factors were included simultaneously in Equation 1, eight of the 35 potential risk variables were dropped from the regression because each one predicts failure perfectly, controlling for all other variables.
- 2) More importantly, the purpose of this analysis was to determine whether respondents' perceptions of *individual* potential benefits and *individual* potential risks were associated

with their willingness to participate in HIV cure-related studies, controlling for extraneous factors. The extraneous factors, in this case, were socio-demographic characteristics and global attitudes towards HIV cure research. It is not the intention of this analysis to determine the association between willingness to participate and perceptions on potential benefits and potential risks, controlling for perceptions of other potential benefits and potential risks. Interpretation of these results would be difficult, and nearly impossible to translate into actionable items for Principal Investigators or implementers. For example, a regression model that includes multiple potential benefit variables might reveal that, controlling for socio-demographic characteristics, individuals that perceive “helping find a cure for HIV” as a very important motivating factor are associated with higher willingness to participate in HIV cure-related studies, controlling for their perception on the motivating importance of “contributing to scientific knowledge,” “helping other people with HIV in the future,” “being compensated for study participation,” “receiving more regular access to medical researchers” and “controlling the viral load in absence of treatment,” simultaneously. The interpretation of the key association (between helping find a cure for HIV and willingness to participate) is obscured when attempting to understand the multiple layers of other perceptions that are controlled for simultaneously, some of which are also correlated with the key independent variable. Instead, by only including one key independent variable in the regression model at a time, controlling only for socio-demographic characteristics and global attitudes of the respondent towards HIV cure research, it was possible to identify which perceptions of potential benefits and potential risks were associated with willingness to participate. This allowed translating the results into recommendations on which benefits and risks Principal Investigators or implementers should focus on while recruiting and enrolling potential HIV cure research volunteers.

Since the dependent variable is a binary variable, we estimated logistic regression models.

The coefficients  $\beta_b$ ,  $\beta_r$ , and  $\beta_c$  estimated the odds ratio of willingness to participate perceiving a potential benefit  $b$  as a very important motivator, perceiving potential risk  $r$  as very likely to discourage participation, and socio-demographic characteristic  $c$ , respectively, controlling for all other variables. Whether the odds ratio estimates were greater than or less than 1 indicated whether participants with those specific perceptions were more likely or less likely, respectively, to be very willing to participate (in all types of HIV cure-related studies). For example, an odds ratio estimate of 1.5 indicated that participants perceiving a potential benefit  $b$  as a “very important” motivating factor to considering participating in HIV cure-related studies was associated with a 50% greater likelihood that they are willing to participate in all 14 types of studies than others who did not perceive that benefit  $b$  is a “very important” motivating factor, *ceteris paribus*.

After a logistic model is estimated, the statistical significance of the odds ratio of the key independent variable is tested. The null hypothesis is that the odds ratio is equal to 1.0, and the alternative hypothesis was that it was not equal to 1.0, thus using a two-tailed test. If the p-value was 0.05 or lower, statistical association was established, revealing the potential benefits and potential risks that were statistically associated with willingness or unwillingness to participate, controlling for socio-demographic characteristics and individuals’ global attitudes towards HIV cure research. The odds ratio for the key independent variable in each model is reported in the Results section, alongside its 95% confidence interval and p-value.

I tested the hypothesis that the odds ratio estimates for the potential benefit variables,  $\beta_b$ , would be greater than 1.0, indicating that there was a positive correlation between perceiving a specific potential benefit as a “very important” motivating factor and a person’s willingness to participate in all types of HIV cure-related studies. Likewise, I test the hypothesis that the odds ratio estimates for the potential risk variables,  $\beta_r$ , would be less than 1.0, indicating that individuals who

perceive a specific potential risk as “very likely to discourage” them from considering participation in HIV cure-related studies are less likely to be willing to participate in studies.

Specific potential benefits and potential risks that were statistically associated with willingness to participate in HIV cure-related studies were noted and discussed. Unfortunately, it was very difficult to infer causality solely using cross-sectional regression models. Collecting longitudinal data among actual study participants was beyond the scope of my research, however. The results of my logistic models can be used to detect and explore associations between perceptions of benefits/risks and willingness to participate in HIV cure-related studies, but not to infer causality.

- 3) Multivariate logistic models involving the number of potential benefits perceived as very important motivating factors and the number of potential risks perceived to be very likely to discourage participation as the key independent variables

In addition to estimating several multivariate models using perception of a potential benefit or potential risk as the sole key independent variable in the model, I also estimated multivariate logistic regression models that used the total number of potential benefits (or grouped benefits) that were deemed to be “very important” motivating factors, and the total number of potential risks (or grouped risks) that were deemed to be “very likely” to discourage participation as the key independent variables, controlling for socio-demographic characteristics and global attitude towards HIV cure research. Thus, a new model is estimated as follows:

$$\ln(WTP_i / (1 - WTP_i)) = \alpha + \beta_m NB_i + \beta_n NR_i + \sum \beta_c \text{Control}_{ci} \quad i = 1, \dots, n; \quad c = 1, \dots, C \quad [3]$$

where  $NB_i$  is the tally of potential benefits that individual  $i$  perceives to be “very important” motivating factors to considering participating in HIV cure-related studies;  $NR_i$  is the tally of potential risks that individual  $i$  perceives to be “very likely” to discourage them from considering participating in HIV cure-related studies;  $\text{Control}_{ci}$  is the same vector of control variables estimated

in Equation 1; and  $\alpha$  is the model's baseline constant. Robust standard errors are estimated in all of the models, to control for potential heteroskedasticity.

The greater the number  $NB_i$ , the more potential benefits an individual considers to be very important as motivating factors. This may reveal a larger sense of optimism and hope inherent in the individual considering participation in HIV cure-related studies. Conversely, the greater the number  $NR_i$ , the more potential risks an individual considers to be very likely to discourage them from participating in HIV cure-related studies. In other words, the more potential risks and problems the individual perceives as obstacles to participating in HIV cure-related studies.

In this model, the coefficients  $\beta_m$  and  $\beta_n$  estimated the odds ratio of willingness to participate for each additional potential benefit that was perceived to be a "very important" motivating factor and for each additional potential risk that was perceived to be "very likely" to discourage participation, on average and *ceteris paribus*. I tested the hypothesis that the odds ratio estimate for  $\beta_m$  would be greater than 1.0, indicating that a respondent that identifies more potential benefits as "very important" in their motivation to consider participating in HIV cure-related studies was more likely to very willing to participate in studies. I also tested the hypothesis that the odds ratio estimate for  $\beta_n$  would be less than 1.0, indicating that a respondent that identifies more potential risks as "very likely to discourage" them from considering participating in HIV cure-related studies was less likely to very willing to participate in studies (or, more accurately, was more likely to have a lower willingness to participate in HIV cure-related studies, for fear of multiple potential risks).

### **Presentation of Quantitative Results**

Results from the baseline descriptive data analysis were tabulated and illustrated using charts and histograms (see Results section for details). The results of the bivariate analyses were presented in the form of tables that listed the categories of each categorical variable, the sample



size within each category and the binary dependent variable of willingness to participate, the odds ratio of willingness to participate and its 95% confidence interval for each category, and the p-value for the odds ratio. Continuous variables, such as age and percent of life living with HIV diagnosis, are presented in these tables as continuous variables as well as categorical variables that split the sample size across a few categories. Finally, the results of the multivariate logistics regression models were presented in tables that listed the key independent variables and control variables' odds ratio estimates, their 95% confidence intervals, and p-values. Because 56 models were estimated using individual potential benefits (21 models) and potential risks (35 models) as the sole key independent variables in the regression model, to be succinct, I only presented the odds ratio, 95% confidence interval and p-value for the key independent variable in each of the models, and not for the control variables, although the full set of control variables from Model 1 were also included in the 56 models with key independent variables.

All p-values that were 0.05 or lower were denoted using asterixes.

I provided a narrative explanation of the variables under analysis, and the interpretations of the bivariate association and multivariate regression analyses, noting which variables were statistically significantly correlated with willingness to participate in HIV cure-related studies, controlling for socio-demographic characteristics. The hypothesis that risk factors were negatively associated with willingness to participate in HIV cure-related studies (hence they deterred participation), and benefit factors were positively associated with willingness to participate (hence they motivated participation) were tested and summarized. Where tests of significance either confirmed or rejected my hypotheses, I noted them in the narrative whenever possible.

### **Qualitative Data Management and Analysis: Key Informant Interviews<sup>13</sup>**

The information obtained from the key informant interviews was qualitative in nature. Qualitative data allowed me to explore the meanings and depths behind reasons to want or refuse to participate in HIV cure-related studies, as well as perceptions around risks and benefits of participation and practical challenges to implement HIV cure-related studies.

#### **Qualitative Data Management**

For the qualitative data, the units of analysis were patient-participants who were living with HIV, clinician-researchers, and policy-makers (regulators), broadly defined. Each key informant interview was assigned a unique identification number. Key informant interviews with patient-participants were assigned number 101 and above; with researchers/clinicians 201 and above and with policy-makers (regulators) 301 and above. Most key informant interviews, contingent upon receiving permission from study participants, were digitally recorded for the purpose of transcription. I performed transcriptions *verbatim* and as soon as possible following each interview to augment accuracy of the transcripts (or took detailed notes and rewrote them immediately afterwards when study participants refused to be recorded). Furthermore, I personally verified each transcript against the corresponding audio recording and kept a journal to record reflections and notes following each interview. I typed all transcripts in Word processing documents, using a key informant interview worksheet.

I employed the following steps to perform qualitative data analysis from the key informant interviews:<sup>14</sup>

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<sup>13</sup>Focus group discussions are deferred

<sup>14</sup>Ibid.

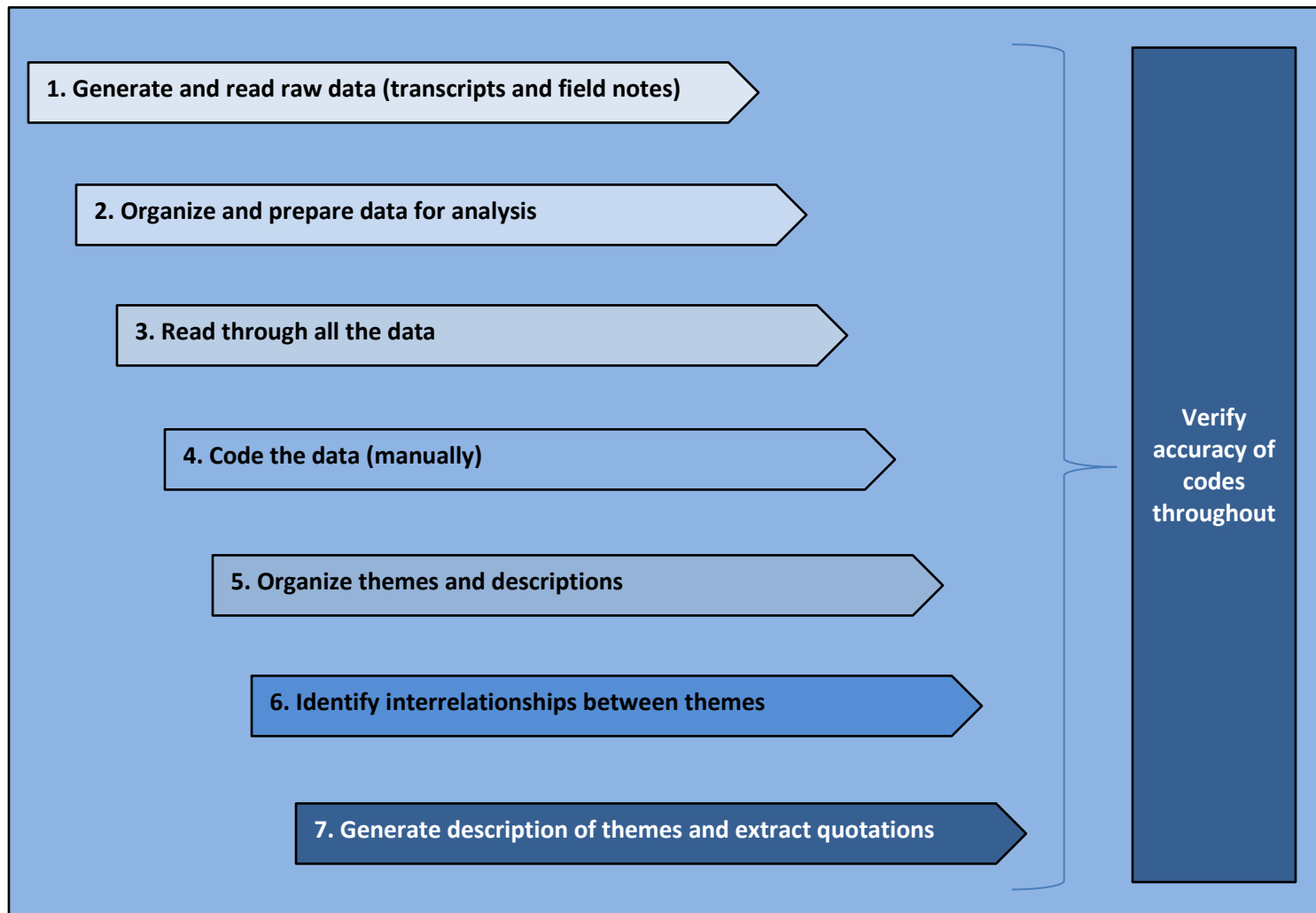


Figure 5. Flow of Qualitative Data Analysis (Adapted from Creswell, Chapter 9, Qualitative Methods, p. 197)

Since “[b]eing there is best” [45], I was present for all the key informant interviews. I also personally transcribed all interviews to ensure accuracy of the data. These provisions ultimately improved analysis since they allowed me to have a very “extensive experience with the data” [45]. I performed the transcribed-based content analysis either manually using a low-cost and low-technology option, also referred to as the “classic analysis strategy” [45]. Manual qualitative data analysis included the long-table approach in Word, combined with a color-coding technique, to derive key themes. I devised a numbering system in order to retrieve key quotes efficiently and to identify the data source as needed.

### **Qualitative Data Analysis**

The qualitative data analysis was situated at the juncture between phenomenology and grounded theory [42]. In fact, I was most inspired by the phenomenological approach, which sought to understand the lived experiences of individuals and capture the essence of a phenomenon. Furthermore, phenomenology focuses on the analysis of significant statements, the generation of meaningful text units and the creation of an essence description [42]. Grounded theory further informed my qualitative data analysis, as I sought to understand the realities grounded in the views of the study participants [42].

The coding process was a key step in the qualitative data analysis process. Codes have been referred to in the literature as “themes,” “categories,” “labels,” “thematic units,” “concepts” and “tags” [46], among others. Codes serve to ascribe meaning to the descriptive information obtained during key informant interviews and to categorize the inferential data obtained during the study. During the analysis phase, I assigned themes or codes to “chunks of data, usually phrases, sentences or paragraphs that [were] connected to a specific context or setting” [46]. I characterized participants’ verbatim statements according to thematic content. The interpretative approach used was both deductive and inductive. I used a combination of *a priori* (or existing, pre-determined)

codes and data-driven (or emergent, latent) codes [42] [46]. Code development and ascertainment was an iterative process during the qualitative data analysis. These key informant interview topics served as headings in the qualitative findings section of my dissertation. They also helped drive the plan for change, leadership and implementation. Each central theme was extrapolated using related sub-themes.

Furthermore, I developed simple *a priori* codebook that contained three components: code name, description and an example [46] (not shown). The final qualitative data analysis narrative includes the synthesis of *a priori* codes as well as the synthesis of data-driven, emergent codes. The qualitative data analysis used mainly an inductive approach, during which themes were revealed. In this sense, I aspired to “build (...) patterns, categories and themes from the bottom up by organizing the data into increasingly more abstract units of information” [42]. The inductive method thus required a conscientious back and forth between the themes and the dataset until I had identified the core themes. I then used a more deductive approach to re-examine the data and assess whether there was evidence to support the key themes [42]. Thus, both induction and deduction played a role in the qualitative data analysis. Codes and their descriptions were iteratively developed, compared and assessed throughout the study.

Main techniques for identifying themes and sub-themes included: repetitions, uses of transitions, similarities and differences, omissions/pauses, apparent importance/significance and metaphors/analogies [47]. Other possible methods included frequency of themes, specificity, emotions of participants and extensiveness of coverage [45]. I paid attention to dominant patterns in the speech, but also to “unique or rare events that [had] major consequences” [45]. While “[n]ot everything [was] worthy of analysis,” [45] I focused on sections of the discourse that had the highest salience and relevance. I supplemented the transcript-based analysis with my field notes. Finally, I embraced the process of coding as an opportunity for the data to be 1) reduced and simplified; 2)

expanded (via linkages between concepts); 3) transformed (via conversion into meaningful units) and 4) re-conceptualized (via redefinition of conceptual framework) [46].

### **Presentation of Qualitative Data and Interpretation of Results**

While I used the themes to answer the main research questions, I also strived to “honor the worldview of informants” [48]. I presented the qualitative findings in a narrative format and used adjunct visuals, such as tables, to complement the discussion, and these emerged logically and organically from the data. Each core theme has a narrative summary, supported by careful selection of quotations and specific evidence and endorsements. I also highlighted expected and unexpected findings and lessons learned whenever possible.

### **Reliability and Validity**

As described above, I conducted the coding of the data and performed all the transcriptions in order to ensure consistency and validity during the analysis. I also asked my co-investigator to review the main themes and descriptions for congruity on a periodic basis. I used peer debriefing during the study to enhance the accuracy of the accounts. While there was no ultimate proof of validity and reliability, I attempted to maximize them via a diligent effort at a systematic and meticulous analysis of the data. Qualitative data analysis and the selection of key themes required judgments on my part. I was partial in that I wished to derive recommendations to ensure the ethical and effective implementation of HIV cure-related studies, and to ensure that the voices of the patient-participants were adequately and conscientiously represented.

### **Comparison between Quantitative and Qualitative Study Results**

Both quantitative and qualitative study results, taken together, provided evidence as to the factors that would either facilitate or deter participation in and affect implementation of HIV cure-related studies. Qualitative findings revealed barriers or facilitators to participation that were not previously considered in the quantitative survey. Following the quantitative and qualitative results

sections, I wrote a discussion section inspired from my review of the literature to explore where themes agreed or diverged. The discussion section also highlights the implications of the study findings as well as the opportunities and barriers to implementation, change and leadership. I used the key themes to inform my plan for change, as well as discussions, practice and possible policies affecting the participation of potential HIV-positive volunteers in cure-related studies and the implementation of studies in general. I focused on creating added value and identified the questions that required further research and inquiry, as well as new and emerging priorities for the field. I endeavored to determine how the data were actionable and focused on the areas of influence that were under my control. I also separated the study results from the recommendations that could be derived from them.

## CHAPTER 4 | QUANTITATIVE SURVEY RESULTS

The quantitative survey results are presented in three sections, with key findings summarized after each section:

- ⇒ In the first section, descriptive statistics from the sample of 400 survey respondents are presented. Because primary data from potential HIV cure-related studies are rare, the descriptive statistics obtained from this survey provide a rare glimpse at their attitudes and perceptions, and can be very informative to clinician-researchers and policy-makers in designing and recruiting for HIV cure studies in the future. Below, I summarized the key results from the descriptive statistics, drawing attention to particular results that revealed important findings.
- ⇒ In the second section, bivariate associations of various factors with respondents' willingness to participate – the dependent variable – are presented. The statistical significance and magnitude of the bivariate associations between respondents' willingness to participate in all types of HIV cure-related studies and their perceptions of the importance of potential benefits in motivating their participation, their perceptions of the likelihood that certain potential risks could deter their participation, and their socio-demographic characteristics and global attitudes towards HIV cure research are examined.
- ⇒ In the third section, I presented the results of the multivariate regression analyses. The statistical significance and magnitude of the associations between willingness to participate and the respondents' perceptions of the importance of each potential benefit and potential risk are examined, controlling for the socio-demographic characteristics.

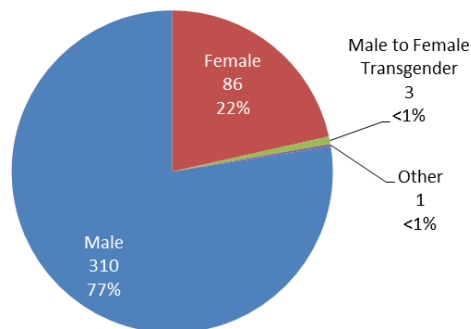


## Descriptive Statistics

**Table 3. Survey Sample Size**

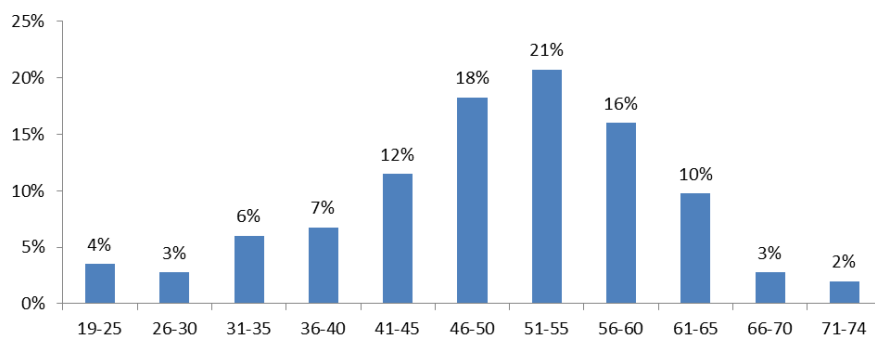
Survey responses	Number
Respondents who completed the survey	343
Respondents who partially completed the survey (at least through the question of willingness to participate in HIV cure studies)	57
Respondents identifying they are ineligible to participate in the survey	9
<i>Total survey responses</i>	<i>409</i>
<i>Total survey responses included in the analysis</i>	<i>400</i>

After excluding five survey responses because of incompleteness of the responses, we recruited 409 study participants, of which 400 were eligible for the study and thus included in the analysis (Table 3). Of those, 343 respondents completed the survey by answering all questions and 57 partially completed the survey, but answered at least one question of interest regarding HIV cure research. Most questions were answered by more than 350 respondents. We did not make all the survey questions mandatory as this might have affected the survey completion and caused significant attrition issues. This was a convenience sample derived from willing respondents who had access to HIV treatment/cure listservs from which they were recruited. This sample was not representative of the entire community of people living with HIV in the United States. We discuss the limitations of the survey further in the Discussion section.



**Figure 6. Gender of Respondents (n=400)**

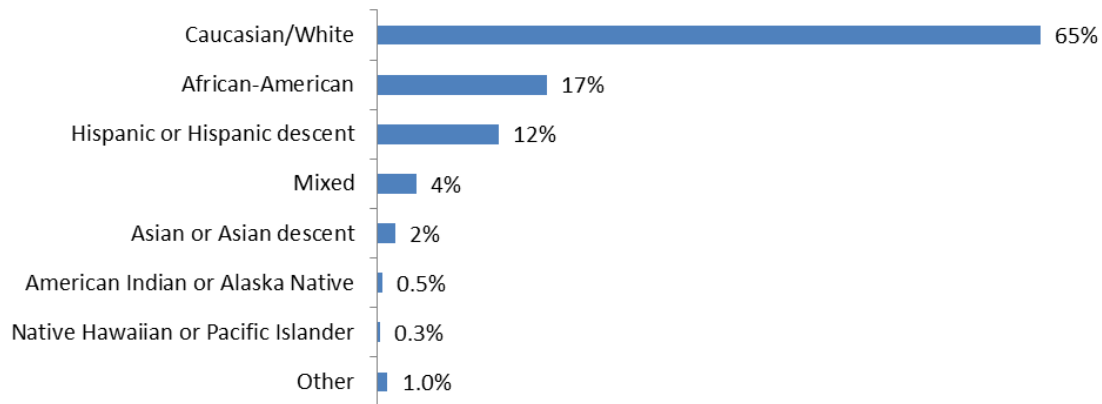
The gender of the respondents is represented in Figure 7. We recruited 77% males, 22% females and <1% transgendered individuals. One individual selected “other” but did not specify his/her gender identification. While this sample is not representative of the population of people living with HIV in the United States, it may reflect those who are interested in HIV cure-related issues. The sample has proportionally more females than a previous U.S. survey conducted in 2010 – 2011[49].



**Figure 7. Age Group of Respondents (n=400)**

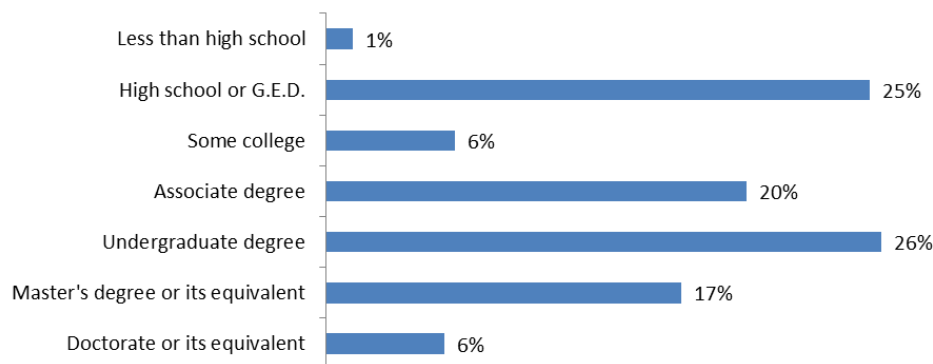
Respondents ranged in ages between 19 and 74 years of age (Figure 8). The average age was 50 years old and the median was 51 years. The highest proportion of survey respondents were between the ages of 46 and 60 years old. This may again reflect those with an interest in HIV cure-related research in the United States. Younger ages may have been under-represented. The sample

derived may reflect the aging population of people living with HIV in the United States and this should be kept in mind for future HIV cure study design.



**Figure 8. Ethnicity of Respondents (n=400)**

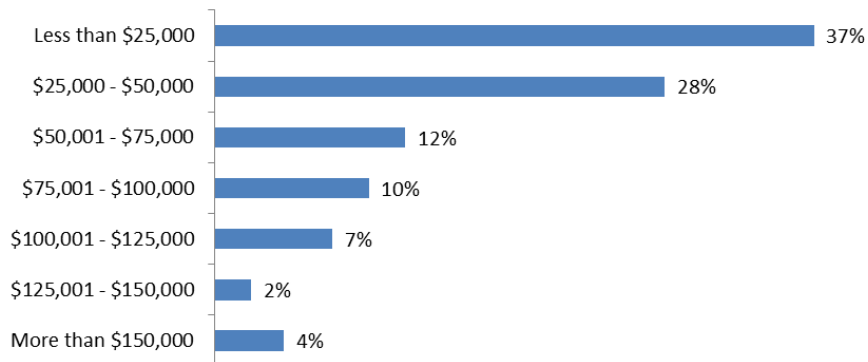
Ethnicity of survey respondents is reflected in Figure 9. We obtained a sample that was ethnically diverse: 65% Caucasians/Whites, 17% African-Americans/Blacks, 12% Hispanic/Hispanic descent, and 4% mixed. This sample was also proportionally more diverse than the one derived from the previously completed U.S. survey on willingness to participate in HIV cure-related studies [49].



**Figure 9. Highest Level of Education Completed (n=399)**

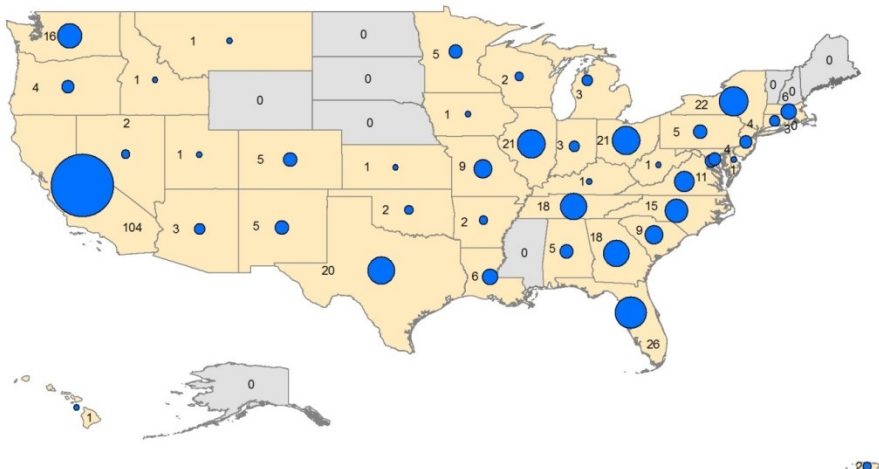
Nearly all survey respondents had at least a high school or GED degree, 6% had some college, 20% had an associate degree, 26% had completed an undergraduate degree, 17% had completed a master's degree or its equivalent and 6% had completed a doctorate degree (Figure

10). Compared to the previous U.S. survey [49], we were able to recruit respondents who were of proportionally lower educational backgrounds. This sample may be slightly more representative of the HIV epidemic in the United States, although it may remain biased towards those with greater income, who have access to the internet and HIV cure research information.



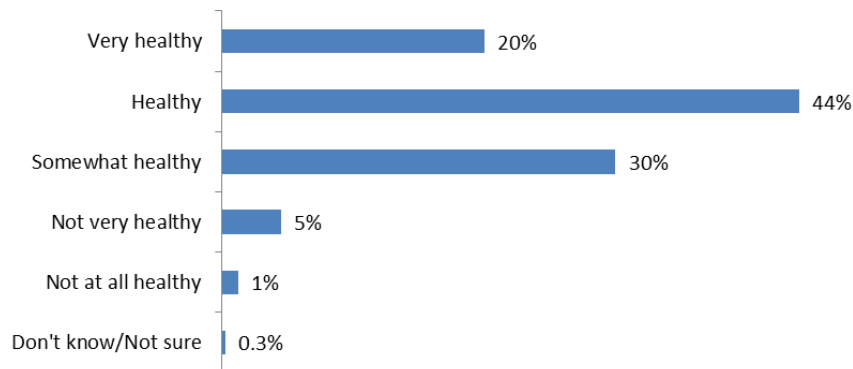
**Figure 10. Yearly Household Income (U.S. Dollars) of Respondents (n=399)**

Yearly household incomes of survey respondents are depicted in Figure 11. More than one-third (37%) earned less than \$25,000 annually and another third (35%) earned more than \$50,000 annually.

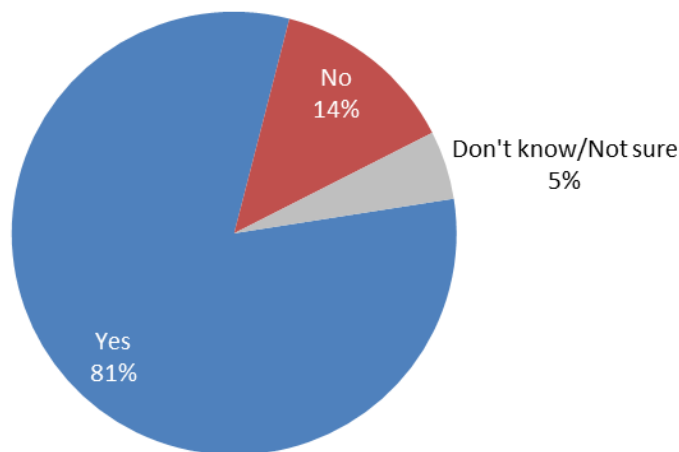


**Figure 11. Residence of Survey Respondents (n=394)**

The map in Figure 12 shows the geographic distribution of the survey respondents. There were 38 states represented in the survey. The highest recruiter sites were California (n = 104), Florida (n = 26) and New York (n = 22). Outside of the continental United States, two respondents were from Puerto Rico. There were 6 respondents did not specify their place of residence.

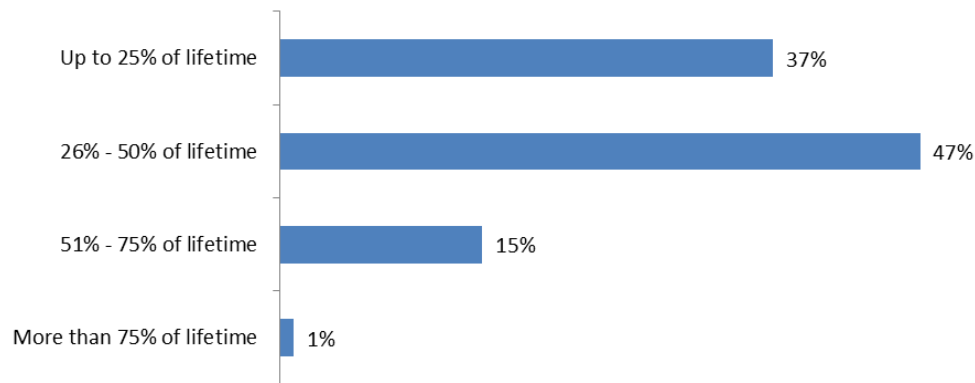


**Figure 12. Self-Reported Health Status of Respondents (n=400)**



**Figure 13. Respondents' Feeling of Control over Health Care (n=400)**

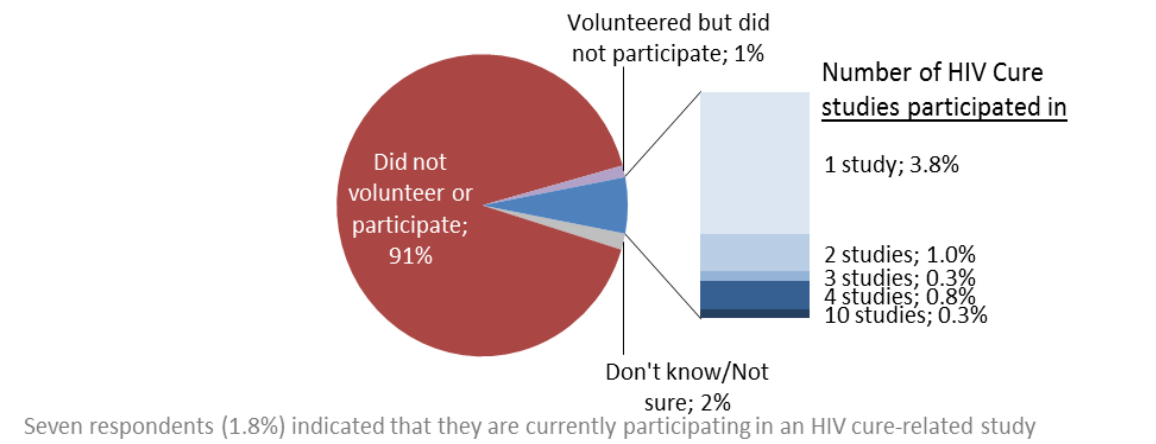
Most survey respondents (94%) described themselves as either very healthy, healthy or somewhat healthy (Figure 13). This may be because most (98%) of them were also taking HIV medication (2% were not taking HIV medication) (data not shown). Most (81%) also indicated that they had control over their own health, compared to 14% who did not have control (5% don't know/not sure) (Figure 14).



**Figure 14. Percentage of Respondents' Lifetime Living with HIV Diagnosis (n=394)**

Our survey included respondents who have been diagnosed with HIV for less than a year (3%) and up to 36 years. Half of the respondents have lived with an HIV diagnosis for 18 years or more. The distribution of years since first diagnosis is mostly uniform between <1 year and 30 years. We calculated the percentage of respondents' lifetime living with an HIV diagnosis by dividing the difference between the number of years lived with HIV and the age of the respondents (Figure 15). If a respondent was first diagnosed with HIV in 2015, we used 0.5 in the numerator (instead of zero). The largest group (47%) had lived with HIV for 26 – 50% of their lifetime, followed with those who lived with HIV for up to 25% of their lifetime (37%). A significant minority of respondents (16%) have lived with HIV for more than half of their lifetime.

Volunteering for and participation in previous HIV treatment research was relatively high, at 44%, compared with 55% who never volunteered to take part in an HIV treatment study (figure not shown). Volunteering for a study does not necessarily mean that the respondent actually participated in a study, but is indicative of their interest in participating in HIV studies.

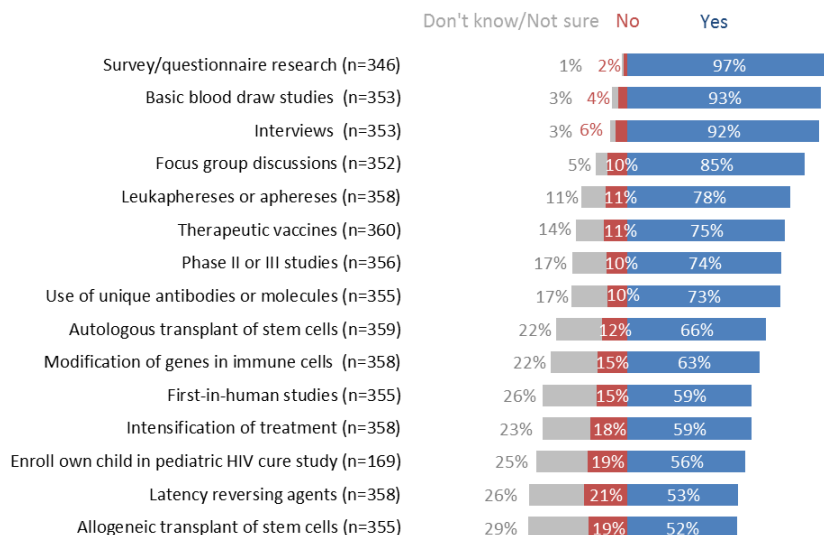


**Figure 15. Respondents have Ever Been in or Volunteered for an HIV Cure Study (n=400)**

In comparison, a smaller proportion of survey respondents had ever volunteered for or participated in HIV cure-related studies (7%), compared with 91% who had never volunteered nor participated (Figure 16). A total of 6.2% indicated that they actually participated in at least one HIV cure study. We did not define “HIV cure research participation” so this figure reflected the participants’ own interpretation of HIV cure-related research. Only 7 out of 400 survey respondents were currently enrolled in an HIV cure-related study.

With regards to general interest in HIV cure research, 97% of respondents said that they were interested (versus 1% that answered no) and 95% answered that they were generally interested in medical issues (versus 3% that were specifically not interested) (data not shown).

## Willingness to Consider Participating in HIV Cure-Related Studies



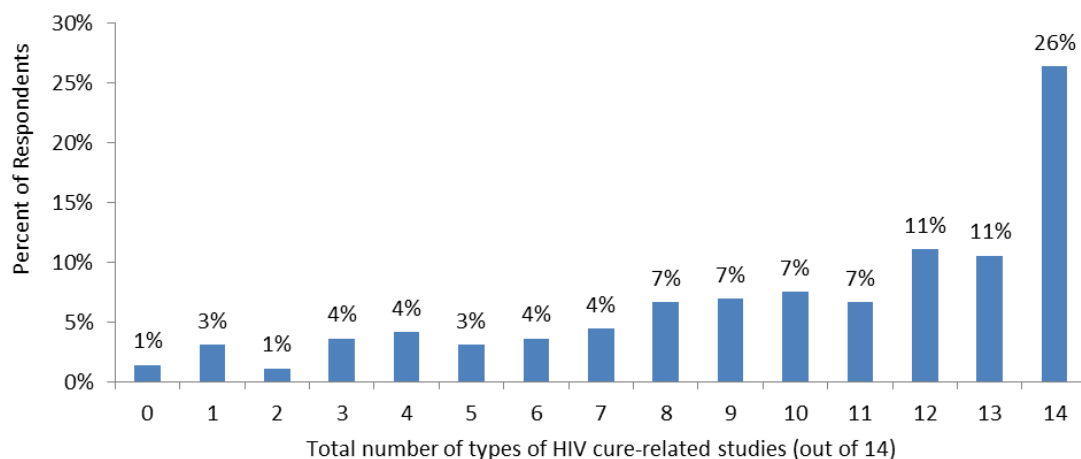
**Figure 16. Willingness to Consider Participating in HIV Cure-Related Studies**

We asked survey respondents to indicate whether they would consider participating in 14 different types of HIV cure-related studies (Figure 17). We provided the definitions of these different cure strategies in lay terms and used the survey as an educational opportunity. Respondents were able to answer “Yes”, “No”, or “Don’t know/not sure” for any and all 14 types of studies, or skip any of the questions. The response rate for each of the 14 types was approximately n = 350 – 360 out of a possible 400. In addition, we asked a separate question asking if respondents would be willing to enroll their infant living with HIV in a pediatric HIV cure-related study, which resulted in a much smaller response rate (n=169). For each of the main 14 types of HIV cure-related studies, more than 50% of those who responded indicated they would be willing to participate in that study type. The highest rejection rate was 21% for studies that involve latency reversing agents. For many study types, the response rate for “Don’t know/not sure” exceeded the response rate for “No.”

Willingness to participate may not reflect actual participation in the future, the inclusion/exclusion criteria of studies, the geographical availability and the studies that participants



would qualify for or enter. However, the graph shows the hierarchy of the different kinds of studies that potential participants would be explicitly willing to join. Respondents were more willing to participate in simple studies (e.g. surveys, basic blood draws, interviews and focus groups) than in studies that are seemingly riskiest modalities (e.g. transplanting stem cells, use of latency-reversing agents and intensification of HIV treatment). The higher the level of intervention, the lower the willingness to participate rate and the greater the rejection rate and the unsure rate are. These data may underscore the need to better educate potential volunteers about the different types of HIV cure studies and their potential risks. While most studies currently enrolling participants are pilot studies with small number of participants, these data should be kept in mind as studies get scaled up.



**Figure 17. Total Number of Types of HIV Cure-Related Studies respondents are Willing to Consider Participating in (n=361)**

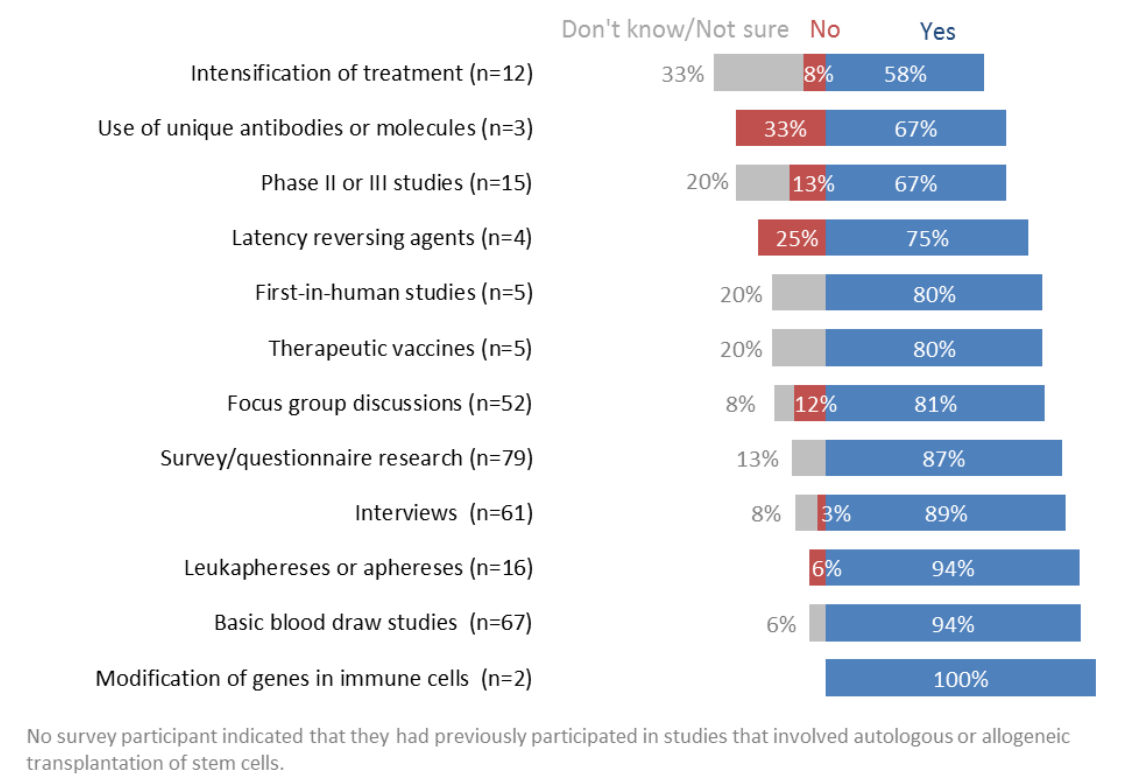
A total of 361 respondents answered “Yes” or “No” to being willing to participate in at least one of the 14 types of studies (Figure 18). Of the 361 respondents, 26% indicated that they would be willing to participate in all 14 types of studies, while the other 74% were willing to participate in some (or none) of the studies but not all 14. This makes up the dependent variable in the bivariate and multivariate quantitative analysis. Respondents who were willing to participate in all 14 types of

studies are defined as “very willing to participate” in HIV cure-related studies, while the other 74% are defined as “relatively less willing to participate.” It is important to remember that the relatively less willing to participate respondents may be willing to participate in several types of HIV cure-related studies, but they are simply not yet willing to participate in *all* types of studies that we asked about. In general, nearly half (48%) were willing to participate in at least 12 of the 14 types of studies, and only 1% were expressly unwilling to participate in *any* type of HIV cure-related studies, including the lowest risk modalities.

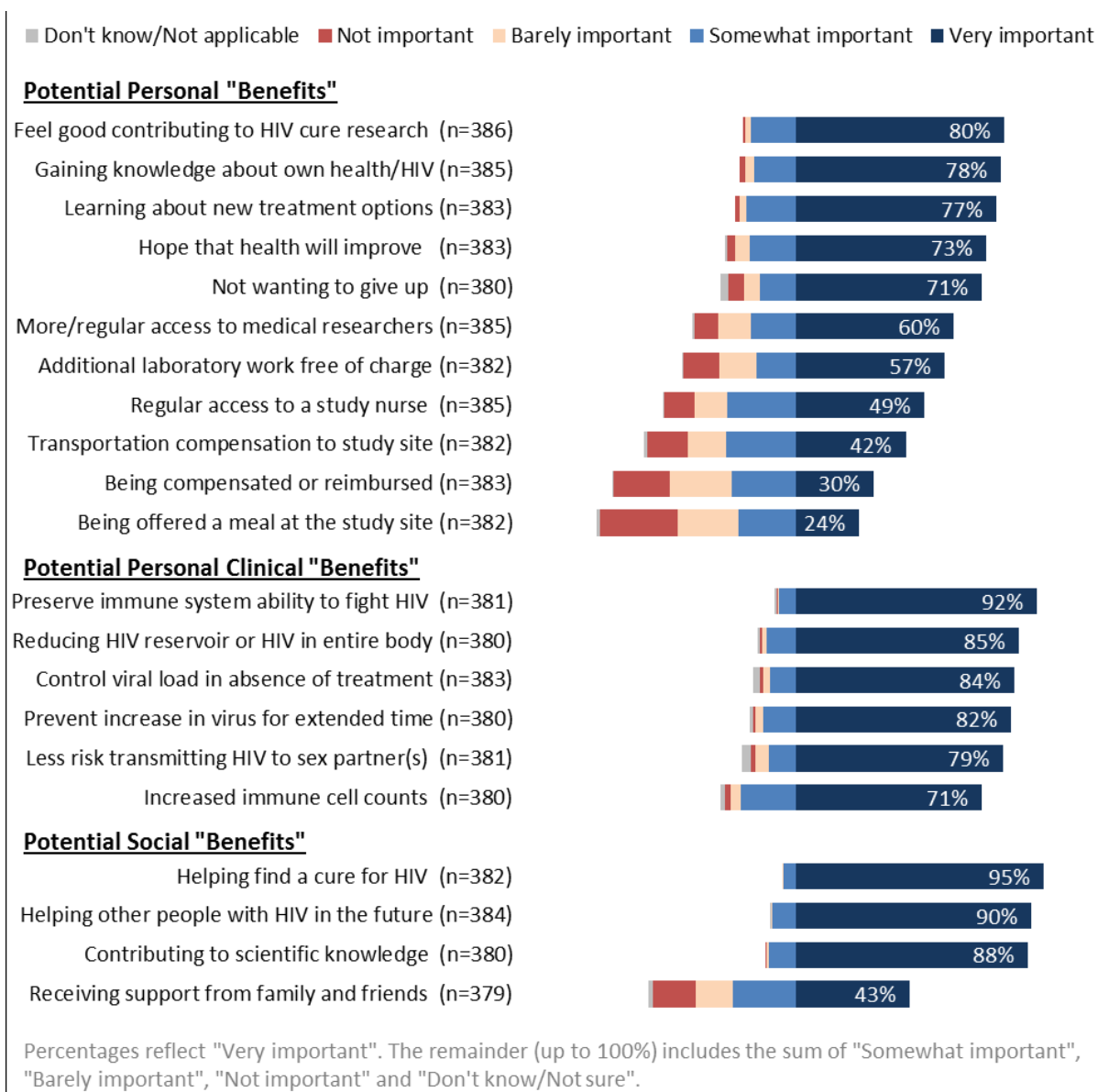
We compared two sets of questions: considering participation in the different types of HIV cure-related studies, given that one had previously participated in a similar (HIV or non-HIV) health study in the past (Figure 19). The sample size was too small to make any significant observations or comparisons for many types of studies and we should be cautious when interpreting claims based on a sample of 2, 3, 4 or 5 people for some of the types of studies (e.g. gene therapy, unique antibodies or molecules, latency-reversing agents, therapeutic vaccines or first-in-human studies). Nonetheless, based on their prior experience, data show that most participants would be willing to participate in HIV cure studies that are similar to studies they had participated in the past. Participants are most reluctant, however, to consider participating in future HIV cure-related studies that would involve: 1) intensification of treatment, 2) phase II or III studies or 3) focus group discussions (red bars in Figure 19 below).

Using Likert scales, we asked participants to indicate which potential benefits would either be very important, somewhat important, barely important or not at all important in their motivation to consider participating in HIV cure-related studies. Figure 19 below shows each factor in relation to the others, but also shows the relative importance of the “personal benefits,” “clinical benefits” and “social benefits” categories compared to each other. The perceived clinical benefits or social

benefits appear to be more important motivators, on average, than personal benefits when considered as a category.



**Figure 18. Willingness to Consider Participating in HIV Cure-Related Studies after Having Previously Participated in Similar (HIV or non-HIV) Health Study in the Past**



**Figure 19. Importance of Factors to Motivate Considering Participating in HIV Cure-Related Studies**

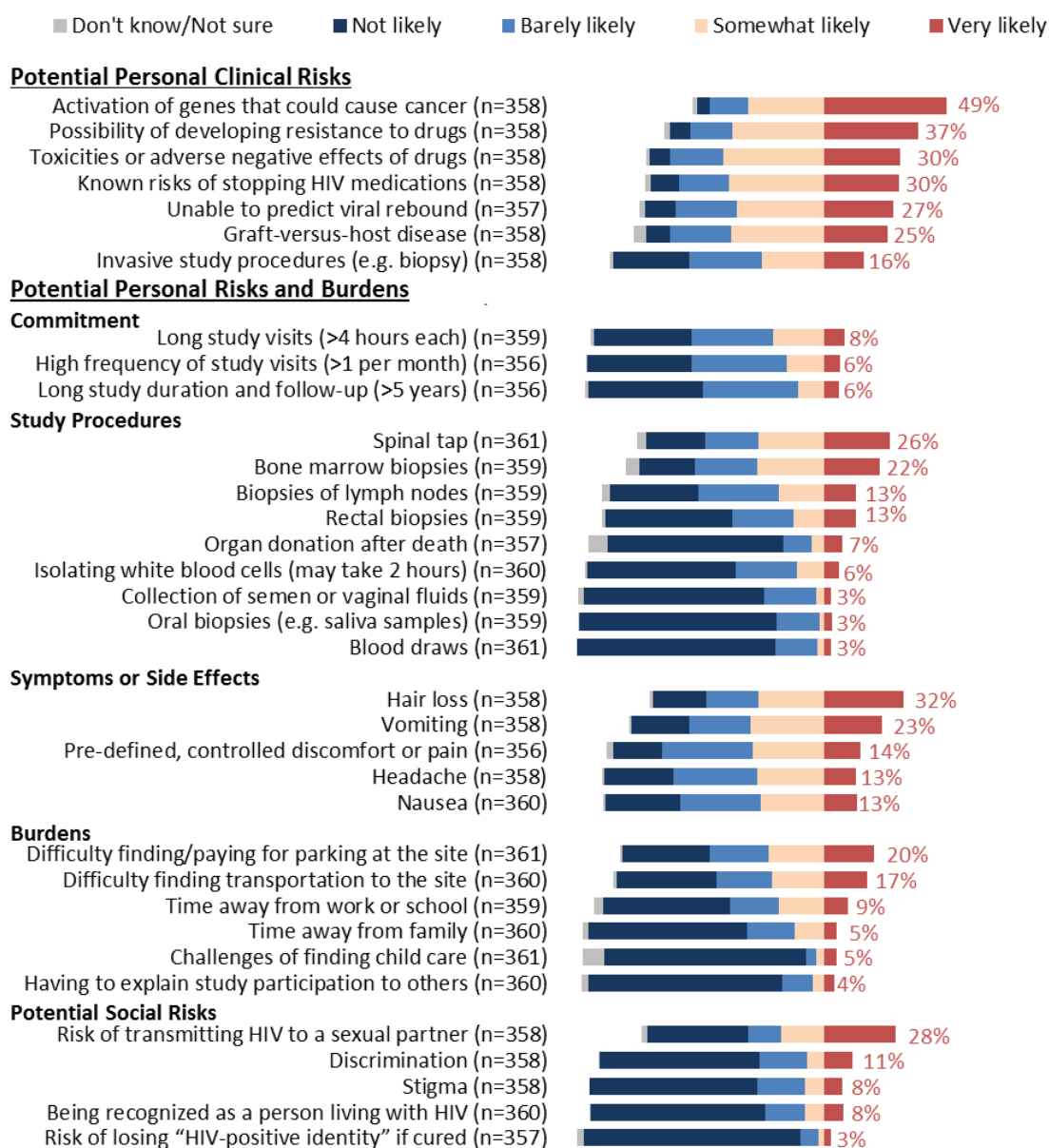
Highlighting specific motivational factors (Figure 20 above), we note that:

- ⇒ Although HIV cure studies confer little to no benefit, it is possible that potential study participants still perceive the likelihood of benefits when deciding to join studies.
- ⇒ The data show that we should not underestimate the importance of emotional and mental benefits in HIV cure research participation, since feeling good about contributing to HIV cure research is the most popular perceived personal benefit (80% very likely to

motivate), and social benefits of helping find a cure for HIV, helping other people with HIV in the future and contributing to scientific knowledge were three of the four highest ranked benefits overall (95%, 90% and 88% very likely to motivate, respectively).

- ⇒ Potential participants value gaining knowledge about their health (78% very likely to motivate). This is interesting as most of the research data are not given to the study participants individually. This raises questions about the need to communicate study data (in the aggregate) and advancements in science to study participants and may highlight the importance of clinical contact factors for study participants.
- ⇒ Hope that health will improve was also a strong motivating factor. Again, research may not confer direct clinical benefits and in fact, there is the possibility of harm when advancing medical knowledge. The high rating of this factor underscores the need to protect against the risk of therapeutic and curative misconception.
- ⇒ There are also perceived potential personal clinical benefits, such as the desire to improve one's immune system.
- ⇒ Reducing the HIV reservoir was perceived as a clinical benefit although we know from research that a reservoir decrease may not confer any direct clinical benefit. Study participants would need a substantial (logs worth) reduction in the size of their proviral DNA replication-competent HIV reservoir in order to reduce time to viral rebound. Scientists need to be careful how reservoir reductions are discussed in the informed consent forms.
- ⇒ Compensation in the form of meals, reimbursements and transportation costs were the three lowest ranked motivating factors overall.

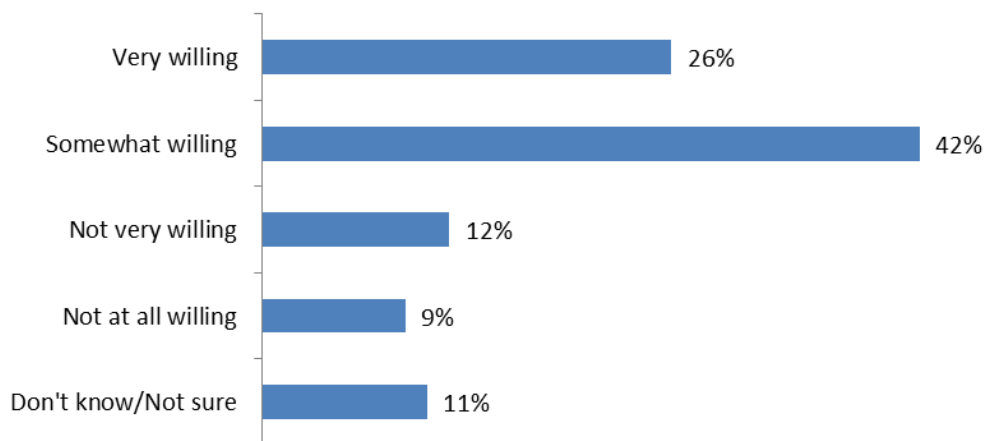
## Likelihood of Factors to Discourage Considering Participation in HIV Cure-Related Studies



Percentages reflect "Very likely to discourage". The remainder (up to 100%) includes the sum of "Somewhat likely to discourage", "Barely likely to discourage", "Not likely to discourage" and "Don't know/Not sure".

**Figure 20. Likelihood of Factors to Discourage Considering Participation in HIV Cure-Related Studies**

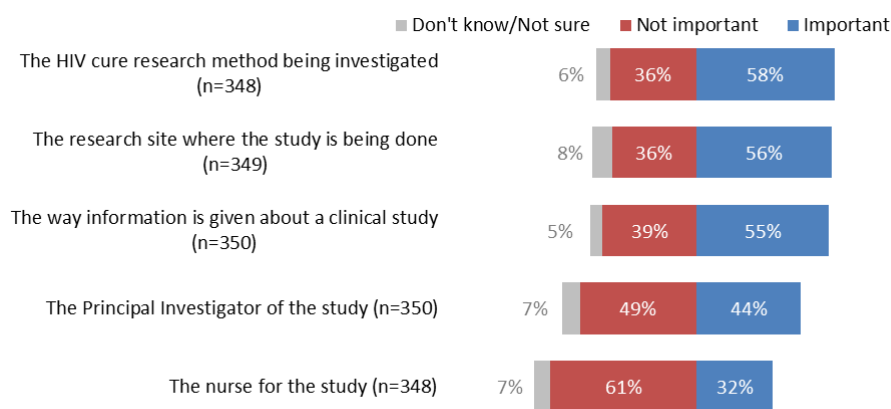
In terms of the perceived risks likely to discourage considering participating in HIV cure research, personal clinical risks appeared to be more likely to demotivate than personal risks or burdens or potential social risks (Figure 21). Activation of genes that would cause cancer (49% very likely to discourage) and the possibility of developing resistance to HIV treatment (37% very likely to discourage) were the most prevalent deterrents. The need for intense commitment did not appear to be strong deterrents of participation. Spinal tap (26% very likely to discourage) and bone marrow biopsies (22% very likely to discourage) were the least favorite study procedures. Hair loss (32% very likely to discourage) was a stronger possible deterrent than more immediate symptoms/side effects, such as vomiting (23%), pain (14%), headache (13%) or nausea (13%). The burden categories reveal that we should not underestimate the importance of addressing possible obstacles like transportation or parking to encourage participation. Finally, the risk of transmitting HIV to others (in the case of an unsuspected viral rebound) was a real possible deterrent (28% very likely to discourage), and may speak to the desire of study participants to “do no harm” during their study participation.



**Figure 21. Willingness to Stop HIV Treatment as Part of an HIV Cure-Related Study (n=359)**

An important feature of some HIV cure research design is the need to interrupt treatment to assess time to viral rebound or predictors of rebound. Among the survey respondents, 68% of

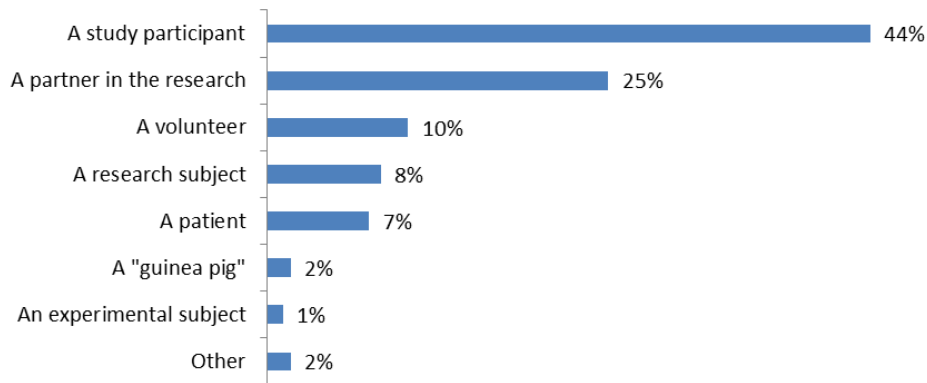
potential HIV cure research participants were very willing or somewhat willing to stop treatment as part of HIV cure research (Figure 22). These numbers are somewhat higher than those obtained in the previous U.S. survey, whereas one third (34%) of respondents stated that they would be very willing or willing to participate in a study that involved treatment interruption, compared to 34% who said that they would be somewhat willing and 32% said that they would not be at all willing [49]. These results may reflect the different study sample used or the need to better educate potential study participants about the possible risks of treatment interruption.



**Figure 22. Importance of Factors in Making a Decision about Considering Participation in an HIV Cure-Related Study**

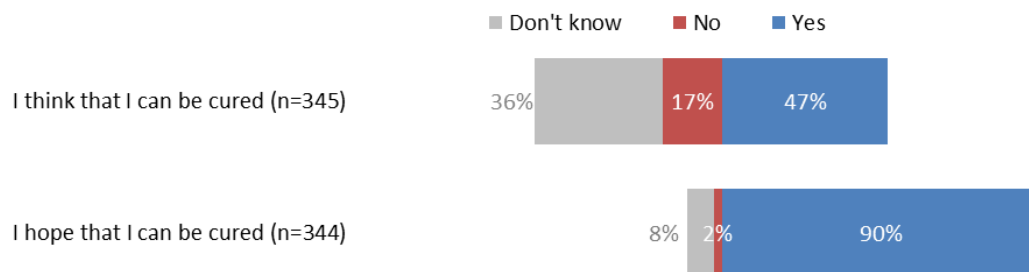
Survey participants rated the importance of various practical factors in making a decision to participate in an HIV cure study (Figure 23). The HIV cure research modality being investigated (58%) was slightly more important than the research site (56%), the way information was given (55%), the Principal Investigator (44%) or the study nurse of the study (32%).





**Figure 23. How would Participants Most Likely Describe Themselves in they were to Participate in an HIV Cure-Related Study (n=348)**

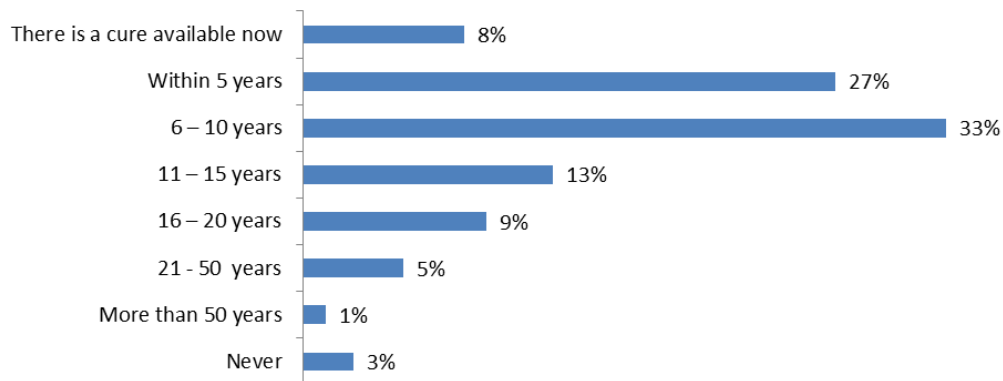
Potential HIV cure research volunteers would also prefer to be described as “study participants” (44%), “partners in research” (25%) or “volunteers” (10%), as opposed to “research subjects” (8%), “patients” (7%) or “guinea pig” (Figure 24). These appellations show the importance of treating study participants with respect and to be careful with terms used to describe them and are consistent with the qualitative study results.



**Figure 24. Personal Beliefs about an HIV Cure**

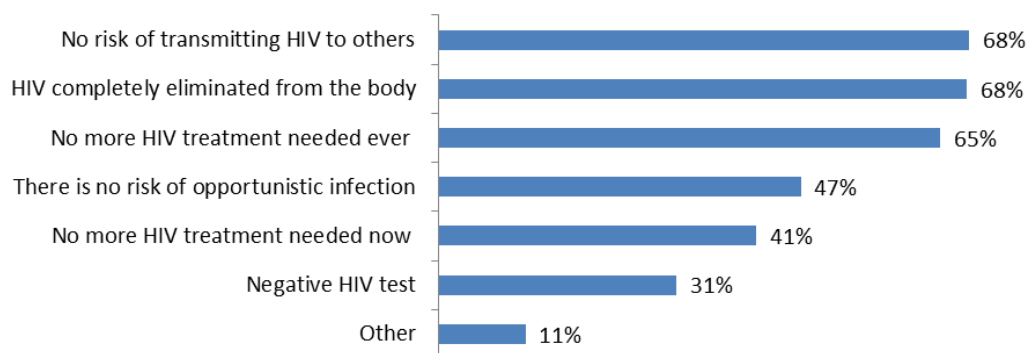
Furthermore, we asked survey respondents to answer whether they thought they could be cured versus whether they hoped they could be cured. The hope of being cured (90% of survey respondents) was higher than the expected possibility that one could actually be cured (47% of

study respondents). Hope to be cured – now or in the future – may possibly be a strong motivating factor in whether to join a study.



**Figure 25. How Many Years Do Participants Think it will take to Find a Cure for HIV (n=350)**

We were surprised to find that 8% of participants thought a cure for HIV infection was presently in existence (Figure 26). This finding seems incompatible with the fact that our convenience sample has regular access to HIV-related information about treatment or cure. The majority of survey respondents thought a cure would be available within 5 years (27%) or in 6 – 10 years (33%). Close to a third (27%) thought a cure would take between 11 – 50 years to be discovered. A tiny fraction (3%) thought a cure would never materialize.



Percentages sum to more than 100% because several participants selected more than one answer.

**Figure 26. What does a Cure Mean to Participants? (n=350)**

A cure for HIV infection should meet the expectations of the people living with HIV. We thus asked the survey respondents to report what a cure meant to them (categories were provided). Not transmitting HIV to others (68%), completely eliminating HIV from the body (68%) and no more HIV treatment needed (65%) emerged as the three strongest categories, above the practical factors of no longer testing positive on the antibody HIV test (31%).

In summary, key descriptive findings from the survey include:

- ⇒ Willingness to participate in HIV cure-related research is high, but may not translate into actual research participation. Willingness decreases as the risk of HIV cure-related studies increases. Potential study volunteers should be better informed about possible risks of studies.
- ⇒ Although HIV cure studies confer no expectation of direct benefit, potential volunteers may still perceive the likelihood of benefits when deciding to join studies. Emotional, mental and psychosocial factors (e.g. feeling good about contributing to the biomedical HIV cure research agenda) should not be underestimated.
- ⇒ The survey results confirm that a mixture of social altruism and perceived personal benefits motivate participation in HIV cure research. Willingness to interrupt HIV treatment as part of cure study design remains high.
- ⇒ Given that a minority of survey respondents (8%) thought a cure was currently available, heightened education efforts are warranted. Possible meanings of an HIV cure should also be explored further.

### **Bivariate Association Analyses**

The results of the descriptive statistics revealed that 26% of the survey respondents were “very willing” to participate in HIV cure-related studies, defined as the group of respondents who explicitly indicated that they would be willing to participate in all 14 types of studies proposed in the

survey. The remaining 74% of the survey respondents were “relatively less willing to participate” in HIV cure-related studies. The survey results also revealed that 21 potential benefits of participating in HIV cure studies motivated respondents to varying degrees: as few as 24% of respondents and as high as 95% of respondents perceived specific potential benefits as “very important” motivating factors in their consideration of whether to participate in HIV cure studies, depending on the potential benefit. The correlation between each of the 21 dichotomous independent variables (perception of an individual potential benefit as a “very important” motivating factor for participation) and the dichotomous dependent variable (willingness to participate in all types of HIV cure-related studies) was statistically tested using univariate logistic regression analysis.

Table 4 below displays the sample size of survey participants who responded to both the dependent willingness to participate (WTP) question and the individual potential benefits questions, alongside the percent of the sample who perceived the individual potential benefit as a “very important” motivating factor in their consideration of whether to participate in HIV cure related studies. For all potential benefits, 26 – 27% of the sample were “very willing” to participate in studies. The odds ratio of participants being “very willing to participate” and claiming that potential benefit was “very important” versus “somewhat important”, “barely important” or “not important” is shown in the Table 4 below. The statistical significance of the odds ratio is shown as the p-value. Correlations that were statistically significant at the 5% level are identified with asterisks in the last column.

**Table 4. Bivariate Association between Perceptions of Potential Benefits as Very Important Motivators and Willingness to Participate (WTP) in all Types of HIV Cure-Related Studies**

Potential benefit	n (answered WTP and benefits question)	% claiming that benefit is a "very important" motivator	Odds ratio (95% CI) for sample claiming that benefit is "very important"	p-value
<b>Potential Personal Benefits</b>				
Feel good contributing to HIV cure research	349	79%	3.62 (1.66-7.87)	0.001***
Gaining knowledge about own health/HIV	349	77%	1.61 (0.88-2.95)	0.126
Learning about new treatment options	346	75%	1.91 (1.05-3.50)	0.035*
Not wanting to give up	336	72%	1.47 (0.84-2.57)	0.175
Hope that health will improve	346	71%	1.12 (0.66-1.92)	0.666
More/regular access to medical researchers	346	57%	1.96 (1.18-3.24)	0.009**
Additional laboratory work free of charge	346	53%	1.85 (1.13-3.02)	0.015*
Regular access to a study nurse	347	46%	1.67 (1.03-2.69)	0.036*
Transportation compensation to study site	344	41%	1.03 (0.64-1.68)	0.890
Being compensated or reimbursed	346	29%	0.87 (0.51-1.49)	0.615
Being offered a meal at the study site	344	22%	1.10 (0.63-1.94)	0.730
<b>Potential Personal Clinical Benefits</b>				
Preserve immune system ability to fight HIV	345	92%	0.92 (0.39-2.16)	0.841
Reducing HIV reservoir or HIV in entire body	342	85%	2.48 (1.07-5.74)	0.034*
Control viral load in absence of treatment	339	85%	1.87 (0.87-4.01)	0.110
Prevent increase in virus for extended time	340	82%	1.86 (0.92-3.75)	0.083
Less risk transmitting HIV to sex partner(s)	334	81%	1.79 (0.91-3.54)	0.093
Increased immune cell counts	341	71%	2.12 (1.18-3.83)	0.012*
<b>Potential Social Benefits</b>				
Helping find a cure for HIV	348	95%	Perfect +ve corr.	0.000***
Helping other people with HIV in the future	348	91%	2.81 (0.96-8.23)	0.059
Contributing to scientific knowledge	347	88%	2.91 (1.10-7.65)	0.031*
Receiving support from family and friends	338	42%	1.20 (0.74-1.95)	0.467

\*\*\* Statistically significant at the 0.1% level. \*\* Statistically significant at the 1% level. \* Statistically significant at the 5% level. 95% confidence intervals are estimated using robust standard errors.

Out of the perceptions of 21 potential benefits asked about in the survey, 9 were statistically significantly correlated with willingness to participate. The p-value for these nine variables were lower than 0.05, thereby rejecting the null hypothesis that willingness to participate is independent of whether respondents believed that the potential benefit was “very important” in motivating them to consider participating. This includes one potential benefit that was perfectly correlated with willingness to participate. All respondents who were “very willing to participate” ranked helping to find a cure for HIV as a “very important” motivating factor to considering participation in HIV cure-related studies.

The odds ratios for the other eight potential benefits that were statistically correlated with willingness to participate were always greater than 1.0, indicating a positive correlation between perception that the potential benefit is a “very important” motivator and willingness to participate. Respondents who perceived feeling good about contributing to HIV cure-related research as a “very important” motivating factor were 3.62 times as likely to be “very willing” to participate in HIV cure-related studies than respondents who did not perceive the potential benefit as “very important.” This potential benefit had the largest association with willingness to participate in terms of magnitude (after the perfect correlation of helping find a cure for HIV). The perceptions of potential benefits that were positively and statistically significantly correlated with willingness to participate included, in descending order of magnitude:

1. Helping find a cure for HIV
2. Feeling good about contributing to HIV cure-related research
3. Contributing to scientific knowledge
4. Reducing the amount of HIV in the entire body or making the HIV reservoir (site where HIV can persist) smaller
5. Increasing immune cell counts

6. Having more regular access to medical doctors or researchers
7. Learning about new treatment options
8. Additional laboratory work done free of charge, such as viral load or CD4+ count testing
9. Having more regular access to a study nurse

It is noteworthy that the three potential benefits that had the strongest positive correlations were all altruistic/emotional benefits. Respondents who were strongly motivated by doing a greater good were much more likely to be very willing to participate in HIV cure-related studies than individuals who did not share a similar sense of motivation. The motivating factors of compensation, gaining knowledge, receiving support from family and friends, and several potential personal clinical benefits were not statistically correlated with willingness to participate.

On the list of 35 potential risks, the survey results revealed that as few as 3% of respondents and as high as 49% of respondents perceived specific potential risks as “very likely to discourage” them from considering participation in HIV cure-related studies, depending on the potential risk. The correlation between each of the 35 dichotomous independent variables (perception of an individual potential risk as “very likely to discourage” participation) and the dichotomous dependent variable (willingness to participate in all types of HIV cure-related studies) was statistically tested using univariate logistic regression analysis.

Table 5 below displays the sample size of respondents who responded to both the dependent willingness to participate (WTP) question and the individual potential risks questions, alongside the percent of the sample who perceived the individual potential risk as “very likely to discourage” participation in HIV cure-related studies. For all potential risks, 26 – 28% of the sample were “very willing” to participate in studies.

The odds ratio of participants being “very willing to participate” and claiming a potential risk as “very likely to discourage” participation versus “somewhat likely”, “barely likely” or “not likely” is shown in the Table 5 below. The statistical significance of the odds ratio is shown as the p-value. Correlations that were statistically significant at the 5% level are identified with asterisks in the last column.



**Table 5. Bivariate Association between Perceptions of Potential Risks as Very Likely to Discourage Participation and Willingness to Participate (WTP) in all Types of HIV Cure-Related Studies**

Potential risk	n (answered WTP and risk questions)	% claiming that risk is "very likely" to discourage participation	Odds ratio (95% CI) for sample claiming that benefit is "very important"	p-value
<b>Potential Personal Clinical Risks</b>				
Activation of genes that could cause cancer	324	49%	0.23 (0.13-0.41)	0.000***
Possibility of developing resistance to drugs	322	38%	0.36 (0.20-0.64)	0.001***
Toxicities or adverse negative effects of drugs	324	31%	0.21 (0.10-0.43)	0.000***
Known risks of stopping HIV medications	324	29%	0.27 (0.14-0.54)	0.000***
Unable to predict viral rebound	322	27%	0.28 (0.14-0.57)	0.000***
Graft-versus-host disease	313	26%	0.16 (0.07-0.38)	0.000***
Invasive study procedures (e.g. biopsy)	324	16%	0.26 (0.10-0.68)	0.006**
<b>Potential Personal Risks: Commitment</b>				
Long study visits (>4 hours each)	326	9%	0.31 (0.09-1.04)	0.058
High frequency of study visits (>1 per month)	325	6%	0.27 (0.06-1.20)	0.084
Long study duration and follow-up (>5 years)	324	6%	0.71 (0.23-2.21)	0.558
<b>Potential Personal Risks: Study Procedures</b>				
Spinal tap	321	27%	0.09 (0.03-0.26)	0.000***
Bone marrow biopsies	312	24%	0.24 (0.11-0.52)	0.000***
Biopsies of lymph nodes	321	13%	0.18 (0.05-0.60)	0.005**
Rectal biopsies	325	13%	0.26 (0.09-0.75)	0.012*
Organ donation after death	303	7%	0.41 (0.12-1.44)	0.166
Isolating white blood cells (may take 2 hours)	326	6%	0.15 (0.02-1.16)	0.069
Collection of semen or vaginal fluids	323	3%	0.76 (0.15-3.72)	0.732
Oral biopsies (e.g. saliva samples)	328	3%	0.30 (0.04-2.40)	0.256
Blood draws	331	2%	0.92 (0.18-4.64)	0.918

**Potential Personal Risks: Symptoms or Side Effects**

Hair loss	324	33%	0.40 (0.22-0.71)	0.002**
Vomiting	326	24%	0.11 (0.04-0.30)	0.000***
Pre-defined, controlled discomfort or pain	318	14%	0.10 (0.02-0.41)	0.000***
Nausea	327	14%	0.16 (0.05-0.53)	0.003**
Headache	328	13%	0.18 (0.05-0.60)	0.005**

**Potential Personal Risks: Burdens**

Difficulty finding/paying for parking at the site	326	19%	0.40 (0.19-0.85)	0.017*
Difficulty finding transportation to the site	325	16%	0.45 (0.20-0.99)	0.047*
Time away from work or school	318	10%	0.49 (0.18-1.32)	0.157
Time away from family	322	5%	0.65 (0.18-2.37)	0.517
Challenges of finding child care	303	5%	1.06 (0.32-3.49)	0.919
Having to explain study participation to others	319	4%	0.52 (0.11-2.43)	0.408

**Potential Social Risks**

Risk of transmitting HIV to a sexual partner	321	29%	0.69 (0.39-1.22)	0.197
Discrimination	327	10%	0.36 (0.12-1.05)	0.062
Stigma	328	7%	0.42 (0.12-1.45)	0.168
Being recognized as a person living with HIV	330	7%	0.39 (0.11-1.35)	0.138
Risk of losing "HIV-positive identity" if cured	319	3%	0.93 (0.18-4.70)	0.931

\*\*\* Statistically significant at the 0.1% level. \*\* Statistically significant at the 1% level. \* Statistically significant at the 5% level. 95% confidence intervals are estimated using robust standard errors.

Out of the perceptions of 35 potential risks asked about in the survey, 18 were statistically significantly correlated with willingness to participate. The p-value for these variables were lower than 0.05, thereby rejecting the null hypothesis that willingness to participate was independent of whether the respondent believed that the potential risk was “very likely to discourage” them to consider participating. The odds ratios for these 18 potential risks are always less than 1.0, indicating a negative correlation between perception that the potential risk is “very likely to discourage” participation and willingness to participate, as expected. Respondents who perceived having a spinal tap as a study procedure as “very likely to discourage” their participation are only 9% as likely to be very willing to participate in HIV cure-related studies as respondents who did not share their strong rejection of spinal tap procedures. Similarly odds ratios were calculated for potential risk factors of vomiting or having pre-defined, controlled discomfort/pain as symptoms or side effects of studies. These three potential risks had the largest associations with willingness to participate in terms of magnitude.

The perceptions of potential risks that were negatively and statistically significantly correlated with willingness to participate include, in descending order of magnitude:

1. Spinal tap as a study procedure
2. Pre-defined, limited and controlled potential discomfort and/or pain as a side effect or symptom
3. Vomiting as a side effect or symptom
4. Graft-versus-host disease (GVHD), a possible complication from allogeneic (foreign) stem cells transplants
5. Nausea as a side effect or symptom
6. Biopsies of one of the participant’s lymph nodes (organs than contain immune cells) as a study procedure

7. Headache as a side effect or symptom
8. Toxicities or adverse negative effects of the drugs being studied
9. Activation of genes in the body that could cause cancer
10. Bone marrow biopsies as a study procedure
11. Invasive study procedures such as biopsy or sample of tissue from one of the lymph nodes
12. Rectal biopsies via sigmoidoscopy or colonoscopy as a study procedure
13. Known risks of stopping HIV medications such as the potential for a rapid increase/rebound in the viral load
14. Having no way to predict the risk of having the virus become detectable again in the participant (viral rebound)
15. Possibility of developing resistance to the drugs during a structured treatment interruption
16. Hair loss as a side effect or symptom
17. Difficulty finding or having to pay for parking at the clinical research site
18. Difficulty finding transportation to the clinical research site

All of the potential personal clinical risks and all of the potential personal risks involving symptoms and side effects were statistically significantly correlated with deterrence to participate. Likewise, all of the invasive study procedures (i.e. biopsies and spinal taps) and transportation risks were statistically significantly correlated with deterrence to participate. Individuals who perceived these factors as “very likely to discourage” their participation were less likely to be willing to participate in studies than individuals who are not as concerned with these factors. Or, in other words, individuals who were relatively less willing to participate in HIV cure-related studies were statistically more concerned about the potential risks of these particular factors than respondents who were very willing to participate. It is worthwhile to note that short-term and immediate risks, such as those involving pain or discomfort temporarily, have stronger correlation with deterrence to

participate in terms of magnitude than some of the longer-term risks, such as the potential for enabling cancer or developing viral rebounds over time in the bivariate analyses. This seemed to be the opposite when looking merely at the descriptive data.

Conversely, none of the potential risks regarding commitment levels, burdens of time and non-transportation logistics, non-invasive study procedures, or potential social risks were statistically significantly correlated with willingness to participate (although perception that discrimination was very likely to discourage participation was negatively statistically correlated with willingness to participate at the 10% level but not the 5% level). All but one of these potential risk factors were “very likely to discourage” participation for only 10% or less of respondents. Risk factors that were more popular (i.e. that worried larger proportions of the respondent sample) were statistically correlated with deterrence to participate.

Finally, the correlation between various socio-demographic characteristics and willingness to participate in all types of HIV cure-related studies was statistically tested using univariate logistic regression analysis. Table 6 below breaks down the sample by all categories for each characteristics variable, displaying the sample size in each category (summing up to 100% within each categorical variable) alongside the number and percent of the sample who were very willing or relatively less willing to participate in HIV cure-related studies. The odds ratios of participants being “very willing to participate” for each category within the characteristics variables is shown in Table 6. The statistical significance of each odds ratio, as well as the overall statistical significance of the correlation of the categorical variable and willingness to participate is shown as p-values. Correlations that were statistically significant at the 5% level are identified with asterisks in the last column.

**Table 6. Bivariate Association between Socio-Demographic Characteristics and Willingness to Participate in All Types of HIV Cure-Related Studies**

Variable	n	Willingness to participate in all types of HIV cure-related studies		Odds ratio (95% CI)	p-value
		Yes (very willing to participate)	No (relatively less willing to participate)		
<b>Gender</b>					<i>0.283</i>
Male	284 (79%)	78 (27%)	206 (73%)	1.00	
Female	73 (20%)	15 (21%)	58 (79%)	0.68 (0.37-1.28)	0.232
Transgender male to female, Other	4 (1%)	2 (50%)	2 (50%)	2.64 (0.37-19.07)	0.336
<b>Age</b>					<i>0.064</i>
19-29	19 (5%)	6 (32%)	13 (68%)	1.00	
30-39	42 (12%)	17 (40%)	25 (60%)	1.47 (0.47-4.64)	0.508
40-49	91 (25%)	27 (30%)	64 (70%)	0.91 (0.31-2.66)	0.869
50-59	142 (39%)	34 (24%)	108 (76%)	0.68 (0.24-1.93)	0.471
60+	67 (19%)	11 (16%)	56 (84%)	0.43 (0.13-1.36)	0.150
As a continuous variable	361 (100%)			0.97 (0.95-0.99)	0.005**
<b>Ethnicity</b>					<i>0.224</i>
Caucasian/White	240 (66%)	71 (30%)	169 (70%)	1.00	
African-American	52 (14%)	12 (23%)	40 (77%)	0.71 (0.35-1.44)	0.347
Hispanic or Hispanic descent	43 (12%)	8 (19%)	35 (81%)	0.54 (0.24-1.23)	0.144
Other	12 (3%)	1 (8%)	11 (92%)	0.22 (0.03-1.71)	0.146
Mixed	14 (4%)	3 (21%)	11 (79%)	0.65 (0.18-2.40)	0.517
<b>Education</b>					<i>0.356</i>
High school or G.E.D., or less	89 (25%)	27 (30%)	62 (70%)	1.00	
Some college / Associate degree	90 (25%)	26 (29%)	64 (71%)	0.93 (0.49-1.77)	0.832
Undergraduate degree	97 (27%)	26 (27%)	71 (73%)	0.84 (0.44-1.59)	0.594
Master's degree or its equivalent	62 (17%)	11 (18%)	51 (82%)	0.50 (0.22-1.09)	0.082

Doctorate or its equivalent	22 (6%)	4 (18%)	18 (82%)	0.51 (0.16-1.65)	0.261
<b>Household Income</b>					0.471
Less than \$25,000	127 (35%)	32 (25%)	95 (75%)	1.00	
\$25,000 - \$50,000	100 (28%)	31 (31%)	69 (69%)	1.33 (0.74-2.39)	0.333
\$50,001 - \$75,000	45 (13%)	10 (22%)	35 (78%)	0.85 (0.38-1.90)	0.690
\$75,001 - \$100,000	35 (10%)	7 (20%)	28 (80%)	0.74 (0.30-1.86)	0.525
\$100,001 - \$125,000	28 (8%)	10 (36%)	18 (64%)	1.65 (0.69-3.94)	0.260
\$125,001 - \$150,000	9 (3%)	3 (33%)	6 (67%)	1.48 (0.35-6.28)	0.592
More than \$150,000	16 (4%)	2 (13%)	14 (88%)	0.42 (0.09-1.97)	0.273
<b>Region</b>					0.699
Northeast	39 (11%)	9 (23%)	30 (77%)	1.00	
Midwest	62 (17%)	13 (21%)	49 (79%)	0.88 (0.34-2.32)	0.803
South	126 (35%)	35 (28%)	91 (72%)	1.28 (0.55-2.97)	0.562
West	130 (36%)	36 (28%)	94 (72%)	1.28 (0.55-2.95)	0.568
<b>Current Health Status</b>					<0.001***
Very healthy	68 (19%)	16 (24%)	52 (76%)	1.00	
Healthy	162 (45%)	50 (31%)	112 (69%)	1.45 (0.76-2.78)	0.263
Somewhat healthy	110 (31%)	17 (15%)	93 (85%)	0.59 (0.28-1.27)	0.181
Not very healthy/Not at all healthy	20 (6%)	12 (60%)	8 (40%)	4.88 (1.70-14.01)	0.003**
<b>In Control Over Own Health Care</b>					0.666
No	48 (14%)	14 (29%)	34 (71%)	1.00	
Yes	298 (86%)	78 (26%)	220 (74%)	0.86 (0.44-1.69)	0.663
<b>Taking Medication for HIV</b>					0.892
No	7 (2%)	2 (29%)	5 (71%)	1.00	
Yes	354 (98%)	93 (26%)	261 (74%)	0.89 (0.17-4.67)	0.891
<b>Percent of Life Living with HIV</b>					
<b>Diagnosis</b>					<0.001***
Up to 25%	129 (36%)	53 (41%)	76 (59%)	1.00	
26-50%	171 (48%)	29 (17%)	142 (83%)	0.29 (0.17-0.50)	<0.001***
More than 50%	56 (16%)	12 (21%)	44 (79%)	0.39 (0.19-0.81)	0.012*

As a continuous variable	356 (100%)			0.07 (0.02-0.28)	<0.001***
<b>Ever Volunteered for an HIV Treatment Study</b>					0.075
No	199 (56%)	60 (30%)	139 (70%)	1.00	
Yes	156 (44%)	34 (22%)	122 (78%)	0.65 (0.40-1.05)	0.078
<b>Ever Volunteered for an HIV Cure Study</b>					0.014*
No	329 (93%)	93 (28%)	236 (72%)	1.00	
Yes	25 (7%)	2 (8%)	23 (92%)	0.22 (0.05-0.95)	0.043*
<b>Generally Interested in HIV Cure Research</b>					
No	5 (1%)	0 (0%)	5 (100%)	Perfect +ve correlation	
Yes	346 (99%)	95 (27%)	251 (73%)		

\*\*\* Statistically significant at the 0.1% level. \*\* Statistically significant at the 1% level. \* Statistically significant at the 5% level. 95% confidence intervals are estimated using robust standard errors.



Of all of the different individual-level characteristics, only five were statistically correlated with willingness to participate in HIV cure-related studies at the 5% level:

- ⇒ Respondents who described their current health status as “not at all healthy” or “not very healthy” were nearly five times more likely to be very willing to participate in all types of HIV cure related studies than respondents who self-described as “very healthy.”
- ⇒ Respondents who have lived with an HIV diagnosis for larger proportions of their life were much less likely to be very willing to participate in HIV cure-related studies than respondents whose HIV status were relatively new. Respondents who have lived more than half of their lives with an HIV diagnosis were only 39% as likely to be very willing to participate in HIV cure-related studies as respondents who have lived less than a quarter of their life with an HIV diagnosis.
- ⇒ When age was analyzed as a continuous variable, older-aged respondents were less likely to be very willing to participate in HIV cure-related studies than younger-aged respondents.
- ⇒ Respondents who have ever volunteered for or been in an HIV cure study were less likely (only 22% as likely) to be very willing to participate in all types of HIV cure-related studies than respondents who have never volunteered for an HIV cure study in the past.
- ⇒ General interest in HIV cure research is perfectly and positively correlated with willingness to participate. All respondents who were very willing to participate in HIV cure-related studies were generally interested in HIV cure research. Only five respondents were not generally interested in HIV cure research, and all five were relatively less willing to participate in HIV cure studies.

Gender, ethnicity, education (on average), household income, region, control over own health care, and taking medications for HIV were not statistically correlated with willingness to participate in HIV cure-related studies in the bivariate analyses. Having a Master’s degree, and

having ever volunteered for or been in an HIV *treatment* study was statistically significantly correlated with willingness to participate at the 10% level but not the 5% level.

In summary, key bivariate results from the survey include:

- ⇒ Perceptions of nine potential benefits as “very important” motivating factors for considering participation in HIV cure-related studies were positively and statistically significantly correlated with willingness to participate. Individuals who cared about these specific factors were more likely to be willing to participate in HIV cure-related studies than others.
- ⇒ The potential benefits that were positively correlated with willingness to participate came from all three groups of benefits: personal benefits, personal clinical benefits, and social benefits.
- ⇒ The three potential benefits that had the strongest positive correlations were all altruistic/emotional benefits. Respondents who were strongly motivated by doing a greater good were much more likely to be very willing to participate in HIV cure-related studies than individuals who did not share a similar sense of motivation.
- ⇒ Perception of the importance of compensation was not correlated with willingness to participate.
- ⇒ Perceptions of 18 potential risks as “very likely to discourage” participation in HIV cure-related studies were negatively and statistically significantly correlated with deterrence to participate. Individuals who were more concerned about these particular potential risks were relatively less willing to participate in HIV studies than individuals who were not as concerned about these risks.
- ⇒ The potential risks that were negatively correlated with willingness to participate were potential personal clinical risks, symptoms and side effects, invasive study procedures, and transportation logistics.

- ⇒ Short-term and immediate risks, such as those that involved pain or discomfort temporarily, had stronger correlation with willingness to participate in terms of magnitude than some of the longer-term risks, such as the potential for enabling cancer or developing viral rebounds over time. The three potential risks that had the strongest negative correlations were the use of spinal tap as a study procedure, or symptoms/side effects of vomiting or pre-defined, controlled pain or discomfort.
- ⇒ None of the potential risks regarding commitment levels, burdens of time and non-transportation logistics, non-invasive study procedures, or potential social risks were statistically significantly correlated with willingness to participate.
- ⇒ Poor current health status, younger age, living with HIV diagnosis for smaller proportions of lifetime, general interest in HIV cure research, and having not ever previously volunteered for or participated in an HIV cure study were positively and statistically significantly correlated with higher willingness to participate in HIV cure-related studies.
- ⇒ Gender, ethnicity, education (for the most part), household income, region, control over own health care, and taking medication for HIV were not statistically correlated with willingness to participate in HIV cure-related studies.

### **Multivariate Regression Analyses**

Bivariate associations that were statistically significant may be caused by an indirect link between the independent and dependent variables. This is particularly possible because socio-demographic characteristics were also shown to be statistically correlated with willingness to participate. Thus, cross-sectional multivariate logistic regression models were estimated to assess the statistical significance and magnitude of the correlation between perceptions of potential benefits/risks and respondents' willingness to participate in all types of HIV cure-related studies, controlling for extraneous socio-demographic characteristics.

A total of 58 logistic regression models were estimated. In all models, the dependent variable was whether the respondent was very willing to participate in HIV cure-related studies versus relatively less willing to participate. In the first model, Model 1, willingness to participate was regressed only on the control variables, comprised of individual-level socio-demographic characteristic and attitudes towards HIV cure research. Several versions of this model were iteratively fitted, adjusting the combination of and construct of the control variables as described in the Methods section. The model (Model 1) that best fitted the data is shown in Table 7 below. Hence, for all subsequent models (Models 2 – 58), the same control variables were included as used and shown in Model 1 (Table 7) below.

**Table 7. Multivariate Logistic Regression of Willingness to Participate in All Types of HIV Cure-Related Studies on Individual-Level Socio-Demographic Characteristics (Model 1)**

Control Variable	Odds Ratio	95% CI	<i>p</i> -value
Male (vs. female, transgender, other)	1.17	(0.57-2.43)	0.666
Age	0.97*	(0.94-0.99)	0.014
Ethnicity (vs. Caucasian/White)			
African American	0.64	(0.25-1.60)	0.337
Hispanic	0.45	(0.16-1.25)	0.128
Mixed or Other	0.41	(0.12-1.38)	0.149
Highest education attainment level (vs. some college or less)			
Bachelor's degree	0.78	(0.40-1.50)	0.453
Graduate degree	0.42*	(0.19-0.95)	0.038
Annual household income (vs. up to \$25,000)			
\$26-\$50k/year	1.20	(0.62-2.33)	0.584
\$51-\$75k/year	0.58	(0.22-1.51)	0.265
\$76-\$100k/year	0.74	(0.24-2.28)	0.603
\$101-\$125k/year	1.82	(0.63-5.25)	0.268
\$126-\$150k/year	1.76	(0.38-8.27)	0.473
More than \$150k/year	0.17	(0.03-1.01)	0.052
Region (vs. West)			
Northeast	0.71	(0.28-1.83)	0.480
Midwest	0.48	(0.21-1.11)	0.088
South	0.60	(0.31-1.16)	0.132
Consider self to be "not at all healthy or not very	4.45*	(1.36-14.5)	0.014

healthy" (vs. healthier)			
Have control over own health care (vs. no)	1.35	(0.60-3.06)	0.467
Percent of life living with HIV status	0.97**	(0.96-0.99)	0.002
Currently taking medications for HIV	0.89	(0.17-4.67)	0.891
Ever volunteered for an HIV cure study (vs. no)	0.22	(0.05-1.08)	0.063
	n	329	
	Model Prob > chi2	0.0088	

\*\*\* Statistically significant at the 0.1% level. \*\* Statistically significant at the 1% level. \* Statistically significant at the 5% level. 95% confidence intervals are estimated using robust standard errors.

Collectively, the set of socio-demographic variables used in Model 1 were statistically significant, with an overall model  $p$ -value of 0.0088. Although the variable measuring whether the respondent is generally interested in HIV cure research was included in the model, it was dropped due to perfect correlation with the dependent variable after being included in the model with the other control variables. Furthermore, the overall model fit (as determined by a Likelihood-Ratio test of a restricted and unrestricted model) improved when the variable measuring whether the participant was taking medications for HIV was excluded. Thus, this variable is excluded from Model 1 onwards.

The results from Model 1 indicate that only four individual-level characteristics were statistically significantly correlated with willingness to participate. The  $p$ -value for these four variables were lower than 0.05, thereby rejecting the null hypothesis that willingness to participate is independent of the socio-demographic characteristic. These four characteristics are:

1. Respondents who described their current health status as "not at all healthy" or "not very healthy" were 4.45 times more likely to be very willing to participate in all types of HIV cure-related studies than respondents who self-described as "somewhat healthy", "healthy" and "very healthy", on average and controlling for all other socio-demographic characteristics.
2. Respondents who have lived with an HIV diagnosis for larger proportions of their lifetime were less likely to be very willing to participate in HIV cure-related studies than respondents whose HIV status were relatively newer. An increase of one percentage point in the percent

- of life living with HIV status was associated with a 97% odds ratio (a drop of 3 percentage points) in willingness to participate, on average and *ceteris paribus*.
3. Older-aged respondents were less likely to be very willing to participate in HIV cure-related studies than younger-aged respondents. An increase of one year in age was associated with a 97% odds ratio (a drop of 3 percentage points) in willingness to participate, on average and *ceteris paribus*.
  4. Respondents who have completed a graduate degree (Master's degree or higher) were only, on average, 42% as likely as respondents who did not complete an undergraduate degree in being very willing to participate in HIV cure-related studies, *ceteris paribus*. Thus, as educational attainment level increased, willingness to participate decreased, when controlling for all other socio-demographic characteristics.

These results are similar to the results of the bivariate association analysis in that the first three variables were statistically significantly correlated with willingness to participate – and in the same direction – both in one-on-one bivariate associations and in multivariate regressions that control for confounding effects of extraneous factors. After controlling for other variables, however, achieving a Master's degree as the highest educational attainment level became statistically significant at the 5% level, whereas the bivariate association was only statistically significant at the 10% level. Lastly, while having ever volunteered for or been in an HIV cure study was statistically significant at the 5% level in the bivariate association analysis, it was only significant at the 10% level in the multivariate analysis after controlling for other factors. The relative consistency between the bivariate association results and the multivariate regression analysis using control variables implies a strong degree of robustness in the data and the strength of the correlations between these factors and willingness to participate.

Individuals who believed that their health status was relatively poor were 4.45 times more willing to participate in HIV cure-related studies, on average, than individuals who believed their health status was good, *ceteris paribus*. This may be an indication that individuals are more willing to try whatever it takes to eradicate the virus, either for themselves or for society, when they are facing greater health obstacles. Conversely, individuals who have lived with their HIV status longer were less likely to be willing to participate in HIV cure-related studies than individuals who have more recently become infected with HIV. This finding suggests that the longer individuals live with HIV, the more accustomed they become to the virus and the less willing they are to consider participating in some of the more experimental types of HIV cure studies. Interestingly, people who are recently infected with the virus may be more eager and more willing to volunteer for HIV cure related studies. Likewise, younger individuals are, on average, more willing to participate in studies than older individuals. These results were surprising.

Willingness to participate was not statistically correlated with six variables in Model 1 (Table 7): gender, ethnicity, income, region, having control over own health care, and having ever volunteered for an HIV cure study. However, three of these variables were statistically significantly correlated at the 10% level, but not the 5% level, indicating a possible correlation. Household income above \$150,000 (versus income below \$25,000), living in the Midwest (versus the West), and having ever volunteered for an HIV cure study were weakly and negatively associated with willingness to participate in all types of HIV cure-related studies.

To determine which perceptions of the 21 potential benefits described in the survey were associated with willingness to participate in HIV cure studies, controlling for their individual-level characteristics, each of the potential benefits was added as the sole key independent variable to Model 1. This resulted in 21 new regression models (Models 2 through 22), each with the same

control variables shown in Model 1 plus one key independent variable that varied from model to model.

The key independent variable was whether the respondent perceived a specific potential benefit as a “very important” in motivating them to consider participation in HIV cure studies. The results for the key independent variable of all 21 models (Models 2 – 22) are shown in Table 8 below. For the sake of brevity, the odds ratios for the control variables are not shown in this table, although the same control variables shown in Model 1 were included in Models 2 – 22.



**Table 8. Odds Ratios of Willingness to Participate in All Types of HIV Cure-Related Studies and Perception of Potential Benefits as Very Important Motivating Factors for Considering Participation, Controlling for Socio-Demographic Characteristics in 21 Individual Logistic Models (Models 2 – 22)**

Model #	Key Independent (Benefit) Variable	Odds Ratio	95% CI	p-value	n	Model Prob > chi2
<b>Models Including a Potential Personal Benefit and the Control Variables</b>						
Model 2	Feel good contributing to HIV cure research	6.96***	(2.73-17.74)	0.000	319	0.0004
Model 3	Gaining knowledge about own health/HIV	2.06*	(1.04-4.11)	0.039	319	0.0082
Model 4	Learning about new treatment options	1.90	(0.96-3.73)	0.064	316	0.0325
Model 5	Not wanting to give up	1.28	(0.65-2.54)	0.474	307	0.0259
Model 6	Hope that health will improve	1.13	(0.61-2.10)	0.691	317	0.0317
Model 7	More/regular access to medical researchers	1.77	(1.00-3.12)	0.051	316	0.0287
Model 8	Additional laboratory work free of charge	2.32**	(1.29-4.16)	0.005	316	0.0077
Model 9	Regular access to a study nurse	1.65	(0.95-2.86)	0.075	317	0.0303
Model 10	Transportation compensation to study site	1.38	(0.73-2.62)	0.320	314	0.0181
Model 11	Being compensated or reimbursed	1.01	(0.53-1.95)	0.965	316	0.0308
Model 12	Being offered a meal at the study site	1.05	(0.50-2.23)	0.890	314	0.0256
<b>Models Including a Potential Personal Clinical Benefit and the Control Variables</b>						
Model 13	Preserve immune system ability to fight HIV	0.73	(0.28-1.91)	0.516	316	0.0303
Model 14	Reducing HIV reservoir or HIV in entire body	1.93	(0.74-5.04)	0.180	314	0.0214
Model 15	Control viral load in absence of treatment	1.33	(0.54-3.22)	0.534	311	0.0186
Model 16	Prevent increase in virus for extended time	1.54	(0.68-3.51)	0.300	313	0.0295
Model 17	Less risk transmitting HIV to sex partner(s)	1.55	(0.72-3.35)	0.263	305	0.0199
Model 18	Increased immune cell counts	1.87	(0.91-3.85)	0.087	312	0.0220
<b>Models Including a Potential Social Benefit and the Control Variables</b>						
Model 19	Helping find a cure for HIV	Perfect +ve correlation with "very willing to participate"				
Model 20	Helping other people with HIV in the future	2.66	(0.81-8.76)	0.107	318	0.0231
Model 21	Contributing to scientific knowledge	5.37**	(1.64-17.62)	0.006	317	0.0031
Model 22	Receiving support from family and friends	0.97	(0.53-1.78)	0.918	309	0.0536

Each benefit variable was included in a separate model with the control variables listed in Model 1. Odd ratios on the control variables are not displayed. \*\*\* Statistically significant at the 0.1% level. \*\* Statistically significant at the 1% level. \* Statistically significant at the 5% level. Robust standard errors estimated.

As shown in Table 8, perception of potential motivating factors does not always associate with an increase in willingness to participate in HIV cure studies. Of the 21 potential benefits, only five were statistically significantly associated, at the 5% level, with willingness to participate, controlling for socio-demographic factors. This includes one potential benefit, helping find a cure for HIV, which was perfectly and positively correlated with willingness to participate, after controlling for all other factors. The odds ratios for the other four potential benefits were always greater than 1.0, indicating a positive association between perception that the potential benefit was a “very important” motivator and willingness to participate. Respondents who perceived feeling good about contributing to HIV cure-related research as a “very important” motivating factor were nearly 7 times as likely to be “very willing” to participate in HIV cure-related studies than respondents who did not perceive the potential benefit as “very important,” controlling for socio-demographic characteristics. This potential benefit had the largest association with willingness to participate in terms of magnitude (after the perfect correlation of helping find a cure for HIV).

After controlling for socio-demographic characteristics, the following five potential benefits were statistically significantly correlated with willingness to participate, in descending order of magnitude:

1. Helping find a cure for HIV
2. Feeling good about contributing to HIV cure-related research
3. Contributing to scientific knowledge
4. Additional laboratory work done free of charge, such as viral load or CD4+ count testing
5. Getting special/additional knowledge about respondent’s own HIV infection and own health while being in the study

Similar to the outcome of the bivariate association analysis, the three potential benefits that had the strongest positive correlations were all altruistic/emotional benefits: helping find a cure for

HIV, feeling good about contributing to HIV cure research, and contributing to scientific knowledge. In fact, they were the same variables that produced the strongest bivariate associations with willingness to participate, and the strength of these associations remained significant even after controlling for socio-demographic characteristics. The other two statistically significant variables were both personal benefits related to increasing the respondent's knowledge of their own HIV infection.

Interestingly, none of the potential personal clinical benefits were statistically significant after controlling for socio-demographic characteristics (see Models 13 –18), and fewer potential personal benefits were statistically significant than the bivariate association analysis revealed. The significance of the correlation between the perception of those factors and willingness to participate may be indirectly linked through other variables that may have been controlled for among the socio-demographic variables. Nevertheless, there were four more potential benefits that were statistically significantly correlated at the 10% level but not the 5% level, implying a weak association with willingness to participate. These included: learning about new treatment options, increasing immune cell counts, having more regular access to medical doctors or researchers, and having more regular access to a study nurse.

Similar to the previous step, 35 new regression models (Models 23 – 57) were estimated using the control variables in Model 1, and adding each potential risk as the sole key independent variable to each model. The key independent variable was whether the respondent perceived a specific potential risk as “very likely to discourage” them from considering participation in HIV cure studies. The results for the key independent variable of all 35 models (Models 23 – 57) are shown in Table 9 below. Again, for the sake of brevity, the odds ratios for the control variables are not shown in this table, although the same control variables shown in Model 1 were included in Models 23 – 57.

**Table 9. Odds Ratios of Willingness to Participate in All Types of HIV Cure-Related Studies and Perception of Potential Risks as Very Likely to Discourage Participation, Controlling for Socio-Demographic Characteristics in 35 Individual Logistic Models (Models 23 – 57)**

Model #	Key Independent (Risk) Variable	Odds Ratio	95% CI	p-value	n	Model Prob > chi2
<b>Models Including a Potential Personal Clinical Risk and the Control Variables</b>						
Model 23	Activation of genes that could cause cancer	0.23***	(0.12-0.45)	0.000	296	0.0010
Model 24	Possibility of developing resistance to drugs	0.32***	(0.16-0.63)	0.001	296	0.0023
Model 25	Toxicities or adverse negative effects of drugs	0.24***	(0.11-0.51)	0.000	296	0.0040
Model 26	Known risks of stopping HIV medications	0.28***	(0.14-0.59)	0.001	296	0.0028
Model 27	Unable to predict viral rebound	0.30***	(0.14-0.63)	0.001	294	0.0043
Model 28	Graft-versus-host disease	0.16***	(0.07-0.38)	0.000	287	0.0014
Model 29	Invasive study procedures (e.g. biopsy)	0.29**	(0.12-0.73)	0.009	296	0.1539
<b>Models Including a Potential Personal Risk (Commitment) and the Control Variables</b>						
Model 30	Long study visits (>4 hours each)	0.46	(0.13-1.65)	0.234	297	0.0089
Model 31	High frequency of study visits (>1 per month)	0.42	(0.09-1.99)	0.277	296	0.0086
Model 32	Long study duration and follow-up (>5 years)	1.09	(0.26-4.49)	0.910	296	0.0093
<b>Models Including a Potential Personal Risk (Study Procedures) and the Control Variables</b>						
Model 33	Spinal tap	0.07***	(0.02-0.23)	0.000	294	0.0001
Model 34	Bone marrow biopsies	0.21**	(0.08-0.59)	0.003	288	0.0125
Model 35	Biopsies of lymph nodes	0.28	(0.07-1.12)	0.071	292	0.0135
Model 36	Rectal biopsies	0.31*	(0.10-0.96)	0.043	297	0.0088
Model 37	Organ donation after death	0.60	(0.15-2.50)	0.487	278	0.0168
Model 38	Isolating white blood cells (may take 2 hours)	0.23	(0.02-2.34)	0.216	297	0.0107
Model 39	Collection of semen or vaginal fluids	1.65	(0.27-10.06)	0.587	294	0.0352
Model 40	Oral biopsies (e.g. saliva samples)	0.43	(0.03-5.53)	0.518	300	0.0107
Model 41	Blood draws	1.95	(0.27-14.11)	0.508	302	0.0219
<b>Models Including a Potential Personal Risk (Symptoms or Side Effects) and the Control Variables</b>						
Model 42	Hair loss	0.38**	(0.18-0.79)	0.009	296	0.0105
Model 43	Vomiting	0.12***	(0.04-0.33)	0.000	297	0.0001

Model #	Key Independent (Risk) Variable	Odds Ratio	95% CI	p-value	n	Model Prob > chi2
Model 44	Pre-defined, controlled discomfort or pain	0.09**	(0.02-0.43)	0.002	291	0.0037
Model 45	Nausea	0.19**	(0.06-0.62)	0.006	298	0.0028
Model 46	Headache	0.19*	(0.05-0.73)	0.016	299	0.0204
<b>Models Including a Potential Personal Risk (Burdens) and the Control Variables</b>						
Model 47	Difficulty finding/paying for parking at the site	0.36*	(0.16-0.82)	0.015	298	0.0183
Model 48	Difficulty finding transportation to the site	0.30*	(0.11-0.77)	0.013	297	0.0037
Model 49	Time away from work or school	0.35	(0.11-1.07)	0.066	290	0.0494
Model 50	Time away from family	0.63	(0.17-2.32)	0.486	293	0.0231
Model 51	Challenges of finding child care	0.87	(0.25-3.00)	0.825	275	0.0242
Model 52	Having to explain study participation to others	0.34	(0.07-1.61)	0.174	290	0.0263
<b>Models Including a Potential Social Risk and the Control Variables</b>						
Model 53	Risk of transmitting HIV to a sexual partner	0.46*	(0.24-0.91)	0.026	295	0.0135
Model 54	Discrimination	0.23*	(0.06-0.96)	0.043	299	0.0144
Model 55	Stigma	0.33	(0.06-1.90)	0.213	300	0.0191
Model 56	Being recognized as a person living with HIV	0.21	(0.03-1.23)	0.084	302	0.0213
Model 57	Risk of losing "HIV-positive identity" if cured	1.13	(0.21-6.13)	0.891	291	0.0497

Each risk variable was included in a separate model with the control variables listed in Model 1. Odd ratios on the control variables are not displayed. \*\*\* Statistically significant at the 0.1% level. \*\* Statistically significant at the 1% level. \* Statistically significant at the 5% level. Robust standard errors estimated.

Of the 35 potential risks, 19 were statistically significantly correlated, at the 5% level, with willingness to participate, controlling for socio-demographic factors. The odds ratios for all 19 potential risks were always less than 1.0, indicating a negative correlation between perception that the potential risks were “very likely to discourage” the respondents from participating and their willingness to participate in HIV cure studies. Respondents who perceived having a spinal tap as a study procedure as “very likely to discourage” their participation were only 7% as likely to be very willing to participate in HIV cure-related studies as respondents who did not share their strong rejection of spinal tap procedures, *ceteris paribus*. Again, this was the potential risk that had the strongest negative correlation with willingness to participate in terms of magnitude.

After controlling for socio-demographic characteristics, the following potential risks were statistically significantly correlated with deterrence to participate, in descending order of magnitude:

1. Spinal tap as a study procedure
2. Pre-defined, limited and controlled potential discomfort and/or pain as a side effect or symptom
3. Vomiting as a side effect or symptom
4. Graft-versus-host disease (GVHD), a possible complication from allogeneic (foreign) stem cells transplants
5. Headache as a side effect or symptom
6. Nausea as a side effect or symptom
7. Bone marrow biopsies as a study procedure
8. Activation of genes in the body that could cause cancer
9. Discrimination as a potential social risk
10. Toxicities or adverse negative effects of the drugs being studied

11. Known risks of stopping HIV medications such as the potential for a rapid increase/rebound in the viral load
12. Invasive study procedures such as biopsy or sample of tissue from one of the lymph nodes
13. Having no way to predict the risk of having the virus become detectable again in the participant (viral rebound)
14. Difficulty finding transportation to the clinical research site
15. Rectal biopsies via sigmoidoscopy or colonoscopy as a study procedure
16. Possibility of developing resistance to the drugs during a structured treatment interruption
17. Difficulty finding or having to pay for parking at the clinical research site
18. Hair loss as a side effect or symptom
19. Risk of transmitting HIV to a sexual partner

Similar to the outcomes of the bivariate association analysis, all of the potential personal clinical risks and all of the potential personal risks involving symptoms and side effects were statistically significantly correlated with unwillingness to participate, even after controlling for socio-demographic characteristics. The correlation between concern over these types of risks and overall unwillingness to participate in HIV cure-related studies appeared to be universal. Likewise, nearly all of the invasive study procedures (i.e. biopsies and spinal taps) and transportation risks were statistically significantly correlated with deterrence to participate. Finally, two new variables were statistically significantly correlated with willingness to participate that were not in the bivariate association analysis: fear of discrimination and the risk of transmitting HIV to a sexual partner were associated with a lower willingness to participate in studies, *ceteris paribus*.

Again, short-term and immediate risks, such as those that involved pain or discomfort temporarily, have stronger correlation with deterrence to participate in terms of magnitude than some of the longer-term risks, such as the potential for enabling cancer or developing viral rebounds

over time. None of the potential risks regarding commitment levels (Models 30 – 32), burdens of time and non-transportation logistics (Models 49 – 52), or non-invasive study procedures (Models 37 – 41) were statistically significantly correlated with deterrence to participate. There were three potential risks that were statistically significantly correlated at the 10% level but not the 5% level, implying a weak association with deterrence to participate. These included: biopsies of lymph nodes as a study procedure, time away from work or school, and being recognized as a person living with HIV.

Respondents who identified a greater number of potential benefits as “very important” motivating factors were more willing to participate in HIV cure studies than others, as shown in Table 10 below (Model 58, which has an overall model p-value of <0.0001), confirming the hypothesis described in the Methods section. Simultaneously, respondents who identified a greater number of potential risks as “very likely” to discourage participation were less willing to participate in HIV cure-related studies. Controlling for socio-demographic factors, every additional potential benefit respondents considered “very important” was associated with a 13% increase to the odds ratio of being very willing to participate, on average and *ceteris paribus*. Every additional potential risk respondents considered “very likely to discourage” was associated with a 0.82 odds ratio (an 18 percentage point decline) of being very willing to participate, on average and *ceteris paribus*. Both results were statistically significant at the 1% level. Respondents who identified a greater number of potential benefits as “very important” motivating factors may generally be more optimistic and eager to participate in HIV cure-related studies than respondents who only identified a small number of “very important” potential benefits. Conversely, respondents who identified a greater number of potential risks as “very likely to discourage” participation in studies may be generally more risk-averse (or risk-aware) and more cautious about participation in HIV cure studies.



**Table 10. Multivariate Logistic Regression of Willingness to Participate in All Types of HIV Cure-Related Studies and the Number of Potential Benefits Deemed Very Important Motivators and Number of Potential Risks Deemed Very Likely to Discourage Motivation, Controlling for Socio-Demographic Characteristics (Model 58)**

Variable	Odds Ratio	95% CI	p-value
Total number of benefits deemed to be "very important" motivators	1.13**	(1.05-1.22)	0.002
Total number of risks deemed to be "very likely to discourage" participation	0.82***	(0.75-0.90)	0.000
Male (vs. female, transgender, other)	0.84	(0.34-2.06)	0.706
Age	0.97	(0.94-1.01)	0.108
Ethnicity (vs. Caucasian/White)			
African American	0.40	(0.14-1.13)	0.083
Hispanic	0.55	(0.19-1.60)	0.273
Mixed or Other	0.24	(0.05-1.21)	0.084
Highest education attainment level (vs. some college or less)			
Bachelor's degree	0.69	(0.34-1.42)	0.313
Graduate degree	0.47	(0.18-1.22)	0.123
Annual household income (vs. up to \$25,000)			
\$26-\$50k/year	1.18	(0.53-2.59)	0.685
\$51-\$75k/year	0.64	(0.23-1.79)	0.392
\$76-\$100k/year	0.85	(0.28-2.65)	0.785
\$101-\$125k/year	1.44	(0.44-4.64)	0.545
\$126-\$150k/year	1.89	(0.37-9.76)	0.445
More than \$150k/year	0.59	(0.05-6.83)	0.671
Region (vs. West)			
Northeast	0.77	(0.26-2.34)	0.651
Midwest	0.28**	(0.11-0.73)	0.009
South	0.43*	(0.20-0.92)	0.030
Consider self to be "not at all healthy or not very healthy" (vs. healthier)	3.90*	(1.01-15.12)	0.049
Have control over own health care (vs. no)	1.00	(0.41-2.48)	0.991
Percent of life living with HIV status	0.97*	(0.95-0.99)	0.012
Ever volunteered for an HIV cure study (vs. no)	0.30	(0.06-1.49)	0.140
<hr/>			
	n	302	
	Model Prob > chi2	0.0000	

\*\*\* Statistically significant at the 0.1% level. \*\* Statistically significant at the 1% level. \* Statistically significant at the 5% level. 95% confidence intervals are estimated using robust standard errors.

Comparing the results of the control variables in Model 58 and Model 1, without any variables regarding perceptions of potential benefits and potential risks, the percent of life lived with HIV status and self-assessing current health as poor both were consistently statistically significant, and with approximately the same odds ratios. In fact, these two variables were always statistically significant at least at the 10% level in all models (Models 1 – 58). Both were statistically significant at the 5% level in all models, except that self-assessing current health as poor was statistically significant only at the 10% level in Models 17, 27 and 43. In all 58 models, the odds ratios were very consistent with those reported in Models 1 and 58. The unusual consistency of these results attests to the strong validity of the finding.

In Model 1, age and graduate degree attainment were both statistically significant at the 5% level, but neither is in Model 58. In Model 58, region becomes statistically significant (people in the Midwest and South were statistically less willing to participate in HIV cure-related studies, controlling for all other factors), but it was not significant in Model 1. These variables were sometimes statistically significant and sometimes not throughout Models 1 –58. In some models, income above \$150,000 was statistically significant, with an odds ratio below 1.0 attesting deterrence.

In summary, key multivariate results from the survey include:

- ⇒ Even after controlling for socio-demographic characteristics, perceptions of 5 (out of 21) of the potential benefits as “very important” motivating factors were statistically positively correlated with willingness to participate in HIV cure-related studies.
- ⇒ Even after controlling for socio-demographic characteristics, perceptions of 19 (out of 35) of the potential risks as “very likely to discourage” participation were statistically negatively correlated with unwillingness to participate in HIV cure-related studies.

- ⇒ The three potential benefits that had the strongest positive correlations with willingness to participate were all altruistic/emotional benefits. The other two statistically significant variables were both personal benefits related to increasing the respondent's knowledge of their own HIV infection.
- ⇒ None of the potential personal clinical benefits were statistically significant after controlling for socio-demographic characteristics and fewer potential personal benefits were statistically significant than the bivariate association analysis revealed.
- ⇒ All of the potential personal clinical risks and all of the potential personal risks involving symptoms and side effects were statistically significantly negatively correlated with willingness to participate, even after controlling for socio-demographic characteristics. Nearly all of the invasive study procedures (i.e. biopsies and spinal taps) and transportation risks were negatively correlated with willingness to participate, confirming the bivariate association analysis results. Fear of discrimination and the risk of transmitting HIV to a sexual partner were also associated with a lower willingness to participate in studies.
- ⇒ Short-term and immediate risks, such as those that involved pain or discomfort temporarily, had stronger correlation with deterrence to participate in terms of magnitude than some of the longer-term risks, such as the potential for enabling cancer or developing viral rebounds over time.
- ⇒ None of the potential risks regarding commitment levels, burdens of time and non-transportation logistics, or non-invasive study procedures were statistically significantly correlated with willingness to participate.
- ⇒ Respondents who identified a greater number of potential benefits as "very important" motivating factors were more willing to participate in HIV cure-related studies than others. Simultaneously, respondents who identified a greater number of potential risks as "very

- likely” to discourage participation were less willing to participate in HIV cure-related studies. Respondents who identified a greater number of potential benefits as “very important” motivating factors may generally be more optimistic and eager to participate in HIV cure-related studies than respondents who only identified a small number of “very important” potential benefits. Conversely, respondents who identified a greater number of potential risks as “very likely to discourage” participation in studies may generally be more risk-averse (or risk-aware) and more cautious about participating in HIV cure studies.
- ⇒ Respondents who believed that their health status was relatively poor were 3.9 – 4.5 times more willing to participate in HIV cure-related studies, on average and *ceteris paribus*, than respondents who believed their health status was relatively good. This result was consistent across all models.
  - ⇒ The longer respondents lived with HIV, the less willing they were to consider participation in HIV cure-related studies, on average. Or, more accurately, respondents who were more recently-infected with HIV were more willing to participate in experimental HIV cure-related studies. This result is very consistent across all models.
  - ⇒ Age, higher educational level attainment, very high income, and living in the Midwest or South (versus the West and Northeast) were negatively correlated with willingness to participate in HIV cure-related studies in some of the models, but not consistently.
  - ⇒ Gender, ethnicity, having control over one’s own health care, having previously volunteered for HIV cure studies, and the remaining categories for income and education were not correlated with willingness to participate in HIV cure-related studies.
  - ⇒ Even after controlling for socio-demographic characteristics, the results of the multivariate regressions were often similar, and always consistent, with those of the bivariate association analyses, implying robust and consistent analytical results.

## **CHAPTER 5 | QUALITATIVE STUDY RESULTS**

The following section summarizes the qualitative study results from the key informant interviews and the semi-structured questions from the U.S. survey on willingness to participate in HIV cure-related research. First, we summarize factors that would be important for potential study volunteers to consider when joining HIV cure-related studies. We explore possible motivators and deterrents to participation. We then delve into perceived risks, including unacceptable risks of HIV cure-related research studies. We also explore possible concerns about, burdens of and barriers to participation in HIV cure-related research. Additional domains of inquiry include perceptions of safety, perceived benefits and attitudes around analytical treatment interruption. The narrative then transitions towards factors facilitating recruitment, retention and implementation of HIV cure-related research. We devote attention to considerations for the ethical implementation of HIV cure-related research. We conclude by exploring overall expectations around the science and general considerations for the field. We summarized the recommendations received from the key informants for moving the field forward in the plan for change section. These do not figure in the results section in order to avoid redundancies.

Key informant interviews were as follows:

**Table 11. Key Informant Interviews by Type of Informants**

<b>Patient-Participants</b>	<b>n = 12</b>
Male (more willing to participate)	n = 6
Female (more willing to participate)	n = 2
Male (less willing to participate)	n = 1
Female (less willing to participate)	n = 3
<b>Clinician-Researchers</b>	<b>n = 11</b>
Represented institutions <sup>15</sup> were:	
<ul style="list-style-type: none"> <li>• Johns Hopkins University</li> <li>• NIH</li> <li>• University of Pittsburgh</li> <li>• Rush University</li> <li>• USCF</li> <li>• UNC-Chapel Hill</li> <li>• University of Utah</li> <li>• University of Washington</li> </ul>	
<b>Policy-Makers (Broadly Defined)</b>	<b>n = 13</b>
Bioethicists/IRB representatives	n = 6
Regulators	n = 5
Strong community advocates	n = 2

### Factors to Consider during Decision-Making

The narrative around factors to consider when deciding to join HIV cure-related research revealed that HIV “cure” research will definitely not be curative in the short term. Biomedical HIV cure scientists use clinical experiments as probes to try to understand the pathogenesis of the provirus and to identify potential drugs that may eventually lead to a cure, and this should be clearly explained to potential study participants during the informed consent process. Biomedical scientists in turn need to understand why a specific intervention would confer any promise of future “therapeutic benefits” before asking potential candidates to participate in research. A related factor to consider was the quality of the science and strength of the pre-clinical or clinical evidence for the strategy under investigation.

<sup>15</sup>The main HIV cure research modalities were represented, including latency-reversing agents, stem cell transplant/gene therapy, pediatric and combination approaches.

Patient-participants and clinician-researchers highlighted the significant time commitments required for HIV cure research participation as well as potential health factors/constraints, such as the current state of one's health and the potential impact of the HIV cure research strategy on one's health. The current state of one's health could be assessed by looking at a person's immune system or viral load, presence of co-morbidities or mental health status. In general, biomedical HIV cure scientists require very healthy study participants who have not had any viral blips in the recent past, or patients with specific conditions such as lymphomas and associated malignancies. Potential study volunteers also need to consider how the proposed HIV cure strategy will affect their current health status in the short-term and the long-term. When considered in the aggregate, it takes very rare volunteers to both qualify for and agree to participate in HIV cure-related research, because patient-participants need to agree to the time commitments, appointments, study procedures and interventions/medications. Overall, HIV cure research participation was viewed as being extremely complex.

Patient-participants were the only group to have brought up people in their life as a factor to consider when deciding to participate in HIV cure-related research. One respondent explained that he was unattached and therefore was free to participate, while another key informant explained that she would not be willing to participate given her family. Patient-participants and clinician-researchers expressed a tension between willingness/interest to participate in research versus opportunity to join studies. One patient-participant expressed willingness to participate but limited opportunities due to the lack of prominent biomedical HIV cure investigators in his state (e.g. state of Mississippi). Clinician-researchers agreed that the field of HIV cure research was effervescent but that the willingness to participate may exceed actual opportunities given the stringent inclusion/exclusion criteria and geographical access issues. Clinician-researchers expressed

that some of the HIV cure-related studies, such as simple reservoir studies, were very tedious and not as exciting to study volunteers.

The possible risks and no prospect of direct benefits of HIV cure-related studies were also mentioned as important factors to consider during decision-making. The topic of risks was strongly emphasized by both policy-makers/regulators and clinician-researchers, and less so by patient-participants which could be concerning in itself. Clinician-researchers stressed the need for potential study volunteers to have adequate information about potential risks before making decisions. HIV cure research was described as being quite different from and potentially more risky than the well-tolerated HIV treatment that most patients are accustomed to. Study volunteers will not personally benefit but will help advance the field forward in incremental steps. Regulators of HIV cure-related research were adamant that study participants should have no expectation of direct or tangible benefits and should weigh the risks of being in the study, some of which are known and others are unknown. Patient-participants should also evaluate the possible impact of their participation on their immediate and long-term well-being and quality of life. One clinician-researcher conducting pediatric HIV cure-research emphasized that decision-making factors may be different for infants, since they cannot consent for themselves. Therefore, clinician-researchers should pay attention to the education component since “many parents are desperate for their children to be cured or to just get better, particularly if they are very sick” (clinician-research, #205). Thus, factors to consider may vary between types of HIV cure-related research modalities and types of study participants.

Overall, there appeared to be a consensus between clinician-researchers and policy-makers/regulators that potential volunteers should verbalize why they want to participate in HIV cure-related research. Investigators should probe participants wanting to enroll to ensure that they do so with acceptable motivations since the clinical protocols are unlikely to provide them with any



direct benefits at this juncture. Study participants also need to determine how the study will fit in their lifestyle and consider the possibility of risks (or harms) related to study participation.

### **Motivators to HIV Cure-Related Research Participation**

Motivators to study participation ranged from tangible factors (such as compensation) to intangible contributors such as the desire to donate to science and give back, altruistic motives, clinical contact factors and hope (or desperation). Key informant interviews and survey responses revealed the multi-facetedness of the issue of motivation to participate in HIV cure-related research.

The most frequently cited tangible motivator to study participation, particularly among patient-participants, was money or compensation. The most important form of compensation was reimbursement for travel costs. In turn, clinician-researchers acknowledged that HIV cure-related studies tend to be lucrative given their intensity. The topic of study-related compensation will be explored further in the discussion section since it has ethical implications.

The most widely endorsed motivator to HIV cure-research study participation was the desire to contribute to the science or to give back. This was consistent with the quantitative study results. This theme also strongly emerged in key informant interviews with all three groups: patient-participants, clinician-researchers and policy-makers/regulators. Patient-participants were hopeful about HIV cure-related research and wanted to help move medical knowledge forward. One respondent underwent a very risky procedure (e.g. stem cell transplant) and recognized that he played a critical role in answering an important research question. Two respondents stated that since people living with HIV were unable to give blood, clinical study participation was a unique way to give back to society or regain a sense of normalcy despite illness. Other respondents felt that scientists were getting close to finding a cure. One participant wanted to see a cure for HIV materialize so that he would no longer have to take medications. Another African-American/Black respondent said that he wanted to join HIV cure studies to make sure that African-Americans/Blacks

were represented in HIV cure research and wanted to encourage others to participate. The theme of helping find a cure also emerged loud and clear in the semi-structured survey on willingness to participate. Survey respondents were willing to participate to contribute to the body of scientific knowledge around HIV cure research, and no longer requiring antiretroviral medication would be a consequence of drug-free remission. One survey respondent answered that “the potential for a cure for [him/herself]” and “to get cured from HIV” were motivators to participation. In a sense, these responses are more troubling from an ethical standpoint as they may be indicative of the underlying therapeutic or curative misconception. Another survey respondent said that “the simple fact that it’s a cure study is enough.” Therefore, the word ‘cure’ is obviously very alluring and should not be abused. Clinician-researchers recognized that participation in HIV cure-related research provided a positive meaning to an otherwise traumatic diagnosis and wanted to be part of the solution to the disease. Patient-participants, they felt, like to be part of something larger than them and the cure would not materialize and scientific progress would not occur if they did not step forward. One clinician-researcher felt that interacting with patients was by far the most fulfilling aspects of his work since patients were so eager to donate and give back. Policy-makers/regulators also recognized the patients’ desire to contribute to science in order to repay those who have come before them, although stated that these desires may be mixed with the hope of direct benefits. Altruism was ubiquitous as a factor motivating participation in HIV cure-related research. Patient-participants, clinician-researchers and policy-makers/regulators described altruism at length. Some respondents distinguished between social altruism and self-altruism and recognized that altruism may not be pure since participants may have underlying expectations of personal benefits from joining studies. Patient-participants also recognized altruism in others and revealed that personal circumstances (e.g. health status (CD4+ count) or financial situation) may affect altruism. Clinician-researchers expressed gratefulness for the generous altruism of their study participants and agreed

that selflessness cannot be under-estimated in HIV cure-related research participation. Altruistic motives, however, are sometimes mixed with other factors, such as scientific curiosity or the desire for monetary gain. Clinician-researchers said that, compared to HIV treatment research, HIV cure research is far more altruistic. Some HIV cure study participants possess a lot of sophistication and understand the process of participation. One clinician-researcher revealed that some of his study participants possess “pure altruism” because they refuse to enroll in commercial research and only enroll in academic research. Another biomedical scientist recognized that altruism is the key question in HIV cure-related research, and human participation is crucial because pre-clinical models are imperfect and not completely predictive of clinical outcomes in humans. It is difficult, however, to decide when a participant displays “too much altruism” and, thus, there should be safeguards in place to protect participants from taking on “too much” risks. Policy-makers/regulators hoped for altruistic motives in early HIV cure research participation, but feared that some participants may have unrealistic expectations, either real or subconscious, of direct personal benefits. Caution was expressed that there is tremendously variability between participants, and individuals join studies for a combination of factors, and therefore motivations should not be lumped together. The topic of self-altruism was described in terms of the hope that participants can personally benefit from research participation. Since becoming HIV-positive can be a terribly negative and defining event in someone’s life, participating in HIV cure research may help people cope with the difficult feelings related to identity and acquiring HIV. Self-altruism was also discussed as helping one’s future self.

In addition to altruism, key informants recognized that study participants like to interact with research staff and can personally gain from these frequent interactions and personal relationships. Thus, clinical contact factors can be strong motivators to research participation that should not be under-estimated. The way study participants feel treated and whether they feel respected can have a tremendous motivational or demotivational impact. Study participants

appreciated the friendliness, compassion and engagement of research staff and feeling valued for the use of their samples or tissues. Another important clinical contact factor was the availability of the study investigators in case of emergency or when participants had questions, good communication and the reporting of study results in layman's terms.

The narrative of hope (versus desperation) also emerged in the key informant interviews, particularly among patient-participants. One respondent took part in a risky HIV cure study and admitted that the hope to be cured is what drove him to participate. Another respondent said that HIV cure research contributes to giving hope to patients so that they do not give up on themselves. Accounts of hope were sometimes intermingled with optimism. The converse of hope, desperation, emerged in the context of pediatric and adolescent HIV cure research. From a parental perspective, the prospect of lifelong antiretroviral treatment for the child is difficult to accept. When children reach adolescence, parents are concerned with treatment adherence issues and thus would prefer their teenagers to be cured.

Overall, motivators to participation in HIV cure research were multi-faceted. The semi-structured survey revealed additional themes that were not captured during the key informant interviews, such as the scientific method/rationale, the preliminary data, the phase of the research study, how studies will contribute to the overall improvement of the public's health, the reputation of the principal investigator and the institution, the site location, the disclosure or clarity of risks and adequacy of the informed consent, the level of participant education, the study procedures and perceived safety of the intervention, issues with current antiretroviral treatment regimen, and likelihood of scientific progress or success. One survey respondent said that s/he would not join an HIV cure study unless s/he "had the guarantee of being cured," which may be a problematic motivation in early phase research where there is no expectation of cure. Other motivational factors were intangible, like the desire to help end stigma, discrimination and criminalization of HIV. A

subset of survey respondent indicated that no factor would motivate them to participate in HIV cure-related research. Therefore, it is important to remember that some individuals are unwilling to participate and that HIV cure research participation is not for everyone.

### **Deterrents to HIV Cure-Related Research Participation**

For the most part, deterrents to HIV cure-related research participation reflected the aforementioned motivators in the reverse, and were both tangible and intangible in nature. In this section, we summarize the narratives around scientific issues, compensation and time factors, study procedures, perceived risks and side effects and negative clinical contact factors that would deter participation in HIV cure-related research.

As expected, key informants who were in the “less willing” category were rather loquacious as to their reasons for not wanting to participate. Here again, it is important to remember that HIV cure research participation is not for everyone. One key informant explained her rationale for not wanting to participate despite that she strongly supports the HIV cure research agenda. She had lived a fairly normal life with HIV for 25 years and was not willing to risk jeopardizing her current health status, especially given other concerns around aging for which there is no cure. This participant also mentioned wanting to take care of her grandchildren. She preferred to wait until a cure was available before she would take it, since this had been her approach with HIV treatment and it had worked fairly well to date.

Deterrents to HIV cure research participation also related to scientific factors. Sub-themes included the modality under investigation, the scientific merit of the approach, the early phase of experimentation and the stringent exclusion criteria. A survey respondent stated that the concept of a ‘functional cure’ was unremarkable as it sounded more like an expensive treatment with the possibility of spontaneous viral rebound and defeated the purpose of ‘cure’ research. Others survey respondents indicated that the lack of a strong scientific evidence base or rationale or “shoddy

science” would be a deterrent to participation. The early phase of experimentation was also a demotivator for some who did not want to serve as pioneers for potentially risky first-in-human studies. Survey respondents also cited the robust exclusion criteria as a deterrent to joining studies.

Practical or logistical deterrents to participant centered on financial incentives, time commitment issues and location of the research site. Survey respondents stressed that inadequate financial compensation would be a significant deterrent. They felt that study participants should not have to pay for study-related interventions, surgeries or medical bills, including those resulting from long-term complications. Unfair compensation for time, efforts and commitment would deter participation, together with unproductive waiting time at the study clinic and time away from work. Clinician-researchers also recognized time factors to be of importance since studies fit within the realm of experimental medicine and thus require intensive procedures and monitoring. Willing participants may not have the time to commit to a study, so researchers need to be willing to work around people’s schedules. A bioethicist wondered how professionals living with HIV can commit to such intense studies. Further, distance to travel to/from the research site, accessibility and whether participants to have pay for parking affect participation.

Additional deterrents of participation focused around study procedures, possible side effects and risks. Examples of deterring procedures included leukaphereses due to fear of needles, as well as invasive procedures (such as gut or bone marrow biopsies) and the need to interrupt antiretroviral treatment for some studies. Others mentioned “too much cutting” or “major surgeries” as discouraging factors. Overall, it seemed that the more invasive the procedure, the more difficult it would be to recruit study participants. Demotivating side effects included loss of quality of life, long-term, irreversible or debilitating side effects, other unknown adverse side effects or impacts on one’s quality of life. Clinical side effects included increases in viral load, decreases in CD4+ count and cancer, among others. Some patient-participants did not want to risk participating

in a study that would worsen their health since they are proud of having HIV under control. In turn, discouraging risks ranged from potential clinical risks, mental risks or financial risks. Clinical risks included pain or discomfort, becoming resistant to ARVs, developing cancer, needing to give up one's health care provider, becoming infectious, developing AIDS or death. A survey respondent indicated that not having the study risks being well-defined up front was a deterrent to participation, and this will be explored further in the discussion section as it has ethical implications and relates to the topic of uncertainty. Mental risks and financial risks, such as loss in disability insurance status, were reported as possible deterrents.

The three most prevalent negative clinical contact factors that would deter study participation related to the poor treatment of study participants, inadequate communication and breaches in confidentiality. With regards to the former, perceived rudeness, coldness, lack of empathy, unresponsiveness, discrimination or stigma would discourage participation. Survey respondents indicated that they want to feel like important contributors to the study and be treated as partners instead of laboratory rats. Their time should not be taken for granted. Patient-participants stated that nurses can either make or break a study: their enthusiasm and ability to humanize the process is key to being able to enroll study participants. Personal attention was also seen as crucial and it was clear that interpersonal skills, above scientific skills, were required to run effective clinical studies. Example of ineffective communication included perceived dishonesty, withholding information, false claims or lack of communication from researchers. Finally, breaches in confidentiality were seen as serious violations.

In sum, deterrents to participation ranged from practical/logistical concerns, study-related factors and clinical contact factors. As with motivators, this is a deeply multi-dimensional and personal issue and there can be as many demotivators as there are potential study participants. Not captured in the above narrative was the fear of greed from pharmaceutical companies and over-

promotion of HIV cure studies as making breakthroughs in science when there is no cure available. There was also a subgroup of study participants who did not foresee any deterrent to participation and would be willing to participate in *any* HIV cure-related study.

### **Perceived Risks of HIV Cure-Related Research Participation**

Since perceived risks of HIV cure-related research can be such potent demotivators to participation, we exercised more detailed scrutiny on this topic in both the key informant interview and the semi-structured survey responses. The topic was discussed at length with patient-participants, clinician-researchers and policy-makers. It became transparent that clinician-researchers have the most sophisticated understanding of risks related to HIV cure-related research. Policy-makers/regulators appear to have book knowledge of potential risks. A minority of patient-participants also appeared to be knowledgeable about possible risks, but they remained in the clear minority. These findings underscore the need to provide additional information to potential study volunteers about study-related risks in language that is accessible to them.

#### **Clinical or Medical Risks**

Most risks to HIV cure-research participation are perceived to be clinical or medical. Some patient-participants were unable to name specific risks related to HIV cure research participation. For example, one participant said that s/he “[didn’t] think there would be any risks” (more willing patient-participant, #101). One respondent said that the field of HIV cure research presents a brave new world, and admitted that there were a lot of risks but could not name any specific risk (more willing patient-participant, #111). One participant thought that immune reconstitution was a possible risk when in fact immune reconstitution was a good thing and would be a clinical benefit if it were possible: “At this time, I could not think of any risks that could be related to the cure research. Except maybe immune reconstitution. And that was one of the things on top of my list that I was worried about” (more willing patient-participant, #105). Another key informant thought



that the margin of risks was low for HIV cure studies since there are so many strategies being investigated at present (more willing patient-participant, #111). Compared to the clinician-researchers and policy-makers/regulators, patient-participants spent more time on the topic of pain, a more subjective perceived clinical or medical risk and also a deeply personal one. Several conversations touched upon individual, unique medical realities and presence of co-morbidities (e.g. platelet disorder, diabetes, etc.) that could present additional risks. Patient-participants would need to take these concomitant conditions into account when participating in studies. The two most often cited perceived clinical risks of HIV cure research participation were developing resistance to ARVs and cancer. Additional clinical risks pertained to study procedures (such as the need to interrupt treatment), increases in viral loads, decreases in CD4+ count, opportunistic infections, developing AIDS, co-morbidities, becoming 'sick', nausea ("sickness of the stomach"), hair loss and dementia associated with reactivation of the HIV reservoir in the brain. Patient-participants expressed wanting to live long, healthy lives, like HIV-negative people. The prospect of any permanent, irreversible harm, debilitation or death would also be highly demotivating. Finally, uncertainty about possible unknown risks would be a deterrent to participation. A survey respondent said that the possibility of "cure failure" would prevent him/her from participating in studies. We will revisit the topic of therapeutic and curative misconception in the discussion section.

As expected, clinician-researchers had more astute knowledge about possible clinical or medical risks of HIV cure research. The two HIV cure research modalities that were associated with the most clinical or medical risks were latency-reversing agents and stem cell transplant/gene therapy.

**Table 12. Perceived Clinical – Medical Risks by Clinician-Researchers**

<b>Perceived Clinical – Medical Risks by Clinician-Researchers</b>	
<b>General</b>	
<ul style="list-style-type: none"><li>• Risk of procedures; phlebotomies, leukaphereses, invasive biopsies</li><li>• Risk of pain or discomfort</li><li>• Risk that interventions will have unanticipated immediate or delayed toxicities with greater impact to health</li></ul>	
<b>Latency-Reversing Agents</b>	
<ul style="list-style-type: none"><li>• Recorded adverse events (AEs) – mild to moderate on the clinical trial scale</li><li>• Gastro-intestinal side effects, nausea</li><li>• Fatigue</li><li>• Vomiting</li><li>• Anemia</li><li>• Toxicities (bone marrow suppression, myalgia, dysphoria)</li><li>• Long-term toxicities (mutagenicity, carcinogenicity)</li></ul>	
<b>Checkpoint Blockers</b>	
<ul style="list-style-type: none"><li>• Chronic inflammation on the immune system (try to reduce inflammation as an effect on the immune system but then need to worry about infectious risk)</li></ul>	
<b>Stem Cell Transplants/Gene Therapy</b>	
<ul style="list-style-type: none"><li>• Risks of infection/contamination</li><li>• In the longer-term, could do something genetically to cells that will make them more susceptible to give rise to cancer</li></ul>	

Clinician-researchers were adamant about the imperative to reduce or mitigate risks whenever possible. They also cautioned about the need to be careful in interpreting risk information, such as side effects of the compounds, especially outside the context of the disease for which they were previously approved. For example, latency-reversing agents were developed as chemotherapy to treat advanced cancers or malignancies, instead of chronic conditions. Therefore, the assessment of potential risks and/or toxicities is very different between cancer versus HIV. Whereas side effects would be tolerated by oncology doctors, they would become unacceptable for HIV clinicians (clinician-researcher, #207). This was reflected recently in the FDA’s decision to put Panobinostat on clinical hold, proposed to be tested in otherwise healthy people living with HIV doing well on ART. The main concern is that “if you intervene with a potentially toxic drug with unknown benefits with respect to cure, [and] if these drugs have irreversible side effects, then you have induced harm in someone without really providing them with any direct benefit.” Therefore,

clinician-researchers concurred that they need to stay vigilant with regards to emerging data about risks in early phase studies. The history of medical research has taught us that some toxicities simply cannot not be detected in pre-clinical models. Clinician-researchers also referred to the progressive and incremental nature of scientific knowledge. In the gene therapy world, for instance, “ It’s a scary thing to be manipulating DNA and one has to be very aware of the possibility for harm there. [But] as much work has gone into it, it would appear to be safe otherwise it would not have moved on into cure trials” (Clinician-researcher, #208). Besides potential clinical or medical risks, clinician-researchers also referred to possible opportunity risks of joining clinical studies (clinician-researcher, #209). This would mean that if a person living with HIV volunteers in a study, s/he may not be able to participate in a subsequent study of an agent that may prove to be more effective, because one of the exclusion criterion may restrict on the basis of past participation.

What transpired from discussions with clinician-researchers is that we need a lot more nuance when discussing risks related to HIV cure-related research interventions, and each modality, or even each study, should be assessed individually. This is most apparent in the context of pediatric HIV cure studies, for which “Risks [to] infants right now are fairly minimal and basically involve the risks of the antiretroviral drugs. As things change and therapeutics get incorporated into pediatric studies, those risks will change to be more similar to those of adults like adverse events and things like that” (clinician-Researcher, #205). Thus, it is important to emphasize that different HIV cure research strategies have varying levels of risks. Similar to clinician-researchers, policy-makers/regulators were rather comfortable reciting possible risks of HIV cure-related research participation, but their approach appeared to be more didactic, mechanic and categorical than clinician-researchers.

**Table 13. Perceived Clinical – Medical Risks by Policy-Makers/Regulators**

<b>Perceived Clinical – Medical Risks by Policy-Makers/Regulators</b>
<b>General</b> <ul style="list-style-type: none"> <li>• Various toxicities and side effects, known and unknown Could cause immediate/short-term, chronic or delayed/long-term morbidity or mortality (e.g. cancer)</li> <li>• Risks related to the specific intervention and/or agent</li> <li>• Procedure or monitoring-related risks</li> <li>• Risks associated with treatment interruption Risk of viral rebound or reactivation of disease Potential health risks (e.g., reduced T cell levels) if the virus is allowed to replicate freely for an extended period of time Change in the phenotype of the virus Development of resistance to ARVs Transmission of virus to partners</li> <li>• Development of resistance to antiretroviral treatment</li> <li>• Limited treatment options in the future</li> <li>• Permanent harm of the intervention being used</li> <li>• Relative risks (e.g. agent/intervention vs. treatment interruption)</li> <li>• Theoretical risks (e.g. death)</li> </ul> <b>Latency-Reversing Agents</b> <ul style="list-style-type: none"> <li>• Toxicity risks of the specific agent</li> <li>• Possible long-term consequences of reactivating latent virus</li> <li>• Risk of stirring up other potential latent retroviruses or reactivating other viruses (e.g. herpes simplex virus – HSV)</li> </ul> <b>Stem Cell Transplants/Gene Therapy</b> <ul style="list-style-type: none"> <li>• Risks associated with chemotherapy and/or conditioning to ablate immune system</li> </ul>

Compared to the other two groups of key informants, policy-makers/regulators were more concerned with normative categories of risks, such as known vs. unknown risks, short-term vs. long-term risks, and real versus theoretical risks. For example, one regulator said: “Well, it’s the risk of the unknown... right? And also the risks of the known” (bioethicist, #310). Policy-makers recognized the difficult nature of assessing risks in HIV cure-related research, and contrasted this to the HIV treatment field where drugs now have well-quantified risks associated with them. A regulator said that “[We are making] apples to oranges comparisons at times, even within the same modality” (regulator, #309). Clinical studies are designed not for the best medical interest of the individual patient, but to answer a specific research question that will lead to generalizable knowledge (bioethicist, #312). Because people living with HIV are relatively healthy, the risks of the tested HIV

cure research interventions need to remain acceptable and therefore regulators of HIV cure research tend to be more risk-averse (regulator, #307).

### **Social Risks**

Patient-participants were the only category of informants to have discussed possible **social** risks related to HIV cure-related research participation. This is revealing in itself and the possibility of social risks should be emphasized with clinician-researchers and policy-makers/regulators. Examples of social risks included: poor treatment by research staff, transmitting HIV to others, disclosure, media attention, identity risks, losing one's employment, losing access to loved ones or stigma. Patient-participants were concerned that they would be treated poorly or taken for granted by clinician-researchers and that nursing staff would assume that they did not have a career. The risk of transmitting HIV to others in the course of HIV cure-related research experimentation (and unsuspected viral rebound) was cited as a concern. Another perceived social risk was inadvertent disclosure of HIV status, akin to an "outing," and this generated distrust in the patient community. A subset of survey respondents said that they feared their personal information will not be protected properly and could be used for dubious ends. Therefore, Health Insurance Portability and Accountability Act (HIPAA) regulations enforcing the use of de-identified information were perceived as being critically important to be part of a research study. Disclosure of HIV seropositivity remains a challenge for several people in the United States, given the pervasive stigma associated with the disease. Furthermore, other breaches in confidentiality, unwanted media attention or publicity regarding one's HIV status were perceived as serious personal and social risks to study participation. Identity risks were also mentioned, although some respondents answered the question in the reverse, saying that they "would gladly lose [their] HIV-positive identity for a cure" or that they "[couldn't] imagine a single sane person who would fear losing their identity of being an HIV-positive person." Other social risks included losing employment or losing access to loved ones in

the course of study participation. The discourse around potential social risks strengthens the need to capture and address social harm events during HIV cure-related research implementation.

### **Financial Risks**

Besides social risks, there were perceived financial risks related to study participation. Examples included concerns around maintaining disability insurance or income (including private or Social Security), current health care or insurance coverage. One key informant asked whether people living with HIV would be grand-fathered in to these programs, given the high likelihood that HIV remission would not be permanent.

### **Other Perceived Risks**

Other perceived risks included whether participation in one study would conflict with participation in another study. For example, a survey respondent agreed to donate his brain after death and wondered if this would present a conflict. Another survey respondent stated that s/he lives in a highly criminalized neighborhood, and therefore would be afraid to have his/her medication stolen if s/he were to spend too much time away from home. Another patient-participant cited the possibility of medical errors and wanted to ensure that proper safeguards were in place before deciding to participate.

### **No Perceived Risks**

Around 40 (10%) of survey respondents answered “None” or “Not Sure” to the question: “What other potential risks are “very likely to discourage” you from participating in an HIV cure-related study?” It is unclear if all the perceived risks of HIV cure research participation were previously covered in the survey, or whether respondents truly did not perceive any risks to study participation. One respondent said that s/he “[did] not have enough knowledge/information about potential risks to make an informed comment.” Another respondent stated that “finding a cure outweighs the risks.” Yet another person wrote “All I see is benefits in the search for a cure.” From

an ethical standpoint, it is troubling that some potential study volunteers only see benefits to HIV cure research participation, when in reality the risks far outweigh the benefits. These results underscore the need for robust education efforts around possible risks of HIV cure-related research participation in the United States.

### **Riskiest HIV Cure-Related Research Modalities**

In addition to asking key informants about perceived risks, we inquired about the riskiest HIV cure-related research modalities. Clinician-researchers and policy-makers provided substantive considerations compared to patient-participants who did not delve into modality-specific risks. Stem cell transplantation/gene therapy, latency-reversing agents and combinatorial approaches were perceived as being the most high-risk HIV cure-related research strategies.

A number of regulators informed that the FDA policy requires evaluating each study on a case-by-case basis, and therefore it is difficult to determine which HIV cure research strategy is the riskiest. All HIV cure research modalities have the potential for adverse reactions, side effects and toxicities. Regulators of HIV cure research mentioned that their division reviews specific kinds of strategies (e.g. antivirals versus gene therapy). Consequently, it is difficult to know what goes on in the other divisions and each review team has a different opinion about what the riskiest strategies are. It is therefore imperative to follow the science and the data signals and to adopt a case-by-case policy (policy-maker, #309). In order to determine risk levels, it is also crucial to follow study participants for several years – sometimes as long as 10 years or more – in order to assess risk reliably (policy-maker, #303).

#### **Stem Cell Transplants/Gene Therapy**

Stem cell transplants and gene therapy emerged as one of the riskiest HIV cure research strategies, given the already high (25%) mortality associated with transplants. For example, in the Boston patients A and B, the protocol also administered stem cell transplants in two additional

volunteers (patients C and D), who each died from non-HIV related transplant complications. Patient C received a gentler form of chemotherapy than Timothy Brown, but died from Hogkin lymphoma six months after his stem cell transplantation. Another patient from in Europe underwent myeloablative stem cell transplantation with cells homozygous for the CCR5  $\Delta 32/\Delta 32$  depletion, but passed away with full chimerism prior to treatment interruption, and therefore it was impossible to determine whether he experienced a sustainable remission similar to that of Timothy Brown. His cells were not infectable *in vivo*. While this is no proof for HIV cure, it may indicate that something was working to prevent his cells from getting infected with the virus (clinician-researcher, #206).

Bone marrow transplants for patients who do not have cancer are particularly risky, between the conditioning procedures and the receipt of genetically modified cells. Relative to other HIV cure research strategies, stem cell transplants have been associated with the largest reduction in the size of the HIV reservoir, and thus may have the highest chance of ‘succeeding’ in chronically infected patients (policy-maker, #306). Zinc finger nucleases were one type of gene therapy that was categorized as being ‘risky’, especially when combined with treatment interruption, since any interference with the human genome was perceived as unnerving (clinician-researcher, #205).

#### **Latency-Reversing Agents**

Latency-reversing drugs, or “shock and kill” approaches, were perceived as being very risky as they attempt to knock latently infected cells out of latency and reactivate quiescent virus. These drugs are borrowed from oncology and have “nasty” side effects; and yet have not been associated with any substantial reduction in the size of the replication-competent HIV proviral DNA reservoir. They have led to transient increases in cell-associated HIV RNA, but they also target important host enzymes and processes and may act in ways that could cause secondary malignancies (clinician-researcher, #302).



### **Combination Approaches**

Clinician-researchers recognized that combination approaches would be most likely to lead to sustainable ART-free remission of HIV. This may increase the risks incrementally, but may not necessarily compound them (clinician-researcher, #201). Risks also depend on the specific compound, the dose of the compound and the duration of the intervention. With combination approaches, it is difficult to understand the relative contribution of each agent.

Overall, stem-cell transplants, latency-reversing drugs and combination approaches were perceived as the riskiest. In retrospect, this interview question was highly controversial for some. Clinician-researchers seemed highly allegiant to their own HIV cure research modality and would never admit that it was “the riskiest.” Asking (and answering) this question was a political act, in a sense. Most scientists referred to “the other type of strategy” as being the riskiest, likely because it was most unknown to them. A biomedical scientist clearly performing high risk gene therapy research said that treatment interruptions was the riskiest aspect of HIV cure-related research. In sum, the field should always refer back to the best available information at any given time. Given the experimental nature of the interventions, there are high barriers to bringing interventions or compounds into human studies. The field of HIV research is victim to its own success, in a way, since antiretroviral treatment is so well tolerated, and the patient population of interest is healthy. The possibility of exposing patients to anything too risky or toxic appears unethical, and HIV cure research protocols need to have clear safety and tolerability criteria and signals that can get acted upon promptly during HIV cure-related research conduct.

### **“Too Much” or Unacceptable Risks of HIV Cure Research Participation**

Perceptions of what would constitute “too much” or unacceptable risks were assessed using multiple data sources, including key informant interviews and survey responses. Narratives cut across a number of topics that are summarized below. Overall, perceptions of inadmissible risks

were variable and subjective. Each group of stakeholders brought a unique perspective to the inquiry.

### **Regulations and Clinical Holds**

Policy-makers/regulators confirmed that the evaluation of first-in-human (or investigational new drug (IND)) protocols is their primary responsibility. If the FDA does not consider a protocol to be agreeable, the agency will issue a set of recommendations to the clinical investigator(s) and will use the clinical hold if necessary (policy-maker, #309). There is a category of “too much” risk in HIV cure-related studies and protocols have been placed on clinical hold in the past (policy-maker, #302). The assessment is usually based on the available evidence or the strong biological plausibility of possible severe adverse drug reactions (policy-maker, #302), even though this is more a judgement call than a clear science. If severe adverse drug reactions would be expected in more than 2 – 3% of participants, this may be “too much” risk (policy-maker, #302). The FDA recognized, however, that there are “black boxes” in the field and this is why the agency remains conservative (policy-maker, #303). For repurposed drugs reserved for metastatic cancer used in otherwise “healthy people,” there needs to be a clear rationale for moving specific doses of compound forward (policy-maker, #303).

Policy-makers/regulators referred back to the regulations. There are two possible scenarios that would constitute “too much risk:” 1) insufficient information to assess risk – either insufficient data from animal/pre-clinical studies to make a good assessment about safety, optimal dose or duration of product, or 2) insufficient benefits to outweigh the risks (policy-maker, #307). Furthermore, risks would be deemed unacceptable if the procedure or drug was known to be significantly toxic and there would be no counter-balancing procedure to reduce risk (policy-maker, #309), or if a drug was known to be toxic without strong evidence that it would deplete the HIV reservoir (policy-maker, #309). Regulators would further be concerned if the study failed to include

a well thought-of study design, with insightful endpoints and with the prospect of interpretable results to advance the field (policy-maker, #309). For example, HIV DNA (or bulk, “junk” DNA) as a measure for reservoir reduction may not be interpretable, since only a minority of DNA cells will produce viable or inducible HIV provirus and the measure will not be sensitive enough to yield interpretable results (policy-maker, #309). The FDA would expect interpretable endpoints looking at replication-competent provirus instead of background noise and indicators of uninducible virus (policy-maker, #309). A bioethicist stated that the field should also look up to IRBs to make sure that unacceptable studies do not occur (bioethicist, #310).

### **Patient-Participant Perspectives**

The perspectives of patient-participants are particularly revealing when it comes to assessing unacceptable risks in HIV cure research. There was tremendous variability in the responses, contingent upon each patient-participant’s risk threshold. For some, the mere fact that HIV cure studies were in the early phase of investigation presented “too much” risk. Any first-in-human study that did not have an established underlying proof-of-concept in a pre-clinical animal model would be unacceptable. Other potential volunteers pointed out specific clinical risk thresholds that would be inadmissible, such as increases in viral load above a specific level (e.g. detectable, rebound, vengeful multiplication, etc.). Correspondingly, a decrease in CD4+ T cells below a specific threshold would be unwarranted, although the acceptable CD4+ count level varied between respondents (e.g. less than 100, 200 (AIDS criterion), 500, 800, etc.). Furthermore, patient-participants conceded being averse to pain; therefore, for some, any painful procedure would constitute “too much” risk. Amongst the most popular unacceptable risks were cancer, permanent or irreversible side-effects, hospitalization, debilitation or death.

### **Unacceptable Strategies**

The two most often cited “unacceptable” HIV cure research strategies were stem cell transplants and anti-PD1 interventions. One patient-participant explained that since he was healthy, he would not be willing to go to the extreme of what Timothy Brown or the Boston patient B have done and this is where he drew the line. Clinician-researchers felt that stem cell transplants in otherwise healthy participants who were stable and suppressed on ART are already going too far, especially as scientists are not yet sure what exactly cured Timothy Brown (clinician-researcher, #201). A researcher who performs stem cell transplant stated that treatment interruption during the transplantation (similar to what Timothy Brown had) is too risky, and that ART should be maintained during the transplantation since there is no benefit of stopping ART during the transplant and engraftment will be enhanced. Maintaining ART throughout the transplant would also contribute to minimizing risks (personal communication). Few key informants commented on the gene therapy aspect, although it has been described as being rather “star trekky” and likely pushing it. With regards to anti-PD1 approaches, they have shown significant toxicities in non-human primates and studies have ceased in humans (clinician-researcher, #201). With regards to latency-reversing agents, scientists have to be careful not to “poke and go too far,” as this would cause global activation of T cells as what happened in a study in Europe in 2006. A clinician-researcher commented that anything suggesting an irreversible and systemic side effect would be unacceptable; however, it will not be possible to know until interventions are tested in humans so this may remain a circular argument (clinician-researcher, #206). Clinician-researchers commented that we need good monitoring systems in place. Scientists are not being too cautious and they need to carefully balance the risks and benefits of experimentations.

### **Treatment Interruptions and Associated Risks**

Treatment interruptions indicated in some HIV cure research protocols, and their associated risks, were deemed to be unacceptable for a subset of key informants and survey respondents. A clinician-researcher explained that testing latency-reversing agents with treatment interruption would be reckless at this point, since the compounds have not yet been associated with a substantial reduction in the size of the replication-competent proviral HIV DNA reservoir, and therefore viral rebound will be almost certain and automatic (clinician-researcher, #206). Reasons given by survey respondents for viewing treatment interruptions as being unacceptable included: current low CD4+ count and almost guaranteed viral rebound, possibility of losing undetectable status, fear of transmitting HIV to others and developing resistance to ARVs. Since viral rebound is unpredictable, it was perceived as being “too risky” for some, or associated with risk of brain damage or death. Some of the survey respondents were very treatment experienced and did not want to risk losing whatever regimen they had left to viral resistance. Other survey respondents were not willing to accept the risk of HIV becoming untreatable and unmanageable. One patient-participant said that he would need to know there is a rescue plan in place before joining these treatment interruption studies: “I would need to know that there is some sort of... what do they call it... there is a name for it in clinical research but basically a back-up plan. If this happens, if I become resistant and if my CD4+ count gets low and my viral load goes way up.... hmmm, there is a plan of action for things like that” (patient-participant, #106). Thus, despite the high willingness of treatment interruption seen in the survey (e.g. 26% of respondents said they were very willing to interruption treatment), it is important to remember that not all people living with HIV are willing to go off antiretroviral treatment.

### “Healthy Subjects”

The topic of “healthy subjects” generated recent debate and controversy in the HIV cure research field in light of the FDA decision to put a Panobinostat + Interferon study on clinical hold. This debate occurred as I was conducting my key informant interviews and thus shaped some of the responses. A regulator of HIV cure research confirmed that: “HIV-infected patients who are otherwise healthy and on fully suppressive ART have an anticipated life-span approaching that of HIV-uninfected patients. From the standpoint of assessing risk-benefit, the Division has consistently stated that we view HIV reservoir research in this otherwise healthy population to be similar to drug research in healthy volunteers” (policy-maker, #311). There is a fundamental paradox in HIV cure research in that the interventions that will likely lead to a cure are risky (e.g. stem cell transplant or latency-reversing agents), but the potential study volunteers are now considered “healthy subjects” because most are suppressed and undetectable for HIV. Therefore, the possibility of harms must be minimized to the fullest.

We discussed the topic of “healthy subjects” with key informants. A patient-participant expressed the dilemma eloquently: “for the younger, healthier ones... I don’t know. We are going to expose people to modulators, to drugs that are approved for cancer or chemo... I know that those doses are a lot lower but there are fears of immune reactivation, lymphoma, cancers, inflammatory issues, auto-immune diseases... We don’t know. But obviously if we knew, we would not be doing the studies” (patient-participant, #102). Clinician-researchers also recognized the conundrum of “otherwise healthy subjects.” One key informant was rather voluble on the topic:

*Where we hit some issues today is that patients living with HIV are doing tremendously well. They are living into their... you know... a normal life span (...) So the question is how do you think adding on these additional very toxic agents to try to test the concepts of HIV cure, whether it is a LRA, a checkpoint inhibitor or a stem cell therapy. How do you go forward in somebody who is doing well clinically and then ask them to take this? (...) We are now in 2015, a very different landscape. I mean... if we had been looking at cure... you know 10 years ago, it would have been very different because you now have one pill once a day for HIV therapy. So the issue is you have great therapies today, people are doing well on their therapy and the reason why we came to the*

*whole structured – the ATIs of – 10 – 15 years ago was because of the burnout of taking 15 pills a day, the fatigue and all the side effects of the drugs you are dealing with, whether they be metabolic lipodystrophies and so on... that's a different landscape in 2015 having all the drugs you have and combinations now moving into the era of the integrase inhibitors and so on and I think that what's changed so much in terms of how you're thinking about this... You've got a great ability to treat and deal with the patients so even if you are just going to test a concept you know you want to make sure it's safe and can be given to the patients safely in terms of the fact that these people are doing well and no longer.. they are no longer gonna die in a month or two. They are going to live a healthy life. If they are infected today, they can live up to their 70s.*  
– Clinician-Researcher (#210)

The background of safety and efficacy provided by ART thus confer a fundamental tension for HIV cure researchers, since potential volunteers tend to be relatively healthy and suppressed (“the almost cured”). Latency-reversing drugs would be tested in individuals with high CD4+ counts. This compares to other modalities, such as gene therapy research that would enroll participants experiencing treatment failure or stem cell transplants that would enroll participants with lymphomas or other cancers already requiring a transplant.

The Panobinostat clinical hold provided one of the best cases to study this issue in real-time. Obviously, the barriers to move compounds into humans increase if undetectable HIV disease is considered a state of normal health or restoration of health with regards to their long-term prognosis. A regulator of HIV cure research explained that the FDA sees a difference between “healthy volunteers and stable HIV-infected adults” (policy-maker, #311). This goes back to the early HIV cure studies having no prospect of direct clinical benefits and therefore study participants need to have a good life expectancy and treatment options (policy-maker, #311); however, this subset of participants paradoxically also has the most to lose from HIV cure research participation. Clinician-researchers need to find a delicate balance between the safety of the experimental agents and the efficacy they are hoping for. The FDA thus tends to remain conservative and researchers should not give one dose more or a longer duration of a dose than is necessary to study a proof-of-concept

(policy-maker, #311). In the case of the Panobinostat study, the dose was arbitrary<sup>16</sup> (policy-maker, #311). The FDA viewed this as a perfect storm of a problematic situation whereas “the combination of a highly toxic drug with potentially life-threatening risks, no anticipated benefit, and insufficient data to know if modifications of trial design (such as lowering dose or total drug exposure) would substantially lower participant’s risks” (policy-maker, #311). The FDA had no choice but to place the Panobinostat + Interferon study on clinical hold.

The risk profile is very dissimilar for people living with HIV who have successful treatment alternatives than for advanced cancer patients. The FDA considers suppressed people living with HIV as “healthy volunteers” in terms of risks and benefits. Clinical investigators must start studying new compounds at low dose, or with very small cohorts (sometimes a single patient cohort). The grading of risks is different from cancer to HIV and separate scales are used since there is a different risk/benefit assessment in advanced cancer patients (policy-maker, #311). Because the optimal dose is not always known for new possible “HIV reservoir reduction” or “HIV remission” agents, the FDA employs a more conservative approach. It was explained to me that protocols are reviewed on a case-by-case basis (policy-maker, #306). Whether an IND gets approved “depends on the overall scenario and the study population” (policy-maker, #306).

Clinician-researchers supported the need for case-by-case evaluations. For example, one of them said that “drugs that are known to cause immuno-suppression or to increase risk of later malignancies. (...) I would evaluate [these] on a case-by-case basis. Long-term health risks are something that I generally advise against without knowing additional information that would

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<sup>16</sup>The label indication for Panobinostat (Parydak) in refractory multiple myeloma is 20 mg given every other day for 3 doses per week for Weeks 1 and 2 of each 21-day cycle for 8 cycles, in combination with bortezomib and dexamethasone. Although the mg dose was the same in the Panobinostat + Interferon study, important differences were that investigators were proposing to give 3 doses every 4 weeks (in contrast to 6 doses every 3 weeks) and not giving bortezomib and dexamethasone.



mitigate the risks. I think we can go too far with what we do with individuals” (clinician-researcher, #209). Another biomedical researcher studying the gene therapy approach commented that:

*That really has to be on a case-by-case basis. Clearly, we’ve done some things like that in terms of the inclusion/exclusion criteria [in our studies]. Clearly some of the transplant-based gene therapy approaches that require heavy conditioning are obviously only appropriate in situations where people need those kinds of chemotherapy for some type of cancer or something like that and that’s why some of our trials have been limited to those from the beginning. The risks and benefits are very personal decisions. There are risks in a number of things. We’ve seen risks in the CAR T-cell world that have been used for cancer, but some people are talking about that for HIV cure. There have been substantial toxicities with immune immuno-modulators. LRAs like the HDACis may have deleterious effects on cellular gene expression that have been under-appreciated. We are obligated ethically and I hope people take that seriously in terms of really having a conversation with potential participants to get that across. There is an enormous benefit to the field when people are willing to take some of that risk on. There is not any study that I would tell people absolutely do NOT think about this as a blanket statement. There are a lot checks and balances in our system now – thank Goodness – to prevent unethical or dangerous studies from ever getting started in our country, so that’s a good thing.*  
– Clinician-Researcher (#208)

The topic of “healthy subject” will likely continue to generate debate in the field of HIV cure research. Clearly, it appears that a case-by-case analysis of the participant population, the proposed intervention, the dose and the duration of the product is warranted. The FDA examines the safety of each proposed intervention and ensures reasonable risk-benefit ratios for what is being investigated. We will explore risk-benefit ratio assessment further in the qualitative analysis section, and again in the discussion section.

### **Beyond Clinical Risks: Social and Financial Risks**

Patient-participants also touched upon potential social and financial risks that would be unacceptable. These included significant changes in quality of life, such as not being able to exercise, walk or speak, increased fatigue and lack of normalcy. A study participant was not willing to relocate to participate in a study, because it would cause a major disruption in his lifestyle (more willing patient-participant, #107). A subset of survey respondents indicated that becoming detectable for HIV and increased risk of passing HIV to sexual partners would be unacceptable. Other social risks

included inability to work, care for family and media attention. Unacceptable financial risks were also identified such as insufficient compensation for the required biopsies and interventions.

One of the discussants said that the interview question was “very challenging (...) because too much risk is a subjective analysis (...) Certainly, that is a lot of risk even though it may be[that] we will find out everything that we need to find out. That’s an individual choice. It’s very hard to answer that. It’s for each person and their stage of life (...) I have had a very healthy experience. I have certainly have had a medical roller coaster for over 10 years, but manageable. But also my emotional personality, I am able to cope with that, compared to someone who might be in late stage of life. They might be willing to take less risks than I might [be willing to] take” (more willing patient-participant, #112). Clinician-researchers also expressed the importance of case-by-case analyses for individual participants. For example, one stated that “I think this is relative to the patient so if they are very ill, then I don’t think/know that there would be a definition of too much risk for them. But if they are very healthy (...) and their therapy is working and they are suppressed, then these would be the ideal patients to be in a cure studies. [I am] [n]ot sure where the line is for too much and I am not sure there is a line. That’s a personal opinion and again brings the idea of patient education and everyone needs to make that decision for themselves” (clinician-researcher, #205). Similarly, another clinician-researcher said that “there are variations from patients to patients. Not all investigators are created the same and not all patients are [either]. And some patients can handle the anxiety of the treatment interruptions better than others. Some might not be good candidates for (...) the gene therapy trials that are around. I would not say that there are ethical differences between the types of trials, but certainly different trials appeal to different types of patients” (clinician-researcher, #211). Willingness to take risks is thus a very personal choice, and the entire make-up of the potential volunteer, including physical and mental state, should be taken

into account. Clinician-researchers should also respect the autonomy of study candidates when making decisions to participate.

Further, policy-makers/regulators also recognized the subjective nature of unacceptable risks. For example, a policy-maker admitted that “This is a hard question and I know some people may have views on risk thresholds. Only a handful of people have tried to evaluate risk thresholds in HIV. Let people give kidneys, let people sky-dive, let people volunteer for the military so why can’t we let people take on similar levels of risk in research? (...) David Resnick argued that we should not allow for more than 1% risk of serious harm or death; yes it is arbitrary but we need to pick something. [This is][r]eally gonna depend on the nature of the study, the benefits and the science, [and] how the risks are being managed and controlled” (policy-maker, #301). Another bioethicist asked us to “Imagine a situation where someone knew they would die in three months, and if the worst risk of the cure trial is to die within one month, then it would make sense for such a person to volunteer in a cure study because s/he may die sooner. But they would have died in a fantastically significant way helping humanity. They could do something really crucial for society and it would be rational to take on that level of risk” (policy-maker, #312). Similarly, another policy-maker said:

*Too much for whom? This is one of the things that I don’t know how much has come up in terms of actual studies. It comes up as a thought experiment. Patients who are run through all the HIV drugs, [with] high viral loads with current regimens, definitely need an intervention but will be poor candidates for HIV cure studies (...) The paradox [is] that those who need these the most may not be able to join trials. They need an interventions; they may be willing to take on more risks; like cancer patients who are more willing to take risks. It could be the only option they have. What makes people feel uncomfortable about HIV cure research is because people are doing so well on HIV treatment. (...) A lot of the time, risk assessment is done in an imaginative way. We just don’t have enough data. Decision making is not entirely rational. We do not have a rational process to evaluate the risks/benefits for these interventions and a way to decide on the ethical questions. [These] [q]uestions have not yet been solved.*  
– Policy-Maker (#304)

Similar discussions occurred with bioethicists and IRB representatives. The question of “too much risk” is one that will be difficult to answer and that can never be answered definitely once and for all. It is difficult to draw a line with risk thresholds, and the determination of what is “too much”

depends on the intervention, the population being studied and the pre-clinical work leading up to the human study. As evidenced with phase III HIV vaccine candidates that scientists thought were protective, yet resulted in increased risk of HIV acquisition, the field of HIV cure research may witness surprises (policy-maker, #305). Risk thresholds will also vary depending on the value of the scientific intervention for society, but limits have to be placed to preserve trust in the research enterprise (policy-maker, #312).

What compounds the difficulty in determining risk thresholds in HIV cure research is the scientific uncertainty. Not having a good indication of what all the risks are – including some of the unknown risks – make the assessment more challenging. Interestingly, a subset of HIV-positive participants said that they would not place any upper threshold on risks in HIV cure-related research. Three patient-participant key informants (#105, #108, #109) (out of 12) said that they could not think of anything that would be “too much” risk and that they would undergo stem cell transplants or ingest latency-reversing drugs. They expressed that they would be “willing to do whatever it takes” (more willing patient-participant, #105). A couple of HIV veterans said that they took a lot of risks in their lives, and this is what has kept them alive. They are willing to do anything because this is how they have managed to survive up to now (personal communication). Similarly, 26 of the 400 survey respondents indicated that nothing would be “too much” risk for them, and this may have ethical implications that we will explore further in the discussion section. A clinician-researcher said that “[nothing] that has been seriously proposed out there that is probably too risky for anyone to consider. There are the crazy ideas outside of scientific thoughts, like ozone or bleach years ago – horrible things. [But] [o]verall, I think that some of the ideas that people are discussing in terms of cure, that have become mainstream, have been vetted quite a bit and we sort of know pluses and minuses and the weak points of each” (clinician-researcher, #208).

In sum, the topic of “too much” or unacceptable risk in HIV cure research generated a rich debate among all types of key informants. The question remains open and the process for determining risk thresholds becomes more of a thought process than a definite line researchers (and participants) cannot cross. As biomedical scientists continue to diversify and scale-up HIV cure clinical studies, perhaps they should never let go of the question of what is “too much” risk.

### **Concerns, Burdens and Barriers around HIV Cure-Related Research Participation**

We asked key informants to describe some of the main concerns they had with regards to HIV cure-related research. This question was meant to anticipate some of the possible unforeseen or unintended consequences of the HIV cure research enterprise. Most of the concerns related to the terminology of ‘cure’, safety issues and impacts on current health, treatment interruptions and circumstances after study participation or post cure discovery.

First, the word ‘cure’ was disturbing for some since HIV cure studies will not be curative in the short or medium term. A patient-participant summarized the issue beautifully: “There is a big concern that the word cure (...) you know using the word cure in any study provides a bias to the patients who think there is a benefit to them. The word cure is hot, sexy and it gets enrollment... but it may give unrealistic expectations to patients. We’ve talked a lot about that and I don’t think we have found a solution. The word cure is there to stay. The alternative is the word remission. We have come back and forth. My only concern is that some patients may be joining thinking they will get benefits. But most studies have risks and that is the ethical part that concerns me” (more willing patient-participant, #102). The related risk of curative misconception was highlighted as a concern by clinician-researchers. Clearly, the word ‘cure’ generates excitement as an aspirational goal; however, potential volunteers may believe there is a chance that they will get cured. The case report of Timothy Brown being cured may complicate the matter: “And some patients think that they will be the next Berlin patient. (...)There is often more of a focus on the exciting science than on

the potential harm to the participant” (clinician-researcher, #207). While it is difficult to abandon the word ‘cure’ to describe this research, most of the people living with HIV today will not be cured. It is thus important to keep this in mind when discussing these types of studies.

Patient-participants and clinician-researchers expressed genuine concerns about safety. Patient-participants were concerned about how the HIV cure experiment would affect their current health status. Patient-participants who were less willing to participate in HIV cure research expressed greater causes for concerns. For example, a discussant said that: “If I am participating in that kind of study and get sicker and sicker because I participate, that would be the only thing that would keep me from doing it. Getting sicker quicker” (less willing patient-participant, #104). Similarly, another respondent stated that: “Just the concern of HIV spiking or just the implications of not having the treatment or some weird thing coming up that was not thought about happening or was not planned” (less willing patient-participant, #110). Clinician-researchers also discussed some of the concerns that their study participants have about safety and health impacts of HIV cure research interventions. For instance, a clinician-researcher studying latency-reversing agents said that “Some of the patients are concerned that they will have the same side effects as people going through chemotherapy. They are [also] concerned about side effects of [the] leukaphereses. It is good that patients are concerned about these things, because these are not risks to be taken lightly” (clinician-researcher, #202). A clinician-researcher studying the effects of stem cell transplants stated that: “There are folks that we have on the cancer protocols, sort of the Tim Brown [type], treat the cancer and find out what happens with the HIV at the same time. One of the very important question is will any of this interfere with our cancer treatment? People often ask that and the answer is no. The really important thing is that the first thing being treated is the cancer. People ask about additional toxicities. We have other questions about whether this will make HIV worse. There is a variety of things and not one that stands out” (clinician-researcher, #208). Additional

concerns are expressed with regards to the impact of treatment interruptions, and these will be summarized in the treatment interruption section (below). Combination approaches have also engendered concerns among stakeholders, since factors may be accentuated when combining HIV cure-related strategies. There are concerns that combination interventions will complicate the process of informed consent since they will be more difficult to explain to potential study participants. It will be more difficult to elucidate the distinct effect of each component when strategies are combined. There were also concerns with the freedom to collaborate between stakeholders on these combinations, as some interventions may be restricted by intellectual property rights. Overall, the fact that key informants expressed concerns related to HIV cure research is indicative that they are cognizant of the potential risks and consequences of the research. Stakeholders voicing concerns is a healthy component of the process to ensure that HIV cure-related studies are implemented with minimal unintended or unanticipated consequences.

Additional concerns were expressed with regards to the consequences of study participation, such as long-term possible side effects and risks, including mutagenicity, carcinogenicity and teratogenicity. The very prospect of having a “failed cure” was also troubling for some. Worries were communicated for the post-study participation period: “Once the study is over, you can’t get the drugs anymore. If I find out that I have to take medication for the rest of my life, or not have to take medications, it would be nice to know. Also, you need to ensure that people are not left hanging dry after the study is over – whether it succeeds or not. Whether it be with medication or immuno-suppressive drugs” (more willing patient-participant, #107). From a translational implementation standpoint, it was interesting to find that some people living with HIV are already thinking about what a world with a cure for HIV would look like, and what some of the anticipated and unanticipated effects may be. Concerns emerged with regards to whether the cure will be mandated as standard of care, what the monitoring will look like, impacts on families and

relationships, and costs associated with cure. The cure for HIV was compared with the cure for HCV which has become an expensive standard of care (more willing patient-participant, #107). These concerns may be compounded given that the population of people living with HIV is aging in the United States. For example, a respondent examined some of the possible consequences of a world with a cure:

*And you find that you have a cure. Then, everything else changes. Now, is it going to be mandated that everyone takes this cure? And then you have to follow people for a long time. You have to see what happens. You have to see the side effects. The good and the bad. There may not be any. What happens then? Then it's other things that are put into place. Then it will cost more to take care of these people who have HIV. Then what happens? They can't rely on the... well, on the system to take care of them anymore. That's sad. You still need to put something into place for the people who are sick. Or now they have to find their own job skills and go to work because they are not dying anymore. I am not saying that it can't happen. It can happen. After it's a proven fact... then would I be willing to take it? Sure. That's one less disease that I have to deal with. Now I have to deal with old age disease.... You know, high blood pressure and all that. And there's no cure for that.*

– Less Willing Patient-Participant (#104)

As biomedical scientists get closer to finding a cure for HIV infection, it will be important to anticipate some of the consequences of having a drug-free remission for HIV for individuals, families and the health care system. Perhaps there can be lessons to be drawn from previous cures. A couple of key informants, however, admitted having “no concerns at all.” One of them stated that: “I believe that people who are involved in HIV cure research are really looking for helping the millions of people on this planet that are dealing with it. I don't think that a Tuskegee is coming, at least I hope not” (more willing patient-participant, #111). Another discussant said the he was “trusting of the medical research world to do what's appropriate” (more willing patient-participant, #112). These findings show that there is heterogeneity in the types of concerns people have around HIV cure research. The snapshot of possible concerns is diverse, yet raises the need to prevent unwanted or unintended consequences, harms and impacts on health. We will also need to manage the risks of failed cures (which will be very high initially), post-study participation realities and



impacts on the health care system. The field should also be tremendously cautious with the use of the word 'cure'.

### **Perceived Burdens of HIV Cure-Related Research Participation**

The main burdens associated with HIV cure research participation touched upon side effects, time commitments and intensity of study visits, as well as travel-related constraints. Two examples of side effects under the rubric of burdens – as opposed to risks – were skin rash or diarrhea. Other side effects were mentioned as perceived risks (above).

Significant time commitments were mentioned by both patient-participants and clinician-researchers. Taking time away from work and finding time for study visits were significant burdens. Clinician-researchers mentioned that time commitments are real deterrents to study participation. They recognized that patient-participants lead complex lives. The complicated study procedures may not fit in their schedules. This is especially true for women with children or child-care responsibilities. Furthermore, some of these studies may only be adequate for individuals who are not working, but these are also usually not the people who are on the healthy side of the spectrum, hence another paradox (clinician-researcher, #202).

The intensity of study visits was described extensively by most clinician-researchers. The main reasons for the intense nature of HIV cure research are the need for serial blood draws or leukaphereses, frequent monitoring (especially with treatment interruptions), numerous biopsies in some cases (e.g. gut, bone marrow, rectal, cervical, lymph node biopsies or lumbar punctures). Furthermore, given that the HIV reservoir is present at extremely low levels, in only 1 in a million infected cells, large amounts of blood must be drawn. HIV cure research participation can cause significant disruption to normal activities. Consequently, key informants commented that study participants should be compensated adequately for these time-intensive protocols and women should also receive compensation for child care (more willing patient-participant, #102).

Travel to and from the research site was also perceived as an important burden by patient-participants and clinician-researchers. This finding is consistent with the results from the U.S. survey on willingness to participate, where the difficulty of finding transportation to the site (17% very likely to discourage participation) and of finding parking at the site (20% very likely to discourage participation) were cited as the most frequent burdens of research participation. Other travel-associated burdens included having to go to another city, finding lodging or parking, and planning for public transportation. A clinician-researcher said that transportation issues are the most significant deterrents to study participation for some of her participants (clinician-researcher, #202).

HIV cure research teams must proactively address potential burdens of study participation, included side effects, time constraints, intensity of visits and travel/transportation realities for study volunteers. Helping alleviate burdens may go a long way in helping study participants attend the required study visits. Small steps such as enough advance notice for study visits, gas cards and bus passes can go a long way to ensure that travel burdens are minimized. One patient-participant wished for a mobile leukapheresis machine to come to his home regularly to help remove some of the burdens of study visits. Overall, clinician-researchers appreciated the “personal sacrifice” from their patient-participants.

#### **Perceived Barriers to HIV Cure Research Participation**

A topic related to burdens of HIV cure research participation was barriers. There was some overlap in the responses between burdens and barriers. For this reason, the themes related to time commitments and intensity of study visits were only discussed in the burdens section (above). The most prevalent types of barriers to study participation included: general barriers (including geographical availability) and other logistical aspects, finding study participants, stringent inclusion/exclusion criteria and stigma.

With regards to general barriers and access issues, some key informants recognized that barriers are not unique to HIV cure research, but applied to clinical research generally (policy-makers, #307, #310). Examples of general barriers included lack of information about the study, difficulty navigating the research setting or understanding the difference between treatment and research. Geographical access to HIV cure studies are real barriers to participation and the willingness exceeds availability of studies in some areas. Not all major U.S. cities have an HIV cure research site. Some potential volunteers reported that they would be willing to travel to a different city in order to participate in research. Besides allowing travel, another solution given was to engage additional clinics as satellite sites, although this strategy was not endorsed by all clinician-researchers who said that HIV cure research is very specialized and should only be performed at sites that are sufficiently well-equipped (clinician-researcher, #204). Other logistical barriers, besides time commitments and transportation, included flexibility of the workplace to facilitate study visits.

Finding study participants was another barrier identified, especially for HIV cure research strategies that require very specific types of study participants, such as those dealing dually with HIV and cancer (requiring a stem cell transplant) or acutely infected individuals who would qualify for early ART protocols (in Fiebig stages I – V) (clinician-researchers, #204, #205). Key informants recognized that enrollment in early phase HIV cure studies is different than for phase III trials. Compared to advanced HIV prevention trials that have fallback methods (e.g. condoms), the calculus may be different for HIV-infected volunteers who may be harmed as a result of participation. Furthermore, a policy-maker warned against exploiting participants who have no treatment option and may qualify for some of the gene therapy trials meant for candidates with advanced treatment failure (policy-maker, #305). For pediatric HIV cure studies, the success of prevention-of-mother-to-child transmission means that there are fewer infants infected with HIV in the United States:

*From the pediatric perspective, a good thing is that we know how to prevent mother-to-child transmission for the most part, thanks to prophylaxis. So that's a barrier because we don't have that many infants infected with HIV, so not many can be involved in HIV cure studies, at least in the United States. What you end up having are very few individuals who are eligible to be enrolled in these studies and they tend to have other factors associated with them, such as low socio-economic status and reasons why women were not on ART in the first place that interfere in their ability to participate in HIV cure studies. It's a complicated system of access to care and the mother's status.*

– Clinician-Researcher (#205)

Recruitment of pediatric HIV cure participants touches upon delicate issues around treatment and access to care for women living with HIV in the United States. Factors that make infants seropositive and thus eligible for studies are tied to additional social vulnerabilities.

Robust inclusion/exclusion criteria were also mentioned as possible barriers to participation. A patient-participant who was extremely willing to participate in HIV cure research said that he would be excluded from most protocols since he was also positive for Hepatitis B and had multiple drug resistance (more willing patient-participant, #102). Inclusion/exclusion criteria were also recognized by policy-makers as major barriers to participation. Clinician-researchers provided the main reasons why candidates fail screening. We will discuss this topic further in the recruitment section (below). Overall, most HIV cure research protocols mandate that participants be “super health or super sick” (more willing patient-participant, #102), but usually the people in the middle of the spectrum are the ones who are most willing to participate, another paradox (personal communication).

Clinician-researchers admitted to doing a bit of self-selection when approaching candidates for HIV cure-related studies. A double-edge sword was exposed in that investigators want study volunteers who are reliable and have their life together, but these individuals have job and are thus less available to participate in research (clinician-researcher, #202). It may also be possible that researchers select candidates on the basis of who is best positioned to respond to a specific agent or intervention, although this should not drive their decisions (personal communication).

Stigma was stated as a major barrier to HIV cure research participation, and even with robust HIV treatment (or cure), stigma would not disappear. HIV/AIDS is still viewed as a gay man's disease in the United States (more willing patient-participant, #101; less willing patient-participant, #104). Another root cause of stigma was lack of understanding about the disease, including transmission routes (more willing patient-participant, #101). A woman living with HIV described her deep and personal experience with stigma:

*I keep coming back to the issue of stigma. If there were not as much stigma, more people would seek help. More people would get treatment. More people would feel supported. I feel very vulnerable when it comes to this issue. I don't tell people because I feel very vulnerable. I actually had a doctor one time, who said: "How did you get that?" "How did that happen?" you know. Oh my God, do you realize how inappropriate that was! I felt so exposed. There is a lot of education that needs to happen for the community as a whole but also people who are working with the patients. I don't talk about it and I keep it to myself. I think stigma is the biggest issue that is always going to be in the way of getting women involved, especially women who are not the usual face of HIV.*

– More Willing Patient-Participant (#109)

In this account, stigma was associated with feelings of vulnerability, even in the health care setting. Stigma is also associated with ongoing issues around disclosure, rejection and discrimination. Some of the stigma may be internalized or externalized and has a profound impact on whether patient-participants decide to join HIV cure research.

Clinician-researchers indicated that most of their patients remember the exact time when they were diagnosed with HIV, since it was such a marking even in their lives:

*Taking a step back, being diagnosed with HIV, you know, as a clinician, when a patient comes in and they are diagnosed, our first visit is largely spent going through and talking about that diagnosis. What I found is if I try to do a lot more, like explain labs and explain how the clinic works and if I start treatment or prevention at that point, they fail, and it's largely because people really struggle with this diagnosis and [this is] normal and healthy. This disease carries tremendous stigma even though it's treatable. People will tell you the exact day, the moment, the hour when they were diagnosed. They can remember all of these things because it's such as life-changing event. Also in a very personal way, people acquiring HIV sexually or using drugs, these are behaviors... (...) It becomes a part of their lives*

– Clinician-Researcher (#206)

The above quotation reveals that stigma cannot be dissociated with the therapeutic trajectory of individual patients and decisions of whether to participate in research may factor in

perceptions of stigma. Clearly, stigma remains a real problem for people living in the United States and more needs to be done around it to demystify the disease (policy-makers, #301, #308). This finding is also consistent with the one of the quantitative study results, which showed that discrimination was a major deterrent of study participation. Stigma and discrimination reduction should be addressed as part of ethical study design and implementation.

In sum, it may be important to consider that barriers to study participation can exist at multiple levels: structural, personal, social, economic and cultural. Our key informant interviews only touched upon a small number of possible barriers, such as geographical access, logistics, finding the right participants, inclusion/exclusion parameters, stigma and other possible impediments. It may be important to conduct actual empirical studies that examine *actual* barriers to HIV cure research participation.

### **Safest HIV Cure-Related Research Strategies**

Since we investigated perceptions of risks (above), we felt it was also important to inquire about perceptions of safety. We hereby summarized general considerations for assessing safety, including the need for case-by-case analyses. We also outline the HIV cure strategies that were perceived to be “safer” compared to others.

#### **General Considerations**

Policy-makers/regulators provided general philosophic considerations for the determination of safety (and risks). They indicated that safety is based on both the risks of the intervention and the population selected for the study (policy-maker, #311). Safety cannot be defined simply by looking at the HIV cure research method, but it is based on a combination of procedure(s), intervention(s) and patient considerations (policy-maker, #311). Even an HIV cure research strategy that is considered “high-risk” may become safer if performed in the right population. For example:

*A bone marrow transplant would be considered high risk in a participant for whom bone marrow transplantation was not clinically indicated. However, for an HIV-infected patient with a malignancy that requires bone marrow transplantation, the additional risks related to such a study may be minimal to moderate. For such a patient, the risk of participating in a study involving bone marrow transplantation may be less than for an otherwise healthy HIV infected patient who is taking part in a kick and kill related clinical study.*

– Policy-Maker (#311)

Thus, assessments of safety are relative. This is why the FDA performs case-by-case analyses to determine whether an intervention is “safe enough” to move forward, although no specific IND could be discussed given the confidential and proprietary nature of the information. A regulator said that he “would not classify one modality over the other as necessarily risky or safe. (...) Just because something is gene therapy or chemotherapy does not mean it is worst or safe” (policy-maker, #302). Therefore, protocols need to be evaluated on a case-by-case basis because they are different. Reviewers of HIV cure research try to learn as much as possible about safety profiles of interventions and agree to keep an open mind, because “the jury is kinda out of what will cure HIV” (policy-maker, #304). Furthermore, one cannot assume that lowering the dose of a drug will increase safety. The evidence needs to be present and this is what reviewers of HIV cure protocols look for. Most of the compounds have long development programs and substantial data on how different doses react in the body. The FDA recommended leveraging that information as much as possible to avoid working blind.

### **Perceived Safe HIV Cure Research Strategies**

Key informants perceived specific HIV cure research modalities to be on the safer side of the spectrum, including early ART, vaccinations/immune-based strategies, monoclonal antibodies and reservoir assessments. Early ART were considered safest and logical, because the drugs are already FDA-approved and have already proven to be potent at stopping viral replication. Vaccinations or immune-based therapies were also considered safe, particularly those that use *ex vivo* expanded autologous cell systems because they do not introduce foreign agents in the body. Monoclonal

antibodies also received the safety vote by the three groups of key informants, despite the dearth of long-term safety information on them. Reasons for why monoclonal antibodies were perceived as relatively safe were that they do not interfere with DNA replication but can kill infected cells. They have a different mechanism of action than antiretroviral treatment, such as blocking entry. This is also a growing industry with over 50 licensed monoclonal antibodies available to date. Monoclonal antibodies, however, have gaps in coverage and therefore must be used in combination. Of the latency-reversing agents, two clinician-researchers mentioned that disulfiram was the safest agent since it has a good tolerability profile and is already FDA-approved to treat alcoholism; however, it was not proven effective at reducing the HIV reservoir (clinician-researchers, #204, #207). Reservoir assessments were also considered safe since they are observational and do not require administration of any foreign agents. Interestingly, a minority of key informants said that none of the HIV cure research strategies were safe at this time (policy-maker, #309).

To sum up, this section explored perceptions of safety around HIV cure-related research strategies. We summarized considerations for assessing safety and described specific HIV cure-related strategies that are perceived to be safer.

### **Perceived Benefits of HIV Cure Research Participation**

We assessed perceptions of benefits in HIV cure research using key informant interviews and survey responses. This topic generated rich answers from the three groups of key informants. Policy-makers were adamant that there should be no expectation of direct benefits in HIV cure research. Societal benefits of knowledge generation around HIV cure research were highlighted by all groups of informants. The most commonly cited personal benefits of HIV cure research participation were psychological and intangible in nature. Some patient-participants perceived the likelihood of clinical benefits, which raised ethical issues around therapeutic or curative misconception. As with risk perceptions, there was tremendous variability around perceptions of



benefits in HIV cure studies. Some patient-participants may have confused the questions of benefits of participating in HIV cure research with the potential benefits of an eventual cure.

### **No Expectation of Direct Benefits**

Policy-makers stated decisively that HIV cure research confer no anticipation of direct benefit to study participants, since the aim is to pursue generalizable scientific knowledge (policy-maker, #311). Very unlikely will HIV cure research interventions change the course of HIV disease for participants. Research may actually increase the likelihood of harms (policy-maker, #312). If there are any benefits, these will likely be indirect from engagement with the research staff or screening tests that may help identify health problems. Even when scientists tell participants that there is no expectation of direct benefit, it is possible that volunteers still expect direct benefits to occur and become disappointed when the cure does not materialize (policy-maker, #303). Expectations of personal benefits are thus wrong reasons for joining HIV cure studies (clinician-researcher, #313). This is why it is important to manage expectations around what the science can deliver in early-phase studies and to provide adequate education to prospective study participants.

### **Societal Benefits**

The main societal benefits of HIV cure research participation related to advancing scientific knowledge around HIV cure. Given that HIV cure research remains in the early stage, the societal benefits of finding additional information about HIV latency or basic aspects of virology and immunology are paramount. Contributing to the biomedical HIV cure research agenda and helping future generations was one of the most commonly cited benefits of the research by survey respondents. Studying diverse minority populations also helps ensure that the data are generalizable. Some of the survey respondents recognized that HIV cure research may have applications to other diseases or conditions. Another perceived social benefit of participating in HIV

cure research identified by survey respondents was contributing to **reducing stigma** around the disease.

### **Personal Benefits**

The most prominent perceived personal benefits to HIV cure research participation pertained to psychological, emotional and mental benefits of contributing to finding a cure. This was consistent with the quantitative survey results. These intangible benefits were recognized by all three groups of key informants. It was felt that psychological benefits should not be discounted as they lead to overall improvements in the quality of life and removal from isolation after a difficult diagnosis. People living with HIV felt it was “the right thing to do” to participate in HIV cure research and felt pride and self-esteem for being able to be a part of it. A participant who underwent a risky stem cell transplant expressed that he felt tremendous emotional benefits after helping further medical knowledge (more willing patient-participant, #112). Another participant was proud of the fact that investigators developed a special assay for her and that scientists were speaking to her directly (personal communication). Furthermore, some study participants valued their experience in a clinical study and these benefits may have nothing to do with the intervention itself. There can also be psychological benefits of being in regular contact with clinical staff, of being treated like a human beings and feeling valued as a result of research participation (policy-maker, #304). Survey respondents also expressed a sense of duty, the need to give back and help others, satisfaction in being “pioneers” and feeling empowered about their condition. The need for additional qualitative research in this area was identified (policy-maker, #304)

There were perceived clinical benefits of HIV cure research participation. The most commonly cited example was the Sangamo study, which resulted in increased CD4 +T lymphocyte cells amongst study participants (more willing patient-participant, #102; clinician-researcher, #208). While HIV was not completely gone at the end of the study, the body was able to control it better

(clinician-researcher, #208). These unexpected clinical benefits, or “off target positive clinical effects” (personal communication) may demonstrate a missing element in HIV cure research: that clinical benefits short of a cure for HIV may emerge and be beneficial. The Sangamo study reveals the importance of intermediate successes along the way to finding a cure and may encourage potential volunteers to participate (clinician-researcher, #208). Early ART has also been associated with clinical benefits and encourage individuals at higher risk for HIV acquisition to come in earlier for diagnosis and treatment.

Additional clinical benefits of HIV cure research participation were mentioned in the survey, although some of the respondents may have confused the question of benefits of research participation with the potential benefits of an eventual cure. Responses such as “taking charge of my own health,” “staying healthy,” “increased life expectancy,” “not having to take medications” and “being potentially one of the first people cured” may be problematic from an ethical standpoint. Besides the example of the Sangamo study, there are no direct clinical benefits to be expected from participation in HIV cure research. Furthermore, some survey respondents mixed the desire to help advance HIV cure research with the expectation of personal benefits. Examples of mixed statements included: “mostly the possible benefits to myself as well as others in the HIV community,” “helping myself and others” and “knowing that I did something to contribute to help people including myself manage HIV.”

An unexpected personal benefit of study participation that emerged from the survey responses was acquiring information about HIV and being able to educate others. People living with HIV saw benefits from learning about cutting-edge HIV research and felt that this information could bolster their advocacy work. Armed with this information, participants felt that they could refer peers to HIV cure studies. Survey respondents also identified other personal benefits to participation, including getting support from others and being able to offer hope. Other perceived

benefits to study participants were actually requirements and expectations of clinical studies and are interesting from an ethical standpoint, such as reimbursements, “knowledge about the risks involved in studies such as the possibility of virus rebound or creating resistance to current ARV” (survey respondent), “privacy and confidentiality” (survey respondent) and that “studies be professionally/scientifically conducted and based on previous (animal) studies” (survey respondent). Statements such as “receiving free nights in a fancy hotel, more money on gift cards and more retreats for everyone to share their stories” may indicate that some potential study volunteers are misled about the purpose of research.

Some of the survey respondents stated that one of the benefits of their participation in HIV cure research would be ensuring that under-represented populations, like women and people of color, get included and represented in studies. The simple fact of knowing that women and minority populations are part of the research would be sufficient to confer a benefit because people know their group is being represented. Other diverse benefits included “satisfying curiosity,” “leaving a legacy” and “having a second chance at life” (survey respondents). Despite the rich perceptions of benefits identified, the likelihood of harms in HIV cure research remains real. One of the survey respondents described his own personal story of harm as a result of research participation:

*I have participated in a vaccine trial through [University] in [City] from 1993 to 1995 and was given placebo instead of GP120. I have also been involved with Dr. [Name of Investigator]'s 'elite controller' research and [University] with Dr. [Name of Investigator] since 2006. I have only taken antiretrovirals for a very short period back in 1999—2000 and remained virtually undetectable for the virus all on my own. I currently have only Medicare part A and do not have a doctor nor am I taking any prescription meds whatsoever. The clinical research I was dedicated to at [University] will no longer allow me to participate since I do not have a primary care physician....this I view as a slap in the face after all the tissue and blood I have donated, along with many cardiology procedures done to me over the past decade*  
— Survey Respondent

This section described perceived benefits of HIV cure research from three types of key informants. These benefits are sometimes embedded with vulnerabilities and risks of harm. According to policy-makers, there should be no expectation of direct benefits in HIV cure research.

Societal benefits included generation of scientific knowledge and contribution to stigma reduction. Psychological personal benefits resulting from HIV cure research participation should not be underestimated. Additional perceived benefits of HIV cure research participation may raise ethical questions that will be examined further in the discussion section. Volunteers may conflate benefits from what is to be expected as part of clinical studies by regulations.

### **“Risk-Benefit Ratios” and Equipoise in HIV Cure Research**

We asked key informants to describe what a “favorable risk-benefit ratio” in HIV cure research meant to them. We received diverse answers from the three types of key informants. For the most part, the balance was tilted towards risks in HIV cure studies. We found that it was difficult to derive objective measures for risk-benefit assessments given the complex nature of the interventions.

Clinician-researchers said that when discussing risks and benefits with study participants, they stress that “the benefits are usually zero [and] it’s usually just about the risks” (clinician-researcher, #204). The benefits are accrued to society instead of the individuals. Therefore, the risk-benefit calculus entails looking at the risks for the individual participants versus the benefits in terms of knowledge to society (clinician-researcher, #204). Only if one “cured a macaque would it be easier to justify exposing people to risks in that case” (clinician-researcher, #209). In the absence of potential known clinical benefits, the thresholds of safety and efficacy remain high to move the field forward. Clinician-researchers agreed that it is too early to come up with anything that would not be subjective at this point (clinician-researchers, #208, #209). One of the key informants explained the complexity of making risk-benefit assessments in HIV cure research given the incremental nature of the research:

*I hope nobody has a real answer to that. I don't think it's easy to imagine having a simple equation that can take you there. It seems to me that it's pretty easy for us to calculate risks and benefits... you know... (...) [We] know the risks and benefits of conventional treatment. We don't really know all of them yet, obviously, but to me, one of the issues here is that you know... it's unlikely that many investigators with some of the trials that are going on now would expect those trials to right there find a cure. You know... I don't think many people would expect that a trial with the latest kind of approach to shock and kill will be suddenly curative. Most of us expect that (...) the trials that we do in this part of the epidemic will give us incremental information. We know that most of the trials will not result in any evidence of clinical remission or do anything to the estimate that we have of the reservoir size. But, if they are well designed, and well conducted and well analyzed, they will move us along to making progress. So the risks and benefits to the participant in that setting is that I am willing to ask somebody to take a risk... that this will ultimately move us to the point where we do have a cure. The benefits are more ultimate and societal than they are individual and immediate. But how do you really put a number on that, that's really hard. So I think again, working with social scientists and social psychologists to make sure that we are explaining that correctly, and it's a tough concept. We need to make sure that we are not enrolling people in trials under false pretenses. That's really an important part of this.*

– Clinician-Researcher, #211

Clearly, HIV cure research protocols are evolving and what is done in one study is used to inform the next study. It is important to guard against enrolling study participants under false pretense. When investigators write informed consent forms, they should state bluntly that there are no expectations of benefits (or cure) to the individual participants for the foreseeable future (clinician-researcher, #206). Most study participants tend to be comfortable with this concept (clinician-researcher, #206). As HIV cure research strategies advance in the translational pathway, however, it may become more important to develop metrics around risks and benefits (clinician-researcher, #208).

Similarly, policy-makers said that HIV cure research strategies have a risk-benefit profile contingent upon the characteristics of the product/intervention, the type of participants, the stage of disease and the standard of care available (policy-makers, #307, #311). Policy-makers were in general agreement with clinician-researchers that it is difficult to obtain an objective risk-benefit measure. Investigators need to focus on the risks of what they are doing and most HIV cure studies present greater than minimal risks (policy-maker, #301). While the regulations do not include clear risk thresholds, scientists must ensure that risks are justified and work towards minimizing those

risks (policy-maker, #301). A bioethicist explained the difficulty of performing the risk-benefit calculus. He said that juxtaposing personal risks with societal benefits would be akin to comparing apples to oranges:

*Do you mean a number... or a concept? (...) I don't think that you would derive a number that would be rationally justified, that we derived in some way by principles of ethics. We are not there. (...) There are several reasons why we are not there. One is [that we are] comparing apples and oranges. How do you weigh against each other medical harms on one hand and psychosocial benefits on the other? We just in general do not have very good tools for assessing those things. That's one thing. The other thing is that we lack factual information. We do not know the likely impact on the psychosocial of the person and it is going to be very hard to come up with reliable numbers on this. We don't have a simple balance.*

– Bioethicist (#312)

Risk-benefit assessments in HIV cure research thus remain subjective measures given that we are dealing with a lot of hypothetical and theoretical risks and benefits. Deriving a neat risk-benefit ratio becomes almost impossible. One policy-maker rejected the concept of risks-benefits and preferred to speak in terms of “investments” (policy-maker, #303). Another policy-maker referred to the case-by-case analyses performed by the FDA (policy-maker, #306). Overall, there was a consensus that the field is evolving rapidly and risks and benefits remain in flux, and this is another reason why reviewing HIV cure studies is a challenging task for regulators (policy-maker, #306). It is almost impossible to apply a consistent algorithmic approach (policy-maker, #311). “At the end of the day, you have to satisfy yourself that the potential benefits outweigh the risks” (bioethicist, #310).

Key informants also recognized that some of the risk-benefit assessments are specific to the individual participants (clinician-researcher, #205). Individuals have different risk thresholds, and this is compounded with the fact that each intervention is unique. All in all, some of the patient-participants interviewed described the thought process for how they were making some of risk-benefit or “personal balance account[50]” calculations:

*If the risk-benefit ratio was like 20 – 80% versus 80 – 20% (...) If the research could really could make a change as far as the disease is concerned – but maybe it could hurt me, but ultimately there is a 1 in 5 chance, but I happened to be that 1, and if what you could learn from me would totally change the world... It's an opportunity to help a situation.*

– More Willing Patient-Participant (#103)

*Well, Timothy Brown was in salvage therapy. He had failed everything. So his risk-benefit ratio was good.*

– More Willing Patient-Participant (#102)

*That's kind of tough for me to answer. They all have some risk, but like everything, it's a calculated risk. The stem cell transplant for me is a bit too risky personally, but the mAb that would be okay. With the kick and kill strategy, I could afford to take a hit with my virus so I would be willing to have some health repercussions from something like that. So I think that everything has risk, but the most extreme and radical things are what tend to unnerve me. The stem cell transplant for me is extremely radical and I would only undertake it if my life were at serious risk.*

– More Willing Patient-Participant (#111)

Even though there are no objective risk-benefit ratios, it is apparent from the accounts of people living with HIV that subjective assessments of risks versus benefits come into play when making decisions about whether to join clinical HIV cure studies. This raises the need to have deep and nuanced discussions with potential participants about the different types of HIV cure strategies, the specific study protocols and the possible risks and benefits (or lack thereof). Perhaps even a matrix approach would be indicated in order to determine which studies would be truly altruistic.

### **Equipoise**

A topic closely related to the risk-benefit ratio was that of equipoise. We asked clinician-researchers and policy-makers to discuss the role of equipoise in HIV cure research. There was variability in the responses, ranging from “equipoise applies,” to “it depends” and “equipoise does not apply at all.” Understanding the thought processes around equipoise as it relates to HIV cure research proved to be an engaging exercise in ethics. In fact, a clinician-researcher defined equipoise as “the concept in a trial (...) [where] you are going in without any preconceived notion that the treatment is going to work or not” (clinician-researcher, #206). This concept is what allows researchers to randomize study participants from an ethical standpoint. For example, one group will



receive treatment and the other group will receive placebo (clinician-researcher, #206). Equipoise relates to “questions for which we do not have solid answers” (clinician-researcher, #206). In the field of HIV cure research, equipoise would need to come with a “reasonable assumption (...) about what we currently know and what we don’t know about the way the reservoir can be reactivated and the next step which would be to see clearance” (clinician-researcher, #206).

A number of policy-makers and clinician-researchers agreed that equipoise was relevant to the HIV cure research field. A policy-maker said that equipoise is “an element that we always consider in any research submitted for review by the FDA. There has to be some level of equipoise [and we] cannot quantify that” (policy-maker, #307). Equipoise ensures that a study remains unbiased and promotes a healthy sense of skepticism that the proposed intervention may or may not work (policy-maker, #307). Equipoise was viewed as being imperative to justify moving a study forward. Likewise, a bioethicist said that equipoise is “probably the trickiest ethical issue in [his] mind, especially [for] someone who is tolerating ART quite well and [has] the infection (...) under control” (bioethicist, #310). He referred to the infectious disease doctors who may not agree with their patients joining HIV cure studies if their clinical management is under control: “why take and why forego proven treatments that are well tolerated for the chance that something may be better?,” he asked (bioethicist, #310). He forewarned that HIV cure research has to be informed with the absolute best available evidence at any given time. A third policy-maker thought equipoise was a useful concept when it relates to the standard of care discussion (policy-maker, #304). For HIV, there is a standard of care for treatment and clinical management of the disease, but no cure standard of care. She asked whether it made sense to allow experimental studies that disrupted standard HIV treatment, and said that equipoise may become more useful when HIV cure interventions start to work (policy-maker, #304).

Two clinician-researchers expressed that equipoise is absolutely relevant to HIV cure research because it guarantees total objectivity about whether something may work or not. One said: “equipoise is the word of the day for cure research. I don’t think anybody has the knowledge to be able to say in advance whether or not there is likely to be benefits” (clinician-researcher, #209). From this researcher’s standpoint, equipoise meant that there is no evidence to suggest one outcome versus another, so equipoise is applicable to HIV cure research. Similarly, another researcher said that equipoise is pertinent because investigators should not be “biased in thinking [they] will be curing people because there is not a good track record for this kind of research” (clinician-researcher, #207). Equipoise was deemed applicable because success remains limited in finding a cure, with the exception of Timothy Brown who was cured via an allogeneic bone marrow transplant (clinician-researcher, #207).

In contrast, a policy maker was categorical that equipoise did not apply to HIV cure research or clinical research in general. He believed that equipoise was a fallacy that did not necessarily lead to ethical studies:

*I do not believe in the need for equipoise in clinical trials in general. I think it’s a mistake of my fellow bioethicists. (...) Equipoise is the concept that before the trial begins the different arms of the trial will not be expected... there won’t be a difference in the prospects given our partial information about the effectiveness of the interventions... and the risks of the intervention... There won’t be a difference in the prospect (...) that we place on the different arms and on how people will fair on the different arms of the trial. The onus is on the people who believe in equipoise to explain why we need that requirement. They seldom give an argument. They assume that equipoise is needed without justifying why. That’s a shame. They assume that equipoise is a requirement but they do not give arguments. There are trials that would not be ethical even with equipoise.*

– Bioethicist (#312)

Most of the arguments against the use of equipoise in HIV cure research pertained to the fact that there is no comparator in the HIV cure field that we can use. Furthermore, the field remains in the early phase of experimentation, and equipoise is more useful for later-phase randomized controlled trials. The current comparison in HIV cure research is between highly

effective HIV treatment (one pill per day) with an HIV cure research modality of unknown safety and efficacy. This is not an “apples to apples comparison” (bioethicist, #305). A bioethicist said that it is “not fair to ask” the equipoise question at this time in HIV cure research because we cannot compare an early-phase HIV cure research strategy with a therapy that keeps the virus suppressed (bioethicist, #205). Compared to HIV prevention research such as HIV vaccine trials, these can be justified ethically using equipoise because there are effective prevention methods, such as condoms or pre-exposure prophylaxis, that can serve as the comparators for equipoise. On the HIV cure side, there is no robust comparator. Treatment is not cure. As a result, any attempt at making a comparison becomes impossible and misguided (bioethicist, #305). In HIV cure research, the key question is not so much one of equipoise, but of getting an accurate representation of the risks that people are being asked to take on and how these can be justified vis-à-vis the potential scientific benefits that have to be gained (bioethicist, #305).

In a similar thought process, clinician-researchers stated that equipoise does not apply to HIV cure research because the modalities being tested are not proven therapies (clinician-researcher, #203). Equipoise applies when we compare two therapies. For the START trial[51], HIV-positive participants were randomized to early versus late HIV treatment. In contrast, HIV cure research studies do not test established therapies. They are short-term pathogenesis, virologic, immunologic, reservoir and latency reversal studies for which there is zero therapeutic benefit to be expected (clinician-research, #203). Correspondingly, another clinician-researcher described the thought process that goes on in determining the best use of equipoise:

*I use the term a lot in randomized clinical trials to make sure that I feel in my heart and in my head that I could recommend either course of treatment to somebody that I really care for like a close relative. If I can't do that, if I feel like I should have one treatment versus the other, or that I would want my brother to be treated with one versus the other, then I do not have equipoise. So to me, that is a very important question in a randomized clinical trial. If I am thinking about equipoise in the context of treatment on a trial versus treatment off a trial, I am not sure how I would answer that. We have a pretty good sense of what's going to happen off a trial. I can take one pill once a day with the current drugs with a reasonable expectation that I am going to be*

*fully suppressed and I am adherent and that suppression will continue indefinitely. We know the state of current treatment. With investigational treatment, like what are talking about here, there is risk. I would say... hmmm I would not try to say that I have equipoise. (...) The question becomes given societal needs or potential benefits of finding a cure, with informed consent, would it be ethical for a person to participate in research where the intervention would not be better than the treatment itself. And you know, people are willing to do different things. If they sense that the risk is small, and the benefits may be not to the individual but to society, and if we explain that, then that's why we do research and that's why people participate in research. They are willing to, for the benefit of society, take a personal risk. And it's our responsibility as investigators to make sure that we are designing trials that limit the risks as much as we possible and that we are communicating all we can to the participants.*

– Clinician-Researcher (#211)

For this particular clinician-researcher, the topic of equipoise is a deeply personal one. In agreement with the policy-makers, equipoise is most applicable to randomized clinical trials with established therapies, as opposed to early-phase experiments. Given that the state of current antiretroviral treatment is well-characterized, the key implementation and ethical question becomes clearly communicating potential risks to study participants and attempting to minimize those risks.

On the topic of equipoise, most of the key informants fell somewhere in the middle of the spectrum, saying that it whether it applies depends on the study, the intervention and the population. A policy-maker said that there is equipoise for some studies but not others and this is contingent upon the particular protocol (policy-maker, #311). Instead of equipoise, what is sometimes helpful are futility rules and safety endpoints that minimize risks (policy-maker, #306). A policy-maker/regulator provided the example of seeing the first five participants on a treatment interruption study having a viral rebound within 3 – 4 weeks – this would provide a clear futility signal. Instead of equipoise, futility rules and robust safety signals can add objectivity to a study and rigor on how to move forward. Correspondingly, most clinician-researchers were equivocal on the topic of equipoise and said that it depended on the study because of the intense regulatory environment of clinical research in the United States (clinician-researcher, #203). Most HIV cure studies up to this point have not used double-blind, placebo-controlled design, so equipoise has not been a practical concept, especially for gene therapy studies that do not have control arms

(clinician-researcher, #208). Unless one is trying to prove non-inferiority, equipoise may not apply (clinician-researcher, #208). In some cases, study participants act as their own controls, so study designs are complex – and equipoise may or may not apply (clinician-researcher, #208). Equipoise may become more relevant as studies progress and HIV cure research interventions get more efficacious. Then, it would make sense to have trial arms, such as one set of zinc finger versus another set of HDAC inhibitors or different combinations (clinician-researcher, #208). At this time, it may be premature to require equipoise since HIV cure research is in the early phase (clinician-researchers, #208, #210). There has only been one person cured of HIV, so drug-free remission remains an aspirational goal with no proven efficacy. The two Boston patients and the Mississippi child no longer meet the ‘cure’ criterion and we are too early for any true successes (clinician-researcher, #210). A clinician-researcher commented that: “for the field as a whole, it is relatively balanced when we compare the risks and the prospect of benefits for the greater good” (clinician-researcher, #201). This may indicate that the entire field of HIV cure research is in a state of equipoise, as opposed to specific studies.

No other topic related to equipoise polarizes the HIV cure research field more than analytical treatment interruptions. In the next section, we examine perceptions of a variety of stakeholders around treatment interruptions.

### **Perceptions of Treatment Interruptions**

We asked patient-participants, clinician-researchers and policy-makers to provide their thoughts on the topic of treatment interruptions. We summarize general attitudes around treatment interruptions, possible motivators for undergoing treatment interruptions, as well as concerns and considerations to ensure that they are implemented ethically and effectively.

### **General Attitudes around Treatment Interruptions**

First, stakeholders are divided on the topics of whether treatment interruptions are warranted in HIV cure research. One group of stakeholders was adamant that treatment interruptions should not be done, while others explained that they could be performed under certain conditions. A clinician-researcher performing very high risk gene therapy research expressed serious concerns with treatment interruptions because study participants will relapse if they are taken off therapy (clinician-researcher, #208). Limits of reservoir detection are not sensitive enough to determine whether all the HIV provirus has been taken out of the cells. If HIV were to rebound, this may reset the entire reservoir to its initial level and the 'purging' benefit will be lost (clinician-researcher, #208). Likewise, another clinician-researcher said that it is premature to implement treatment interruptions, especially in the pediatric patient population (clinician-researcher, #205). There are risks of drug resistance with perinatally infected children who will need to take ART for the rest of their lives. If treatment is interrupted and resistance to the current regimen develops, they will have one fewer option (clinician-researcher, #205). The appropriateness of treatment interruptions is further complicated by the fact that there may be no direct clinical benefit of reducing the size of the HIV reservoir. Some researchers rely on very sensitive assays, such as the quantitative viral outgrowth assay (QVOA), without the need for treatment interruptions, to determine if experimental agents had any effect on the size of the replication-competent HIV proviral DNA reservoir. But these assays are not sensitive enough to detect every latently infected cell and they do not serve as clinical endpoints like treatment interruptions (and delayed time to viral rebounds). Reservoir assays remain surrogate endpoints that scientists use to determine if the HIV reservoir was perturbed in any way and whether these perturbations are meaningful at all. In the absence of potent 'curative' agents, some scientists prefer to rely on these surrogate markers, instead of causing unnecessary harms resulting from ART interruptions. Since latency-reversing

agents have not yet been associated with a substantial reduction in the size of the replication-competent HIV reservoir, it is best to rely on those assays and not combine these experimental latency-reversing compounds with treatment interruptions given the overall compounded risks (clinician-researcher, #206). Furthermore, some of the people living with HIV have worked very hard to become undetectable (clinician-researcher, #202). They are proud of their high CD4+ count and are not willing to risk progressing to AIDS or having a viral spike due to a treatment interruption. Since HIV cure research remains in the early phase of experimentation, they prefer to stay on ART for the time being until interventions become more efficacious at depleting the HIV reservoir.

On the contrary, there are clinician-researchers who believe in the need for treatment interruptions at this time, under specific conditions. For study participants undergoing treatment interruptions, there should be close monitoring to assess viral rebound (#207). Participants should be clearly informed about the potential risks, including the possibility of developing resistance to ARVs (clinician-researcher, #201) or the increased risks of cardiovascular events (clinician-researcher, #207). Furthermore, treatment should resume if the viral load rises up to a certain threshold (clinician-researcher, #201). A clinician-researcher explained his rationale for supporting treatment interruptions:

*I think they can be done cautiously and with very careful monitoring. Because if they're not done, I don't think [that] we will be able to convince anybody that we have achieved an ART-free remission. I don't think any of the current biomarkers or surrogate markers are predictive of a change in duration of ART-free remission. We really do have to move forward with ATIs as the key indicator of whether we have achieved what we are striving for. With that being said, there are all kinds of ATIs, and I am in favor of intensively monitored antiretroviral pauses which means that we monitor them until there is appearance of viremia and we monitor frequently enough [so] that there is no risk of acute antiretroviral syndrome, and we put patients on therapy before the viral load gets very high. Obviously there is risk that the logistics will break down and that won't occur. But I think that if it is done carefully, it can occur. There is proof in the literature that ATIs can be done carefully and not expose people to risk. There is some risks they will reset the relationship between host and virus and expand the reservoir from what it was before. I don't believe it that and I can explain why but it's a lengthy explanation. I don't think the reservoir accumulates very quickly. There has to be prolonged high levels of viremia to generate the reservoir and by prolonged, I mean weeks.*

– Clinician-Researcher (#209)

Based on this account, treatment interruptions can be a clinical endpoint of choice to determine whether sustained ART-free remission has occurred. Furthermore, precautions can be taken to minimize risks. All other measures of ‘cure’ or ‘reservoir depletion’ remain surrogate endpoints. Ultimately the success of interventions aimed at achieving ART-free remission will be judged by their ability to show clinically meaningful results. One of the most clinically relevant endpoint is delaying the time to viral rebound and perhaps a predictive value can be derived from this outcome. Some scientists are working to identify surrogate markers that could predict viral rebound, although not everyone agree about the necessity (and the ethics) of such studies (personal communication). Furthermore, in some cases, treatment interruptions may carry fewer risks than the actual interventions under investigation (clinician-researcher, #207), so the entire risk profile of a study should be taken into account. All in all, treatment interruptions remain “the best outcome measure that we have and we need to deploy [them] very thoughtfully and carefully” (clinician-researcher, #206).

#### **Motivations for Treatment Interruptions**

We asked key informants about possible motivations for treatment interruptions. Some of the responses mirrored the motivations for joining HIV cure studies in general – such as helping find a cure, the desire for forward scientific movement and financial incentives – while others were unique to treatment interruptions, including past experiences with the same. One of the patient-participants interviewed explained that he went off treatment because it was part of the stem cell transplant protocol (patient-participant #112). He would not have been able to participate had he refused to be off treatment since it was the only way to test whether the intervention worked. In his case, there was a desire to comply with the study requirements and to help scientists prove the premise on which the protocol was predicated. Most motivators around treatment interruptions centered on helping find a cure or derive evidence. Some of the patient-participants said that they



were very healthy and virally suppressed, and thus would be good candidates for treatment interruption studies that could help advance science (more willing patient-participants, #101). Treatment interruption “would be just like any other risk in the study” (policy-maker, #301). Furthermore, two patient-participants interviewed had prior experience with treatment interruptions. Due to the fact that they maintained stable CD4+ counts off treatment (more willing patient-participant, #105) and became rapidly undetectable after resuming treatment (more willing patient-participant, #109), they would not be afraid to go off treatment again.

Furthermore, the three groups of key informants wanted definite forward scientific movement resulting from treatment interruption protocols, so that the risks could be justified vis-à-vis the incremental scientific knowledge gained. The scientific and social value ethics criterion was clearly reflected in these narratives. A clinician-researcher expressed that, if we are mandating treatment interruption, “we need to make sure that we are going to learn something” (clinician-researcher, #204). A policy-maker said that treatment interruptions may become more attractive when there are major breakthroughs in science, such as a proof-of-concepts established in animal models (policy-maker, #306). As the potential for direct clinical benefits increases, so does the appeal for treatment interruptions (policy-maker, #306). Timothy Brown, in his personal account [52], recognized that having interrupted treatment is what helped demonstrate the scientific breakthrough of his cure: “I stopped taking my HIV medication on the day of the transplant. (This is important because a continuation of antiretroviral therapy would have meant that no one would have known for a long time that I as cured of HIV.)” Finally, another motivator for stopping HIV treatment are the financial incentives, (more willing patient-participants, #107, #109), similar to what we found under the general motivators for HIV cure research participation.

The topic of “drug holidays” as a motivating factor emerged in some of the interviews. For some patient-participants, being off treatment for a defined period of time may be attractive

because they experience “treatment fatigue” (policy-makers, #302, #303). A policy-making explained the phenomenon as follows:

*[Some] people have different reservations about taking drugs. For example, in the START trial, when they started enrolling, patients did not have trouble being randomized to delaying treatment. They found more people who wanted to delay treatment. My caution would be that we should not presume that not all patients are really excited about being on treatment all the time. Some people may be glad to be off the drug for some time (...) People have different attitudes.*

– Policy-Maker (#304)

This statement reveals that there may exist a phenotype of study participants for whom treatment interruptions are attractive or easier to tolerate. Perhaps these are the types of participants that should be approached for ART interruption studies. While treatment fatigue may be real, asking people to do something they would not normally do (e.g. coming off treatment) just to qualify for a study may be unethical, however. Similarly, scientists need to ensure that participants understand that the study is likely not going to cure them before they come off their antiretroviral medications. Treatment interruptions must be done with caution, and while there are participants who may be better suited for these types of protocols, treatment interruptions are clearly not for everyone.

### **Concerns around Treatment Interruptions**

Below, we compiled the main **concerns** around treatment interruptions expressed by the three groups of key informants. We used a summary table because we felt that it more clearly encapsulated the compendium of concerns uncovered as part of the study. From a study implementation standpoint, this may provide a checklist for clinical investigators to use during protocol design and/or the informed consent to ensure that all possible concerns are addressed with the different groups of stakeholders.

**Table 14. Concerns around Treatment Interruption**

<b>Concerns around Treatment Interruptions</b>
<b>From Patient-Participants:</b> <ul style="list-style-type: none"><li>• Study participants unknowingly going from being undetectable to being detectable (“ticking time bomb”) (more willing patient-participant, #102)</li><li>• Risk of developing resistance to ARVs (ATIs not recommended for patients on salvage therapy) (more willing patient-participant, #102)</li><li>• Increased risk of opportunistic infections (more willing patient-participant, #107)</li></ul>
<b>From Clinician-Researchers:</b> <ul style="list-style-type: none"><li>• It is possible to minimize the risks but not completely eliminate them. Virus can re-emerge from a single or multiple clones leading to increased viremia (clinician-researcher, #201)</li><li>• Need sensitive enough ways to measure recrudescence (clinician-researcher, #204)</li><li>• Need to concomitantly enhance the immune system in a durable manner (clinician-researcher, #204)</li><li>• Kinetics of rebound and or viremia are unknown (e.g. Mississippi child was asymptomatic during rebound) (clinician-researcher, #205)</li><li>• Additional risks for acutely infected participants (e.g. repopulation of the HIV reservoir, virus diversification, impairment of the HIV-specific immune response (personal communication)</li></ul>
<b>From Policy-Makers</b> <ul style="list-style-type: none"><li>• Older populations may be more concerned with interrupting drugs because they have fewer options available at this point (policy-maker, #311)</li><li>• Unsuspected drug resistance could spread, potentially causing public health disaster (policy-maker, #311)</li><li>• Cost to the community for late failure (parallel to PrEP in terms of monitoring) (personal communication)</li><li>• Spontaneous failures have a huge impact on when (and whether) interventions can become cost-effective (personal communication)</li></ul>
<b>Shared concerns:</b> <ul style="list-style-type: none"><li>• Risk of transmission to others during an unsuspected relapse of viremia (too heavy of a burden to be in an HIV cure study?)</li></ul>

### **Considerations for Treatment Interruptions**

Similarly, we used a table to summarize the various considerations for treatment interruptions that emerged as part of the key informant interviews. This table may provide a checklist to HIV cure research practitioners for possible ways to implement treatment interruptions in an ethical and effective manner to optimize their application.

**Table 15. Considerations for Implementation of Treatment Interruptions**

<b>Considerations for Implementation of Treatment Interruptions</b>
<b>From Patient-Participants:</b> <ul style="list-style-type: none"> <li>• Adequate support to study participants enrolled in treatment interruption protocols (less willing patient-participant, #110)</li> <li>• Is there a maximal amount when participants can be off treatment safely? (more willing patient-participant, #102)</li> </ul>
<b>From Clinician-Researchers:</b> <ul style="list-style-type: none"> <li>• Need to continue research to obtain sensitive measures of the HIV reservoir, including tissues (clinician-researchers, #203, #211)</li> <li>• Need criteria or matrix for when treatment interruptions may be indicated (e.g. vaccinations; early ART; if think cured someone) and when they are not (e.g. latency-reversing agents; TLR agonists) (clinician-researcher, #204)</li> <li>• Functional cure (e.g. ART-free clinical remission demonstrated by treatment interruption) is more likely than sterilizing cure; need to implement in the experimental (and potentially real-world) setting (clinician-researcher, #211)</li> <li>• Treatment interruptions are not indicated for infants as they face a prospect of lifelong ART and need all treatment options possible (clinician-researcher, #205)</li> <li>• When should treatment interruptions be the primary endpoint? (personal communication)</li> <li>• What is the actual endpoint – the time to viral rebound or the viral set point post-rebound? (personal communication)</li> <li>• Does monitoring antiretroviral pause actually increase risks? (personal communication)</li> <li>• Should control arms undergo treatment interruptions? (personal communication)</li> <li>• HIV reservoir reduction of 2 logs or less will not delay time to viral rebound by much; need at least 3 – 4 logs worth reduction for ~1 year ART-free remission (personal communication)</li> <li>• How to account for tremendous patient-to-patient variability and stochastic nature of viral rebound? (personal communication)</li> </ul>
<b>From Policy-Makers</b> <ul style="list-style-type: none"> <li>• Establish relationship between reservoir assays and time to viral rebound determinations (policy-maker, #309)</li> <li>• Which participants to enroll in treatment interruption studies <ul style="list-style-type: none"> <li>Appropriate CD4+ threshold prior to ATI</li> <li>Plan for ART restart for clinical issues, pre-determined CD4+ or HIV RNA thresholds</li> <li>Minimum duration of ART to test hypothesis</li> <li>Assure acceptable ART alternatives beyond current regimen in case of development of resistance</li> <li>Address issues related to variable half-life of components of ART regimen</li> <li>Counsel study participants on risk of HIV transmission during treatment interruptions</li> <li>Criteria to define therapeutic success after treatment interruptions? (personal communication)</li> </ul> </li> </ul>
<b>Shared Considerations:</b> <ul style="list-style-type: none"> <li>• Intensive and frequent monitoring (e.g. viral load, CD4+ count)</li> <li>• Need back-up regimen for study participants in case ART resistance develops</li> </ul>

- Provision and criteria for reinstituting antiretroviral treatment
  - Provision of information to study participants about potential risks (e.g. informed consent process)
- 

We assessed perceptions of treatment interruptions among our group of stakeholders. We highlighted the general attitudes, possible motivators, concerns and considerations around treatment interruptions. The latter two were provided in a tabular format (above) to facilitate the ethical and effective implementation of treatment interruptions as part of HIV cure studies that mandate them.

### **Factors Facilitating Recruitment in, Retention in and Implementation of HIV Cure Studies**

As HIV cure studies get scaled up in the United States and around the world, it is important to understand the factors that can facilitate recruitment of people living with HIV in these studies. The table below provides the compilation of recommendations to improve recruitment of study participants in HIV cure studies. We felt that this way of summarizing the information was most useful from a clinical study management and implementation standpoint. Checklists are known to enhance organization, motivation, productivity and delegation. The tabular format allows us to clearly and quickly see what needs to be done to facilitate recruitment and can in turn directly inform the plan for change.

**Table 16. Possible Recommendations to Facilitate Recruitment in HIV Cure Studies**

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**Possible Recommendations to Facilitate Recruitment in HIV Cure Studies**

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**Overcoming Logistical and Stigma Barriers:**

- ✓ Flexible study clinic hours
- ✓ Remove transportation and parking barriers
- ✓ Address stigma-related issues

**Inclusion/Exclusion Criteria and Study Design Issues:**

- ✓ Liberalize entry criteria whenever possible
- ✓ Minimize intensity of study visits whenever possible
- ✓ Ensure adequate sample size to test research question (especially for small pilot studies)

**Safety and Efficacy Issues:**

- ✓ Have adequate pre-clinical safety data or robust proof-of-concepts from animal models
- ✓ Clearly communicate potential risks to study participants (during informed consent process)
- ✓ Ensure adequate risk-benefit (or risk-knowledge) ratio
- ✓ Ensure that robust risk mitigation strategies are in place

**Screening and Recruitment Process:**

- ✓ Hire research screener dedicated to recruit study participants (link between clinical care and research efforts)
- ✓ Maintain regular communications with and build a referral process from the infectious disease doctors (frontier out in the community)
- ✓ Find people where they are (e.g. support groups)
- ✓ Maintain regular contacts and provide frequent updates about new studies even if candidates did not qualify for previous studies (e.g. emails)
- ✓ Build authentic relationships with potential study participants
- ✓ Build a recruitment 'apt' to match potential study participants with clinical researchers
- ✓ Maintain up-to-date and robust databases of potential study participants (e.g. registries of individuals who have HIV and cancer and need CCR5 transplants; registries of potential donors with  $\Delta 32/\Delta 32$  CCR5 mutations)

**Clinical Contact Factors:**

- ✓ Maintain trust between study participants and clinical researchers
- ✓ Have one-on-one conversations (personalized approach)
- ✓ Create a more level playing field between investigators and potential study participants

**Peer Recruitment, Community Outreach and Education:**

- ✓ Have previous study participants act as peer recruiters (e.g. story telling) – but exercise caution with issues of confidentiality when using peers
- ✓ Maintain “patient voice” in recruitment activities
- ✓ Implementation education activities to manage expectations without crushing hope
- ✓ Incorporate long-term research perspective into educational programs
- ✓ Involve primary care physicians in education activities around HIV cure research
- ✓ Utilize existing platforms where the HIV community is already engaging and raise awareness of HIV cure research in the (HIV) community
- ✓ Ask for regular feedback and do not be afraid to have a dialogue
- ✓ Employ social media wherever logical

**Post-Study Issues:**

- ✓ Provide assistance to pay for study-related complications (e.g. following treatment interruptions) if issues (e.g. resistance) come up (may require more expensive drugs)

**Special Recruitment Considerations for Women:**

- ✓ Take into consideration the fact that women are also care-givers; provide additional support if needed
- ✓ Proactively address issues related to reproductive health risks in HIV cure research
- ✓ Ensure that the HIV cure research equipment is compatible with women's anatomy (e.g. smaller veins and may be knocked out of studies due to newer models of leukapheresis machines)
- ✓ Make HIV cure studies (and meetings) relevant to women

**Special Recruitment Considerations for Minorities:**

- ✓ Make sure that "under-to-reach" populations do not become self-fulfilling prophecies
  - ✓ Do not make the diversity of study participants in HIV cure research an afterthought and learn lessons from HIV treatment trials
- 

Table 16 above summarizes the key recommendations received by the key informants to facilitate recruitment in HIV cure studies. We focused on practical aspects to facilitate the effective recruitment of study participants in HIV cure research. The action plan provided considerations to overcome logistical and stigma barriers to participation, study design issues, safety and efficacy aspects, screening and recruitment efforts, clinical contact factors and peer recruitment and community outreach components. We also provided special considerations for recruiting women and minorities. This list may be expanded or modified by practitioners as different elements are found to be relevant to recruitment of study participants in HIV cure-related studies. Similarly, as more study participants get enrolled into studies, we need to understand the factors that can facilitate retention of study participants. Below, we provide a summary of recommendations from key informants on this topic. Table 17 provides a clear checklist of what can be done to facilitate retention of study participants in HIV cure clinical studies. Most of the considerations relate to clinical contact and safety factors.

**Table 17. Possible Recommendations to Facilitate Retention in HIV Cure Studies**

<b>Possible Recommendations to Facilitate Retention<sup>17</sup> in HIV Cure Studies</b>
<b>Clinical Contact Factors:</b> <ul style="list-style-type: none"> <li>✓ Explain importance of adhering to the study protocol and explain at the outset what will be involved in terms of time and effort</li> <li>✓ Treat study participants with respect (including respecting their time and schedule)</li> <li>✓ Show gratitude</li> <li>✓ Be kind (basic kindness); good bedside manners</li> <li>✓ Treat study participants like normal people</li> <li>✓ Continued communication (e.g. safety labs; progress to date)</li> <li>✓ Ensure an open, collegial atmosphere (study participants as partners and collaborators in research)</li> <li>✓ Maintain regular contacts with study participants (e.g. phone calls, text messages) (should be IRB-approved); obtain information technology support</li> <li>✓ Listen to the study participants</li> <li>✓ Validate study participants' experience and make them feel valued and appreciated for what they are doing</li> <li>✓ Care about study participants' needs (e.g. mental health, health insurance, housing)</li> </ul>
<b>Safety Considerations:</b> <ul style="list-style-type: none"> <li>✓ Explain the importance of long-term follow-up (e.g. treatment interruptions; monitoring of carcinogenicity, mutagenicity, teratogenicity)</li> <li>✓ Ensure that the proper follow-up registries are in place and adhered to (e.g. cancer registries, etc.)<sup>18</sup></li> </ul>
<b>Design Issues and Study Procedures:</b> <ul style="list-style-type: none"> <li>✓ Only perform study procedures when they are absolutely needed</li> <li>✓ Cut down the number of study visits that are not critical</li> <li>✓ Avoid very painful or uncomfortable conditions</li> <li>✓ Ensure fair, adequate IRB-approved compensation for study visits (without being coercive)</li> </ul>
<b>Overcoming Logistical and Stigma Barriers:</b> <ul style="list-style-type: none"> <li>✓ Flexible study clinic hours</li> <li>✓ Remove transportation and parking barriers</li> <li>✓ Sufficient advance notices of days and times of study visits</li> <li>✓ Address stigma-related issues</li> <li>✓ Understand the reasons why study participants are dropping out</li> <li>✓ Provide ongoing support whenever necessary and facilitate study visits</li> <li>✓ Consider having a mobile van to go see study participants for lighter study visits</li> </ul>

<sup>17</sup> Retention was found to be “not applicable” for some of the HIV cure research modalities that are irreversible, such as gene therapy/stem cell transplant. Once a study participant commits, they are in all the way and this becomes a one-way decision (clinician-researcher, #208). For other studies where salvage therapy is needed, losing people to follow-up may not be an option.

<sup>18</sup> Study participants who take part in a latency-reversing agent study must be registered in a cancer database.



Table 17 above provides a succinct checklist of possible factors that may facilitate retention of study participants in HIV cure studies. Most of the issues identified related to clinical contact factors or safety issues. As there is no magic bullet, implementers of HIV cure research need to remain vigilant as to the factors that ensure adequate follow-up of participants and statistical study power, despite small numbers. Further, one of the aims of the study was to derive factors that could facilitate effective implementation of HIV cure studies. Table 18 summarizes the key recommendations from stakeholders on factors that would help execute such studies. The checklist is not exhaustive and can be augmented or amended as necessary by HIV cure research implementers.

**Table 18. Recommendations to Help Execute HIV Cure Studies Effectively**

<b>Recommendations to Help Execute HIV Cure Studies Effectively</b>
<p>Trial Design Issues (Early Phase Development HIV Cure Studies):</p> <ul style="list-style-type: none"> <li>✓ Consider toxicity profile in study drug(s) selection</li> <li>✓ Conservative enrollment criteria and stopping rules for safety-related issues (e.g. participants, cohorts and overall study)</li> <li>✓ Informed consent (IC) process that fully addresses potential risks and conveys no expectation of individual benefits and time-intensity of studies <ul style="list-style-type: none"> <li>Consider using assessment of understanding as component of IC process</li> </ul> </li> <li>✓ Start with small number of subjects</li> <li>✓ Stagger enrollment into two or more cohorts with progression (including dose escalation) based on acceptable safety from earlier (sentinel) cohorts</li> <li>✓ Use lowest dose and duration necessary</li> <li>✓ Provide any safety-exposure data available to support dose selection</li> <li>✓ Consider drug interaction related to antiretroviral treatment</li> <li>✓ Provide adequate scientific justification (e.g. supportive data from animal studies or justification of why animal studies are not feasible or supportive)</li> <li>✓ Support for selection of assays that will be used</li> <li>✓ If possible, incorporate of a control group to aid interpretability of the data generated</li> <li>✓ Proper selection of the study population <ul style="list-style-type: none"> <li>Allow scientific hypotheses of interest to be tested while maintaining acceptable safety balance</li> <li>Enroll participants on stable ART with higher CD4+ counts and undetectable HIV RNA (e.g. participants best able to tolerate study treatments and treatment interruptions)</li> <li>Overlapping populations of interest (e.g. stem cell transplantation (SCT) in participant for whom SCT is already indicated for cancer treatment)</li> <li>All studies: mechanism for long-term follow-up of participants administered</li> </ul> </li> </ul>

- 
- products with potential long-term risks (including products known to be genotoxic, mutagenic and/or carcinogenic)
  - ✓ Clear rationale for conducting the study (e.g. avoid redundancies) – regimen, dose, duration and study population
  - ✓ Ensure clarity of study procedures (e.g. avoid vague language subjective to different interpretations)
  - ✓ Ensure clearly defined and appropriate study endpoints and well-characterized assays for assessing endpoints
  - ✓ Plan for rationally designed combinations
  - ✓ Work closely with FDA during the pre-IND stage
  - ✓ Scientific success (e.g. answering research question and advancing scientific knowledge) does not equate with having a ‘curative’ intervention – criteria for success will not be ‘curative’
  - Systems make the maximum benefits of people’s participation
  - Learn from ‘failures’

**Study Conduct:**

- ✓ Promote good recruitment and retention practices (see above)
- ✓ Prioritize planning and organization
- ✓ Be willing to be flexible
- ✓ Conduct dry runs of study visits
- ✓ Implement one-time leukapheresis protocol before asking study participants to commit to long-term follow-up
- ✓ Provide fair compensation for study visits
- ✓ Ensure the processing of specimens does not break down

**Safety Issues:**

- ✓ Implement robust risk mitigation strategies
  - Stopping rules for treatment arms that fail to show an effect or associated with development of serious adverse events (SAEs)
- ✓ Enroll study participants who have an alternative ART regimen in case their current ART regimen gets compromised

**Efficacy Issues:**

- ✓ Ensure good baseline (and follow-up) data for all the samples

**Interpersonal, Communication and Management Issues:**

- ✓ Ensure good communication between investigational team, clinical staff and study participants
- ✓ Communicate honestly
- ✓ Ensure emergency contacts outside of regular office hours
- ✓ Ensure investigators have enough time to supervise study operations
- ✓ Build very strong and highly trained clinical study teams (including study coordinator)
- ✓ Have adequate time for face-to-face interactions between principal investigators or nurse and study participants
- ✓ Diverse clinical research study workforce
- ✓ Place study participants first (e.g. respect for persons)
- ✓ View study participants as holistic individuals
- ✓ Ensure study participants are comfortable during study visits
- ✓ Provide adequate support to study participants, including mental support and social services if needed
- ✓ Insure health insurance status of study participants does not get affected as a result of study participation
- ✓ Build long-term partnerships and trust with health care providers (and their patients)

– even if they do not qualify for studies)

**Community and Education Issues:**

- ✓ Forethought around community engagement
- ✓ Ensure positive collaboration with the community from beginning to end
  - Ensure patient group provides feedback on protocol
  - Make patients feel a part of the research process (true partnerships)
- ✓ Share study outcomes (aggregate findings) to study participants and community in lay terms (results dissemination)
- ✓ Include education component as part of study implementation and community engagement
- ✓ Educate from a place of compassion

**Boarder Considerations for the Field:**

- ✓ Set realistic expectations for the study with clinical study team and study participants
- ✓ Incrementalism and planning for the long-term are key; let science drive the next sets of experiments
- ✓ Be careful about how result findings are reported in press releases and the media
- ✓ Consider standardizing endpoints between studies to derive more power from small numbers (e.g. requires agreement)
- ✓ Conduct clinical studies as part of well-established networks with well-resourced and deep infrastructure in place (e.g. ACTG)
- ✓ Build strong research collaborations
- ✓ Bring scalability of HIV cure approaches to the forefront of study design
- ✓ Ensure that the health care system would be able to provide the level of monitoring needed for ART-free remission cases (becomes an implementation question)

**Developing Country Considerations:**

- ✓ Identify which HIV cure research strategies are best suited for the developing world (e.g. early ART, pediatric HIV cure studies)
- ✓ Invest in capacity building, technology transfers and research partnerships
- ✓ Informed consent issues (lower literacy levels combined with difficult scientific concepts)
- ✓ Ensure access to treatment (and prevention-of-mother-to-child transmission interventions) to those who need them; invest in health-systems strengthening
- ✓ Continue HIV prevention and HIV treatment research (and implementation science) even as try to find a cure for HIV
- ✓ Understand that there can be different co-morbidities that could affect safety and efficacy
- ✓ Appreciate the different set of implementation and ethical considerations (e.g. ethics of incentives)
- ✓ Appreciate cultural and socio-economic differences

**Funding Issues and Policy Issues:**

- ✓ No HIV cure research without funding; long horizon requires funding and investment
  - ✓ Revise HIV criminalization laws and lobby U.S. Congress to update Ryan White Care Act to remove criminalization provisions in the law
-

Table 18 above consolidated the main considerations to help facilitate the implementation of HIV cure studies. Recommendations were compiled into the following categories: study design issues, study conduct, safety and efficacy issues, interpersonal, community and management factors, community and education, broad considerations for the field and developing country considerations, and funding and policy issues.

### Expectations and Hopes in HIV Cure Research

We asked potential study participants to describe their expectations from the HIV cure study experience as well as their hopes related to HIV cure research. Table 19 below summarizes the main expectations of people living with HIV while participating in HIV cure research. The most common expectations related to study conduct such as adequate support, clinical contact factors and scientific progress or forward movement as a result of HIV cure study participation.

**Table 19. Main Expectations from the Study Participation Experience**

Main Expectations from the Study Participation Experience
<b>Study Conduct:</b> <ul style="list-style-type: none"> <li>✓ "I would expect <b>constant follow-up</b> and <b>support</b>. (...) Also, the researchers should <b>communicate</b> with our current HIV providers, for sure." (Patient-Participant, #110)</li> <li>✓ "I would expect <b>quality</b> of the study" (Patient-Participant, #101)</li> </ul>
<b>Clinical Contact Factors:</b> <ul style="list-style-type: none"> <li>✓ "I would expect to <b>be treated like a normal person</b>, not like someone with HIV" (Patient-Participant #108)</li> <li>✓ "I would expect people to <b>care about my well-being</b>" (Patient-Participant, #110)</li> <li>✓ "I would expect to <b>know what's going on</b>. I would need to know why people are taking my blood." (Patient-Participant, #108)</li> </ul>
<b>Scientific Progress:</b> <ul style="list-style-type: none"> <li>✓ "If I were to be accepted to participate, I would expect <b>forward movement</b>. Like I would expect some kind of outcome that would be beneficial to the world. Even if it is not the outcome that I am after. Trial and error is definitely part of the study. But if I participate in the research and I am not cured and there were all these risks and I end up getting a different genotype and drop below 200 T cells and my viral load runs up to like a million. That's what I would expect. <b>Forward movement</b>. Whether I were cured or not. Knowing that <b>forward movement</b> happened is what would make it all worth it." (Patient-Participant, #103)</li> </ul>

We also asked study participants and clinician-researchers about “curative” expectations. As early HIV cure research will not be curative, it is important to better understand how “hopes to be cured” factor into decisions to participate in research in order to avoid therapeutic misconception. There was a broad range of responses from study participants. Some of study participants had no expectation of being cured from HIV cure-related research, while others expected to be cured. Among the study participants who had no expectations of being cured, they realized that a cure for HIV is a long-term endeavor that may not materialize for another 20 years. They understood the incremental nature of the science and that HIV cure studies are scientific experiments that meant to be iterative. One study participant mentioned that she would still practice safe sexual practices regardless of whether she was found cured or not (patient-participant, #108). Another study participant alluded to the fact that there is a belief that pharmaceutical companies are hiding the cure (patient-participant, #102). There has also been much abuse in the past related to “miracle HIV cures” – in the United States and abroad, mostly Africa. Other people believe that HIV is a conspiracy created by the government and it is difficult to combat these misperceptions in the community.

In contrast, one patient-participant reported that he would expect to be cured from HIV cure studies. His expectation for a cure was very high and he thought that the science had evolved to be close to finding a cure for HIV infection. This example points to the possible existence of curative misconception among potential volunteers and would need to be investigated further. Expectations to be cured from HIV cure research should be distinguished from hopes of finding a cure – one day. Some of the study participants thought a cure for HIV would be possible in the future. This was an important motivator to participation in HIV cure research, but these individuals did not necessary think that they would be cured right away or as a result of research participation.

Clinician-researchers mentioned emphasizing to study participants that HIV cure research will not be curative. They recognized the double-edged sword of using the expression “HIV cure research” – while HIV cure-related research will not cure them, study participants need to understand that a cure is a goal that scientists are working towards. One clinician-researcher referred to the fact that participation in HIV cure research is part of a therapeutic journey for study participants, who have gone through a transformative diagnosis and can find meaning in HIV cure research participation (clinician-researcher, #206). Study participants also recognize what HIV research can provide over time given the discovery of potent antiretroviral treatment and a cure for HIV would be the next logical scientific step. One clinician-researcher emphasized the importance of letting study participants know what they are not cured in order to avoid unwanted public health consequences resulting from patients stopping their medications, thinking they have been cured (clinician-researcher, #210). Further, clinician-researchers emphasized that the informed consent process is an important step to explain to study participants that they will not be cured. It is also imperative to understand the reasons behind study participation. One clinician-researcher said that he asks volunteers to repeat back what they understand the possible outcomes of HIV cure research participation to be (clinician-researcher, #207). While the *hope* to be cured is prevalent, it does not necessarily mean that study participants think they will be cured right away. It is important to listen to the language used by study participants to understand the hopes and meanings that motivate them and whether these are irrational or not. Participants who are very sophisticated and well-informed may still have hopes to find a cure or to be cured, and bring these hopes with them in the study interactions. While there should be a conservation assumption that everyone participating in HIV cure research can believe in the possibility of a cure for HIV one day, what is more dangerous are the cognitive dissonance or the unrealistic or irrational hope or optimism that may prevail, as explained by a policy maker/bioethicist:

*It is like cognitive dissonance – they understand that there is no risk/benefit to them, no magic bullet but they keep at the back of their mind that something really cool might happen. There are people who are genuinely motivated because they want to help science and the field (...) But some people have denial or dissonance that they may get something out of it (...) The few reasons that would make me pause would be the unrealistic optimism [and] the source of unrealistic optimism is human nature. I did not want to use the term therapeutic misconception because it is too strong of a phrase. It was brilliantly coined originally; a brilliant thought; oftentimes true, but it implies that one fully believes something will happen. What I am talking about is not that someone fully believes that they will get cured. This is early phase research and there is no direct benefit. People do not think they will get cured. They know that there is no direct benefit but people still hope for something great to happen anyway.*  
– Policy-Maker (#304)

In sum, there was a broad range of opinions expressed with regards to expectations from HIV cure research participation and hopes to be cured. Clinical research implementers should safeguard against unrealistic or irrational hopes and more subtle cognitive dissonance that study participants will derive direct clinical benefits. They should also try to better understand the motivations behind study participation and whether they are rational or not. Study participants should not enroll in study because of the hype or the perception of direct clinical benefits in terms of HIV control.

### **Factors Facilitating Ethical Implementation of HIV Cure Research**

One of the study aims was to derive factors that could facilitate the ethical implementation of HIV cure studies. Below, we summarized the main recommendations from stakeholders on the factors that could help promote the ethical conduct of HIV cure research. The checklist represents a cross-section of the responses given. It is by no mean exhaustive and can be augmented or amended as necessary by bioethicists and implementers of HIV cure research.

**Table 20. Recommendations to Facilitate Ethical Implementation of HIV Cure Studies**

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**Recommendations to Facilitate Ethical Implementation of HIV Cure Studies**

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**Design Issues and Requirements of Research Ethics:**

- ✓ Research should meet all the requirements of research ethics (per regulations)
  - Ensure safety of study participants is paramount while minimizing risks
  - Adequate risk-benefit ratio (balance between benefit to society and risks to individuals)
  - Thoughtful review by proper regulatory bodies (e.g. FDA, IRBs, Recombinant DNA Advisory Committee (RAC)); Data Safety Monitoring Board (DSMB)
- ✓ Proper study design with strong scientific underpinning
  - Ensure that the bar is held high when it comes to study designs
  - Ensure people can call on improper study designs
- ✓ Study conducted with the highest ethical standards possible
- ✓ Strong foundation in the possibility that something definite will be learned from the research
- ✓ Get as much scientific information as possible from HIV cure experiments and honor people's participation so that we have learned as much as possible
- ✓ Sample size ethics
  - Reduce duplication of similar studies (to put the fewest number of participants at risk)
- ✓ Clear futility criteria
- ✓ Need for long-term follow-up of study participants, especially during treatment interruptions
- ✓ Fairly compensate study participants

**Safety Considerations:**

- ✓ Clear safety endpoints monitored frequently
- ✓ Minimizing harm as a result of research participation; not subjecting study participants to unnecessary risks

**Informed Consent Considerations:**

- ✓ Risk undertaken is understood by study participants and is appropriate compared to potential benefits that can be gained
- ✓ Ensure "true" informed consent – participants should be well-informed of risks and should not expect direct benefits in most cases
- ✓ Observe balance between explaining what the risks are in terms that are easy to understand, but still accurate
- ✓ Separate optional informed consent for ancillary procedures (e.g. sigmoidoscopy, etc.)
- ✓ Informed consent should be a continuous process throughout the study

**Treatment of Study Participants and Clinical Contact Factors**

- ✓ Strong confidentiality
- ✓ Basic respect and consideration
- ✓ Study participants treated like people and not like a disease
- ✓ Honest communication with participants during study
- ✓ "Mental health analysis" of study participants to ensure that they are in the right mindset and resilient enough prior to joining studies

**Fair Representation of Study Participants**

- ✓ Study participants should be representatives of those living with HIV (justice)

**Collaboration and Partnerships:**

- ✓ Need a true partnership between the researchers and the study participants



- ✓ Investigators, IRBs, FDA and patient advocates need to work together as much as possible
- ✓ Need for more collaboration between scientists and standardized endpoints
- ✓ Collaboration with social scientists through study implementation

**Community Input and Education:**

- ✓ Community members should review study protocols
- ✓ Plan for long-term community engagement
- ✓ Education at every levels – community members, individuals interacting with the study participants and IRB representatives

**General Considerations:**

- ✓ Constantly asking what makes HIV cure research ethical and never letting go of the question
  - ✓ Be cautious about any claims for a cure unless there has been  $\geq 5$  years of follow-up
  - ✓ Make sense of the data that we have or from large studies (such as the START trial result) and what they mean for HIV treatment and cure research; focus on treatment adherence
- 

Table 20 above consolidates the main considerations received from key informants to facilitate the ethical implementation of HIV cure studies. Recommendations were compiled into the following categories: design issues and requirements of research ethics, safety considerations, informed consent, treatment and representation of study participants, collaboration and partnerships, community input and education and general considerations.

**General Considerations in HIV Cure Research**

The final qualitative results section summarizes general considerations for HIV cure research that emerged during the key informant interviews. These factors did not belong to a specific question or category but were still felt relevant to the effective and ethical implementation of HIV cure research. Most of the reflections pertained to the rationale for HIV cure research, the meanings of HIV cure and the language/terminology around HIV cure research.

**Justification for HIV Cure Research**

Some of the key informants alluded to the fact that scientists need to continually be able to justify the need for HIV cure-related research – ethically, scientifically, and logistically (clinician-researcher, #209). The field needs to be able to defend why money is going towards HIV cure research when tremendous gaps exist in HIV prevention and HIV treatment. It was felt that scientists

need to come up with a consistent rationale for why a cure for HIV infection is required by the scientific community. There further needs to be more granularity as to what an actual HIV cure would look like and how HIV cure would be defined (clinician-researcher, #204). Knowing why the pursuit of an HIV cure is important – including the challenges around HIV treatment adherence, negotiation of the HIV ‘care continuum’, HIV drug resistance and cumulative toxicities over time, and the fact that HIV treatment may not be economically and logistically feasible for the 35 million+ people infected with HIV around the world– are some of the facts that are needed to help the community understand why HIV cure scientists are searching for the holy grail.

### **Meanings of HIV Cure**

Key informants – particularly patient-participants – felt that it was necessary to pay attention to the different meanings of HIV cure. A cure for HIV may have different meanings for different groups of stakeholders – including, but not limited to: not transmitting HIV to others, not having to take HIV medication, testing negative on the HIV antibody test or no longer harboring replication-competent HIV virus. Key informants wanted a better understanding of what HIV cure meant in different contexts (policy-maker, #310). There can be discrepant notions of cures and meanings of cure between study participants, scientists and policy-makers/regulators. It was felt that these needed to be reconciled and better understood.

The meaning of HIV cure research was highlighted by one of the two Boston patients interviewed as part of this study when he explained his transition from “feeling cured” after receiving a bone marrow transplant to “no longer being cured” following his viral rebound:

*Although the study failed and mine is an emotionally monumental failure. I am very biased here. There was a period for few months where I felt like I was HIV-negative because of the study... (...) Even if the study itself was a failure at that time, in that it did not find a cure at that moment, it still moved the field forward. The personal side is so touching.*  
– More Willing Patient-Participant (#112)

For a moment, the Boston patient thought he was actually cured of HIV and that he was HIV-negative. He “felt” cured even though he was not cured. Despite the viral rebound, he still considered the study a success because it answered an important scientific question. It took several months for the virus to become undetectable and for him to be virally suppressed again. The study participant had to cope with the reality of being “HIV-positive” and “detectable” again after thinking he was cured. The emotional toll of “feeling cured” and then “not being cured” should be taken into considerations when designing studies. The different meanings of HIV cure should also be examined further. Despite that study participants may “feel” cured, they may not be cured in reality and this may have implications for HIV cure research implementation.

Interestingly, one study participant felt that getting HIV is what cured him:

*I have to be honest with you. Having HIV is part of what cured me. Like, there is a moment that I was told that I was positive. I stopped being the person I was and started to be the person I wanted to be. As far as healing, I would be worried that curing someone would take that away. You know... like perhaps counseling would be an important point of that. (...) There are people who have been living with it since 1983. Almost 30 years of this one lifetime and getting used to something. There will need to be re-adjustment and counseling. Maybe not everyone of them. But a psychological evaluation at the beginning would probably be a smart start. And support. They would also need to go back to the clinic to monitor their viral load to make sure that they are still cured. And having the support of the other participants would be really important. They need to share their stories in order to adjust and grow. This is part of their story and their therapeutic journey.*

– More Willing Patient-Participant (#103)

This quote reveals the need to better understand meanings around HIV cure and identities surrounding HIV-positive diagnoses. Cure is also closely intertwined with discourse around healing and therapeutic trajectories. Meanings around HIV cure should be further explored via formative research. A case in point could be the disconnect between scientists who target functional cures and study participants who wish for a sterilizing cure.

### Language of HIV Cure Research

Beyond the meaning of HIV cure research, narratives focused on the language used to describe HIV cure. Several respondents felt that it was like learning a new language with its own set of rules. The use of language is particularly important when interacting with the community. Even the vocabulary used in scientific manuscript changes rapidly. Key informants felt that it was important to define what was meant up front and to be cognizant of the perspectives of community members, otherwise communication can rapidly break down (clinician-researcher, #205). The term HIV cure research was thought to be a misnomer because the term is divorced from its existence : “Oh, we don’t really think we are going to cure you but the title is HIV cure whatsoever” (policy-maker, #311). The “kick and kill” approach was also misleading, since scientists are simply trying to poke latently infected cells and clear out latent virus (policy-maker, #311). The “kick and kill” approach was described as a “cure study that won’t cure them with an anti-cancer drug” (clinician-researcher, #202). The term functional “cure” was problematic and incongruous, because of the word “cure” is used to describe someone still living with HIV (patient-participant, #103; policy-maker, #311). The term remission was more clearly understood, in that it implies that the virus can come back (more willing patient-participant, #103).

Key informants felt that the word cure had tremendous powerful appeal but can be misleading. Cure is different than treatment research, and one should distinguish between cure as an “intervention” and a “state of being.” One key informant felt that the word “cure” was more problematic with respect to study participants themselves, as there was a tendency to sometimes only hear the word cure and get excited about what the science can deliver. The cure terminology should not be used as a form of false advertising, and more nuanced terms, such as “viral reservoir research,” should be used instead (clinician-researcher, #207). Key informant also pointed out that there were inconsistent interpretations between cure, eradication, post-treatment control,

sterilizing versus functional cure and virological suppression off treatment (VSOT) (and its various permutations). These various appellations of HIV cure research were found to be unwieldy for the development and regulatory processes because they failed to define clear endpoint criteria and did not offer a framework for standardized measurement of an HIV cure. Overall, there was a general consensus that more precise language and nomenclature was needed to advance HIV cure drug development and the regulatory aspects associated with HIV cure research. Other examples were provided of problematic terminology in HIV cure research (not reported here).

Overall, we need to bridge the divide between scientists and community and better understand how study participants understand HIV cure research terminology. Further, key informants felt that the debate and nuances should also be accomplished in the press as much as possible. Community advocates have a role to play in policing the language. There should be an ongoing dialogue around the terminology used to describe HIV cure concepts as the field evolves. After all, “it’s not all about the lab science. It’s about the context as well” (clinician-researcher, #211).

In summary, key qualitative study results were as follows:

- ⇒ Factors affecting decision making are multi-faceted. Key motivators to HIV cure-related research participation related to tangible motivators as well as the desire to contribute to HIV cure science and give back. Altruism was also a significant motivator to participation. Important deterrents to HIV cure research participation related to the modality under investigation, the early phase of experimentation, practical and logistical deterrents, study visit procedures, side effects and potential risks, and negative clinical contact factors, among others.
- ⇒ Perceived risks of HIV cure-related research participation included clinical or medical risks, opportunity risks, social risks, financial risks and other perceived risks. The perceived riskiest

- HIV cure-related research strategies were stem cell transplant/gene therapy, latency-reversing agents and combinatorial approaches. “Too much” or unacceptable risks were also assessed.
- ⇒ Main concerns around HIV cure-related research encompassed unforeseen or unintended consequences, impacts on health and circumstances after study participation or post-cure discovery. There were perceived burdens of HIV cure-research participation, including, but not limited to side effects, time commitments, intensity of study visits and travel-related constraints. Perceived barriers to HIV cure research participation included general barriers (such as geographical availability), logistical aspects, finding study participants, stigma and other miscellaneous barriers.
  - ⇒ The perceived safest HIV cure-related research strategies were early ART, monoclonal antibodies and reservoir assessments.
  - ⇒ Perceived benefits of HIV cure research participation included none, societal benefits such as advancing scientific knowledge, personal benefits (such as psychological, emotional and mental benefits), clinical benefits (for some), and the acquisition of information around HIV cure research.
  - ⇒ Interpretations of “risk-benefit ratios” were discussed among the variety of key informants, and the balance tilted towards greater risks in HIV cure studies. It was difficult to derive an objective measure for risk-benefit assessments. We discussed equipoise with clinician-researchers and policy-makers. A range of opinions was expressed and proved to be a meaningful engagement with research ethics concepts.
  - ⇒ We inquired about perceptions of treatment interruptions, and summarized general attitudes around treatment interruptions, possible motivators as well as concerns and considerations to ensure the effective and ethical implementation of these interventions.

- ⇒ We prepared a checklist of factors facilitating recruitment and retention in HIV cure-related studies. We also summarized factors facilitating the effective implementation of HIV cure-related studies.
- ⇒ We conveyed general expectations from the HIV cure research experience as well as hopes related to HIV cure research. Besides the topic of therapeutic or curative misconception, we learned about the risk of cognitive dissonance and unrealistic or irrational hope and optimism.
- ⇒ We compiled a checklist of factors facilitating the ethical implementation of HIV cure studies, according to key informants.
- ⇒ We highlighted general key considerations for the field of HIV cure research, such as the need to constantly justify HIV cure research, assess the meanings of HIV cure and cautiously use HIV cure-related terminology.

## CHAPTER 6 | DISCUSSION OF STUDY RESULTS

This dissertation section reviews the implications of the main quantitative and qualitative study results as well as significance for the effective and ethical implementation of HIV cure studies. Overall, there was a convergence and complementarity between the quantitative and qualitative datasets, despite slight contradictions noted. The mixed methods approach added tremendous richness to the inquiry. In fact, the use of a mixed methods approach was critical to better understand factors that can facilitate participation of people living with HIV in cure research in the United States. We showed that mixed methods deepened our understanding of meanings that were not captured in the quantitative data analysis. In turn, issues were identified in the qualitative data that were not captured quantitatively *a priori*, and this limited our ability to identify more convergent issues. For examples, perceptions around risks and benefits were only limited to the categories provided by the survey, but qualitative interviews delved deeper into perceptions and nuances of unacceptable risks. Formative inquiry can help uncover the rich context that surround decision-making in HIV cure clinical studies. Much more research will be needed to understand the key elements of motivation related to actual decision making processes in early HIV cure research, including participants' reasons for participation (or refusal) and their experiences related to participation.

After discussing study results, we engage with principles of ethics and implementation science to inform the conduct of HIV cure studies. While the results section was biased towards descriptive ethics, we explore some normative ethical aspects in the discussion [53]. We complete the chapter by examining the strengths and limitations of the research.



## Discussion of Quantitative Findings

Survey respondents indicated whether they would be willing to participate in 14 different types of HIV cure-related studies. It remains unclear if survey respondents fully understood the risks and benefits of HIV cure-related research participation. The result that >50% of people would be willing to join all 14 types of HIV cure-related studies was surprising, as we would have expected a greater skewness towards risk aversion. The high apparent willingness to participate in HIV cure research underscores the need to better educate study candidates about the potential risks of different types of studies, since the desire to participate does not necessarily mean *informed* participation. There may be individuals who rationally want to participate in studies who perhaps should not participate, as highlighted in the key informant interviews. Nevertheless, the seemingly riskiest modalities appeared to have been the least popular altogether, as expected. This finding was in agreement with the published literature that if more risks are expected in clinical studies, volunteers are more likely to decline participation [54][50].

Although HIV cure studies conferred little to no benefit, it is possible that study participants *still* perceived the likelihood of benefits when deciding to join studies. Data showed the importance of not under-estimating the contribution of emotional and mental benefits in HIV cure research participation. Participation in HIV cure research may truly change the meaning of one's HIV diagnosis from a traumatic to a meaningful, empowering experience. Our finding that social and personal benefits were most often psychological in nature was consistent with similar studies from the HIV prevention and treatment literature [55] and with the *Voice of the Patient* report prepared by the FDA's patient-focused drug development on HIV cure [43]. Furthermore, the finding that most common perceived benefits of participation are emotional and psychological suggests that HIV cure scientists should strongly appeal to the scientific altruism of study participants when conducting recruitment efforts.

In terms of the perceived risks likely to discourage HIV cure research participation, personal clinical risks were more likely to demotivate participation than personal risks, burdens or potential social risks in the descriptive analysis. Survey respondents viewed long-term risks as more worrisome than short-term risks. In contrast, when looking at the bivariate and multivariate results, short-term and immediate risks had stronger correlation with deterrence to participate in terms of magnitude than some of the longer-term risks, such as the potential for enabling cancer or developing viral rebounds over time in the bivariate analyses. This finding is more consistent with what transpired in FDA's *Voice of the Patient* report [43], where study participants reported making decisions to participate based on short-term impacts as opposed to long-term risks, although this report relied on anecdotal evidence.

The need for intense time commitments for study visits did not appear to be strong demotivators of participation in the survey. This finding was inconsistent with key informant interview narratives. Clearly, the degree of burdens and efforts imposed on study participants (such as site visits and study procedures) place a strain on a person's willingness to participate. The risk of transmitting HIV to others (in the case of an unsuspected viral rebound) was a real possible demotivator (28% very likely to discourage) and may speak to the study volunteers's desire to "do no harm" when participating in research. This result was reminiscent of a similar prior survey conducted among >450 people living with HIV in the Netherlands, which suggested that no longer being able to transmit HIV to sexual partners was a more desirable outcome of HIV cure than stopping HIV treatment [41]. Similarly, in the McMahon *et al.* survey, conducted among 20 participants who completed a Vorinostat study in Australia, the greatest possible benefit to an HIV cure was placed on stopping HIV transmission (47% of respondents) [56]. There is also a parallel to be drawn between the desire to no longer be infectious in HIV cure research with the HIV vaccine and prevention literature. In a study on willingness to participate in HIV vaccine trials, protection

against HIV from vaccines was associated with a high (75%) willingness to enroll in studies [57].

From a trial implementation and ethical standpoint, we should emphasize to study participants that HIV risk reduction practices should not be relaxed during study participation –in both prevention or cure-related research [57].

Like previous surveys on willingness to participate in HIV cure research [49][58], we asked about willingness to interrupt treatment as part of HIV cure research. We found that 68% of potential HIV cure research participants were very willing or somewhat willing to stop treatment as part of HIV cure research. These numbers were slightly higher than those obtained in Arnold *et al.* survey [49], whereas one third (34%) of the 2,262 respondents stated that they would be very willing or willing to participate in a study that involved treatment interruption, compared to 34% who said that they would be somewhat willing and 32% said that they would not be at all willing. Our data are more aligned with a more recent (2014) survey conducted in the United Kingdom with 982 people living with HIV, where treatment interruption was found acceptable for 62% of study respondents [58]. The results that we obtained on the treatment interruption variable may reflect the different study samples used or the need to better educate potential study participants about the possible risks of treatment interruption. It is clear that health risks such as those related to treatment interruptions create barriers to study enrollment and may increase the difficulty of implementing HIV cure-related studies ethically. More formative research is needed to explore the influence of altruism in willingness to undergo risks such as treatment interruptions.

It was surprising that 8% of participants thought a cure for HIV infection was presently in existence. This finding was incompatible with the fact that our convenience sample had regular access to HIV-related information about treatment or cure. It may have been indicative of the inflated HIV cure news that people hear in the media. Furthermore, the awareness of Timothy Brown's cure likely must have skewed the results as to whether people thought a cure for HIV was

presently available, although his cure remains a unique case report. The finding underscores the need to better support educational programs around HIV cure-related research, especially as the HIV cure science gets scaled up and more complex in the United States and around the world. We need to encourage HIV cure scientists and universities to report on the incremental nature of HIV cure science development in a responsible way, in press releases or other media. We also need to do a much better job at being consistent with portraying a realistic picture of the science without generating false hopes. Expectations around what HIV cure science can deliver should be managed, without unduly crushing the hope. We also need to find a balance between engaging communities now versus getting ready for the long journey ahead and not burning out people living with HIV and community advocates.

### **Discussion of Bivariate Study Results**

The bivariate study results revealed that nine potential benefits were “very important” motivators to participation in HIV cure-related studies as they significantly correlated with willingness to participate. The potential benefits that were positively correlated with willingness came from all three categories of benefits: personal benefits, personal clinical benefits and social benefits. Those with the strongest positive associations were altruistic and emotional in nature, thus underscoring again the need to appeal to study participant’s altruistic motives when conducting recruitment efforts.

There were 18 potential risks that were “very likely to discourage” study participation in HIV cure research, and all were statistically significantly correlated with unwillingness to participate. The potential risks that were negatively correlated with willingness were personal clinical risks, symptoms and side effects, invasive study procedures and transportation logistics, and these results were consistent with those from the qualitative analysis. None of the potential risks and burdens

such as time commitment levels, non-transportation logistics, non-invasive study procedures and potential social risks were statistically significantly associated with unwillingness to participate.

Interestingly, general interest in HIV cure research was perfectly and positively associated with willingness to participate. Thus, more HIV cure-related research recruitment efforts should focus on the individuals and communities who are actively engaged in HIV treatment and cure studies, such as those who are obtaining information about HIV cure research (e.g. such as the CUREiculum) or those who have already volunteered but are not currently enrolled in other HIV treatment or cure studies at present. These individuals may also be able to recruit peers in studies, although there are confidentiality issues to be aware of.

### **Discussion of Multivariate Study Results**

Multivariate analyses showed that, after controlling for socio-demographic characteristics, perceptions of 5 (out of 21) of the potential benefits were “very important” motivators to participation in HIV cure studies. Three potential benefits with the strongest positive associations were altruistic and emotional benefits and two were personal benefits related to increasing the respondent’s knowledge of their own HIV infection. HIV cure researchers should focus on these benefits when recruiting for higher-risk studies in order to improve enrollment and enhance participants’ satisfaction in joining studies.

After controlling for socio-demographic characteristics, 19 (out of 35) of the potential risks were “very likely” to discourage participation in HIV cure-related studies. All of these risks involved symptoms and side effects. Further, nearly all of the invasive study procedures, such as biopsies and spinal taps, and transportation risks were negatively correlated with willingness to participate, confirming the bivariate analysis results. Fear of discrimination and risk of transmitting HIV to sexual partners were associated with deterrence to participate. HIV cure scientists should address the risk

of discrimination and properly counsel study participants about sexual transmission risks of HIV as part of research design.

Interestingly, willingness to participate was not statistically corrected with six socio-demographic variables: gender, ethnicity, income, region, having control over own health care, and having even volunteered for an HIV cure study. This is interesting given that women and non-whites have traditionally been under-represented in HIV cure studies[30][29]. It may be that despite their willingness to participate, women and non-whites have to overcome other barriers to participation. Despite the lack of statistical significance, HIV cure scientists should still exert special efforts to recruit these groups in HIV cure-related research since the willingness is there. This is also where we need to exercise caution with interpretation of the data.

People who were recently infected with the virus were more eager and more willing to volunteer for HIV cure-related studies. Younger individuals were also, on average, more willing to participate in studies than older people living with HIV. These results were surprising, given that older individuals have done everything to stay alive and well up to this point. Given that the population of people living with HIV is aging in the United States, HIV cure scientists should exert special efforts to recruit younger and newly infected individuals as these individuals will be the primary targets of HIV cure research initiatives in the future. Further, people who believed that their health status was relatively poor were 3.6 – 4.5 times more willing to participate in HIV cure-related studies, on average and *ceteris paribus*. The finding may indicate that people who are sicker are more willing to help advance the science or try whatever it takes to eradicate the virus, either for themselves or for society, when faced with greater health obstacles. This is paradoxical given that HIV cure studies focused on the “healthier subjects” who have the least to gain (and the more to lose) from HIV cure research participation.

## **Discussion of Qualitative Findings**

The study employed a semi-structured survey (with people living with HIV) and key informant interviews (with people living with HIV, clinician-researchers and policy-makers) to elicit a range of opinions around factors that influence participation in HIV cure research. We were able to explore these factors in greater depth along with the implications for the effective and ethical implementation of HIV cure research. We used a non-probabilistic purposive recruiting strategy for the qualitative interviews. Implementation issues and implications raised were best explored via rich dialogue. In our systematic qualitative analysis (above), we used quotations as the primary form of evidence to support our interpretation of the raw data [44].

Our exploration of the perspectives of key informants uncovered that participation in HIV cure research is a complex multi-dimensional experience. The qualitative analysis revealed that it was difficult to adhere to the strict dichotomy of risks/deterrents versus benefits/motivators to participation. Several themes were revealed as part of the inquiry that stretched beyond risks and benefits as factors influencing decisions to participate in HIV cure studies. It is thus important to appreciate the entire clinical study experience and overall quality of life of people living with HIV when designing and implementing HIV cure research. Furthermore, study participants, clinician-researchers and policy-makers/regulators ascribed meanings to HIV cure research. Undoubtedly, formative research to assess those understandings may provide an empirical foundation to facilitate recruitment and retention of people living with HIV in studies and community engagement efforts that support long-term HIV cure clinical developments.

Among the key findings from the qualitative data, we found that motivators to HIV cure-related research participation were both tangible and intangible in nature, with psychological, emotional and mental benefits playing a significant role. This finding was consistent with what has been found in the early-phase cancer literature [59] and with our quantitative data. Deterrents to

HIV cure-related research participation were manifold but centered on perceived risks, negative clinical contact factors and practical and logistical obstacles to participation. Concerns, barriers and burdens of HIV cure research participation were revealed. We found that the risk-benefit ratio was biased towards risks and that study participants should not expect any direct clinical benefits from study participation. We gathered perceptions around analytical treatment interruptions that complemented the quantitative survey data.

On a more practical level, we derived lists of factors facilitating the recruitment, retention and effective implementation of HIV cure studies. The qualitative research also described factors facilitating the *ethical* implementation of HIV cure research, and these will be further explored later in this chapter. We learned about the perceived roles of study participants, clinician-researchers and policy-makers, along with general expectations around and hopes related to the HIV cure research experience. We also obtained general key considerations for the field of HIV cure research, such as the need to manage expectations and to use language thoughtfully.

All-inclusively, qualitative data showed that decisions to enter HIV cure studies were “often relational, dynamic, iterative, provisional and/or conditional” [60]. In that regard, HIV cure research is not different than other types of medical research where complex decisions must be taken in the face of scientific uncertainty [60] [59]. While we attempted to understand willingness to participate in HIV cure research on a community or societal level, it is clear that decisions to participate are deeply individual and personal. Key informant interviews with study participants showed that there are both extremely willing and extremely unwilling individuals and that willingness to participate falls on a spectrum. Despite the tremendous altruism shown, there is clearly a phenotype of people living HIV for whom participation in HIV cure research is absolutely out of the question – either due to risk aversion, lack of interest, concomitant medical conditions or other reasons. There is another



phenotype of people living with HIV who do not place any upper limits on acceptable risks and would do anything to help move the field forward.

Furthermore, decisions to participate in studies are not divorced from the impact of HIV on the daily life of study participants or their views on currently available therapeutic options [43]. A case in point was that one of the most feared risks of participation in HIV cure research, as revealed during the qualitative interviews, was that HIV could rebound and become unmanageable. People living with HIV appreciate the potency and ease of using currently available HIV drugs. Furthermore, it is important to interpret the study results in view of the fact that intentions around HIV cure research participation may never be truly absolute and once-and-for-all. Even Timothy Brown, in his personal account of how he became the Berlin Patient, reported being unenthusiastic about whether to participate in research because he did not want to become a guinea pig:

*I said “No” to the transplant thinking that it would not be necessary were the leukemia to remain in remission because I could continue to take my antiretroviral medication indefinitely. I did not need to be a guinea pig and risk my life receiving a transplant that might kill me. The survival rate for stem cell transplant is not great; normally it is about 50/50.(...) This is important because a continuation of antiretroviral therapy would have meant that no one would have known for a long time that I was cured of HIV (...) The recovery from that [second transplant] did not go well. I became delirious, nearly went blind, and was almost paralyzed. [52]*

As illustrated by this quote, willingness and intentions to participate in research must be interpreted carefully, because even the most willing study participants may have reservations about participation. In turn, decliners may have openness towards participation. Key informant interviews further emphasized the critical importance of clinical contact factors in decisions to participate. As with the cancer field, developing positive, meaningful researcher – participant interactions may be important to facilitate recruitment in research, as opposed to wide marketing of HIV cure studies. Furthermore, from a clinical and public health perspective, much of the U.S. population of people living with HIV is aging. There is a greater need to better understand how the challenges of treating

other chronic conditions – such as diabetes, cancer, cardiovascular events – impact decisions, eligibility or risks to participate in HIV cure studies [43].

One aspect of the qualitative research that was most intriguing was discovering perceptions of risks (and benefits) in HIV cure studies. The inquiry richly complemented the survey results. It was surprising to find that latency-reversing agents were considered to be amongst the riskiest HIV cure strategies in both the survey and the key informant interviews, as I had previously reported that “This method may represent the safest, most scalable, and accessible strategy to eradicating HIV-1 in the longer-term” [11] based on previous work with the Collaboratory of AIDS Researchers for Eradication (CARE). Narratives around perceived risks and benefits of HIV cure modalities revealed possible disagreements between clinician-researchers and the perceptions of study participants added a degree of complexity to the inquiry. The fact that potential study participants weighed perceived social benefits with clinical risks was in alignment with Verheggen’s “personal balance account” assessment underlying decisions to participate in clinical studies [54][50], although the calculus may not be systematic. Unquestionably, perceptions of what represent “too much” or unacceptable risks should be taken into account when designing studies as they influence the ethical development and implementation of research.

One topic that received more attention was that of (social) altruism, an important motivator to HIV cure research participation. This is consistent with connected bodies of literature, including HIV prevention research [61]. Altruism is defined as “individual[s] weighing potential social benefits for research participation over and above any personal risks associated with trial participation” [61]. In social altruism, study participants feel that the social benefits of study participation outweigh potential personal, health, clinical or social risks [61]. There is a positive relationship between altruism and quality of life in the HIV prevention field, as research participation adds purpose and meaning to someone’s life [61]. It was found that nurturing a sense of altruism among study

participant could increase recruitment in trials, and altruism is very important in clinical studies that involve greater personal risks [61]. Nevertheless, in our key informant interviews, wishes to contribute to scientific knowledge around HIV cure were often mixed with desires for personal benefits. The topic of mixed altruism (or personal, self-altruism) has been under-explored in research around decision-making toward HIV cure clinical studies. While study participants may be motivated to join studies for perceived personal benefits, they can still understand that the overall intent of the endeavor is to gather generalizable scientific knowledge [37].

Stigma was another important topic discussed during the key informant interviews. It was no surprise that stigma deterred participation in HIV cure research, as it also discourages access to HIV testing, uptake of HIV care and initiation and compliance to HIV treatment [62]. In our study, stigma and discrimination were both a social risk and a major barrier to HIV cure research participation. Key informant described their close and personal encounters with HIV-related stigma in daily life. More work should be done to understand and reduce stigma as part of ethical HIV cure research design and implementation.

The next portion of the discussion reflects on the implications of our findings as they relate to key concepts in research ethics. The inquiry contributes to the aim of understanding factors facilitating the ethical implementation of HIV cure studies. Subsequently, we consider the effective implementation of HIV cure studies.

### **Reflections on the Ethical Implementation of HIV Cure Studies**

In their *Principles of Biomedical Ethics* [63], Beauchamp and Childress describe that “ethics is a generic term for several ways of examining the moral life (page 9).” Biomedical ethics involves collecting information, assessing its reliability, identifying moral dilemmas and mapping out solutions to the ethical challenges that have been identified [63]. Unquestionably, HIV cure studies are cutting-edge and they are challenging, not just from a scientific standpoint, but also ethically.

They involve long-standing questions in bioethics such as the protection of research participants, minimization of risks or harms and distribution of burdens and benefits [64]. Yet, no absolutes exist for the ideas of right and wrong at any given time. Ethics and moral behaviors must engage with the situations and they are a function of time and space [65]. They may create obligations where the law remains silent [63].

Bioethics involve hierarchical levels such as ethical theories (integrated bodies of principles that govern choices – such as utilitarianism or deontological theories), principles (general concepts that serve to justify rules – such as respect for persons), rules (specific to context) and judgments and actions (expressed in decisions, verdicts or conclusions) [63]. In our inquiry of factors that facilitate participation of people living with HIV in cure research, we focus on discussing ethical principles as they have the most direct application. The Belmont Report summarizes ethical principles and guidelines for research involving human participants into three core principles: respects for persons, beneficence and justice [34]. The Belmont Report provides a useful framework to organize our inquiry around the ethical implementation of HIV cure research, although it may not encompass of all possible requirements for ethical research [27].<sup>19</sup>

### **Principle of Respect for Persons**

According to the Belmont report, we show respect for persons by honoring their right to make informed and voluntary choices [64]. The principle of respect for persons is embodied in the informed consent (or informed refusal) to participate in research [63]. There are issues of autonomous decision-making in research, however, that extend beyond the step of informed consent. Beauchamp and Childress argued that there is a distinction between autonomous agents

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<sup>19</sup>Emanuel and colleagues highlighted 7 requirements for ethical research: 1) value, 2) scientific validity, 3) fair selection of subjects, 4) favorable risk-benefit ratio, 5) independent review, 6) informed consent and 7) respect for enrolled subjects. We explore some these requirements using the overarching organization of the Belmont Report.

and autonomous choices: “Being autonomous and choosing autonomously are not the same as being respected as an autonomous agent. To respect an autonomous agent is, first, to recognize that person’s capacities and perspectives, including his or her right to hold views, to make choices, and to take actions based on personal values and beliefs.” [63] In medical research, respecting a participant as an autonomous agent requires an obligation to disclose information, to ensure understanding and voluntariness, and to foster autonomous decision-making [63]. Nevertheless, there exist “paradoxes of autonomy” in scientific research given the unequal distribution of research knowledge or the frequently shared nature of decision-making [63].

No other topic has received as much attention in the ethical implementation of research as informed consent. Informed consent is a fundamental component of all important documents dealing with research ethics, including The Nuremberg Code, the Declaration of Helsinki, The Belmont Report and ICH GCP E6. Informed consent has two main components: an informational element and a decisional element. The informational component includes the adequate disclosure of information and comprehension by the study participant. The decisional element refers to the voluntary decision as to whether to participate. As expected, informed consent was one of the most frequent answers to the key informant interview question of “What facilitates the ethical implementation of HIV cure studies?” While necessary for ethical clinician research, authors have argued that informed consent is by no means sufficient. [27] The signature on an informed consent form does not provide any guarantee of a participant’s comprehension of what s/he has signed [50]. Therefore, clinician-researchers must make conscious efforts to communicate clear information to the study participants and answer their questions prior to making a decision to participate. The informed consent form must also state the alternatives to study participation. Furthermore, it is well accepted that informed consent should be an ongoing process and not a one-time event before screening can begin [28][66]. New knowledge may be acquired during the course of a study that

modify risks and benefits and influence a participant's willingness to be retained. While a lot has been written on informed consent, the literature on informed refusal remains relatively silent.

In her essay on "How do Patients Know," Rebecca Kukla argued that the epistemic component of a participant's autonomy is a necessary condition for autonomy [19]. More importantly, participants exercise their autonomy through the act of making a decision *once* they are well-informed. Kukla contends that the participants' practices of collecting information may play a more integral role in autonomy and informed consent. While the bioethics literature has focused on the obligations of researchers to inform the participants, there has been little consideration for the fact that participants often enter the clinical study visits as "active inquirers" who have already been exposed to information, and this information requires "active negotiation, not just passive reception" [19]. HIV cure research implementers should thus not view candidates as mere passive recipients of cure information. In fact, some participants have reported "shopping" for studies as their bodies is what they have to offer and they try to obtain the best deal. HIV cure research participation may even become an enterprise for the more astute and professional research participants who act like empowered consumers of research and also expect a return on investment. The skills and strategies exercised by potential volunteers to access, assess and balance information is important in the act of decision-making: "we cannot "measure" the autonomy of this choice without attending to whether it resulted from a competent, responsible process of inquiry – that is, whether the patient manifested autonomy not only during the moment of choice itself, but also in the epistemological process that led up to that moment" [19]. The act of informed consent goes beyond the exact moment when a study participant signed an informed consent form. S/he has acquired information organically and must negotiate a decision-making pathway. Kukla insisted that competent inquiry requires basic health literacy skills because one cannot understand medical or scientific information unless s/he can access it, and whether the information is understood depends

on how it is presented [19]. What this essay teaches us for the implementation of HIV cure research is that scientists should respect and recognize their participant's capacity for autonomous inquiry. This changes the meaning of patient autonomy and informed consent. Study participants are not mere recipients of information but active inquirer of scientific knowledge.

A related literature has focused on “gist knowledge” – defined as “qualitative, more general cognitive representation of understanding” [67]. This literature focuses on the role of heuristics – or cognitive shortcuts – in medical decision making, suggesting that trade-offs are negotiated by study participants to reduce the cognitive burden of decision-making, even at the risk of reducing decisional accuracy [67]. Gist knowledge is found to have a strong influence in decisions to participate in research, often above verbatim knowledge found in informed consent forms. Furthermore, for good or for bad, study participants may form opinions about HIV cure strategies via other settings, such as the popular media, study recruitment materials or advocacy pieces that contribute to shaping public perceptions around the research [64]. This underscores the need to provide adequate information about HIV science in all platforms.

Similarly, research has found that prospective study participants may have already made a decision as to whether to participate in a clinical study before they come in the door or receive an informed consent form [66]. This shows that the process of informed consent may actually begin before the potential risks, benefits and objectives of a study are explained to a study candidate. HIV cure research implementers should therefore pay attention to the process of recruitment, provided that candidates may have already made a decision to participate before they are consented [66]. Needless to say, the language used in the informed consent form is paramount and there should be conscientious efforts to streamline and increase the readability of informed consent forms.

Additional informed consent considerations related to HIV cure research relate to the fact that some kinds of consent are non-retractable. For example, with gene therapy research, the decision to go into a stem cell transplant is a one-way track decision. Other types of HIV cure research strategies may make informed consent more difficult, such as with pediatric HIV cure research, where a mother would need to provide assent for her child's research participation during labor, although women routinely give or withhold consent for epidurals, C-sections, forceps and oxytocin during labor [32]. The issue of informed consent also becomes complicated for donations that are not tied to a specific study – such as leukaphereses or cell or sample donations that are meant to conduct experiments now or in the future (e.g. for reservoir assessments, effects of latency-reversing agents or other broad purposes), since study participants may not know exactly what they are consenting to.

It is important to explore the topic of shared or joint decision-making in HIV cure research. Oftentimes, a study participant's decision to participate in studies cannot be viewed as a discrete, isolated event, but rather be understood as a set of interactions with the research or medical establishment. The shared decision making literature received extensive attention in the cancer field [60][67][68][69] but less so in the HIV cure research field. Clinician-researchers help study candidates understand that a decision should be made, describe risks, benefits, uncertainties and possible options and work together to make a decision [68]. Shared decision making helps promote (earned) trust between the clinician-researchers and the patient-participants and helps manage uncertainty [67]. As explained by Epstein and colleagues:

*Engaging patients in constructing preferences in the face of complexity, inadequate evidence, and irreducible uncertainty involves more than provision of information and an invitation to choice. It also involves dialogue about the communication process itself; that is, what patients want to know, what information is relevant, how patients prefer to be informed, patient's roles in decision making, and who else (if anyone) should be present. Seen in this way, constructing preferences (...) involves building relationships, providing information, and exploring preferences, which then strengthen relationships, understanding, and involvement in decisions. [60]*



The topic of shared decision making adds a new inflexion to the need for autonomy. In such highly innovative HIV cure research, investigators should try to interact with study participants as study partners and collaborators. Clinician-researchers should not under-estimate the interpersonal dynamics of the informed consent process and the importance of the researcher – participant relationships. This theme clearly emerged in the key informant interviews. Establishing a climate that makes it easier for study participants to ask questions may be more important than having the study candidates understand very fine detail of the disclosed information [63]. Study participants must still be free to make a decision and be free of coercion, manipulation or undue persuasion [63] and they should feel like they can ask questions about their study participation at any time.

#### **Therapeutic Misconception or Fallacy**

Therapeutic misconception or fallacy has received attention in the HIV cure research literature given that most studies are in the early stages of experimentation. Therapeutic misconception refers to the overestimation of clinical benefits resulting from clinical research or an underestimation of the possible risks of harm [37][70]. With therapeutic misconception, there is unrealistic or unreasonable optimism that one can benefit from the research intervention and the experimental research is confused with clinical care[38]. Therapeutic misconception is different than therapeutic misestimation in that study participants overestimate benefits and underestimates the risks [71]. In therapeutic optimism, participants hope for the best possible personal outcome [72]. Most of the research on therapeutic misconception, misestimation and optimism is derived from the cancer field, but also applies to HIV cure research. It is apparently a well-established fact that when an outcome has a low probability, but a very high value, study participants may be inclined to place disproportionate weight on the small odds in decision-making [59]. Not helping the field of HIV cure research is the powerful word “cure.” Cure-associated terminology can lead to false hopes and incorrectly bias risk-benefit assessments. It is difficult for HIV cure scientists to balance the

aspirational language with the reality of first-in-human clinical studies with a low likelihood of individual medical benefit. Some scholars have debated whether to use the word “cure” at all [73]. While the “cure research” language is important to explain the long-term goal and potential future value of the research, not to mention the benefit to society, expressions such as “HIV reservoir research”, “long-term ART-free remission” or “HIV remission research” may be less prone to inducing therapeutic misconception.

The term curative misconception has been distinguished from therapeutic misconception, which is the false belief in the possibility of being cured from an HIV cure research strategy or experiment [73]. Curative misconception could disproportionately influence willingness of people living with HIV to participate in studies, distort perceptions of risks and uncertainties associated with the research interventions [73]. In her analysis of HIV cure-related informed consent forms, Gail Henderson found that long-term aims associated with HIV cure-related research are often presented in overly optimistic terms such as “to achieve HIV remission,” “to eradicate hidden virus... unmask or flush out the latent HIV in your cells,” “to improve the body’s ability to fight infection” and “to remain healthy” [74]. These research objectives are obviously misleading, because HIV cure research experiments will not lead to eradication of latently infected cells at this juncture. HIV cure scientists should replace language in the informed consent forms with more precise and realistic goals, such as “to see if it would be possible to perturb the HIV reservoir.” In order for HIV cure studies to be implemented ethically, it is important for scientists to remain honest because unrealistic expectations can prove harmful and contribute to disappointing and embittering study volunteers when the benefits they hope for fail to materialize. Furthermore, HIV cure clinical studies – such as gene “therapy” or “therapeutic” vaccinations – are not truly therapeutic and we should find better alternatives to name this falsely therapeutic research.

Moreover, with the growing literature on HIV cure research, some accounts are blatantly misinformed and may contribute to creating the perception that a cure is close to being materialized. When peer-reviewed journal articles state that HIV cure can be functional or sterilizing, it implies that scientists already know what a cure for HIV looks like or that a cure is already in existence. For example, the following was recently published by Buell *et al.*:

*HIV cure can be functional, a state whereby HIV positive patients have clinically undetectable viral loads in the absence of therapy, or sterilizing, whereby all traces of the virus, including the reservoir of latently infected CD4+ cells, are permanently removed (...)* Numerous studies have found that HDACis such as Vorinostat, Panobinostat, and Romidepsin are potent inducers of viral transcription from the latent HIV reservoir [62].

In this account, it would have been preferable to use the conditional tense to denote hypotheticals around HIV cure. Furthermore, HDACis – including Vorinostat, Panobinostat, and Romidepsin – have failed to substantially reduce the size of the replication-competent HIV reservoirs, and therefore are not potent inducers of viral transcriptions *in vivo*. Latency-reversing agents very much remain at the proof-of-concept stage and absolutely no claim toward efficacy should be made. These types of statements contribute to inflating hopes and may cause more harm than good. They violate the ethical norms of veracity and non-maleficence [73] and may fuel the belief that a cure for HIV is in existence, as shown in the survey.

Research has shown that therapeutic misconception may be a phenomenon that is difficult to eradicate in early phase experimentation [75]. Oftentimes, study participants may register perceived benefits of study participation, not so much to communicate understanding about actual benefits, but to register optimism about the study, especially when asked to express something positive about study [76]. Nevertheless, perceived benefits of early phase research should be discussed in a nuanced way, especially when they are likely to be limited. There needs to be a balance between getting study participants motivated to participate without overselling the research. There are inherent methodological challenges to assessing therapeutic misconception in

HIV cure clinical studies, and it remains unknown whether specific types of HIV cure modalities are more prone to therapeutic misconception – such as pediatric HIV cure research (e.g. given the near missed cure of the Mississippi child) or stem cell transplant/gene therapy research (given the sterilizing cure of Timothy Brown).

In order to avoid therapeutic misconception, there are specific dimensions that must be understood by study participants, including the scientific purpose of research, study procedures, uncertainty, adherence to the research protocol and the medical staff being researchers [37]. Nancy King and colleagues also provided a helpful checklist of recommendations for informed consent forms using examples from gene therapy research. These are worth revisiting in the context of early HIV cure experiments:

**Table 21. Recommendations for Informed Consent Forms in Early Phase Clinical Studies**

<b>Recommendations for Informed Consent Forms in Early Phase Clinical Studies[77]</b>
<b>Avoid Inconsistent and Confusing Terminology</b> <ul style="list-style-type: none"> <li>✓ Keep terms clear and simple; define them succinctly when necessary</li> <li>✓ Describe potential direct benefits consistently throughout the consent forms, or limit their description to one consent form section only</li> <li>✓ Limit variation in use of terms referring to experimental interventions</li> </ul>
<b>Avoid Misleading “Treatment” Implications</b> <ul style="list-style-type: none"> <li>✓ Present benefit to society as the role of primary goal of the research</li> <li>✓ When direct clinical benefit is not possible or unlikely, say so</li> <li>✓ Describe surrogate endpoints as measurement goals only</li> <li>✓ Consistently use “research” terminology to refer to investigators, study participants and experimental interventions</li> </ul>
<b>Avoid Vagueness about Potential Benefits</b> <ul style="list-style-type: none"> <li>✓ Discuss each type of benefit (societal, direct and inclusion) separately and distinctly</li> <li>✓ When direct benefits are reasonably possible, describe them precisely, including their nature, magnitude, duration, likelihood and limits</li> </ul>

It may also be worth exploring the topic of curative hope, as there is a fine balance between fostering realistic hope and creating unrealistic expectations around the science. As borrowed from the cancer literature, hope is a broad concept that can have different meanings for each person [78]. Hopes can be defined as the feeling that something good will happen. More empirical work and ethical analysis are needed to be able to analyze hopes as they related to reasonable versus

unreasonable expectations in early HIV cure research. Surely, “hopes to be cured” should not be part of decision-making or the referral process in these early-phase HIV cure clinical experiments [11]. Related to hopes, HIV cure scientists must avoid deceiving study participants [27]; however, research has found that study participants can also commit deception while participating in research by failing to disclose important or accurate information to scientists. [79]. Self-reported endpoint data are known to be spurious.

### **Revisiting the Principle of Respect for Persons**

We explored the principle respect for persons in terms of ensuring true informed consent and avoiding therapeutic misconception. Respect for autonomy means more than just having study participants make decisions, but also respecting their capacity to learn and evaluate values, meanings and context. In a sense, it may be time to adopt a broader and more fluid definition of respect for persons that extend beyond mere autonomy. Respect for participants mean respecting them at all stages of recruitment – including before, during and after study participation [27]. This wider participant-centered focus may be currently missing from the HIV cure research enterprise. Research projects must respect people living with HIV whether or not they enroll in studies. The need for respect must also be reconciled against the fact that experimental interventions are designed to produce generalizable scientific knowledge, and not meant to address participants’ individual health needs. Further, the roles of researchers versus caregiver must constantly be balanced, and deciding upon which one to use at any given time may represent an ever-present ethical dilemma for HIV cure research implementers[80].

Study participants should feel appropriately valued in research beyond the health assessments that they routinely get during study visits. They should feel valued as human beings. One key informant commented that although she was oftentimes called a “valuable biological specimen” – something that could have been completely dehumanizing – however, the way it was

done by the study nurse was with the upmost respect and therefore she felt the opposite of being objectified and dehumanized. She explained that the approach and interaction with the study nurse matter a lot. The respect for persons cannot be achieved solely by relying on procedural safeguards, such as informed consent. There are more subtle issues related to the recruitment, retention and treatment of study participants that stem from interactions with the research staff. HIV cure research implementers must appreciate the entire personal experience and the therapeutic journey of study participants. Some authors have even advocated that study participants should have their own stopping rules for research participation, particularly in the psychosocial dimension [53].

Undoubtedly, HIV cure research participants have undergone a life-altering event and the HIV-positive diagnosis can be troubling. Some participants may be relatively healthy, others not. Some are long-term survivors, while others were newly diagnosed or even acutely infected. It is important to treat the study participants as holistic individuals. In their account on the ethics of talking about HIV cure, Rennie and colleagues remind, invoking Van Eys [81], that there are actually three components of a cure: biological, psychological and social. To truly cure a person requires that all three dimensions are covered. Similarly, borrowed from Chinese medical tradition, Qiao argued that a cure for HIV would not only require the science of eradicating pathogens, but also the art of restoring harmony between mind and body. Healing becomes interpersonal and social, in addition to biological, and involves both HIV participants and their entire social environment (Qiao, Foundation Brocher workshop, May 2014).

Furthermore, as shown in the key informant interviews, we need to be cautious about how study participants are described. People enrolling in early HIV cure research experiments should not bear the degrading label “subject;” instead, they are “participants” or “volunteers” who are actively contributing to the research endeavor. The literature on clinical research participation has also called for more humane and compassionate language in order to minimize the distance between

researchers and participants and to signal “ethical protection” and “trust-based obligations” as opposed to “exploitation” [82]. Research participants can wear multiple hats and serve multiple functions – such as community advisory board members, patient advocates, co-investigators, and volunteers, and these roles may change over time [82]. It is important to embrace these new research relationships at all stages. These may make the upholding of ethical obligations more complex, however, and inflect the very meaning of respect. In short, respect for persons in clinical research is much more than the general requirements of autonomy and informed consent.

### **Principles of Nonmaleficence and Beneficence**

Next, we review the principles of nonmaleficence and beneficence. Nonmaleficence is the concept of not inflicting harm and can be associated with the maxim *Primum non nocere* (“Above all [or first], do not harm”) [63]. It encompasses the moral requirement of protecting the well-being of study participants, providing basic standards of care and ensuring risk-benefit assessments [27][63]. In turn, the principle of beneficence, contained in the Belmont Report [34], refers to the moral obligation of acting for the benefit of study participants [27][63]. In a sense, the principle of beneficence requires positive steps to help others and may even suggest the provision of benefits and acts of kindness, mercy or charity [63]. In the case of HIV cure research, given the high standards of care and tremendous safety of HIV antiretroviral treatment, it becomes difficult to justify the need for low benefit and high risk. HIV research has evolved to attempting to find treatment for very sick individuals, to now searching for a cure for relatively healthy participants. The burden of safety is very high and scientists need robust safety and efficacy data before exposing study participants to risks.

### **Risks in HIV Cure Research**

It is worth exploring the concept of “risks” and “benefits” in the context of HIV cure research. According to Beauchamp and Childress, risks can be both a descriptive and an evaluative concept [63]. Risk analysis is different than risk assessment: risk analysis serves to identify risks whereas risk assessment estimates the probability of a negative event occurring or may evaluate the acceptability or the significance of risks [63]. HIV cure research, in its current early phase, rests on the risk side of the benefit-risk continuum. Our study data revealed that the greater the risks, the more likely potential volunteers are deterred from participating in research. We also asked key informants about perceptions of risks related to various types of HIV cure studies as well as perceptions of “too much risks.” There was tremendous variability in the responses given. The literature has emphasized that potential volunteers’ perceptions of risks may sometimes differ from expert opinions[83]. Overall though, risk perceptions may play a tremendous role in deciding what interventions get moved forward. The more honest investigators are about potential risks and the lack of direct benefits, the more difficult recruiting study participants may become.

HIV cure investigators have an ethical duty to convey risks to potential study participants. According to the ethics literature, two criteria must be fulfilled in order for risks to be accepted. First, risks must be minimized. Second, they must be “reasonable in relation to the importance of the knowledge that may reasonably be expected to result (45 CFR 46.111.(a)(2)” [39]. Risks can result from study interventions but also study visit procedures, and the very monitoring can also add risks [84], together with the deviations from standards of care, as with treatment interruptions. Scholars have appreciated the stochastic nature of risks; for example, interventions that may work in >80% of study participants may also cause harm in <20% of participants [83]. As we increasingly start to embrace a public health and epidemiological approach to HIV cure research, it is important to account for individual variations in risks [83]. We need to minimize risks because unexpected



serious harms to study participants could trigger a crisis of confidence that could set the field back (as with gene therapy research in 1999). We also need to ensure that data points derived from HIV cure research participants, either on their own or in the aggregate, are as valid and informative as possible to move the field forward in order to justify the risks taken by study participants.

The Forum for Collaborative HIV Research, during its June 2014 meeting, provided a framework for how to portray potential risks of participation. Types of risks of HIV cure studies identified and ways to tackle those risks included:

**Table 22. Types of Risks in HIV Cure Research and Ways to Tackle**

<b>Types of Risks in HIV Cure Research and Ways to Tackle</b>	
<b>Types of Risks in HIV Cure Research</b>	
⇒	Risks of highly invasive procedures
⇒	Reproductive risks
⇒	Risks of analytical treatment interruptions (e.g. deviations from standards of care)
⇒	Risks of intensification of ARV treatment
⇒	Risks of antibody formation, viral drift, mutagenesis and blood cancer
⇒	Risks of being ineligible for future trials or treatments
⇒	Risk of loss of private or confidentiality of personal information
[Forum for Collaborative HIV Research, 2014]	
<b>Ways to Tackle Risks in HIV Cure Research</b>	
⇒	Proceed to human experimentation only after rigorous, non-human animal studies, laboratory tests and mathematical modeling
⇒	Develop rigorous criteria for discontinuation and restarting if needed
⇒	Recruit participants who need intervention anyhow (for co-morbidity)
⇒	Recruit participants with allegedly little to lose <sup>20</sup> because they have a terminal condition
⇒	Make sure that we have done as much as we could before interventions go into humans
⇒	Assume that there will be misadventures in some studies; prepare for that
⇒	Focus on known risks because unknown risks are unknown; but know that there are unknown risks
[Adapted from: Forum for Collaborative HIV Research, 2014]	

<sup>20</sup>However, relatively “healthy subjects” may be the ones who have more to lose from HIV cure research participation given their high CD4+ count and low viral load.

The literature has further discussed whether we need to place upper thresholds on risks that are acceptable. A case in point was an AIDS activist who, in 1995, underwent a bone marrow transplantation based on the hypothesis that a baboon's immune cells would resist HIV infection.<sup>21</sup> In our study, there were potential volunteers who did not place any upper limits on acceptable risks. Ethical guidelines are very clear that scientists have an obligation to protect study participants from unjustified or excessive risks [85]. The placement of limits on permissible risks is warranted by the need to protect the research enterprise and the study participants, sometimes from themselves [85]. Currently, IRBs provide the risk determination of risk permissibility, but assessments of risks can vary greatly as there is no objective yardstick with which to assess risks. Furthermore, maximum (or minimal) risks can be flexible concepts – they can be transient and dynamic with the evolving state of knowledge or science [39].

The extreme heterogeneity of clinical study designs and interventions and the great uncertainty of interventions make the reliability of risk-benefit judgements difficult, and call for prudence in exposing otherwise “healthy subjects” to substantial likelihood of serious risks [85]. Scholars have advocated for the standardization of language and methods used to communicate this uncertainty and has promoted participant-centeredness in representing risk uncertainty [86]. The literature is also rather silent, however, on interpreting and communicating risks to others – for example, as in the case of an HIV transmission during an unsuspected viral rebound in HIV cure research. Little has been written about how to evaluate future risks, such as the risk of developing future cancer, or about how the different types of risks, beyond clinical risk, affect overall well-being related to research participation, such as psychological risks, emotional risks, financial risks, identity risks, opportunity risks and social risks. Clinical study implementers are not always good at capturing social harm events either [87].

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<sup>21</sup>See: <http://www.nytimes.com/1995/12/15/us/man-gets-baboon-marrow-in-risky-aids-treatment.html?pagewanted=all>

### **Benefits in HIV Cure Research**

Benefits are oftentimes portrayed as referring to something positive that occurs during study participation [63]. At this time, clinical experiments in HIV cure research are proof-of-concept activities with no expectation of clinical benefit accruing from experimental interventions [11]. Furthermore, whether such experimental interventions, which are thought to be initial steps at attempting to purge persistent HIV infection, will lead to a reduction in the size of the latent reservoir and whether this partial reduction will lead to clinical benefits, remain highly unclear [88]. HIV cure studies are experiments that evaluate basic safety and whether interventions are capable of perturbing the latent HIV reservoir. They are not efficacy studies against disease. They are meant to generate knowledge to benefit future people living with HIV and thus study participation relies fundamentally on altruism [64]. Researchers have the responsibility to report the inherent lack of benefit in early HIV cure-related experiments.

But what constitute benefits, exactly? Would a (temporary) HIV remission even be considered a benefit? Our study showed that potential volunteers still expect tremendous psychological and mental benefits from study participation and that these should not be underestimated. According to the literature, it is important to distinguish between benefits to study participants (e.g. benefits of study participation) from benefits to society (producing scientific knowledge) [75]. Further, advances in science and knowledge may not all translate into actual health or clinical benefits [64]. There is also a distinction between benefits from the interventions, and inclusion benefits (or indirect, collateral benefits) [75]. Examinations, study interventions and laboratory tests should not be considered benefits [66], even these were found to be perceived benefits in our survey.

Interestingly, it is possible that clinical HIV cure studies may have positive clinical off-target effects. A case in point is the study by Tebas and colleagues who evaluated engineering cellular

resistance to HIV. This study observed that zinc-finger nucleases restored and sometimes doubled the study participants' CD4+ T cells [89]. Certainly, explaining possible benefits – or lack thereof – in HIV cure studies can be extremely complex. Besides personal benefits and altruistic societal benefits, there could also be benefits to future self – or delayed personal benefits – in case a cure for HIV could materialize. More empirical research is definitely needed on speculative benefits in HIV cure-related studies.

The Forum for Collaborative HIV Research, during its June 2014 meeting, provided a framework to tackle possible benefits in HIV cure research:

**Table 23. Ways to Tackle Benefits in HIV Cure Research**

<b>Ways to Tackle Benefits in HIV Cure Research</b>	
⇒	Rely on the potential psychosocial benefits to participation
⇒	Rely on the fact that sometimes, early phase studies show clinical effect
⇒	Provide ancillary care
⇒	Insist that the adverse risk-benefit ratios for study participants are justified by the social value of finding a cure for HIV
[Adapted from: Forum for Collaborative HIV Research, 2014]	

### **Risk-Benefit Ratios**

Our study further asked key informants to provide perceptions of risk-benefit ratios in HIV cure research because this most closely embodies the principles of nonmaleficence and beneficence [90]. While risk-benefit ratios may be “best conceived in terms of a ratio between the probability and magnitude of an anticipated benefit and the probability and magnitude of an anticipated harm,” [63]it is important to note that there is no objective, quantifiable measure of risks to benefits. Risk assessments in clinical research require both moral and scientific judgment [91]. Importantly, potential risks to participants must be minimized, and potential risks must be enhanced and benefits to participants and society should be proportionate and outweigh the risks [90]. Undoubtedly, the field of HIV cure research has sharpened debates around risk-benefit assessments. It is difficult to evaluate risks and benefits for novel interventions, particularly when the nature, magnitude,

likelihood or severity of risks are unknown [92]. Instead of the risk-benefit ratio, Weijer has called for a “risk-knowledge calculus” to determine whether the risks of research can be justified against the societal benefits that can be gained from the research [27]. This is reminiscent of the criteria of scientific validity to advance research [27]. Early HIV cure experiments should be designed to answer important scientific questions towards an HIV cure [28]. While the likelihood that there will be benefit will be small, there should be a high likelihood that there will be any scientific progress, or “forward movement” as described by our key informants. Certainly, the NIH is pushing for end-of-pipeline translational research in funding cycles. There may be ethical issues associated with over-emphasizing human studies over cell model or animal experiments given the tremendous uncertainty of outcomes and the newness of the pre-clinical science.

Rid and Wendler provided a constructive framework to evaluate risks and benefits in biomedical research [84]. Their framework provides a process for making risk-benefit evaluations and identifying unresolved questions to evaluate research risks and benefits. The framework can be highly applicable to the field of HIV cure research. The main steps are summarized in Table 24.

**Table 24. Steps to Evaluate Risks and Benefits in Biomedical Research**

<b>Steps to Evaluate Risks and Benefits in Biomedical Research[84]</b>
1. Ensure and enhance the study’s social value
2. Identify the research interventions and procedures used to ensure safety of interventions
3. Evaluate and reduce the risks to participants
4. Evaluate and enhance the potential benefits for participants
5. Evaluate whether the interventions pose net risks
6. Evaluate whether the net risks are justified by the potential benefits of other interventions
7. Evaluate whether the remaining net risks are justified by the study’s social value

### **Equipoise**

We now turn to the topic of equipoise. The term was introduced by the philosopher Charles Fried to denote the “controversy within the scientific community about whether the new intervention is better than standard therapy” [27][92]. The term is usually associated with

randomized clinical trials [39] and its relevance to early phase experiments is unclear. In our study, key informants varied in their responses around the relevance of equipoise – from accepting to denying its relevance in HIV cure research. It is worthwhile to explore the concept – and possible alternatives – further.

Equipoise is one of the prevailing abstract frameworks to evaluate clinical studies. It adopts primarily a therapeutic lens. Advantages of equipoise are that it prevents redundant research and defines some of the prerequisites for conducting clinical research [92][93]. Critiques of clinical equipoise have argued that the concept is insufficient for ethically justifiable clinical trials [93]. In a sense, equipoise is conflicted because it “attempts to have it both ways: to view the clinical trial as a scientific experiment, aimed at producing knowledge that can help improve the care of future patients, and as treatment conducted by physicians who retain fidelity to the principles of therapeutic beneficence” [94]. Equipoise is a highly subjective notion that is biased by the optimism surrounding an intervention [95] and ill-informed when it comes to implementing research in developing countries that lack robust treatment options [96].

Few alternatives to equipoise have been proposed in the literature that may be relevant and applicable to the field of HIV cure research. These are summarized in Table 25.

**Table 25. Alternatives to Equipoise Relevant to HIV Cure Research**

<b>Alternatives to Equipoise Relevant to HIV Cure Research</b>
<ul style="list-style-type: none"> <li>⇒ Carefully investigate <b>all aspects of the design of a clinical study</b>, along with social and cultural context, including the <i><b>motivations of study participants</b></i> [93]</li> <li>⇒ Adapt <b>non-exploitation</b> as central to clinical research ethics [93]</li> <li>⇒ “The pertinent question is not whether the two treatments are in equipoise, but instead whether the <b>potential benefits to third parties</b> are sufficient in this case to justify the less-than-optimal care given to some of the patients in the study” [96]</li> <li>⇒ <b>Modest translational distance criterion</b>: incorporates study-by-study evaluation of the expert scientific community [Kimmelman, in [97]] – similar to what is done by the FDA</li> <li>⇒ <b>Close examination of the entire structure of experiments across the continuum of biomedical research</b> [98]: <ul style="list-style-type: none"> <li>Normative obligations that govern the work of the laboratory researcher at the bench, research with laboratory animals, research with healthy volunteers and research on sick patient-subjects [98]</li> </ul> </li> </ul>

Of the above alternatives to equipoise, my favorite is the one by Joffe and Miller [98], because it calls for a new conception of clinical research ethics based on a scientific orientation. In fact, this framework is much more applicable to HIV cure research than equipoise, which is best suited to randomized clinical trials. The paper defines normative obligations across the *entire* continuum of biomedical research – from laboratory bench work to research with healthy and sick participants. The key benefit of the scientific orientation is the appreciation of the entire translational research spectrum and the insistence on methodological rigor. The scientific framework also clarifies the acceptability of research procedures, such as biopsies, that are important to answer scientific questions that will not provide benefits to participants. The entire emphasis is on professional integrity and scientific value and validity. I recommend that the scientific framework be looked at closer in the context of HIV cure research.

#### **“Healthy Subjects”**

Related to equipoise, the topic of “otherwise healthy subjects” received recent attention given the FDA clinical hold of the Panobinostat + Interferon clinical study, as described in the qualitative results section. HIV cure research embodies the perfect storm of recruiting relatively healthy participants – otherwise “healthy” besides their HIV status –to undergo potentially significant risky interventions. The calculus of what is tolerable is obviously different between sick cancer patients and virally suppressed people living with HIV. Long-term treated HIV disease by no means represents a perfectly “healthy” state, however. That people living with HIV are considered “otherwise healthy” also somewhat conflict with data that co-morbidities are more prevalent in this population, including cardiovascular disease and diabetes. HIV suppression is not the same as being healthy. Moreover, inflammatory diseases occur at much higher rates in people living with HIV, despite their long-term HIV suppression. The cumulative toxic effects of HIV treatment are

unknown, and there are tremendous unmet needs surrounding HIV treatment cascades, both in the United States and globally.

What is more, several people living with HIV may not perceive themselves as “otherwise healthy” volunteers, but instead fragile individuals who may still experience great health risks. Health may become an illusion for several people living with HIV. From an ethical implementation standpoint, it is important to ensure that HIV cure studies include proper safeguards so that if harms occur, procedures in place to mitigate these harms.

### **Standard of Care and Treatment Interruptions**

Duties of nonmaleficence and beneficence require not imposing risks of harm and therefore observing standards of care [63]. Given the fast evolving state of HIV research, standards of care are not static, but evolving constantly with newly emerging drugs. There are also standards of care considerations during and after a clinical study has been completed. In HIV cure research, treatment interruptions go counter to standards of care. It is unclear to what extent treatment interruptions motivate or deter participation in HIV cure studies, although in our study, we asked general willingness to undergo treatment interruptions. It might be that some volunteers find the notion of a “drug holiday” to be a motivating factor, as we saw in the qualitative section. Treatment fatigue has also been reported to exist, although it should not be used as a way to attract volunteers in a study. Furthermore, to prevent sexual transmission of HIV to sexual partners during HIV cure research (and unsuspected viral rebound), it is clear that both standards of care and standards of prevention apply in HIV cure research and more guidelines are needed surrounding both.

### **Scientific Uncertainty**

The literature on biomedical research ethics emphasizes that risks are distinct from scientific uncertainty [63]. While both imply a lack of predictability or knowledge about future outcomes, risks refer to the probability and magnitude about possible future hazards, while uncertainty means the



lack of predictability or knowledge about future outcomes because of insufficient scientific evidence [63]. One author has defined uncertainty as the “subjective consciousness of ignorance” [86]. Early phase research carries inherently more uncertainty [27]. The Institute of Medicine (IOM) outlined three main sources of uncertainty: clinical, statistical and methodological [99]. Clinical uncertainty is derived from the use of randomized clinical trials as the primary methodology. Statistical uncertainty stems from the inability to quantify risks and benefits. Methodological uncertainty results from the pre-clinical and pre-market context [99]. Other sources of uncertainty that have been identified include: probability, ambiguity and complexity uncertainty [86].<sup>22</sup> Doubtlessly, uncertainty has implications for recruitment study participants and for the ethical and effective implementation of clinical studies. It also has scientific, practical and personal implications.

Our study assessed how risks and benefits affected willingness to participate in early HIV cure studies. There will always be a measure of uncertainty in characterizing those risks and benefits – some of which are known, others unknown. How the uncertainty is communicated to and understood by potential study candidates is of key importance and relevance here, especially during recruitment and retention activities. Neither benefits nor risks can ever be defined in absolute terms – they are relative and contingent upon a host of factors. They lie on a dynamic continuum that must take into account the experimental interventions, study population, visit procedures and standards of care. The characterization of the uncertainty is initiated in the pre-clinical phase of experimentation and continues throughout clinical research and marketing of products. It is known that pre-clinical models do not fully predict how compounds will behave in humans, and the interpretation of clinical data in early phase experimentation requires extrapolation and subjective judgment [91].

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<sup>22</sup>See page 16S of the article for a discussion on the probability, ambiguity and complexity with infographic. Politi *et al.* [68] used the categories of stochastic uncertainty (related to chance), ambiguity uncertainty (conflicting strength of scientific evidence) and informational uncertainty (lack of available evidence).

HIV cure research is fraught with uncertainty, as was demonstrated by the cases of the Boston patients [4] and the Mississippi child [100] who experienced a viral rebound following announcement of their “cures.” What if Timothy Brown, who received a donation from a CCR5Δ32/Δ32 donor, were to experience a CXCR4-induced rebound? Scientists just do not know all the factors that predict relapse and viral rebound is highly stochastic. The topic of scientific uncertainty is particularly relevant for study participants who interrupt HIV treatment. Why should they choose to replace a safe, effective drug regimen with uncertainty and unknown risks? HIV cure research participation raises questions around uncertainty management for study participants. Informed consent guidelines around disclosure of scientific uncertainty are unclear. Should scientific uncertainty even become a separate category of disclosure in informed consent forms, along with risks and benefits? In the field of HIV cure research, we simply do not know where all the thresholds of evidence lie. Factors such as small size sizes, observational study designs (as opposed to randomized trials), varying outcome measures and study endpoints exacerbate uncertainty. Communication of uncertainty also has ethical implications, including what is being communicated to the study participants and how the uncertainties are being communicated to them [86]. It is worth borrowing from the scientific uncertainty literature to improve the quality of clinical research decisions. Politi and colleagues [68] offered four steps to facilitate decision-making in situations of uncertainty using a participant-centered approach:

**Table 26. Four Steps to Facilitate Decision-Making in Situations of Uncertainty**

<b>4 Steps to Facilitate Decision-Making in Situations of Uncertainty [68]</b>
1. Allow study participants and clinician-researchers to clarify the decision
2. Explore the decision – options, benefits, risks and uncertainty
3. Identify decision-making needs (information, support, values clarification)
4. Plan next steps focusing on exploring participant values and preferences

Better appreciation of scientific uncertainty is needed to help implement HIV cure studies effectively and ethically. Furthermore, it is important not to conflate the concept of uncertainty with

the extent of risks. Uncertainty should not be mixed with the willingness of study participants to accept those risks, either [99].

### **Gaining Medical Knowledge and Returning Study Results**

Finally, a topic that has received attention in research ethics is that of returning research results to study participants. Do participants have the right to know their individual study results while participating in HIV cure studies – such as their reservoir size? There are three types of study results, including screening results (e.g. diagnostic tests at baseline), study results (e.g. research results) and results from research on stored specimen [74]. In HIV cure research, the last two are emphasized, and these are *research* results, not diagnostic or clinical results. HIV cure studies mostly generate results that are not clinically relevant or even interpretable. Returning surrogate marker results to study participants may risk transmitting information that is confounding or confusing to their clinical care. In the worst case scenario, results could be interpreted as stopping HIV medication, which could be harmful. In HIV cure studies, it may be better for clinician-researchers to communicate *aggregate* study results to participants as opposed to individual results, since research results are only meaningful in their aggregate. Furthermore, clinician-researchers should have a duty to disseminate study results to participants and communities in lay terms. Our key informant interviews showed the importance of having scientists explain results to study participants and their significance. This can be a retention strategy in a study.

### **Principle of Justice**

We next explore the Belmont principle of justice. This principle emphasizes the just distribution of burdens and benefits in clinical research. According to some moral philosophers, justice can be explained in terms of fairness or fair opportunity [63] and contributes a human rights dimension. According to Lo and Grady, the selection of study participants and research sites must be equitable and research sites must have the capacity to carry out procedures safely [28]. While

noble, this principle is violated in research ethics because early phase studies are proof-of-concept, and they can only be conducted at specific research sites with the requisite expertise and capacity. Furthermore, study participants may be excluded if they have conditions that could affect their adherence to the protocol, such as substance abuse, homelessness, and co-morbidities. Therefore, the principle of justice is much more difficult to uphold in early phase HIV cure research experimentation, but remains critical to ensure the generalizability of study results [101].

The principle of justice is important and relates to the ethics of participant selection in research [27]. Emanuel and colleagues discussed some of the dimension of fairness. The scientific goals of the study, not vulnerability or privilege, should drive recruitment decisions [27]. Furthermore, efficiency should not override fairness in recruiting study participants [27]. The issue of access to HIV clinical studies is also relevant here, since access is not equitable and limited by geographical availability (and capacity), means or time. Justice and fairness can be enhanced by paying attention to the processes of recruiting study participants [64].

It is also worth looking at specific groups of study participants who are “under-represented” in research, although these issues are not unique to HIV cure research. Rowena Johnson *et al.* reported that participation in HIV cure studies do not reflect the national or international burden of HIV infection in women, older adults and non-Whites [30]. With regards to women, a study found that they represented a median of 11.1% of participants in HIV cure research [29]. The moral imperative to increase women’s representation in HIV cure studies is supported by the existence of biological differences (such as clinical outcomes), physiological differences and pharmacokinetic responses, as well as social factors. In our survey, while 27% of males were willing to participate in all 14 types of studies versus 21% of females, the difference between males and females was not statistically significant at the 5% level. Thus, in this sample, males and females were as likely to be “very willing to participate” in HIV cure-relate studies (there were more males in the survey sample

than females – 284 versus 73). Still, while overall willingness may not vary, *actual* study participation may differ. Recommendations to help with representation women in HIV cure studies include ensuring that reviewers check for adequate female representation before funding studies, ensuring that female enrollment data are reported consistently, and avoiding “over-protecting” women.

Other groups that have been under-represented are racial minorities. In our survey, people who identified as Caucasians/Whites were slightly more likely to be "very willing to participate" in HIV cure-related studies than people who identified with other ethnicities. We found 30% of Caucasians who were very willing to participate, versus 23% of African-Americans, and 19% of Hispanic or people with Hispanic. The difference between the ethnicities was not statistically significant at the 5% level, however. Factors contributing to overall under-representation of racial minorities in HIV research may include the difficulty navigating the clinical trial system [102] and poor referral rates in studies [101]. Future HIV cure studies certainly need to incorporate strategies to increase representation of minority groups. Authors have also insisted on looking at the role of medical insurance as a barrier to participate in research, as fear of losing insurance is a major deterrent [101]. Other issues to be investigated further include the role of trust issues, awareness and information about clinical studies and characteristics of clinical studies [101]. Further, for some minority groups such as Hispanic populations, lack of access to the health care infrastructure translates into low research participation. Adolescents and children living with HIV are also under-represented and potentially vulnerable.

Another group that is under-represented in research includes transgender women. While the NIH recently created a cross-network transgender working group to address factors that impact transgender inclusion in biomedical HIV studies, there remains issues with transgender persons feeling comfortable and welcome to participate in studies. There are also challenges reported with using consistent and respectful terminology on clinical study data collection instruments. Some

transgender women do not want to be identified as transgender, since their transition to womanhood is complete and they no longer consider themselves transgenders. Other transgendered individuals may experience legal discrimination and social stigma. Other potential groups that require representation are heterosexual men, since they are less likely to participate in HIV clinical studies compared to men who have sex with men [101][103]. Further, while scientists have been focused on reproductive risks to women, little has been written about potential reproductive health risks to men (and infertility may be a possible risk of HIV cure research interventions). Given the aging population of people living with HIV in the United States, it is also important to pay attention to aging issues. Other types of study participants in HIV cure research that may require special attention are: mother-children pairs, women being asked to donate cord blood after giving birth, tissue donors (before or after death) and HIV controllers.

More attention is needed to the group of elite controllers in HIV cure research. In fact, elite or viremic controllers are currently threatened by universal HIV treatment. Public health officials recommend that people living with HIV be placed on treatment, regardless of their ability to suppress the virus. Elite controllers are technically functionally cured, and HIV treatment can actually jeopardize their much “cured” status. This raises serious ethical questions about subjecting individuals who are able to control the virus naturally to the effects of HIV treatment. For physicians not well informed on the subject of elite control of HIV infection, sole reliance on the recommendations from the U.S. Department of Health and Human Services (DHHS) *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* for ART in individuals with greater than 500 CD4+ T cells (as is typical in a majority of elite controllers), may lead to a pointless prescription for ART and to a much greater difficulty to recognize this group in the future – and perhaps even the disappearance of this group that represents the model for functional cure. This is highly paradoxical for a field that is moving towards a cure.

Furthermore, in HIV cure research, there needs to be a much deeper understanding and appreciation for the types of study participants that are needed, in order to facilitate referral. The field has moved beyond simplistic “acutes” versus “chronic” categories and study participants are not homogeneous with regards to age, sex, biology, reservoir size, immune function, treatment initiation, co-morbidities and psychological status. Furthermore, comprehensive care and support are needed for the holistic persons as it is rare that HIV will be the only “infection” that people are dealing with. There are certainly complicating factors in people’s lives and underlying vulnerabilities that need to be taken into account. While people living with HIV may be virally suppressed, they may have uncontrolled diabetes, cancer or cardiovascular disease. The HIV population is also getting older and these associated risks and vulnerabilities should also be taken into account.

Categories of study participants that are considered “vulnerable” per regulations include children, prisoners, pregnant women and mentally disabled persons [104]. Certainly in HIV cure research, children are vulnerable because they cannot provide consent [32]. Pregnant women also have specific vulnerabilities when consenting for HIV cure studies [32]. More research is needed to determine to what extends HIV cure research makes people living with HIV vulnerable. Adding to the burden of participation is the risk of infecting others during an unsuspected viral rebound. One of the key informants asked if the burden of study participation in HIV cure research was too high due to the risk of infecting others. There are also vulnerabilities beyond those that are clinical, such as privacy and confidentiality issues, social vulnerabilities and financial vulnerabilities. While not all HIV cure study participants are “vulnerable” per say, there should be processes in place to determine the extent to which they are “not merely predisposed to harm but actually harmed – vulnerated” as a result of research participation [92].

Finally, it may be worth discussing the topic of coercion and the ethics of incentives in the context of justice for HIV cure research. As the survey results revealed, there is great diversity in the

people living with HIV in the United States. Some live close to the federal poverty line while others do fairly well. Clinical studies have been recognized as a way for people to earn additional income [66]. The ethics literature emphasized that remuneration should be proportionate and recognize participant time and contribution, but should not cloud participants' perceptions of risks and benefits [28]. The ethics of incentives can be improved by engaging community advisory boards in helping evaluate reasonable, non-coercive compensation [105]. Other authors have cautioned that incentives should not undermine the autonomy of study participants [106]. When incentives help study participants overcome barriers to participation, they may actually be "autonomy enhancing" [106].

### **Reflections on the Effective Implementation of HIV Cure Studies**

In addition to seeking factors facilitating the ethical implementation of HIV cure studies, we want to understand preconditions of effective implementation of HIV cure clinical studies. Effective implementation requires the ability to define the need for change, formulate a blueprint for strategic objectives, build a strong research team and communicate the mission and vision. Implementation science can assist with determining factors for effective implementation. As per Rohit Rasmawany, implementation science is a specified set of activities designed to put into practice a program of known dimensions.<sup>23</sup> The primary purpose of implementation science is to promote the successful application of implementation strategies. The goal is to make a difference, improve effectiveness, quality, efficiency and equity (and some of these goals may be in conflict). Yet, providing a set of enabling factors does not suddenly make implementation easy, but it provides a foundation.

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<sup>23</sup>Rasmawani R. Where is Implementation in Implementation Science? Presentation to DrPH Program 13 May 2015.



So why should we care about implementation science in the context of HIV cure research? Should we simply leave the implementation of clinical research protocol and the recruitment of study participants to the individual scientists and study teams? While implementation science has been defined as the study of methods to promote the integration of *existing* interventions and evidence into healthcare policy and practice,<sup>24</sup> I would argue that implementation science is also relevant to the conduct and management of clinical research (e.g. T1 – T2 translational paradigm). We need the HIV cure research field to start thinking in terms of effective implementation and appreciate that the entire translational research continuum – from pre-clinical to clinical research – requires effective implementation strategies. There is also a need to appreciate that issues that occur at the beginning of the translational research pipeline affect the entire implementation pathway, including the application of existing interventions. And it is important to begin to understand these factors early in the translational continuum. In HIV cure research, we must appreciate the entire journey, beyond the mere destination. Recruitment of study participants thus presents the ideal platform to discuss these implementation factors as it touches on a critical implementation question. Without study participants, there is no T1 to T2 translation.

A parallel can be drawn between the adoption of innovations[107] and the desire to participate in them (e.g. decisions to be screened, to be recruited, to go through the informed consent process, to be retained and to participate again – i.e. serial participation). Clinical research provides the setting to begin to understand how innovations and interventions will work in the real world. Furthermore, recruitment in clinical research is increasingly being viewed as a science[66]. The goals of effective implementation could be to remove obstacles to study participation – including recruitment and retention. Many individuals who have participated in clinical trials have reported that what mattered to them more were the study logistics, rather than the risks of the

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<sup>24</sup>Ibid. (NIH definition)

interventions[66], and this is also consistent with our study results. People who cannot make the clinical study fit their lives and their realities must decline study participation[66].

Our qualitative research results highlighted factors that can both facilitate the recruitment and retention of study participants in HIV cure research studies. There are measures that can be taken to facilitate participant accrual in HIV cure clinical studies, and this is consistent with the HIV prevention and treatment literature.[105][101] There is also a science of retaining study participants [60], especially when faced with potentially complex outcomes. Preferences to study participation can be provisional, conditional and evolving, and we must appreciate the entire journey of study participation. No doubt that it would be interesting to conduct additional research on factors facilitating retention of study participants as part of actual HIV cure clinical studies.

Because measuring HIV remission is complex, long-term follow-up of study participants is required. The decision as to which study endpoints to adopt represent another critical implementation science question. Scientists have not yet reached consensus on determining which assay(s) to use for measuring reversal of HIV latency. They remain divided on the use of the quantitative viral outgrowth assay and cellular-associated HIV DNA or RNA, for example. There are also clear limit of surrogate endpoints in HIV cure studies. We discussed the challenges associated with HIV treatment interruption – the ultimate test for a cure – in the qualitative results section. Furthermore, it is possible to make an HIV reservoir undetectable and still get viral rebound (as in the case of the Mississippi child), and open-ended designs that require long-term follow-up can be very worrisome to study participants.

Another question that belongs in the realm of implementation science is that the impact of HIV cure research on health care systems, and potential future impacts once we find a cure for HIV infection. While innovative cures may transform health care services – such as those for tuberculosis, syphilis and now hepatitis C infections – we should not forget that diseases may have

unintended consequences that can be perversely related to the overall intended goal of decreasing disease prevalence.<sup>25</sup> We are reminded of Robert Merton's theory of unintended consequences. Unintended consequences are outcomes that were not originally intended [108]. Furthermore, the terms unintended and unanticipated consequences are not synonymous: unintended implies the lack of purposeful action or causation, while unanticipated means the inability to predict what will happen[108]. These consequences can be desirable or undesirable, direct or indirect, and latent versus obvious[108].

The potentially future impact of an HIV cure and its influence on the health care systems must be carefully considered in the process of translational development, because factors that we did not anticipate can have profound social and health care consequences. For example, the health care system may not be able to handle the level of monitoring required for ART-free remission cases and these tests may be more expensive than HIV treatment. We should therefore advocate taking a health systems approach to HIV cure research. For example, implementation of pediatric HIV cure research should be done with the intent to prevent mother-to-child transmission of HIV in the first place. Similarly, early treatment should be implemented by first attempting to prevent new HIV infections. We should also try to improve early diagnosis and access to HIV treatment for all. Translating clinical research findings into implementation also presents challenges, as we have seen with the findings from the Mississippi child, whereas early treatment (e.g. as close to birth as possible) can be beneficial to prevent negative outcomes, but it is not universally implemented.

Once an effective HIV cure is found, we will need implementation science to determine how best to operationalize it in the real world[41]. For example, the recent example of hepatitis C cures reminds us about the importance of integrating these factors early in cure development. There could be negative impacts of these "high-cost" cures that can exacerbate health care inequalities.

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<sup>25</sup>Tucker J. Notes from Brocher Foundation Meeting May 2014.

There can also be unintended consequences associated with the research enterprise itself.<sup>26</sup> We must plan for and guard against potential unintended consequences of HIV cure research at all stages of the translational continuum.

### **The Role of Implementation Research**

We consulted the implementation science literature to extract factors that may be relevant to the effective implementation of HIV cure research. Implementation science requires an appreciation of both the processes used in the implementation of programs as well as an appreciation of the contextual factors that affect these processes [109]. Implementation science also helps us address or explore *any* aspect of implementation, including factors that affect recruitment or implementation of general. It also offers a window into the actual practical challenges presented by the implementation of HIV cure studies, and draws from various disciplines, including public health, sociology, psychology and management theory [24]. Furthermore, implementation science focuses on leadership and creative problem solving [110].

Table 27 below summarizes implementation science perspectives that are directly relevant to the effective implementation of HIV cure research. It also touches on factors that were described in the qualitative results section. Informed by the literature, it attempts to bridge theory and

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<sup>26</sup>Examples of unintended consequences from the HIV cure research enterprise include:

- Negative results (or viral reactivation with potential drug resistance). This is why consultation with local health authorities in advance of a study (e.g. pediatric or early ART study in resource-limited settings) would be critical, in order to ensure that second-line antiretroviral treatment would be accessible to study volunteers post-participation[32].
- HIV cure research may increase non-adherence to HIV treatment. For example, a study in Tanzania showed that when traditional healers proclaim that they have cured HIV, there were negative consequences to HIV treatment adherence that result[134].
- Possibility that study participants neglect their care thinking they have been cured or HIV providers may view the care of “cured” participants as a lower health priority [135].
- There can be conflicting information about HIV cure from HIV physicians and the media that can present potential health risks in the post-Timothy Brown era. For example, after learning about scientific HIV cure research efforts, people living with HIV may be more willing to pursue experimental interventions and treatments advertised as being able to cure HIV, without the proper biomedical scientific underpinning. There could be increased “quackery” in HIV cure research[136].
- Understanding why study results did not work (or worked) is critically important. Failure to do so may upset study participants if there is a feeling that results remain inconclusive.

practice and provides an appreciation of the complex and multi-faceted factors that affect implementation, beyond mere risks and benefits of interventions. It also provides a foundation for understanding effective implementation.

**Table 27. Factors Relevant in the Effective Implementation of HIV Cure Research – Perspectives and Opportunities from the Implementation Science Literature**

<b>Factor Relevant in the Effective Implementation of HIV Cure Research – Perspectives and Opportunities from the Implementation Science Literature</b>
<p><b>Glasgow RE, Eckstein ET, Elzarrad J. Implementation Science Perspectives and Opportunities for HIV/AIDS Research: Integrating Science, Practice and Policy. JAIDS 2013; 63(1): S26 – S31[23]:</b></p> <ul style="list-style-type: none"> <li>• <b>Risks and benefits</b> incurred</li> <li>• <b>Trialability:</b> whether intervention can be first tested at low risk</li> <li>• <b>Simplicity:</b> difficult of implementing the intervention</li> <li>• <b>Observability:</b> readiness with which we can observe the results of an intervention</li> <li>• <b>Compatibility/congruency:</b> whether intervention can “fit” in a given organization or system</li> <li>• <b>T1 – T4 translation:</b> describes the development of scientific knowledge from basic discovery (T1) to evidence-based guidelines (T2), practice (T3) and improved population health (T4)</li> </ul> <p><b>Feldstein AC, Glasgow RE. A Practical, Robust Implementation and Sustainability Model (PRISM) for Integrating Research Findings into Practice. The Joint Commission Journal on Quality and Patient Safety 2008; 34(4): 228 – 43 [111]:</b></p> <ul style="list-style-type: none"> <li>• Comprehensive, prescriptive and robust, yet practical, model to help researchers understand factors that need to be considered for implementation; predictors of effective implementation</li> <li>• <b>Patient[Participant] perspectives:</b> Patient[Participant]-centered approach – providing choices, addressing barriers, providing access, minimizing burden, getting feedback, understanding demographics, disease burdens, knowledge and beliefs, health literacy</li> <li>• <b>Organizational perspectives:</b> Addressing barriers of frontline staff Coordination between departments and specialties Burden (complexity and cost)</li> <li>• <b>External environment:</b> Regulatory environment Community resources</li> </ul> <p><b>Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering Implementation of Health Services Research Findings into Practice: A Consolidated Framework for Advancing Implementation Science. Implementation Science 2009; 50: 1 – 15[112]:</b></p> <p><b>The intervention</b></p> <ul style="list-style-type: none"> <li>• Intervention source</li> <li>• Evidence strengths and quality</li> <li>• Complexity and cost</li> </ul> <p><b>The inner setting</b></p> <ul style="list-style-type: none"> <li>• <b>Structural characteristics:</b> Implementation team</li> <li>• <b>Networks and communications:</b> Complex role networks and communications have on implementation</li> </ul>

- Communication
- Cohesion
- **Culture**
- **Implementation climate**
  - Absorptive capacity for change
  - Tension for change
  - Compatibility
  - Relative priority
  - Goals and feedback
  - Learning climate
  - Readiness for implementation
  - Leadership engagement

**The outer setting**

- **Patient [participant] needs and resources**
    - Extent to which patient[participant] needs, as well as barriers and facilitators, meet those needs
    - Patient[Participant]-centeredness
  - **External policies and incentives**
    - Policies and regulations
- 

In addition to the implementation science frameworks provided above, there are additional implementation science concepts that could inform the field of HIV cure research implementation. Meyers and colleagues[113] have emphasized a quality implementation framework, where effective implementation is documented via manuals, guides, worksheets and toolkits. Braithwaite and colleagues[21] explored emergent success factors, including preparing for change and appreciating the capacity for implementation, resources, leverage and sustainability. They recognized that various stages of implementation do not happen automatically. Certainly, the history of international HIV clinical trial shutdowns – such as pre-exposure prophylaxis in Cameroon, illustrates that clinical trials do not occur on their own and that successful implementation factors must be appreciated.

As we conclude the section on implementation science, there are themes we have not fully explored in the context of effective implementation. These include clinical trial management, adaptive clinical trial design and implementation and capacity for effective research (e.g. basic thresholds of conditions that must be present). Unquestionably, HIV cure clinical research is an

exercise in management. Researchers are often focused on the protocol endpoints, and they are often reluctant to document lessons learned in terms of participant recruitment, retention or overall implementation. Lessons learned are rarely factored in, and short-term funding horizons of grants often preclude the development of best practices. In academia, where most HIV cure research occurs, incentives can be misaligned. Clinical research with people living with HIV requires longer-term visions as opposed to short-term focuses. With industry (e.g. pharmaceutical companies), profitability and the need to mitigate risks often come first. Further, some HIV cure research implementers may also have conflicts of interest due to different types of agreements and engagement – between academia, public-private partnerships, publicly-funded collaboratories with industry sponsors, and various consultancies. As this segment described, the entire context of HIV cure research implementation must be taken into account.

### **Towards a Possible Implementation Ethics Framework in HIV Cure Research**

We now attempt to combine ethical and effective implementation by asking the question: is there an implementation ethics to HIV cure research? The expression “implementation ethics” was coined by Stuart Rennie and Frieda Behets in the context of rationing AIDS care and treatment in sub-Saharan Africa (existing AIDS treatment interventions) [114]. Here, implementation ethics also affect HIV cure research by forcing us to appreciate the ethical pathway to effective implementation. What ethical issues are raised by the implementation of HIV cure research in the United States and around the world? Are there ethical conundrums and factors related to the ethical implementation of research [115]? Do case-by-case analyses of HIV cure protocol – as done by the FDA – constitute an issue in implementation ethics? I argue that HIV cure scientists must adopt on “implementation ethics” in addition to research ethics. For example, a serious safety signal, a demonstration of futility of a specific intervention, emerging information about scientific

details to measure HIV latency or any other factor can affect the dual effective and ethical implementation of research.

Rennie and Behets pointed out that bioethics must keep pace with times and science [114]. As research protocols are implemented, there can be unexpected challenges, dilemmas and conflicts that arise. The “ethical odyssey” of HIV clinical study implementation has been documented in the context of HIV treatment as prevention trials [116]. Ethical challenges arise over the course of a trial implementation that requires deliberation and response, not only from the investigators, but also funders, community members, regulatory bodies and bioethicists. In the case of the HPTN 052 trial, the lack of ART availability at the research site reflected long-standing issues in global justice and access to HIV treatment, and thus the trial was deemed non-coercive. Furthermore, a prevention package had to be developed with broad consensus from stakeholders. As clinical trial data were emerging, scientists had to balance the need for keeping existing public health guidelines current while generating better evidence. Some of the ethical challenges to implementation were anticipated and others were not. Clinical trial implementers in HPTN 052 argued that HIV clinical teams should think about developing “ethics plans” comparable to data management, or statistical analysis plans [116].

In the field of HIV cure research, the implementation of ethical analytical treatment interruptions brings about implementation ethics questions. For example, we must be careful how these “negative” reports of HIV treatment are being interpreted. For example, Buell and colleagues wrote: “A cure for HIV would obviate these intrinsic disadvantages of ART” [62]. Portraying a cure for HIV as mitigating the negative effects of ART for people living with HIV is short-sighted. HIV treatment saves millions of lives each year and there was a time when there was no treatment for HIV at all. While it is true that a cure for HIV may mean the freedom to live without medication, we



must be careful not to categorically reject the benefits of live-saving HIV drugs while advancing HIV cure science. There is a greater need for nuance when describing the “negative” effects of ART.

As illustrated with the HPTN 052 and treatment interruption example, implementation of HIV cure clinical studies engenders questions that are not covered merely by research ethics. Logistical, social, cultural and economic issues affect the ethical and effective implementation of studies – at the individual, institutional, national and even global levels. As with the rationing of AIDS treatment in sub-Saharan Africa, there can also be conflicts between equity and efficiency. While the NIH aspires for a simple, safe and scalable cure,<sup>27</sup> that may be a distant possibility. Further, HIV cure research resources are insufficient to build capacity for research on a broad scale *and* execute research concurrently, so the field must rely on well-equipped sites with reputable investigators. As we discussed under the concept of justice, beyond the “where” question (selection of research sites), we are also confronted with the question of “who” should take part in HIV cure studies. Assuredly, as with the rationing of AIDS treatment, there are difficult trade-offs that must be negotiated in HIV cure research as well. The concept of scalability [117][118] of an HIV cure can also fall under the category of implementation ethics. By scalability, we mean the absorptive capacity of research sites or health care settings. We must pay attention to the scientific, community and participant absorptive capacity for HIV cure research. The concept of cure replicability can also stem from implementation ethics. As we have one case of cure (e.g. Timothy Brown), scientists are devoting significant resources to attempting to replicate that cure and these involve trade-offs.

Other examples that can fall under the realm of implementation ethics may include sample size ethics and side effect ethics (e.g. insufficient sample sizes to detect size effects). With HIV cure

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<sup>27</sup>Simple cure: tertiary care is not needed. Safe cure: not worse than current HIV treatment. Scalable cure: relevant to the millions of people infected with HIV.

research, small studies can only detect large effects. Scientists must attempt to minimize the number of study participants exposed to risk, and they must also maximize the value of small numbers. How do we ensure that scientists do not reject a therapy with a modest benefit just because the study was underpowered to show any meaningful effect? Furthermore, what are the incremental steps and how do we determine if we have the appropriate intermediate endpoints? With small sample sizes, there can be conclusions of uncertain validity because interventions and study populations are subject to undetermined fluctuations. Some clinical investigators pre-screen for agent sensitivity, others do not. With small sample sizes, there can also be negative unknown consequences of serial participation in research if the same study participants are selected over and over again for studies. With small sample sizes, confidentiality and anonymity are even more important. When races/genders are reported in journal articles with small numbers, it may be possible to deduce the identity of the actual study participants. Further, the field of HIV cure research should attempt to use systematic reviews of studies to overcome the effects of small numbers.

Beyond small sample sizes, there are design issues that belong to the class of implementation ethics. In research, the ethical principles of respect, beneficence/nonmaleficence and justice must also be operationalized in study design, protocols and methodologies, as we discussed earlier. Ethically speaking, the most appropriate study designs are those that will address the research questions while exposing study participants to the least risk. A case in point is stem cell transplant research that focuses on curing cancer. Stem cell transplant implementers attempt to learn as much as possible about HIV in the process. Thus, HIV cure scientists run behind hematologists to see what happens to the HIV reservoir following a stem cell transplant. This constitutes a wonderful example of implementation ethics and risk minimization in practice. Risk of

harm is minimized because studies are implemented with cancer patients for whom the transplant is already indicated.

The field of HIV cure research is in great need of standardized endpoints in order to make meaningful comparisons between studies. Currently, HIV cure studies are designed with different endpoints and measures of the HIV reservoir. What is more, the current measures of the HIV reservoir are not sensitive enough to detect very low levels of HIV persistence. A case in point is the Mississippi child who had no detectable replication-competent provirus in her resting CD4+ T cells, yet the HIV came back 27 months following treatment interruption [119]. Furthermore, surrogate endpoints are not clinical endpoints or benefits – and there is little real, if any, clinical benefits in HIV cure research participation. With surrogate endpoints, correlation does not equal causation, and surrogate endpoints do not predict cures. There can be different surrogate markers for different interventions that are difficult to reconcile, and social factors can also impact biomarkers. Issues with describing surrogate endpoints were found in informed consent forms in the context of gene therapy transfer research. These are important to keep in mind with HIV cure research as well. King and colleagues found that surrogate markers were not only described in terms of study objectives, but also mentioned as potential benefits to participation [75]. Referring to surrogate markers as direct benefits is ethically problematic in clinical studies because surrogate endpoints are rarely meaningful in early phase research. They may not have any direct correlation with the clinical endpoints that actually have values for the patients [70]. “A reduction in the size of your HIV reservoir” may be an overstatement in HIV cure research consent forms. Thus, specificity with regards to the lack of benefits about surrogate markers is supreme. Furthermore, there must be clear distinctions between activity of an agent and efficacy of that agent. An agent is showing sign of activity does not mean that it will be efficacious. Being cautious with the portrayal of clinical outcomes will prevent the overestimation of benefits.

Furthermore, HIV viral elimination is an extremely high bar to achieve. There could be intermediate endpoints that may have value for the study participants on the road to complete HIV remission. It would be important for scientists to better understand what these intermediate endpoints would look like. Defining those intermediate endpoints would also be consistent with taking a realistic and progressive approach to HIV cure research. These could include, for example, shorter periods of drug-free remissions, or an increase in CD4+ T cells.

Under the rubric of implementation ethics, it is important to discuss the value of research to society. Authors have argued that to be ethical, clinical research must be valuable, meaning that it would lead to improvements in health [27]. The intervention would also need to be implementable if found effective. Different judgments can be made as to what constitutes “socially valuable” research. Is scientific value a sufficient criterion for social value? Stuart Rennie<sup>28</sup> outlined social value criteria for patients/participants<sup>29</sup> as well as for public health.<sup>30</sup> Further, will HIV cure research save lives? Or should we rely on robust implementation science of existing HIV prevention and treatment interventions that are population-focused instead? Whether a treatment or a cure is experimental or existing, the criterion of likelihood of success is important, because scarce medical resources should be distributed to people who are likely to benefit most from them [63].

Allocation of scarce resources between HIV prevention, treatment and cure research is another implementation ethics issue for the broader field. It relates to principles of distributive justice and responsiveness of research to local health priorities. The utilitarian approach would require us to opt for interventions that would maximize social utility[63]. Approximately 2 million of

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<sup>28</sup>Rennie S. CUREiculum Ethics Module: <http://www.avac.org/cure-curriculum/module14>.

<sup>29</sup>Suspension of lifelong cART and its short and long-term side effects, potential for reduced stigma.

<sup>30</sup>Impact on the HIV epidemic by lowering transmission, reduction of high-cost expenditures related to HIV care and treatment.

new HIV infections occur each year and we should thus not forget about HIV testing. With the release of the START trial results[51], universal HIV treatment is recommended and we have a long way to go to bridge the gaps in the HIV treatment cascade. There are also other infectious diseases that require attention, such as tuberculosis that is now the number one infectious disease killer in the world. Tuberculosis provides a cautionary tale of what can happen even in the existence of a treatment and cure, and enthusiasm for an HIV cure should not go unchecked by the reality of other prevalent infections.

Setting realistic expectations about what the science can deliver is also extremely important. We simply just cannot get carried away with the science and we must adopt a nuanced, incremental approach that is also iterative [11]. As we learned from recent cases, future research will build a stepwise approach on the incremental successes and failures of early studies [13]. The need for prudence is paramount. As a cautionary example, clinicians adopted high-dose chemotherapy with autologous bone marrow transplantation as a therapy for breast cancer in the 1990s, even though the treatment was highly toxic and did not confer any advantage over the standard of care [120]. Continued scrutiny, skepticism, and discourse in ethics and implementation of HIV cure research will be healthy. The field of HIV cure research should also address the rationale for a cure and there should also be independent review of protocols [27][28].

Broader issues of public policy, law and human rights are also brought to the forefront by the prospect of a cure for HIV. Public policy constitutes the set of enforceable guidelines. For example, some authors have emphasized that HIV transmission and criminalization laws in the age of treatment-as-prevention are antiquated and need to be revised [121]. It would be worthwhile to appreciate the interpretation of these laws in the context of HIV cure research, where a study participant may inadvertently transmit HIV to a sexual partner following an analytical treatment interruption. Authors have argued that laws criminalizing HIV transmission can be

counterproductive to a broad human rights-based public health approach [121]. Furthermore, HIV cure research implementation should not be devoid of considerations for basic human rights. Rights are defined in terms of those claims that demand our respect [63].

In sum, this section reviewed potential implementation ethics issues in HIV cure research, including the need to appreciate the inherent ethical odysseys involved, potential trade-offs, scalability and replicability considerations, sample size ethics, study endpoints (including intermediate endpoints), allocation of scarce resources, value of research to society, setting realistic expectations and broader issues of public policy, law and human rights. Choices of moral behavior cannot be made in absolute terms. In the end, the art of the application of ethical reasoning must be required for each individual case. Should HIV cure study implementers be taught about ethics? Eckenweiler goes further by asking us to extend the scope of responsibility for ethical implementation of research to pharmaceutical companies, research funders and elected officials to prevent the perpetuation of vulnerabilities [122]. Implementation ethics is not devoid of politics and must be concerned with issues of patent protections for the commercial enterprise, global trade rights, public health systems and clinical research in resource-limited settings and its implications.

### **Strengths and Limitations of Research**

The strengths and limitations of this dissertation project stem from the selection of research methods under each aim. These are summarized in the table below.<sup>31</sup>

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<sup>31</sup>Strength of focus group discussions (deferred) includes the richness of information. Limitations of focus group discussions include possibility of “group think” and researcher’s bias(es) that shape interpretation of data.

**Table 28. Strengths and Limitations of Methods**

	<b>Strengths</b>	<b>Limitations</b>
<b>Survey</b>	<ul style="list-style-type: none"> <li>• Reach a large pool of respondents efficiently</li> <li>• Anonymity of study respondents</li> </ul>	<ul style="list-style-type: none"> <li>• Cross-sectional data; inferences should be made with caution</li> <li>• Participants recorded <i>stated</i> preferences, not <i>revealed</i> preferences (i.e. reliance on hypotheticals)</li> <li>• Self-reported data (e.g. false HIV-positive)</li> <li>• Possibility of bias due to non-responses or incomplete responses</li> <li>• Inability to control self-selected respondents or veracity of information given</li> <li>• Possibility of sampling errors</li> <li>• May be of low quality</li> </ul>
<b>Document Review</b>	<ul style="list-style-type: none"> <li>• Documents and notes are extant and available</li> <li>• Data collection is not contingent upon having access to study participants</li> </ul>	
<b>Key Informant Interviews</b>	<ul style="list-style-type: none"> <li>• Richness and depth of information collected</li> <li>• Relatively easy to implement</li> <li>• Cost-effective</li> <li>• Allows researcher to establish rapport with key informants and clarify questions</li> <li>• Improves ability to discuss issues in-depth</li> <li>• Expert opinion given</li> </ul>	<ul style="list-style-type: none"> <li>• Possible selection bias (e.g. selecting the “right” key informants may be difficult)</li> <li>• Researcher’s bias that shape interpretation of data; qualitative research is deeply “interpretive”</li> <li>• Possibility of social desirability bias (over-reporting of successful/effective strategies and minimization of those that are less effective)</li> <li>• Lack of generalizability of study findings such as experiences, beliefs, perspectives</li> <li>• Telephone interviews have the drawback of not being in physical proximity to the participants; therefore, visual clues were lost</li> </ul>

Our survey on the willingness to participate in HIV cure studies was very comprehensive and extensive, focused on risks and benefits. The survey was a unique contribution to the field of HIV cure research over previous surveys. The survey appeared to have been somewhat representative of the U.S. population of people living with HIV who would have been genuinely interested in HIV cure research. Possible limitations may have included a biased sample of respondents (e.g. those who had access to HIV cure/treatment listservs and internet). The sample was not representative of the overall population of people living with HIV in the United States and may have excluded those who never or rarely access these listservs. Communities of people living with HIV are highly heterogeneous. While the data represent an aggregate picture, there can be a high degree of variability between individual people living with HIV. Children and adolescents were excluded from the survey due to the need for parental assent. The questionnaire was not available in Spanish. The complexity of the survey wording may have limited full understanding of items, although we mitigated this risk by using survey completion as an educational opportunity and we provided definitions of key concepts. Further, we did not ask about sexual orientation in the survey and assessed whether it affected willingness to participate. We barely included any psychosocial factors such as self-efficacy beliefs that may have proved to be important motivators to participation in HIV therapeutic vaccine trials, such as Remune and ALVAC[103]. We likely missed additional possible motivators and deterrents to participation given the structured nature of the questionnaire. Demographic characteristics such as “having children” as a potential deterrent to study participation were not assessed. We did not directly compensate each study respondent in the survey, and thus lack of financial reward (except for the \$25 gift card drawing for each 25 survey respondents) may have affected motivations to complete the survey. Social desirability bias may have also been an issue, as shown by the high willingness to participate in the 14 categories of HIV cure studies (above 50% for all types, despite the risks). The sample size could have been expanded further to reduce



confidence intervals around point estimates, increase the generalizability of results and stabilize the willingness to participate of different factors. A prospective, longitudinal study, nested within an actual HIV cure study, would have also made the data more valid about actual motivators and deterrents to participation. Another study limitation is that only data from survey respondents were analyzed, while data on study decliners could not be systematically collected. There were 9 survey decliners – the reason was that they did not meet the eligibility criteria (assuming they were HIV-negative). Future HIV cure studies should attempt to compare study decliners with study accepters on various factors to clarify the role of altruism and risks and benefits in decisions to participate in research. Finally, macroscopic factors such as demographic, political, cultural and economic influences could not be assessed in the survey.

With regards to qualitative research, we interviewed a broad range of patient-participants, clinician-researchers and policy-maker key informants. Pharmaceutical company contacts were not represented due to time constraints. The choice for the key informant interviews was based on contact lists based on the perception that they would be interesting key informants or that they would be responsive to the request for an interview.

In order to address some of these limitations, I employed careful validation techniques, including those identified in the validity and reliability sections of the methods section. In retrospect, some of the key informant interview questions may have been leading questions (e.g. “Do you think information about HIV cure research should be shared in your community?”). Furthermore, since qualitative research is deeply interpretive and that personal biases and values may influence the interpretation of results, acknowledging one’s own bias is important. My main bias while conducting this research was the recognition of the need to minimize risks to study participants, while ensuring that the fundamental ethical principles were met such as the fair

selection of research participants, favorable risk-benefit ratio, informed consent and respect for study participants.

While the selection of individuals who were fairly knowledgeable about HIV cure research may have biased the results, recruitment of people living with HIV into social science research is difficult outside of established community networks, unless embedded as part of a clinical study. For convenience of sampling and by necessity as part of the study, not to mention the complexity of the science, I was purposively limiting the sample pool of people living with HIV who may have already been aware of or connected to information about HIV cure studies. As someone who has worked in the field of HIV research for >10 years, and more recently HIV cure research, I have also come to appreciate the upmost importance of the ethical implementation of research. While I strived to maintain objectivity during the data collection and analysis, I was also cognizant that my biases may influence my downstream findings. I was surprised to find that most respondents thought latency-reversing agents were risky, as explained above. In terms of data coding and analysis, codes that were mentioned consistently and discussed in detail during the interviews were identified as themes. Although the key informant interviews represented a wide variety of backgrounds and perspectives, there was a balance between consistency and variability of the ideas expressed. In the end, the data have valuable implications for the ethical and effective implementation of HIV cure studies.

## CHAPTER 7 | PLAN FOR CHANGE/LEADERSHIP/IMPLEMENTATION

*“I have been impressed with the urgency of doing. Knowing is not enough; we must apply. Being willing is not enough; we must do!”*

-Johann Wolfgang von Goethe (1749 – 1832)

### Plan for Change Overview

In the field of HIV cure research, we are witnessing a unique policy window to address emergent implementation and ethical challenges related to participation. It is imperative that we carefully design and plan these studies from the outset, putting participants’ needs and expectations at the forefront in order to avoid unintended and unanticipated consequences. We must further attempt to preserve the public trust in the research towards an HIV cure now, so that any future scientific interventions that arise from it are not tainted by the negative decisions that we make [123].

What are some of the leadership and change opportunities at this juncture, and why do these require leadership? How do the data collected fit in the overall plan for change and create added value in the practice of HIV cure research? And finally, how do the data and evidence collected inform a plan for change, implementation and leadership for the future?

My plan for change is centered around promoting the ethical and effective implementation of HIV cure-related studies through research, public discourse and practical action. I focus on the inherent implications of the research findings as they relate to the implementation of HIV cure-related studies as an emergent field in the social sciences. I also emphasize the need to translate findings into action and describe how the resultant work can be used in practice.

I relied on three main theoretical foundations to implement my plan for change, namely 1) community engagement and participation, 2) implementation science and 3) research ethics; however, these fields overlap as with “implementation ethics” [114][115] (see Discussion section). Further, my plan for change and leadership is informed by four schools of leadership: team and servant leadership, authentic leadership and ethical leadership. During my key informant interviews, I have come to realize the role that implementation leadership and discovery leadership play in HIV cure-related science. The intended practical outcomes include participative processes as well as effective and ethical implementation of HIV cure studies. The plan for change below describes the proposed intersection of these force fields.

For my plan for change/leadership/implementation to be effective, meaningful and relevant, it is imperative that I focus on what I can control. Thus, I intend to use my role as a middle manager to effect change as an emergent process and within evolving systems. According to the literature, middle managers have a key role in strategic change management [124]. Not only do they coordinate and implement strategic programs, but they are also relationship managers, networkers and interpreters of expectations. Additionally, middle managers perform translation, mediation and negotiation tasks, increasing the ability of others around them to respond to change by providing resources, structure and a safe place for learning [124]. Middle managers also work to reduce the impact of problems as they arise and serve as “change intermediaries” and “change catalysts” [124]. Implementing strategic change, however, requires a lot of time and energy [124] and middle managers must find ways to make time to implement the vision. In fact, my most scarce resource at the moment is sufficient time to be able to implement my vision for change.

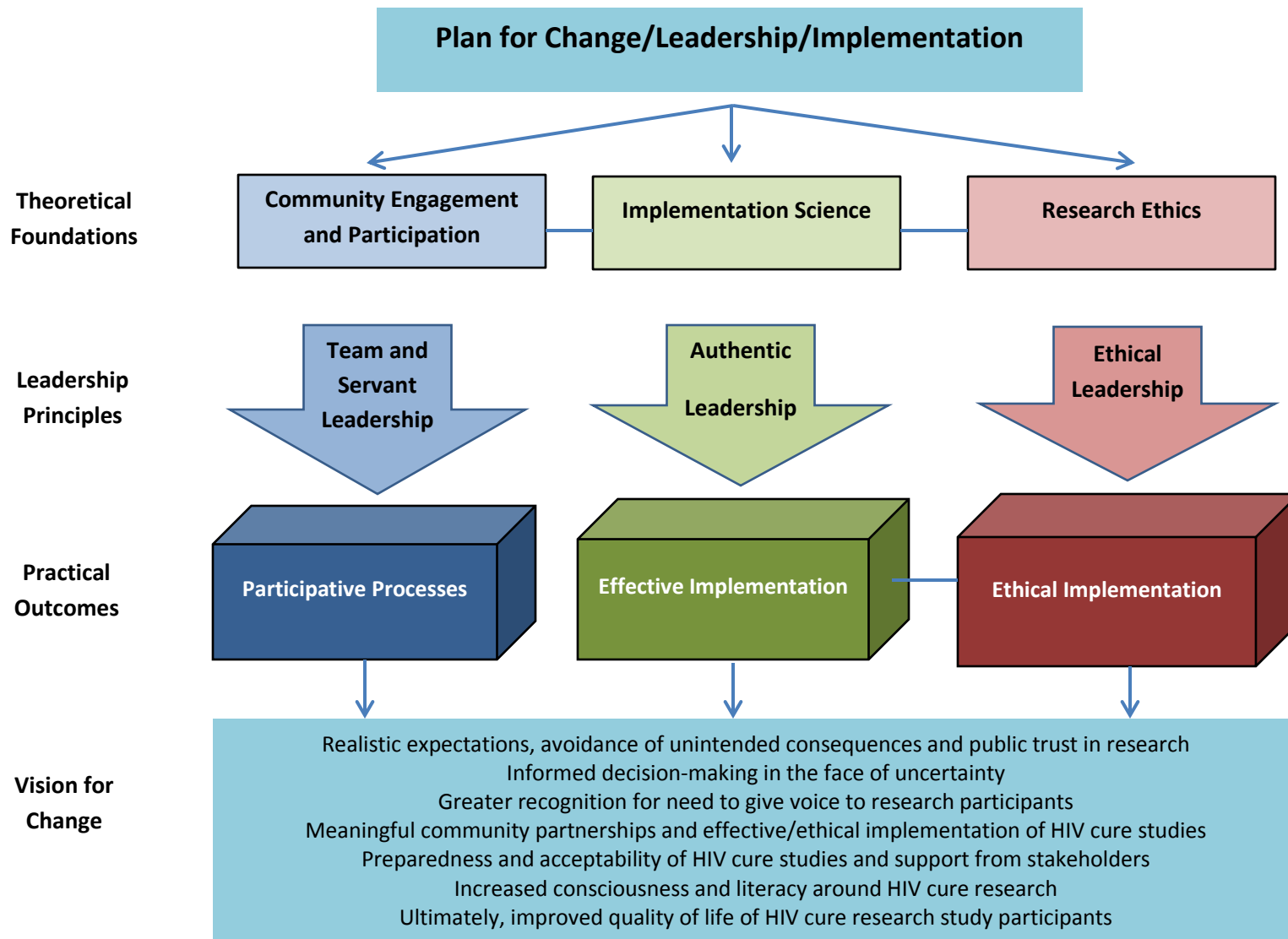


Figure 27. Building Blocks for Proposed Plan for Change/Leadership/Implementation

## Principles of Leading Change and Inspired Actions

The theories of change management that have inspired me thus far include those of Kotter [125], Aguirre [126], Kidder [127] and Kuyvenhoven [124]. Below are the principles that have made an impression on me and that I am incorporating into my toolbox as a public health practitioner. I also included a list of inspired actions that stem from these principles.

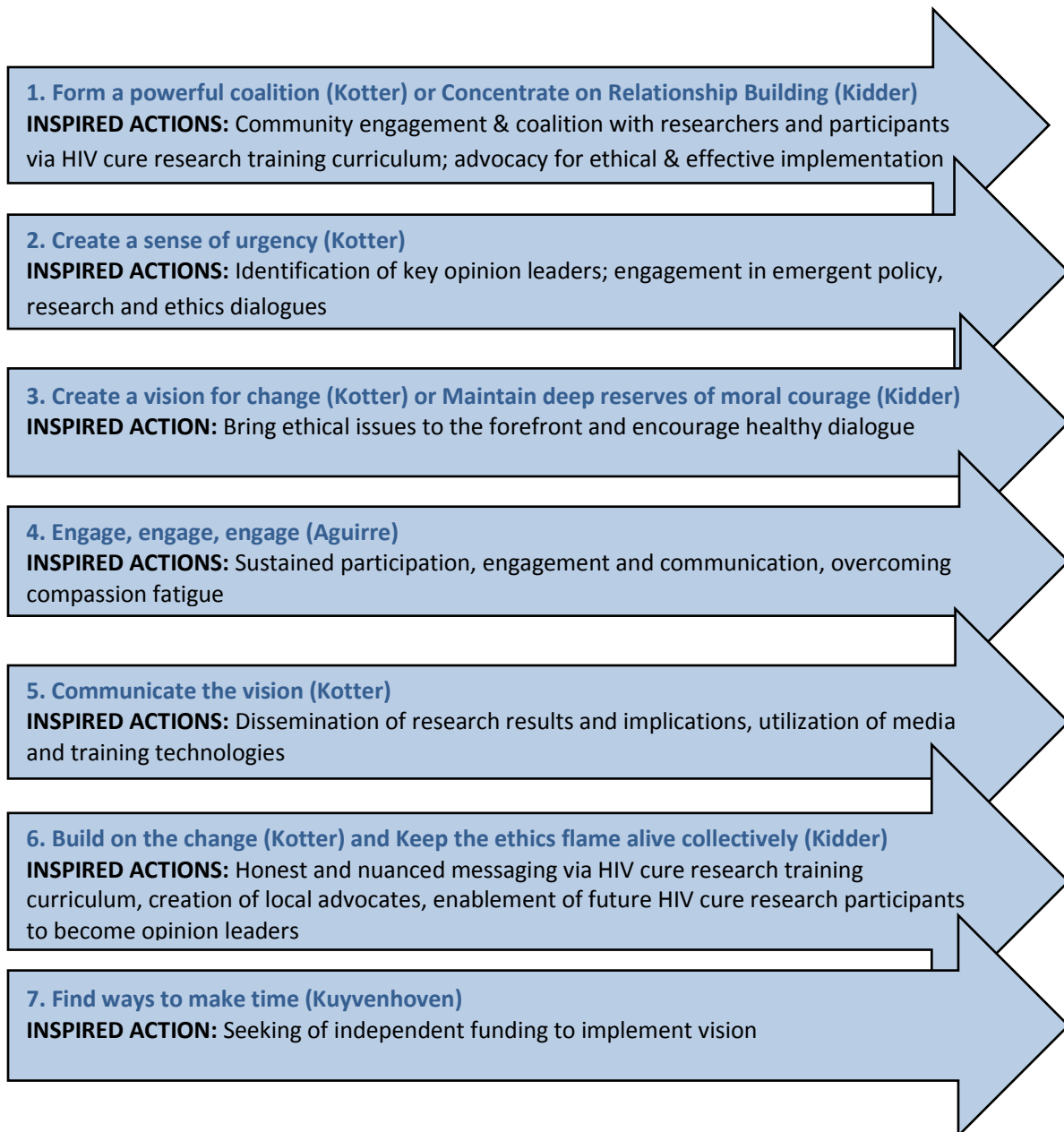


Figure 28. Principles of Leading Change and Inspired Actions

## **Participative Processes**

The first component of my plan for change includes participative approaches, centered around community/stakeholder engagement as well as a patient-centered philosophy. Participative management, in turn, is informed by principles of team and servant leadership. Community engagement and participation of individuals living with HIV should be considered primary in the design of HIV cure research or dissemination of research results, rather than an afterthought. While advocating for opportunities to integrate science, practice and policy in HIV research in general, Glasgow and colleagues argue that researchers and communities will need to establish ways to collaborate effectively moving forward, including the establishment of transdisciplinary and participatory approaches [23]. The determination of best practices in research will need to include considerations for community engagement as a fundamental building block in order to effectively integrate research, policy and practice [23]. Furthermore, the iterative feedback loops between communities and researchers will permit a healthy and open dialogue that will enable opportunities for frontline ownership of the change process [23].

This vision for change is consistent with the new FDA framework on patient-focused drug development [13], which proposes that people living with HIV should be empowered from the outset to make informed choices about HIV cure-related research participation. They should not be mere recipients of the research enterprise, but should actually be actively involved in the design and implementation of studies, as they have something very valuable to contribute. As partners in research, their participation should be regarded as a key success factor driving study implementation, especially since most of them are already virally suppressed thanks to advances in HIV treatment. Most of them are also leading relatively normal lives, are considered “healthy subjects” and their participation in research does not involve an end-of-life care decisions. Furthermore, when they feel that their voices are heard

and responded to, they may have more of a stake in the clinical research enterprise and may be more willing to respond to the inevitable challenges that arise. As ‘frontline people’, they are “rich repositories of knowledge about where potential glitches may occur (...) Not only does more information surfaces [when involving them], but [they] are more invested when they’ve had a hand in developing a plan.” [126]. Active participation and engagement is also known to decrease the likelihood of misunderstandings and can help build support for the research enterprise.

### **Guiding Leadership Theory: Team Leadership [128]**

*“[T]he leader is to do whatever is necessary to take care of the unmet needs of the group.”*

Team or participative leadership theory is informative as it recognizes that teams are composed of individuals who are interdependent. Team leadership, when effective, is also known to lead to better decisions and problem solving as well as greater innovation and creativity. For teams or participative processes to be successful, there needs to be support for the involvement of team members and mechanisms to promote upward communication. Furthermore, teams must encompass the leadership repertoire of the entire team. Processes such as trusting, adapting and learning are given centerstage in team leadership. Effective teams also keep an eye on the larger context. Their tasks include networking, forming alliances, advocating, negotiating, buffering and assessment the environment. Criteria for effective teams or participatory leadership include clear and elevating goals, result-driven structure, unified commitment, devoted team members, collaborative climate, standards of excellence and principled leadership.



### **Guiding Leadership Theory: Servant Leadership [128]**

*“This is not about me... this is about them! (My own interpretation of servant leadership)”*

Although servant leadership involves an inherent paradox and is counterintuitive, it should be the cornerstone of an approach aimed at encouraging greater participation. Servant leaders commit themselves to putting the needs of others at the forefront. They are attentive to the concerns of others, nurture them and empathize with them. Servant leaders are also ethical and develop strong long-term relationships with fellow individuals. By encouraging others to make decisions on their own, building their confidence, servant leaders endeavor to empower others and to bring out the best in them. Core values of servant leadership include respect, trust, empathy, healing, awareness, (ethical) foresight, and stewardship, commitment to the growth of others, building community, humility, emotional intelligence, altruism and humanism. In the end, servant leaders envision a fairer society.

I strongly believe that we can harness the talents of communities of people living with HIV towards a cure. In fact, I would like to help create an addendum to the Good Participatory Guidelines (GPP) [129] for the field of HIV cure research, in collaboration with AVAC. As in the past, community engagement is crucial to help anticipate and resolve ethical challenges as they arise. Communities provide the potential for checks and balances and they allow safe, efficient and effective conduct of research. Focusing on communities also represents a long-term investment in the HIV cure research enterprise. The success will depend upon sound leadership, community and stakeholders already engaged and invested in the research.

### **Effective Implementation**

The second component of my plan for change includes considerations for the effective implementation of HIV cure-related studies. I informed this component with teachings from implementation science and authentic leadership. Appreciative inquiry in the data collection

phase served to identify success factors facilitating implementation of HIV cure studies (see Qualitative Results section for details).

Implementation science seeks to focus attention on the execution, achievement and accomplishment of an action. In a sense, both implementation science and translational research (as in the case of HIV cure-related research) refer both to an ideal and an endeavor: “As an ideal, [they] aim to capture evidence produced by scientific or social scientific processes and get [them] into practice. As an endeavor, [they] recognize that these stages do not happen automatically, often to no great extent, and sometimes not at all” [21]. Yet the provision of a set of factors that either ‘facilitate’ or ‘hinder’ implementation does not necessarily make implementation easy, since implementation occurs in a complex environment [21]. But the knowledge of these factors help prepare for the upcoming change and inform detailed and effective planning.

Effective implementation also includes the intention to avoid unintended consequences and to incorporate lessons learned into practice. Drawing on the law of unintended consequences, careful planning from the outset and knowledge of possible roadblocks and landmines help ensure a more effective implementation of an intervention. For example, in the context of HIV cure research, the topic of analytical treatment interruption or ‘intensively monitored antiretroviral pause’ is deeply controversial at the moment, as we explored in this report. Some argue that treatment interruption is absolutely necessary to assess viral rebound and effectiveness of an intervention, while others contend that it is completely unethical at this early stage of HIV cure research because it may lead to several negative long-term health outcomes. Social sciences studies such as the one presented in this dissertation can be useful to diagnose existing and potential challenges and controversies for the implementation of HIV cure studies.

In turn, path dependency theory provides a useful lense to conceptualize the variables that guide the deployment of an intervention or a set of interventions. The field of HIV cure research is currently ‘exploding’ and will be greatly influenced by the discussions, dialogues and decisions that we have/make at this juncture of the policy window. Path dependency theory provides us the *modus operandi* or instrument to determine how certain policies or decisions are implemented and deemed socially desirable while others are not [130]. It reminds us to keep everything into a historical perspective but also invites (ethical) foresight. Path dependency also supports learning and incremental change, together with an overtone of caution since the deployment of interventions may have long-term, and sometimes negative and irreversible consequences [130]. Path dependency further gives insights into what can lead to sustainable change that survives over time. Consciencious efforts must be made to push the implementation of interventions onto the ‘right’ path.

#### **Guiding Leadership Theory: Authentic Leadership [128]**

*“Authentic leaders are genuine, have a real sense of purpose and serve catalysts for change.”*

Authentic leadership is one of the most practice-oriented leadership theories. Authentic leaders find what is true in themselves, in their organizations and in the world. They focus on locating the problems and selecting appropriate actions to resolve them. They are genuine, have a real sense of purpose and serve as catalysts for change. They proceed with confidence, hope, optimism, resilience and moral reasoning. They also have self-knowledge and self-regulation and analyze information objectively yet act from their heart. They also view leadership as a process and incorporate meaning, mission, structure and appropriate resources into their leadership style.

## Ethical Implementation, Moral Courage and Professional Issues

The third component of my plan for change includes considerations for ethical implementation, moral courage and professional issues in the conduct of HIV cure research as they relate to participation of people living with HIV. I informed this component with teachings from research ethics and ethical leadership. I also attempted to expose how the evidence derived from my research relates to ethics and regulatory principles for the protection of human participants in research, including respect for persons, beneficence and nonmaleficence and justice (see Discussion section for details).

One of my main inspirations for this segment is Rushworth Kidder's book *How Good People Make Tough Choices*. Kidder defines ethics with the concept of "ought." "[Ethics] is not about what you have to do because regulation compels it (...) It's about what you ought to do – have an obligation to do – because it is right." And with ethics, "as with the rest of life, there are no magic answer systems (...) Making ethical decisions depends on judgement, character, moral awareness, perception, discrimination – a whole host of imponderables." [127] In fact, tough choices often operate in territories where laws and regulations do not reach. Kidder teaches us about the need to develop our *ethical fitness* and to embrace our core values, such as responsibility, compassion, honesty, fairness and respect. "What is needed," he says, "is a capacity to recognize the nature of moral challenges and respond with a well-tuned conscience, a lively perception of the difference between right and wrong, and an ability to choose the right and live by it." One is only ready to sustain an effort or change over the long-term if s/he remains mentally engaged with and if s/he ultimately cares about the issue. Of course, this requires a moral compass and moral courage – an attribute essential to leadership. "Developing (...) ethics requires that intelligence fuse with intuition, that the process be internalized, and that decisions be made quickly, authoritatively, and naturally."

## Guiding Leadership Theory: Ethical Leadership [128]

*“And little wonder, finally, that as we practice resolving dilemmas we find ethics to be less a goal than a pathway, less a destination than a trip, less an inoculation than a process.”*

Ethical leadership is rooted in the Greek word *ethos* and translates into conduct and character of a person. Ethics is concerned with the values that individuals or societies find desirable or appropriate. In fact, to implement change carries with it great ethical burden and responsibility. Ethical leaders are those who use authority to pay attention to issues, to frame issues and to facilitate ethical decision-making. Principles of ethical leaderships include respect, service and honesty. Ethical leaders strive to build the community around them.

Thus, embodying ethical action in practice entails meeting the highest ethical standards in each action and interactions. It means having continuous ethical awareness. McCullough [53] outlined several additional ethical principles that should be considered in the face of clinical uncertainty that are highly relevant here:

**Table 29. Ethical Principles under Conditions of Clinical Uncertainty**

Ethical Principles under Conditions of Clinical Uncertainty [53]	
✓	<b>Candor:</b> The professional virtue that obligates the practitioner to acknowledge and correct errors using evidence-based reasoning. Candor is an antidote to enthusiasm.
✓	<b>Enthusiasm:</b> Clinical judgement undisciplined by evidence-based reasoning. Enthusiasm should be regarded as an infectious process in clinical decision making that can spread rapidly between practitioners.
✓	<b>Integrity:</b> The professional virtue that obligates the practitioner to follow standards of intellectual excellence and seek to “always do the right thing.”
✓	<b>Expectation:</b> The belief that a future state of affairs will occur.
✓	<b>Hope:</b> The concept of hope has two components: a probability >0 and <1 that a future state of affairs will occur; and the desire for a future state of affairs.
✓	<b>Prudence:</b> The virtue that schools us in the discipline of identifying our legitimate interests and acting to protect and promote them.
[Adapted from [53]]	

## **Plan for Change/Leadership/Implementation Deliverables**

There are five concrete ways that I hope my dissertation project can help improve practice: 1) through the dissemination of research findings, 2) community engagement and coalition building, 3) involvement in research and policy dialogues around HIV cure research and preparation of considerations, best practices, lessons learned and decision aids for HIV cure research, 4) development and implementation of a comprehensive HIV cure research training curriculum (CUREiculum), and 5) through the identification of future research questions. I describe these five elements below.

### **Dissemination of Research Findings**

I would like to share the findings from my research through the publication of journal articles, submission of abstracts at major international HIV conferences and HIV cure-related workshops and through the preparation of blog posts. I hope that my research findings will be relevant to both HIV cure scientists and communities affected by HIV. Since this is an emergent field, I expect that the data will add to the body of knowledge and advance/inform HIV cure research implementation and policy/ethical considerations. The collection and publication of data will in turn give me more authority, credibility and even legitimacy in the field, and help me be recognized as a 'leader'.

#### **Journal Articles and Abstracts (Formal Channels)**

I would like to prepare manuscripts to be submitted for publication and to present findings at international HIV conferences and HIV cure research workshops. I would like to use the summarized findings (e.g. tables and narratives) for my dissertation research and prepare manuscripts for submission on the topic of barriers/facilitators to participation in HIV cure-related studies in collaboration with the DrPH committee members. The data derived could further generate evidence to support the ethical decision-making and effective implementation

of HIV cure-related studies. Below, I also provide suggestions for future empirical research and hopefully contribute to the formulation of an enhanced research and policy agenda for the social sciences of HIV cure-related research. Ultimately, I aspire to continue studying factors that affect participation in HIV cure studies via a larger prospective, quantitative study of barriers and facilitators to participation and retention.

In addition to publishing manuscripts and presenting at HIV conferences, I plan to disseminate the results to patient advocacy groups, as this would constitute a critical transfer of knowledge. I am also in the process of implementing the focus group discussions with leaders of the national Martin Delaney community advisory board (until June 2016), the results of which will be summarized separately.

Completed manuscripts to peer-reviewed and practice-oriented journals include:

- Framing expectations in early HIV cure research (published in *Trends in Microbiology* in October 2014, lead author with David M. Margolis and Gail E. Henderson) [11]
- Participation in HIV cure-related research: a scoping review of the proxy literature and implications for future research (published in the *Journal of Virus Eradication* in October 2015, lead author with Dr. Sandra Greene) [40]
- Towards a multidisciplinary HIV cure research: integrating social science with biomedical research (published in *Trends in Microbiology* in January 2016, middle author (lead author: Cynthia Grossman)) [41]

Planned manuscripts to peer-reviewed and practice-oriented journals include, but may not be limited to:

- Paper(s) reporting results from semi-structured survey from DrPH dissertation project (e.g. descriptive statistics, bivariate and multivariate results)\*\*

- Paper(s) reporting results from the key informant interviews and discussion section from the DrPH dissertation project\*\*
- Paper on the ethical issues inherent in analytical treatment interruption with the Division of AIDS (DAIDS) of the National Institutes of Health (NIH) (submitted to *Lancet Infectious Diseases*; co-author with Stuart Rennie)
- Paper on the ethics of HIV cure clinical research among acutely infected adults: points for consideration (submitted to the *Journal of the International AIDS Society*, co-author with Stuart Rennie)
- TBD

\*\*direct product of DrPH dissertation research; to discuss with DrPH committee members

Conference abstracts presented and/or submitted:

- Dubé K, Taylor J, Jefferys R, Sharp M, Wakefield S, Handibode J. Results of a community needs assessment and pilot test of a novel HIV Cure research training curriculum. Presented at 2015 IAS Towards an HIV Cure Symposium, July 2015, Vancouver, Canada.
- Taylor J, Handibode J, Sharp M, Jefferys R, Wakefield S, Dubé K. Decoding HIV cure science: A CUREiculum seminar. Presented at the 2015 United States Conference on AIDS, September 2015, Washington, D.C.
- Dubé K, Taylor J, Evans D, Sylla L, Burton A, Skinner A, Greene S. Emerging results of an extensive survey of potential participant's willingness to take risks and donate to HIV cure research in the United States. Presented at 7<sup>th</sup> International Persistence during Therapy Meeting in Miami, Florida on December 10, 2015.
- Sylla L, Taylor J, Evans D, Weiner B, Skinner A, Greene S, Dubé K. Perceived benefits of HIV cure-related research participation in the United States. Abstract submitted to 2016 IAS meeting July 2016. Outcome pending.



- Taylor J, Evans D, Sylla L, Dee L, Weiner B, Skinner A, Greene S, Dubé K. Perceived risks of participating in HIV cure-related research in the United States. Abstract submitted to the 2016 IAS meeting July 2016. Outcome pending.
- Taylor J, Evans D, Sylla L, Dee L, Weiner B, Greene S, Rennie S, Dubé K. What is “too much risk” in HIV cure clinical research in the United States? Abstract submitted to the 2016 IAS meeting July 2016. Outcome pending.
- Dubé K, Evans D, Taylor J, Sylla L, Dee L, Rennie S, Weiner B, Skinner A, Thirumurthy H, Greene S. Multivariate results of an extensive survey of potential volunteers’ willingness to participate in HIV cure-related research in the United States. Abstract submitted to the 2016 IAS meeting July 2016. Outcome pending.
- Evans D, Taylor J, Sylla L, Garner S, Weiner S, Skinner A, Greene S, Rennie S, Dubé K. Treatment interruptions in HIV cure studies in the United States: perceptions, motivations and ethical considerations from potential HIV-positive volunteers. Abstract submitted to the 2016 IAS meeting July 2016. Outcome pending.
- Garner S, Rennie S, Ananworanich J, Dubé K, Margolis D, Sugarman J, Tressler R, Gilbertson A, Dawson L. Interrupting HIV treatment in cure research: scientific and ethical considerations. Abstract submitted to the 2016 IAS meeting July 2016. Outcome pending.
- Dubé K, Weiner B, Taylor J, Garner S, Rennie S. Is there an implementation ethics to HIV cure-related research? Abstract submitted to the 2016 IAS meeting July 2016. Outcome pending.
- Salzwedel J, Hannah S, Taylor J, Dubé K. Community engagement in HIV cure-related research: applying Good Participatory Practice (GPP) principles to community education efforts. Abstract submitted to the IAS 2016 meeting July 2016. Outcome pending.

### **Blog Posts (Informal Channels)**

Furthermore, I hope to be able to use more flexible technologies and blog posts to continue promoting the ethical and effective implementation of HIV cure-related studies. Blog posts are an excellent way to share best practices, lessons learned alerts and to react quickly to issues related to HIV cure-related research implementation. This is also a way to “find my voice” and to contribute to policy dialogues. See blog posts under the searchHIV website at: <http://searchiv.web.unc.edu/blog/>.

### **Community Engagement and Coalition Building/Strengthening**

Community engagement and coalition building/strengthening may prove to be a key ingredient and a chief indicator for change as it relates to HIV cure research implementation. The key principles guiding my community engagement will be co-agency, trust, openness, fairness and shared decision-making in the face of uncertainty. I will continue my community engagement in the National Martin Delaney Collaboratory CAB since I have been elected as a new member in January 2016. I will also continue my involvement in the UNC-CH Center for AIDS Research (CFAR) Community Advisory Board (CAB). Community engagement and coalition building/strengthening will aim to promote the ethical and effective implementation of HIV cure studies and will focus on relationship building and process values. I will encourage fellow CAB members to have a say in research and policy issues that affect them. I further hope to conduct debriefing sessions of my research with CAB members and will ask them what they would like to do with the information.

In fact, a primary driver for my research is the potential utility of the findings for patient advocates. By creating findings that are accessible and useful to patient advocates, and by involving them in the research process, the policy-making and implementation process can be influenced and facilitated in a meaningful grassroots approach. In a sense, I am inspired here

by the teachings of Paulo Freire, whose critical consciousness or *conscientização* emphasizes co-learning, shared leadership and ultimately transformation. Critical consciousness focuses on taking action against the oppressive elements of one's life, on achieving a deep understanding of the world and on exposing social contradictions as a liberating process [131]. Further, because advocates then to be more informed and assertive than the general public, they are more likely to make substantive contributions to research practice and policy [64].

For my plan for change to be successful, coalition building and engagement with opinion leaders, champions and agents of change will be important. In fact, “successful [change and] implementation [are] more likely if leverage and enablers are harnessed.” [21] For example, together with CAB members, we may produce position statements and participatory practice guidelines for HIV cure-related research. Communities are asking for a return to the Denver Principles developed in 1983 aimed at protecting the rights of AIDS patients. One of these rights is for people living with HIV to be included in all AIDS forums with equal credibility as other contributors and to be able to share their lived experiences and knowledge of the disease. In order for community engagement and coalition building to be truly impactful moving forward, it will be important to engage more women and people of color in the process. This is a real challenge facing the entire HIV research field. However, community engagement will not serve as a substitute for true, meaningful social sciences around HIV cure research.

#### **Engagement in and Contribution to Research and Policy and Implementation Dialogues and Development of Tools to Facilitate Research Implementation**

I would like to continue contributing to research and policy dialogues around HIV cure-related research. Ultimately, I would like to find a position that will allow me to become an “ethical voice” in the field of HIV cure research. My aspiration is to be recognized as a leader in the social sciences of HIV cure research and in infectious disease implementation.

There are three mechanisms through which I can accomplish this at the moment:

- ⇒ UNC-CH R01 Team on the Social and Ethical Consequences of HIV Cure Research
- ⇒ Forum for Collaborative HIV Research – Social Sciences Working Group (Patient Recruitment, Education and Informed Consent)
- ⇒ International AIDS Society Psychosocial Working Group

I believe that involvement in and participation to working groups and workshops is what facilitates communication and accelerates progress. Discussions often contribute to the shaping and creation of policy statements and journal articles that are later published. It is also a way to become recognized as a leader in the field. For example, I presented the results of my literature review at the International AIDS Society psychosocial working group meeting in Melbourne, Australia in July 2014. This workshop was dedicated to request increased funding to study crucial social sciences issues around the implementation of HIV cure-related research. I also presented my literature review at the Brocher Fondation workshop in Geneva, Switzerland in May 2014 on the Intended and Unintended Consequences of HIV Cure Research.<sup>32</sup> My literature review was also highlighted at the Forum for Collaborative HIV research HIV cure meeting in Washington, D.C. in June 2014.<sup>33</sup>

An aspirational goal would be to contribute to the development of considerations, best practices, lessons learned and decision aids around HIV cure-related research. While some practitioners argue that it is too early or pretentious to implement firm guidelines at this juncture, others think that some sort of shared guidance has become necessary to minimize unintended consequences. We are waiting for the right “policy window” for this to occur, but it may only be a matter of time before such considerations become necessary. I would like to

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<sup>32</sup> <http://www.brocher.ch/en/events/75/unintended-and-intended-implications-of-hiv-cure-a-social-and-ethical-analysis>

<sup>33</sup> <http://www.hivforum.org/projects/drug-development/hiv-cure-project>

help generate considerations around effective and ethical HIV cure research implementation, focusing on recruitment of study participants. While it is too early to speak in terms of guidelines, perhaps the field is ready to begin discussing best practices. Since we are still in the process of discovery in the field of HIV cure research, it may still be too early for true or emerging consenses at present. Yet, there is tremendous value in fostering dialogue, especially given the current state of the HIV cure research field where so many questions include “well, it depends.” Thus, instead of premature practice guidelines, it may be best to call for more robust dialogues among stakeholders to define a pathway that will eventually lead to normatively sound evidence-based guidelines.

Considerations for effective and ethical implementation of HIV cure-related research could take the form of checklists or decision aids as well as specific recommendations around recruitment. This will obviously take consensus building – and the consensus, if any can be reached, will be evolving. Another useful tool would be the provision of reliable and sustained flow of information about research opportunities as well eligibility requirements for HIV cure-related studies. The development of considerations may be viewed through difference lenses – either as enhancing facilitators (e.g. appreciative inquiry), preventing barriers or contributing to shaping the field in general. In order to meet the translational challenge of moving HIV cure research forward (and later of moving scientific discoveries into practice), we will need to be able to leverage and integrate this information into useful formats.

John Kidder, in his book on ethics, argued that sometimes, what is more powerful is “not necessarily a checklist that is applied in the heat of the moment, but (...) a guide to the underlying structure of ethical decision-making” [127]. These constitute the “widely shared codes of conduct within a profession” [127]. Having a moral compass and simply knowing where one stands on the ethical line can be impactful to set standards.

The following tables summarize responses received from the key informant interviews to the questions:

- ⇒ What guidance is needed for patient-participants wanting to participate in HIV cure studies?
- ⇒ What guidance is needed for clinician-researchers implementing HIV cure studies?
- ⇒ What guidance is needed for policy-makers/regulators regarding HIV cure studies?

Responses to these interview questions were not summarized in the results section. I felt that it was much more appropriate to summarize them in the plan for change section, as they have immediate applicability to facilitating the effective and ethical implementation of HIV cure studies.

**Table 30. Possible Considerations for Stakeholders to Facilitate Effective and Ethical Implementation of HIV Cure Research**

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**Possible Considerations for Stakeholder to Facilitate Effective and Ethical Implementation of HIV Cure Research**

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**General Considerations**

- ⇒ Considerations for language used in HIV cure research
- ⇒ Considerations to facilitate acceptability of HIV cure studies for study participants
- ⇒ Considerations surrounding risks and benefits of HIV cure studies, using a nuanced, matrixed approach to evaluate risk-benefit ratios and ethical considerations across various types of studies
- ⇒ Considerations to address ethical issues in HIV cure studies with analytical treatment interruptions
- ⇒ Advocate for the need to apply lessons learned from previous work as well as consider the unique circumstances raised in HIV cure research (requires careful, nuanced analysis)
- ⇒ Advocate for cross-dialogues and interactions between basic sciences, translational research, animal research, clinical research, bioethicists, social medicine, anthropology, economics, health policy, law (e.g. workshops)
- ⇒ Ensure the right setting to promote dialogue and create safe environments; stay opened to possible landmines (usually find them upon stepping on them)

**For Patient-Participants**

- ⇒ Decision-making algorithm so patient-participants can better understand where they fit in the HIV cure research continuum
- ⇒ Use of technologies for decision-making and help study participants navigate the field (e.g. apt for clinical trial decisions, simple updated websites for knowing what studies are enrolling, use of social media)
- ⇒ Decision aids for HIV cure research<sup>34</sup> or personal decision guides[68] (consult International Patient Decision Aids Standards (IPDAS))
- ⇒ Explore different, more effective mechanisms to present informed consent information to potential study volunteers (e.g. procedural videos, peer education with past study participants, etc.)
- ⇒ Standard list of questions that participants should ask themselves prior to joining HIV cure studies (e.g. values and priorities)
- ⇒ Encourage and facilitate peer-to-peer recruitment in HIV cure studies
- ⇒ Educational materials such HIV/AIDS cure glossaries<sup>35</sup> (also see CUREiculum section below)
  - Make information accessible
  - Press that we are in the early days of research
  - Focus on risks and benefits information, emphasize expectations
  - Emphasize importance of participating in HIV cure studies, focusing on altruistic motives
  - Need more innovative teaching methods (videos, cartoons, infographics)

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<sup>34</sup>Decision aids lead to better knowledge, more accurate perceptions of risks, greater comfort with and participation in decision-making and fewer people remaining undecided [12]. They are also known to decrease anxiety and decisional conflict [137].

<sup>35</sup><http://www.projectinform.org/pdf/HIVCureGlossary.pdf>

- Use educational tools to help relationships between patient-participants and clinician-researchers; organize forums for meaningful interactions
- Debunk myths, misperceptions, misunderstandings and mistaken reporting
- ⇒ Advocate for funding for educational initiatives

#### **For Clinician-Researchers**

- ⇒ Refreshers on ethical research guidelines; draft “ethics plan” [116]
- ⇒ General considerations to facilitate acceptability of HIV cure studies for study participants
- ⇒ Considerations for HIV cure clinical study protocols and designs, including safety monitoring and escalation of interventions, and criteria that the FDA sets
- ⇒ Considerations for risk mitigation plans in early HIV cure studies
- ⇒ Considerations for recruitment materials to ensure that they are ethical and participant-focused, focused on potential risks, benefits, probabilities, uncertainties and alternatives<sup>36</sup>
- ⇒ Standard list of questions that clinician-researchers should use prior to enrolling study participants to ensure readiness
- ⇒ Draft for an informed consent template with proper terminology to be used to describe research
- ⇒ Draft comprehensive checklists for HIV cure research, as assurance of understanding of the informed consent is essential[54]
- ⇒ Tools to help clinician-researchers explain HIV cure research to study participants (e.g. humanoid with images of where the HIV reservoir is)
- ⇒ Education to clinician-researchers about the motivations, needs and interests of study participants
- ⇒ Systems to stay in touch with potential study volunteers, so that if they do not qualify for one study, they may still qualify for other future studies
- ⇒ General rules of behaviors (e.g. since numbers are so small, need to give a lot of consideration and attention to each individual participant; avoid “tokenism” with people living with HIV; cultural competence and sensitivity trainings; communication skills)
- ⇒ Ensure that there is a team about the HIV cure scientists and the participants (e.g. mental health professionals, social workers, etc.)
- ⇒ Better information for HIV providers about available HIV cure studies to facilitate referrals of potential study participants
- ⇒ Advocate for standardization of assessments to allow for better comparability between studies and interpretation of results
- ⇒ Better collaboration between researchers to refer study participants to study (e.g. trans-collaboratory partnerships)

#### **For Policy-Makers/Regulators**

- ⇒ Regulatory considerations for HIV cure research (e.g. pre-IND process, early discussions with clinical investigators)
  - ⇒ Policy and legal considerations for HIV cure research
- 

<sup>36</sup>Recruitment materials need to receive IRB approval. Should funding agencies also require investigators to report their plans for recruiting study participants?





## **Development and Implementation of HIV Cure Research Training Curriculum: The CUREiculum<sup>37</sup>**

With Jessica Salzwedel from AVAC (formerly the AIDS Vaccine Advocacy Coalition), I co-chair a novel, comprehensive HIV cure research training curriculum (the CUREiculum). The CUREiculum is a collaborative project aimed at making HIV cure research science accessible to the community and the HIV research field.

The three main CUREiculum goals are to:

- ⇒ Provide basic scientific knowledge on a range of HIV cure research related topics
- ⇒ Strengthen community capacity to participate in and make decisions about HIV cure research
- ⇒ Promote the ethical development and implementation of HIV cure clinical studies

The objective of the CUREiculum is the creation of an international learning community around HIV cure research and a clearinghouse to disseminate research results in a way that is comprehensible to the lay community. The CUREiculum is a well-coordinated program that brings together scientists and community members to discuss key topics around HIV cure research. The CUREiculum will also introduce transparency and accountability to enhance safeguards around HIV cure research, possibly providing checks and balances. There are currently around 15 modules, focused on the main HIV cure research modalities. In addition to highlighting key research findings, the CUREiculum teaches main ethical and implementation issues (see below) and discusses past and future (planned) HIV cure studies. Powerpoint teaching sets, pre-/post test assessments, webinar series, participatory activities and case studies are prepared and live on a central website. Additionally, the CUREiculum committee

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<sup>37</sup> <http://www.avac.org/cure-curriculum>

organizes town hall meetings at various locations around the United States and around the world, adjacent to major HIV (cure) research conferences and workshops.

There are currently few resources that are dedicated to fostering a broad, informed, credible and informed dialogue between researchers, participants, advocates and the lay community around HIV cure research. The CUREiculum provides a communication infrastructure to facilitate such relationships, since communication is key to developing and implementing change initiatives and to promoting participation. In fact, “[p]olicy analysis is not just an exercise in truth-telling (...). It is a pragmatic and responsible effort to facilitate reasonable discourse about a policy future that is inherently uncertain.” [132] In point of fact, the idea of an educational process in policy making has been recognized. This is where I am to “[take] responsibility for opening up a dialogue and perhaps [try] to infuse it with reason and insight, and then [allow] the political process to take over.” [132] The CUREiculum is definitely a way to expand my moral perimeter and improve on my communication skills. I draw tremendous inspiration and emotional energy from my interactions with scientists and community advocates.

In leading strategic change, John Kotter advised to put in place a structure for change, to permit an honest dialogue and obtain support and to openly address people’s concerns and anxieties and ideas [125]. The CUREiculum aims at doing just that, providing a feedback mechanism to solicit feedback about the HIV cure research process.

Researchers have a vested interest in listening and responding to participants’ concerns and the CUREiculum opens a transparent public and political dialogue about the science. The multi-faceted techniques used has several advantages, encouraging dialogue, clarifying meanings and helping promote ‘buy in’ for ethical science. The CUREiculum is also a product and a process that both researchers and community can rally around while waiting for concrete

scientific results. It provides focus to the community efforts, while encouraging literacy and learning about the science. In response to servant leadership, it is necessary to have a process to give people the knowledge they need in order to sustain the change over time, especially when the science is so complex. The CUREiculum further instils great appreciation and recognition for people living with HIV who take part in HIV cure studies and also ensures that their voices are heard. In a sense, the CUREiculum aims at injecting democracy into the HIV cure research scientific process. It requires “a conscious effort to cultivate mutual respect and trust among collaborating laypeople and technical experts” [64].

There is a growing recognition in the field that researchers and communities need to bridge the epistemic gap to ensure adequate preparedness and acceptability of HIV cure studies. The CUREiculum is an attempt to respond to the growing need for a reliable source of information on HIV cure research and HIV cure research participation. The CUREiculum is entirely evidence-based and is intended as a vehicle for reflective dialogue and to encourage ethical and effective implementation of studies. In fact, [t]he task of any sort of conscious reflection (...) is to make explicit what’s often left unsaid, to help systematize the fragmentary and order the haphazard.” [127] The CUREiculum provides that collaborative and supporting environment and promotes a culture of safety and teamwork.

In addition to co-leading the entire effort, I was able to obtain funding for the initiative via the national Martin Delaney collaboratory community advisory board (programmatic component) in collaboration with AVAC, from January – June 2016. The immediate goal is to revamp the CUREiculum modules that will be relevant to the International AIDS Society 2016 conference in Durban, South Africa (including introduction to HIV cure research, stakeholder and community engagement, informed consent and ethics, pediatric HIV cure research and early antiretroviral treatment). I am also preparing fact sheets to accompany the modules. I

hope to implement the marketing plan for the CUREiculum effort developed as part of HPM 962 class and the business plan developed as part of the HPM 959 class.

The main HIV cure research modalities are covered as part of the CUREiculum. I am leading the module on participation in HIV cure research. I consider the CUREiculum the main product, process and instrument to prepare for change that is within my control. I am in the process of preparing and implementing a needs assessment to better comprehend literacy needs around HIV cure research. In turn, these results will have implications for the informed consent of participants in HIV cure research. I also presented an abstract about the CUREiculum at the 2015 Towards an HIV Cure Symposium meeting of the International AIDS Society in Vancouver, Canada in July 2015 and presented a CUREiculum seminar at the United States Conference on AIDS in Washington, D.C. in September 2015. The CUREiculum concept emerged at the 2014 Conference on Retroviruses and Opportunistic Infections (CROI). The CUREiculum committee officially launched the initiative at the 2015 CROI in Seattle, WA. An update was presented at the pre-CROI 2016 HIV cure community workshop in Boston, MA.

Example CURE-riculum website and products: <http://www.avac.org/cure-curriculum>

# CUREiculum



## What is the CUREiculum?

The CUREiculum is a suite of tools that provides simple, accessible information on HIV cure research, organizing into a systematic format for ongoing or issue-specific learning. The CUREiculum was developed in a multi-collabratory process by leading scientists, community educators and various advocacy organizations who recognized the need for increasing literacy in this exciting arena. The tools are designed for community educators, funders, media and other stakeholders. Fifteen key areas of HIV cure research have been developed into free standing modules.

## Table of Contents

- HIV/AIDS and Cure Basics
- Stakeholder Engagement in HIV Cure Research
- Gene Therapy/ Stem Cell Transplant
- Shock and Kill and Latency-Reversing Agents
- Measuring the Latent HIV Reservoir
- Regulatory Issues in HIV Cure Trials
- Early ART
- Pediatric HIV Cure Research
- Concepts in Basic Sciences and Translational Research - The Main Pathways
- Therapeutic Vaccines and Immune-Based Therapies
- Informed Consent and HIV Cure Research
- Ethics of HIV Cure Research
- Participation in HIV Cure Trials
- Animal Models (*coming soon*)

**Figure 29. The CUREiculum**

As a direct outcome of my DrPH research, I wanted to incorporate nuanced and ethical considerations for various HIV cure research modalities into the CUREiculum. The table below summarizes some of these considerations.

**Table 31. Ethical Considerations for Various HIV Cure Research Modalities – The CUREiculum**

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**Ethical Considerations for Various HIV Cure Research Modalities – The CUREiculum<sup>38</sup>**

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**Latency-Reversing Agents**

- ⇒ May not require analytical treatment interruption in the short-term
- ⇒ But have not been shown to cause a substantial reduction in the size of the replication-competent HIV reservoir to date
- ⇒ Possible consequences of reactivating latently infected cells
- ⇒ Will not be sufficient alone and will need to be paired with an immune strategy
- ⇒ Benefits of research accrue to science and society
- ⇒ Ethical considerations of using anti-cancer drug
- ⇒ Likely need to be used in combination

**Therapeutic Vaccines**

- ⇒ Therapeutic vaccines often (although not always) include ART interruptions to assess if vaccine-induced immune responses can exert an anti-HIV effect in the absence of ART (ethical issues associated with risks of treatment interruptions)
- ⇒ Possible risk that a therapeutic vaccine could increase rather than decrease HIV replication by creating additional CD4+ T cell targets for the virus
- ⇒ Participation in a clinical trial of a therapeutic vaccine candidate may preclude participation in future trials of other therapeutic vaccine candidates
- ⇒ Multiplicity of factors that can influence adaptive immunity (e.g. sex, age and genetics) means that diversity of trial participants is particularly key for understanding the spectrum of potential responses to therapeutic vaccine candidates (as for vaccines generally)
- ⇒ Use of the word “therapeutic” to describe the research is problematic

**Gene Therapy/Stem Cell Transplant**

- ⇒ Gene therapy studies involve different gene editing/modifying techniques
- ⇒ Precision is key – a serious concern if “off target” editing
- ⇒ If the genes other than those targeted are modified (off target editing), the potential for serious adverse events exist, including cancer
- ⇒ Scalability of approach
- ⇒ Risk to participants who are otherwise “healthy”
- ⇒ Potential race and clade differences
- ⇒ Likely need to be used in combination

**Pediatric Studies[32]**

- ⇒ Consent issues during labor and delivery
- ⇒ Pressure to discontinue ART
- ⇒ Drug fatigue in adolescence
- ⇒ Frequency of viral rebound assessment
- ⇒ Ability to emotionally support parent
- ⇒ Higher risk of therapeutic misconception?
- ⇒ Blood volume issues with infants
- ⇒ Ability to assess rebound (e.g. frequency) in case of a treatment interruption
- ⇒ Issues related to consent/assent – infants cannot consent themselves
- ⇒ Drug fatigue in later years of life
- ⇒ Emotional support for the mother – having baby go through this experience is hard
- ⇒ Ability of mothers to provide informed consent for a neonate who would start a

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<sup>38</sup> <http://www.avac.org/cureiculum>

study immediately after delivery – is a woman in labor able to make an informed decision, particularly if she has just learned that she is HIV-positive?

#### **Early Antiretroviral Treatment**<sup>39</sup>

- ⇒ Treatment interruption is not medically necessary and potentially harmful
  - ⇒ Early treatment is not curative but the combination approaches may first be available for those treated early
  - ⇒ Treatment fatigue
  - ⇒ Consenting issues
- 

#### **Possible Avenues for Future Research**

The last component of my plan for change consists in summarizing possible questions for future social sciences research around HIV cure. While HIV cure research will fundamentally be biomedical, I strongly believe that the social sciences can add tremendous value. I will remain a fervent advocate to sound social sciences in HIV cure because I see the synergies between the biomedical and social sciences in HIV cure research. Social sciences guide meaningful community and stakeholder engagement and ensure the ethical conduct of research. They also enhance patient-participant and clinician-researcher communications and ensure basic inclusion of communities. They also facilitate research-policy synergies, assist in health systems preparedness and ultimately help us reduce HIV stigma. Of course, there are also several unresolved conceptual and normative questions related to HIV cure research and research ethics.

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<sup>39</sup>See manuscript led by Gilberton A et al. “The ethics of HIV cure clinical research among acutely infected adults: points of consideration” Submitted to *Journal of the International AIDS Society*. Outcome pending.

**Table 32. Future Possible Social Sciences Questions around HIV Cure Research**

<b>Future Possible Social Sciences Question around HIV Cure Research<sup>40</sup></b>
<b>Meanings of Cure</b> <ul style="list-style-type: none"> <li>❖ What are the various meanings of HIV cure research and how can we reconcile patient-participants, clinician-researchers and policy-makers/regulators' perspectives?</li> <li>❖ What are the various meanings of "success" in HIV cure research (including intermediate outcomes)</li> <li>❖ What do potential participant understand about HIV cure research and how does that affect their willingness to participate?</li> </ul>
<b>Role of Altruism</b> <ul style="list-style-type: none"> <li>❖ What role do altruism (versus desperation), expectations, optimism and hope play in HIV cure research?</li> </ul>
<b>Research with Prospective Study Participants</b> <ul style="list-style-type: none"> <li>❖ How do demographic characteristics (such as age, gender, socio-economic status, nationality) relate to HIV cure understanding, acceptability and willingness to participate?</li> <li>❖ How do people view their health and undersand the purpose and risks of HIV cure studies?</li> <li>❖ Discrete choice experiments borrowing from economic, cognitive psychology and decision-making literature – what are common trends in HIV cure research decision making (e.g. anchoring, judgmental heuristics, defaulting to patterns, etc.)</li> <li>❖ How can we increase recruitment of women and under-represented groups in HIV cure studies?</li> <li>❖ Would asking for long-term follow-up of study participants negatively affect overall recruitment? Or would long-term follow-up make study participants feel better?</li> <li>❖ How can we begin to study therapeutic (or curative) misconception in HIV cure research?</li> <li>❖ Is there rogue HIV cure research participation? What motivations are ethically questionable?</li> <li>❖ How does long-term survival with HIV affect willingness to participate and actual participation in HIV cure research?</li> </ul>
<b>Research with Actual Study Participants</b> <ul style="list-style-type: none"> <li>❖ Research with actual HIV cure research participants, either retrospectively or prospectively as part of actual HIV cure studies (e.g. nested social sciences research); would require collaboration from biomedical HIV cure scientists</li> <li>❖ What does HIV cure research mean for quality of life outcomes (such as Short-Form-36 Health Survey)</li> <li>❖ What factors predict retention in HIV cure studies?</li> </ul>
<b>Research with Study Decliners (more difficult)</b> <ul style="list-style-type: none"> <li>❖ What are some of the reasons people living with HIV decline participation in HIV cure research?</li> </ul>
<b>Research with Clinician-Researchers and Policy-Makers</b> <ul style="list-style-type: none"> <li>❖ How do clinician-researchers and policy-makers view risks in HIV cure research?</li> </ul>

<sup>40</sup>For additional social sciences questions, see the backgrounder document prepared for the NIH-NIHM Meeting on Social, Ethical and Behavioral Issues in HIV Cure Research, 22 – 23 September 2014.



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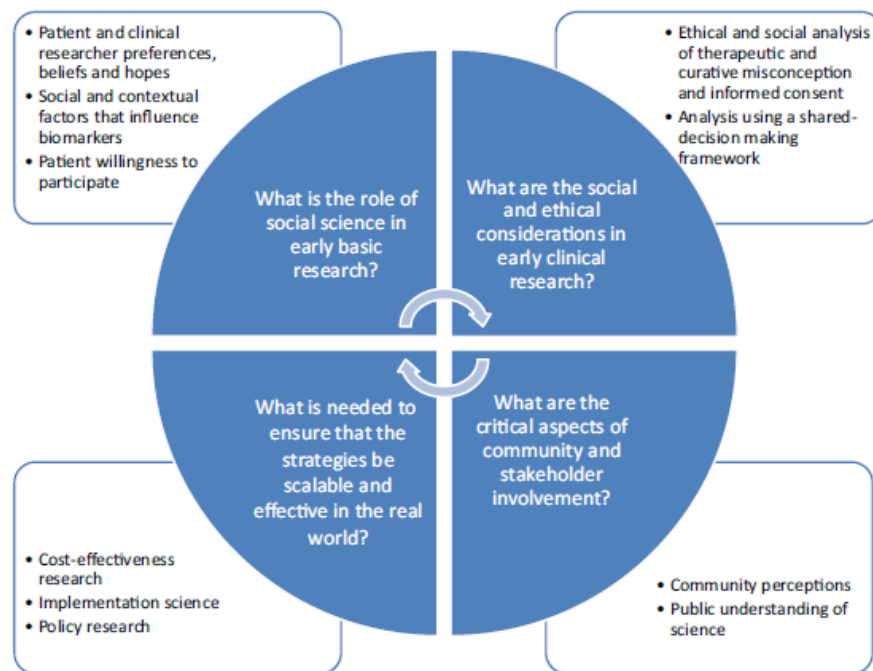
### Research Ethics Questions

- ❖ Are there groups who are more vulnerable than others in HIV cure research?
- ❖ How can HIV cure researchers best measure effective management of scientific uncertainty?
- ❖ How can we prevent unintended consequences of HIV cure research?

### Research Implementation Questions

- ❖ What are some of the benefits of collaboration in HIV cure research and how can we evaluate effective research collaborations?
- 

Additional critical questions to be addressed in the integration of the social sciences and the biomedical research agenda can be found in the Grossman *et al.* article championing multidisciplinary HIV cure research [41]:



Trends in Microbiology

**Figure 30. Critical Questions to Address in the Integration of Social Science in the HIV Cure Research Agenda[41]**

## CHAPTER 8 | CONCLUDING REMARKS

*“Cure is far more complex as a concept than getting rid of the disease.” – Van Eys*



**Figure 31. Research with Ebola Survivors**

Photo Credit: Karine Dubé – Monrovia, Liberia

To conclude, my ultimate goal and vision for change would entail greater recognition on the part of the entire HIV cure research community of the importance of giving a voice to study participants and to address their unique concerns. This would in turn lead to more effective and ethical implementation of HIV cure studies, stronger community partnerships and greater preparedness for and acceptability of HIV cure studies in the long haul. Ethical implementation of HIV cure research starts with setting realistic expectations for these studies as well as conscious attempts to avoid unwanted consequences. Moving forward, it will be important to foster public trust in the research and ensure true informed consent of study participants in the face of scientific uncertainty. A long-term investment in a sound HIV cure research enterprise will require a meaningful involvement of people living with HIV, together with servant and participatory leadership skills, better articulated ethical considerations and support from a wide range of

stakeholders. I hope that my dissertation research will, in a small way, facilitate the design and implementation of effective and ethical HIV cure-related studies by helping understand factors that affect participation in research. I also hope that the plan for change will make a small difference in the lives of potential study participants.

With my DrPH, I aspire to become more adept at contributing to the social sciences of infectious disease research in both an academic setting and in a practical way. The skills learned in my DrPH courses and throughout the dissertation process will make me a more effective manager of clinical research and student of the social sciences. The DrPH program will also allow me to implement my vision of a comprehensive international HIV cure research training curriculum with greater energy and focus. Ultimately, I aspire to obtain a faculty position to be able to contribute to the social sciences related to infectious diseases and inspire students to implement positive change. I also want to be a continuous student of consilience [133], infectious diseases and the social sciences.

I started my DrPH journey in Mozambique, where I was developing research capacity for HIV vaccine trials. I transitioned to working on the social sciences of HIV cure research and completed the program working with Ebola survivors in Liberia. In a way, I feel like I have come full circle and that I have covered the spectrum of public health, from ultimate prevention research (e.g. vaccines) to cure and research. The issues identified in my DrPH dissertation have ramifications that extend far beyond HIV. I now hope to be able to contribute the skills learned to implementing a successful natural history study with Ebola survivors in Liberia funded by the Bill and Melinda Gates Foundation. I have grown cognizant of the factors that influence the effective and ethical implementation of infectious disease research in general. I see many parallels between HIV research and Ebola research. In fact, the way Ebola was talked in the recent outbreak in West Africa was reminiscent of the early days of the AIDS epidemic, when fear, isolationism and xenophobia were

predominant in the public discourse and there was little in the way of accurate and meaningful information. Hopefully, the Ebola survivor study will help generate more accurate information about long-term Ebola disease and implications for public health and the lives of survivors. There are so many issues that apply to both HIV and Ebola research, including the need to reduce stigma and discrimination and to foster altruism among study participants. HIV and Ebola research represent an opportunity to find hope in what have been enormous tragedies in the lives of patient-participants.

Furthermore, Ed Wilson's concept of consilience [133] changed the way I work as a public health practitioner. I now fully appreciate the complex matrix of social, ethical, experiential and evidence-based related factors in the implementation of infectious disease clinical studies. My literature review examined the lessons learned from proxy fields of study. I hope to continue this personal journey of consilience throughout my career as a public health practitioner and scholar. I consider the implementation of infectious disease research not simply as a scientific matter, but also a social and deeply moral one. Researchers need to have tremendous insights into both the personal and the scientific dimensions of a disease. The following quote from Rebecca Dressler has inspired my work:

*It would be acknowledging that research results are not simply numbers, but descriptions of real events in real lives. It would be an act that could remind researchers of the human side of their investigation and perhaps encourage greater sensitivity toward participants at other points in the research process. This is the sort of insight that advocates could contribute to research ethics. Advocates could help ethicists see research from the point of view of research participants and patients in the community.[64]*

No matter whether I work on HIV, Ebola or other public health issues, I want to remain attuned to the realities, perceptions, motivations, desires, fears and vulnerabilities experienced by the people who live with the infection or condition. Throughout the process of investigation, I grew increasingly convinced that study participants have much to offer clinical research scientists and also bioethicists. People living with HIV are hungry to know where they fit in the HIV cure research

agenda. More work needs to be done to discover what study participants value or resent and what they appreciate or would change about their research experience.

HIV cure research is an extremely complex field, and no one knows what the cure will look like. It is important to acknowledge that advocacy around HIV has changed tremendously in 30+ years of research. HIV cure research is very different than the research conducted in the early days of the HIV epidemic. Now, most people living with HIV are doing well on treatment and desperation does not drive research participation. It will take an enormous appreciation for the altruism of the “otherwise healthy volunteers” to advance the field of HIV cure research. As the study showed, those who may most want the cure (the “least healthy”) are also the ones who are also the least likely to qualify for studies, paradoxically. With Ebola research, most of the survivors are convalescent cases who are “functionally cured.” Scientists are still trying to determine the mechanism of Ebola persistence and the significance of the diagnostic and research tests. Sexual transmission of Ebola has occurred. New vaccine, treatment and cure research is currently occurring in West Africa, and there is a greater need to uncover the psychosocial consequences of having survived Ebola. With HIV, much remains to be done to close the prevention and the treatment cascade gap. With both diseases, we must appreciate the entire public health continuum of what it will take to eradicate infections, together with meaningful community engagement efforts to get there and listening to the voices of the patients.

All things considered, I am extremely appreciative to have been part of the DrPH journey at UNC-Chapel Hill. The DrPH program has given me a calmer confidence to continue pursuing my passions and has made me a better-rounded person. I am extremely thankful and feel very blessed to be a student in this truly amazing program and to have been a part of ‘C9’.

## APPENDIX 1: LIST OF RECRUITMENT CHANNELS AND/OR KEY INFORMANTS

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### PATIENTS/PARTICIPANTS

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The list of patient/participant key informants was derived from the survey and remains strictly confidential.

#### Possible recruitment sources for HIV-positive patients/participants:

- Immune-based therapy listserv (ibt-listserv)
  - Martin Delaney Collaboratories Community Advisory Board (CAB) listserv (mdc-national-listserv)  
Collaboratory of AIDS Researchers for Eradication Community Advisory Board (CARE CAB)  
Delaney AIDS Research Enterprise Community Advisory Board (DARE CAB)  
defeatHIV Community Advisory Board (defeatHIV CAB)
  - AIDS Treatment Activist Coalition (AVAC) listserv (ATAC-drug dev listserv)
  - AIDS Clinical Trials Group Community Advisory Board (ACTG CAB)
  - Center for AIDS Research Community Advisory Board (CFAR CAB)
  - Women's HIV Interagency Study (WHIS)
  - Referrals by study participants; see participant lists below.
- 

#### Participant lists from:

- Forum for Collaborative HIV Research – Regulatory Pathway for HIV Cure Research: Developing Consensus; Washington D.C. (June 17, 2014)
- NIH/NIHM Think Tank on Social, Ethical and Behavioral Issues regarding HIV Cure Research; Bethesda, MD (September 22 – 23, 2014)
- NIH-Sponsored Workshop on HIV Cure Research; Bethesda, MD (October 15 – 17, 2014)

## **APPENDIX 2: SAMPLE RECRUITMENT EMAILS/SCRIPTS FOR LISTSERVS (APPROVED BY UNC IRB)**

### **Key Informant Interviews**

#### **A Request for your Participation**

Dear [Name],

In order to learn about the factors affecting participation in HIV cure studies, we are [conducting a series of interviews with clinicians/researchers or stakeholders/regulators like yourself] or [implementing a survey with potential study participants].

Attached, you will find a document that describes the main goal of this research study and includes information that you will need in order to provide your informed consent, should you agree to participate. You will be asked to provide your verbal consent [on the next page or over the phone prior to our interview].

If you choose to participate in the [survey or interview], we are the only persons who will have access to your responses. Your name will not be disclosed to anyone and will not be used in any report or summary that comes from this [survey or interview]. Records of the [survey or interview] will be stored electronically in password-protected files. Any hard copy information linked to an individual's response to interview questions will be stored in a locked file.

If you agree to participate, we will send you a copy of the [verbal] informed consent form, together with a list of the possible interview questions, to better help you prepare.

[Interview only: Would you be available on [Date] at [Time] to conduct a call? If this date/time is not convenient for you, can you please suggest a day/time when you would be available? Please confirm the best phone number we should use for this call. If you have any questions in the interim, please feel free to contact us as well.]

Thank you very much for considering participating in this study to discuss factors that influence participation in HIV cure studies as well as effective and ethical implementation of these studies.

We know that you are very busy, and we greatly appreciate your time and assistance with this effort.

Sincerely,  
Karine [and Jeff]

**Enclosure:** Dissertation Project Fact Sheet



### APPENDIX 3: PROJECT FACT SHEET (APPROVED BY UNC IRB)



This research study seeks to examine the factors that influence the participation of HIV-positive patients/participants into HIV cure-related studies. By HIV cure research, we mean any investigation that evaluates a therapeutic intervention that would control or eliminate HIV infection to the point where no more HIV treatment would be required to preserve health. There are two main approaches being investigated: 1) a sterilizing cure, which would clear all latent viral reservoirs in the body (eradication); and 2) a functional cure, which would allow a person's immune response to control HIV without medication. A functional cure may be easier to achieve than a completely sterilizing cure. In addition, most of the HIV cure-related research modalities remain in the very early-stage of development. We do not have a lot of information about what factors influence HIV positive patients/participants to participate (or refuse to participate) in these cure-related studies.

The U.S. Food and Drug Administration (FDA) recently launched a new initiative aimed at placing the needs and perspectives of HIV positive patients/participants at the forefront of the drug development process for an HIV cure. The U.S. government and other funders are also investing more money into HIV cure research than ever before. As of [April 2015], there were more than [100] ongoing HIV cure-related clinical studies conducted around the world.

The social sciences have not kept the pace with the basic, translational and clinical research. It is important to understand the factors that would motivate or deter HIV positive patients/participants to enter these studies to ensure that they are implemented effectively and ethically.

We also wish to engage individuals living with HIV in a significant and sustained dialogue to understand their concerns, perceptions and understandings of HIV cure studies. The perspectives of clinicians/researchers implementing these studies as well as other stakeholders are also critical in order to ensure that we preserve the public trust in the HIV cure research agenda.

**Thus, this study has three main objectives:**

1. To better understand the factors that act as motivators and/or deterrents of participation in HIV cure studies;
2. To explore how various stakeholders perceive the risks and benefits of HIV cure studies; and
3. To understand some of the practical or pragmatic issues that affect participation of HIV positive patients/participants in cure studies.

The findings generated from this dialogue will be used to create recommendations as well as decision/communication aids in order to facilitate the effective and ethical implementation of HIV cure studies. Since HIV cure studies are complex, we wish to avoid unintended harm or consequences during the design and implementation phases. The tools generated from this research will be shared with various stakeholders working on HIV cure studies.

We thank you in advance for your participation and support.

## **APPENDIX 4: INFORMED CONSENT FORMS (APPROVED BY UNC IRB)**

### **1. Patient/Participant**

Participant ID#: \_\_\_\_

#### **Title of Study:**

*Assessing Factors Affecting Participation in HIV Cure Research: Implications for Effective and Ethical Implementation*

#### **Co-Investigators:**

Karine Dubé, MPhil, DrPH (candidate), Department of Health Policy and Administration and Collaboratory of AIDS Researchers for Eradication (CARE), Institute of Global Health and Infectious Diseases (IGHID), The University of North Carolina at Chapel Hill (UNC-CH)  
Jeffrey Taylor, Collaboratory of AIDS Researchers for Eradication (CARE)

**Informed consent (5 – 10 minutes):** *Online for semi-structured survey; Verbal for interview or focus group discussion*

#### **Purpose:**

Throughout this interview, we want to know your opinions about HIV cure studies. We want to more fully understand patients' perceptions, attitudes and understandings of HIV cure studies, with an emphasis on exploring facilitators and barriers to participation in research studies. We would also like to make recommendations to facilitate implementation of these studies. We will first ask you some questions about demographics and then ask for your opinions about HIV cure studies, such as the factors that (would) either motivate you or deter you from participating in HIV cure research. We also want to know more about your perceptions of the risks and benefits of HIV cure studies. Finally, we would like to hear about the practical challenges of implementing these studies or about any concerns that you have. You can choose not to answer, but any support will be appreciated. This interview will take approximately 30 – 45 minutes to complete.

The University of North Carolina at Chapel Hill Institutional Review Board (IRB) approved this study.

#### **Potential Benefits and Harms:**

There is no direct or indirect harm that could result from your participation in this study. Throughout your participation in this study, you may benefit by being able to explore some important issues or questions related to HIV cure studies.

#### **Voluntary Participation and Anonymity:**

Participation in this study is voluntary. You may refuse to join or withdraw from the study at any time. We will maintain your anonymity at all times during this study. No information that you share will ever be traceable back to you. The final reports will provide only aggregated data. All data files will be stored on a

password-protected laptop and held in a secure location. We will destroy all files – including audio files – once the final analysis is completed.

If you agree to have this interview recorded, we will record it using a digital recorder. If you do not want to have this interview recorded, you can still participate and we will take notes.

**Compensation:** There is no compensation from participating in the key informant interviews.

**Consent:** Do you have any question at this time about participating in this study?

I, \_\_\_\_\_ (survey participant or interviewee's name), understand that I am being asked to participate in a research study conducted by the University of North Carolina at Chapel Hill to answer questions related to my attitudes and perceptions about HIV cure studies. I understand that it is my voluntary choice to participate in this study. I also understand that I may refuse to answer during the interview and/or withdraw from the study at any time. A summary of the results will be made available to me upon completion of the study, should I request a copy. I understand what this study involves and I freely agree to take part.

**Consent given:** Yes ☐ No ☐ **Date:**

\_\_\_\_\_

**Agreement to Record:** Yes ☐ No ☐ N/A ☐ **Date:**

\_\_\_\_\_

If you have any questions or concerns, either prior to or following your participation, please do not hesitate to contact us.

Karine Dubé at (919) 962-0993 or by e-mail at [karine\\_dube@med.unc.edu](mailto:karine_dube@med.unc.edu).

Jeff Taylor at 760-835-1926 or by email at [jefftaylorps@gmail.com](mailto:jefftaylorps@gmail.com).

UNC-CH IRB and Office of Human Research Ethics, CB #7097, Medical School Building 52, 105 Mason Farm Road, Chapel Hill, NC 27599; Phone: 919-966-3113

## **2. Clinician/Researcher**

**Participant ID#:** \_\_\_\_

**Title of Study:** *Assessing Factors Affecting Participation in HIV Cure Research: Implications for Effective and Ethical Implementation*

**Co-Investigators:**

Karine Dubé, MPhil, DrPH (candidate), Department of Health Policy and Administration and Collaboratory of AIDS Researchers for Eradication (CARE), Institute of Global Health and Infectious Diseases (IGHID), The University of North Carolina at Chapel Hill (UNC-CH)  
Jeffrey Taylor, Collaboratory of AIDS Researchers for Eradication (CARE)

**Informed consent (5 – 10 minutes):** *Verbal for interview*

**Purpose:**

Throughout this interview, we want to know your opinions about HIV cure studies. We want to more fully understand your patients'/participants' perceptions, attitudes and understandings of HIV cure studies, with an emphasis on exploring facilitators and barriers to participation in research studies. We would also like to make recommendations to facilitate implementation of these studies. We will first ask you some questions about the factors that would motivate you or deter your patients/participants from taking part in HIV cure research. We also want to know more about your perceptions of the risks and benefits of HIV cure studies and the factors that lead you to refer possible participants in HIV cure studies. Finally, we would like to hear about the practical challenges of implementing these studies or about any concerns that you have. You can choose not to answer, but any support will be appreciated. This interview will take approximately 30 – 45 minutes to complete.

The University of North Carolina at Chapel Hill Institutional Review Board (IRB) approved this study.

**Potential Benefits and Harms:**

There is no direct or indirect harm that could result from your participation in this study. Throughout your participation in this study, you may benefit by being able to explore some important issues or questions related to HIV cure studies.

**Voluntary Participation and Anonymity:**

Participation in this study is voluntary. You may refuse to join or withdraw from the study at any time. We will maintain your anonymity at all times during this study. No information that you share will ever be traceable back to you, and the final reports will provide only aggregated data. All data files will be stored on a password-protected laptop and held in a secure location. We will destroy all files – including audio files – once the final analysis is completed.

If you agree to have this interview recorded, we will record it using a digital recorder. If you do not want to have this interview recorded, you can still participate and we will take notes.

**Compensation:** There is no compensation from participating in the key informant interviews.

**Consent:** Do you have any question at this time about participating in this study?

I, \_\_\_\_\_ (survey participant or interviewee's name), understand that I am being asked to participate in a study conducted by the University of North Carolina at Chapel Hill to answer questions related to my perceptions about HIV cure studies. I understand that it is my voluntary choice to participate in this study. I also understand that I may refuse to answer during the interview and/or withdraw from the study at any time. A summary of the results will be made available to me upon

completion of the study, should I request a copy. I understand what this study involves and I freely agree to take part.

Consent given: Yes ☐ No ☐ Date: \_\_\_\_\_

Agreement to Record: Yes ☐ No ☐ N/A ☐ Date: \_\_\_\_\_

If you have any questions or concerns, either prior to or following your participation, please do not hesitate to contact us.

Karine Dubé at (919) 962-0993 or by e-mail at [karine\\_dube@med.unc.edu](mailto:karine_dube@med.unc.edu).

Jeff Taylor at 760-835-1926 or by email at [jefftaylorps@gmail.com](mailto:jefftaylorps@gmail.com).

UNC-CH IRB and Office of Human Research Ethics, CB #7097, Medical School Building 52, 105

Mason Farm Road, Chapel Hill, NC 27599; Phone: 919-966-3113

### 3. Policy-Maker/Regulator

Participant ID#: \_\_\_\_\_

**Title of Study:** *Assessing Factors Affecting Participation in HIV Cure-Related Research: Implications for Effective and Ethical Implementation*

#### Co-Investigators:

Karine Dubé, MPhil, DrPH (candidate), Department of Health Policy and Administration and Collaboratory of AIDS Researchers for Eradication (CARE), Institute of Global Health and Infectious Diseases (IGHID), The University of North Carolina at Chapel Hill (UNC-CH)

Jeffrey Taylor, Collaboratory of AIDS Researchers for Eradication (CARE) Community Advisory Board (CAB)

**Informed consent (5 – 10 minutes):** *Verbal for interview*

**Purpose:**

Throughout this interview, we want to know your opinions about HIV cure studies. We want to more fully understand your perceptions, attitudes and understandings of HIV cure studies, with an emphasis on exploring facilitators and barriers to participation in studies and practical challenges of implementing these research studies. We would also like to make recommendations to facilitate implementation of these studies. We will ask you some questions about perceptions of the risks and benefits of HIV cure research. Finally, we would also like to hear about any concerns that you have. You can choose not to answer, but any support will be appreciated. This interview will take approximately 30 – 45 minutes to complete.

The University of North Carolina at Chapel Hill Institutional Review Board (IRB) approved this study.

**Potential Benefits and Harms:**

There is no direct or indirect harm that could result from your participation in this study. Throughout your participation in this study, you may benefit by being able to explore some important issues or questions related to HIV cure studies.

**Voluntary Participation and Anonymity:**

Participation in this study is voluntary. You may refuse to join or withdraw from the study at any time. We will maintain your anonymity at all times during this study. No information that you share will ever be traceable back to you, and the final reports will provide only aggregated data. All data files will be stored on a password-protected laptop and held in a secure location. We will destroy all files – including audio files – once the final analysis is completed.

If you agree to have this interview recorded, we will record it using a digital recorder. If you do not want to have this interview recorded, you can still participate and we will take notes.

**Compensation:** There is no compensation from participating in the key informant interviews.

**Consent:** Do you have any question at this time about participating in this study?

I, \_\_\_\_\_ (survey participant or interviewee's name), understand that I am being asked to participate in a study conducted by the University of North Carolina at Chapel Hill to answer questions related to my perceptions about HIV cure studies. I understand that it is my voluntary choice to participate in this study. I also understand that I may refuse to answer during the interview and/or withdraw from the study at any time. A summary of the results will be made available to me upon completion of the study, should I request a copy. I understand what this study involves and I freely agree to take part.

Consent given:

Yes ☐

No ☐

Date:

\_\_\_\_\_

Agreement to Record:

Yes ☐

No ☐

N/A ☐

Date:

\_\_\_\_\_

If you have any questions or concerns, either prior to or following your participation, please do not hesitate to contact us.

Karine Dubé at (919) 259-2489 or by e-mail at [karine\\_dube@med.unc.edu](mailto:karine_dube@med.unc.edu).

Jeff Taylor at 760-835-1926 or by email at [jefftaylorps@gmail.com](mailto:jefftaylorps@gmail.com).

UNC-CH IRB and Office of Human Research Ethics, CB #7097, Medical School Building 52, 105 Mason Farm Road, Chapel Hill, NC 27599; Phone: 919-966-3113

## **APPENDIX 5: PATIENT/PARTICIPANT QUESTIONNAIRE (APPROVED BY UNC IRB)**

### **AMENDED SURVEY v2.0 – APPROVED BY UNC IRB 30 AUGUST 2015**

#### **Social Sciences Survey on HIV Cure Research: Your Opinion Matters**

There has been an increase in HIV cure research in the recent years. We would like to find out how people living with HIV (or potential HIV cure research volunteers) perceive HIV cure research, including their willingness to participate in HIV cure studies. We would also like to find out what would help implement HIV cure studies. Your answers to these questions will be kept strictly confidential.

**You are eligible to complete this survey if you:**

- Are at least 18 years of age
- Are living with HIV
- Are willing to give your opinion about HIV cure research
- Live in the United States

**We are interested to find out what you think about:**

- The possible risks and benefits of HIV cure research
- How willing you would be to volunteer in clinical studies related to HIV cure research
- How willing you would be to take risks as part of HIV cure research
- Things you think could help or hinder HIV cure studies

Note: By answering the questions in this survey, you are not obligated to actually participate in any HIV cure study. This survey will assess whether you would be willing to participate in different types of HIV cure-related clinical studies, but you will not be signed up for a study as a result of this survey.

#### **HIV Cure Research**

By HIV cure research, we mean studying anything that could help control or eliminate HIV to the point that medications would no longer be needed to keep someone healthy.

**There are two main approaches being investigated:**

- 1) A sterilizing cure, which would clear HIV from the body (eradication); and
- 2) A functional cure, which would allow a person's immune response to control HIV without medication.

#### **Engaging People Living with HIV in Dialogue**

We wish to find out what people think about HIV cure studies. The understanding of perspectives of people living with HIV is important in establishing and maintaining public trust in and support for the HIV cure research agenda.



### Informing Implementation of HIV Cure Research

The findings generated from this study will be used to help conduct HIV cure-related studies. Since HIV cure-related studies are complex, we wish to avoid unintended consequences during the design and implementation of research.

#### Time to Complete

This survey will take from 45 – 60 minutes to complete.

#### Thank You and Questions

We thank you in advance for your participation and support. If you have any questions about this survey, please feel free to contact Karine Dubé ([karinedube2003@gmail.com](mailto:karinedube2003@gmail.com)) or Jeff Taylor ([jefftaylorps@gmail.com](mailto:jefftaylorps@gmail.com)).

#### Prize Drawing

At the end of the survey, you have the opportunity to enter a prize drawing (\$USD 25 for each 25 survey respondents – either VISA™, Target™ or Starbucks™ gift card). If you want to be considered for the drawing, you will need to provide an email address or a phone number to be contacted if you win.

Would you like to go ahead with the survey?	Yes
	No
If Yes, please proceed to survey.	
If No, can you please tell us why you do not wish to participate? This will end the survey for you.	Do not have time No interest Do not meet the eligibility criteria Other, Specify_____

### Demographic Characteristics

What is your gender?	Female Male Transgender (male to female) Transgender (female to male) Other, Specify _____
What is your age?	(Years)
What is your ethnicity?	Caucasian/White African-American Hispanic or Hispanic descent American Indian or Alaska Native Native Hawaiian or Other Pacific Islander Asian descent Other, Specify _____ Mixed, Specify _____
What is the highest level of education that you completed?	Less than high school High school or G.E.D. Associate's degree Undergraduate degree Master's degree Doctorate or doctoral-level degree (e.g. PhD, MD, JD, etc.) Other, Specify _____
What is your yearly household income (in U.S. dollars)?	<\$25,000 \$25,000 – \$50,000 \$50,001 – \$75,000 \$75,001 – \$100,000 >\$100,000
In which U.S. state or territory do you live in ?	(Select from a list of state abbreviations and territory initials)

### Health Perceptions

How would you describe your current health status?	Very healthy Healthy Somewhat healthy Not very healthy Not at all healthy
Do you feel you have control over your own health care?	Yes No I don't know/not sure
Are you currently taking HIV medication?	Yes No I don't know/not sure

## History

<p>Have you ever participated in any of the following types of health research studies (whether HIV related or non-HIV related)? Please select all that apply.</p>	<ul style="list-style-type: none"> <li>• Survey research</li> <li>• Interviews</li> <li>• Focus group discussions</li> <li>• Basic blood draw studies</li> <li>• Laboratory procedure where selected immune cells are separated out from your blood and the rest of your blood is returned to your veins</li> <li>• Studies that involve agents that could reactivate HIV that has become dormant inside your cells (“latency reversing agents”)</li> <li>• Studies that involve the modification of some of your genes in your immune cells</li> <li>• Studies that involve a transplantation of your (“autologous”) stem cells</li> <li>• Studies that involve a transplantation or someone else’s (“allogeneic”) stem cells</li> <li>• Studies that involve therapeutic vaccines (vaccines that control disease in people already infected rather than vaccines that prevent infection)</li> <li>• Studies that involve the intensification of treatment or taking more than 3 different classes of drugs at the same time</li> <li>• Studies that involve the use of unique antibodies, proteins or molecules (for example, antibodies that have dual functions)</li> <li>• Studies that involve totally new treatments or approaches (“first-in-human” studies)</li> <li>• Studies about safety and efficacy (or phase II or III studies)</li> </ul>
<p>In what year were you diagnosed with HIV?</p>	<p>(Year) I don’t remember</p>
<p>Have you ever been in (or volunteered for) an HIV treatment study?</p>	<p>Yes No I don’t know/not sure</p>
<p>Have you ever been in (or volunteered for) an HIV cure study of any kind? If No, skip to X (question on general interest in HIV cure research).</p>	<p>Yes No I don’t know/not sure</p>
<p>If Yes: How many HIV cure-related studies have you participated in?</p>	<p>(Number)</p>
<p>Can you please name the HIV cure research that you participated in?</p>	<p>(Name(s))</p>
<p>Are you currently participating in an HIV cure-related study?</p>	<p>Yes, Specify _____ No I don’t know/not sure/don’t want to disclose</p>
<p>Are you generally interested in HIV cure research?</p>	<p>Yes No I don’t know/not sure</p>
<p>Are you generally interested in medical issues?</p>	<p>Yes No I don’t know/not sure</p>

### Types of HIV Cure Studies

Would you consider participating in any of the following HIV cure-related studies – now or in the future? Note: There is no obligation to participate in HIV cure-related studies if you answer “Yes”	
Survey research	Yes No I don't know
Interviews	Yes No I don't know
Focus group discussions	Yes No I don't know
Basic blood draw studies	Yes No I don't know
Laboratory procedure where selected immune cells are separated out from your blood and the rest of your blood is returned to your veins (leukapheresis or apheresis)	Yes No I don't know
Studies that involve agents that could reactivate HIV that has become dormant inside your cells (“latency reversing agents”)	Yes No I don't know
Studies that would involve the modification of some of your genes in your immune cells	Yes No I don't know
Studies that would involve a transplantation of your (“autologous”) stem cells	Yes No I don't know
Studies that would involve a transplantation or someone else’s (“allogeneic”) stem cells	Yes No I don't know
Studies that would involve therapeutic vaccines (vaccines that control disease in people already infected rather than vaccines that prevent infection)	Yes No I don't know
Studies that would involve the intensification of treatment or taking more than 3 different classes of drugs at the same time	Yes No I don't know
Studies that would involve the use of unique antibodies, proteins or molecules (for example, antibodies that have dual functions)	Yes No I don't know
Studies that would involve totally new treatments or approaches (“first-in-human” studies)	Yes No I don't know
Studies about safety and efficacy (or phase II or III studies)	Yes No I don't know
If you had an infant living with HIV, would you let them participate in a pediatric HIV cure-related study (for example, ARV treatment as close to birth as possible)?	Yes No I don't know I don't have an infant (not

	applicable)
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### Potential Personal Benefits

How important are the following to your motivation to participate in HIV cure studies?	
Getting special/additional knowledge about your own HIV infection and your own health from being in the study	Very important Somewhat important Barely important Not important I don't know/not applicable
Having (more) regular access to medical doctors/researchers	Very important Somewhat important Barely important Not important I don't know/not applicable
Have regular access to a study nurse	Very important Somewhat important Barely important Not important I don't know/not applicable
Feeling good about contributing to HIV cure-related research	Very important Somewhat important Barely important Not important I don't know/not applicable
Hope that your health will improve	Very important Somewhat important Barely important Not important I don't know/not applicable
Not wanting to give up	Very important Somewhat important Barely important Not important I don't know/not applicable
Being compensated or reimbursed for participation in a study	Very important Somewhat important Barely important Not important I don't know/not applicable
Learning about new treatment options	Very important Somewhat important Barely important Not important I don't know/not applicable
Additional laboratory work done free of charge, such as viral load or CD4+ count testing	Very important Somewhat important Barely important Not important I don't know/not applicable

Being offered a meal at the study site	Very important Somewhat important Barely important Not important I don't know/not applicable
Receiving gas money, transportation compensation or public transportation passes to help come to the study site	Very important Somewhat important Barely important Not important I don't know/not applicable

#### Potential Personal Clinical Benefits

How important are the following clinical factors to your motivation to participate in an HIV cure-related study?	
Increased immune cell counts	Very important Somewhat important Barely important Not important I don't know/not applicable
Reducing the amount of HIV in your entire body (not just your blood) – or making your HIV reservoir (site where HIV can persist) smaller	Very important Somewhat important Barely important Not important I don't know/not applicable
Controlling the amount of virus in your body in the absence of treatment	Very important Somewhat important Barely important Not important I don't know/not applicable
Not having the amount of virus in your body increase for an extended period of time (i.e. one year)	Very important Somewhat important Barely important Not important I don't know/not applicable
Having your immune system preserve its ability to fight HIV	Very important Somewhat important Barely important Not important I don't know/not applicable
Less risk of transmitting HIV to your sexual partner(s)	Very important Somewhat important Barely important Not important I don't know/not applicable

### Potential Social Benefits

How important are the following factors to your motivation to participate in an HIV cure-related study?	
Helping other people with HIV in the future	Very important Somewhat important Barely important Not important I don't know
Helping find a cure for HIV	Very important Somewhat important Barely important Not important I don't know
Contributing to scientific knowledge	Very important Somewhat important Barely important Not important I don't know
Receiving support from your family and friends	Very important Somewhat important Barely important Not important I don't know

### Other Potential Benefits

What other potential benefits are “very important” to your motivation to participate in an HIV cure-related study? \_\_\_\_\_

### Potential Personal Clinical Risks

How likely will any of the following potential risks discourage you from participating in an HIV cure-related study?	
Known risks of stopping HIV medications (such as the potential for a rapid increase in your viral load or “rebound”)	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know
Toxicities or adverse negative effects of the drug(s) being studied	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know
Possibility of developing resistance to the drug(s) during a structured treatment interruption	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know

Having no way to predict the risk of having your virus become detectable again (“viral rebound”)	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don’t know
Activation of genes in your body that could cause cancer	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don’t know
Graft-versus-host disease (or GVHD) (a possible complication from allogeneic (foreign) stem cells transplants, although rare)	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don’t know
Invasive study procedures (such as a biopsy or sample of tissue from one of your lymph nodes) )	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don’t know

#### Perceptions of Clinical Risks

How willing would you be to stop your HIV treatment as part of an HIV cure-related study?	Very willing Somewhat willing Not very willing Not willing I don’t know
What level of CD4 count would be acceptable to you if your CD4 count were to decrease as a result of your participation in the study?	500 cells 350 cells 200 cells Other, Specify _____ cells I would not go off treatment I don’t know
What do you think would be “too much” risk for you to be in an HIV cure-related study?	(Text Field)

#### Other Potential Personal Risks and Burdens

How likely will any of the following potential risks discourage you from participating in an HIV cure-related study?	
Long (more than 4 hours) study visit(s)	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision)



	I don't know
High frequency of study visits (more than 1 time per month)	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know
Long (more than 5 years) duration of study and follow-up	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know
<b><u>Study Procedures:</u></b>	
Blood draws	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know
Procedures that separate your white blood cells from the rest of your blood cells (may take up to 2 hours)	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know
Spinal tap ("lumbar punctures")	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know
Biopsies of one of your lymph nodes, organs that contain immune cells	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know
Collection of semen or vaginal fluids	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know
Rectal biopsies (via sigmoidoscopy or colonoscopy)	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know

Oral biopsies (such as saliva samples taken from your mouth)	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know
Bone marrow biopsies	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know
Organ donation after death	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know
<b>Symptoms or Side Effects:</b>	
Nausea	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know
Vomiting	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know
Headache	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know
Hair loss	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know
Pre-defined, limited and controlled potential discomfort and/or pain	Very likely to discourage Somewhat likely to discourage Barely likely to discourage

	Not likely to discourage (does not affect my decision) I don't know
<b><u>Burdens:</u></b>	
Difficulty finding transportation to the clinical research site	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know
Difficulty finding or having to pay for parking at the clinical research site	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know
Challenges of finding child care	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know
Time away from your work or school	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know
Time away from your family	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know
Having to explain your study participation to your partner(s) or others	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know

### Potential Social Risks

How likely will any of the following potential risks discourage you from participating in an HIV cure-related study?	
Being recognized as a person living with HIV	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know
Risk of transmitting HIV to a sexual partner	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know
Stigma	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know
Discrimination	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know
If there is a cure, the risk of losing your "HIV-positive identity"	Very likely to discourage Somewhat likely to discourage Barely likely to discourage Not likely to discourage (does not affect my decision) I don't know

### Other Potential Risks

What other potential risks are "very likely to discourage" you from participating in an HIV cure-related study? \_\_\_\_\_

### Factors Affecting Participation

Are any of the following factors important to you in making a decision about whether to consider participating in an HIV cure-related study?	
The Principal investigator of the study (the physician in charge of the study)	Yes No I don't know
The nurse for the study	Yes No I don't know
The research site where the study is being done	Yes No

	I don't know
The way the information is given about a clinical study	Yes No I don't know
The HIV cure research method being investigated	Yes No I don't know

#### Facilitators of Participation and Implementation

What (other) factor(s) are likely to make you want to participate in HIV cure-related studies?	(Text)
In your opinion, what factors would help with the conduct of an HIV cure-related study?	(Text)

#### Barriers to Participation and Implementation

What (other) factors are likely to make you <u>NOT</u> want to participate in an HIV cure-related study?	(Text)
In your opinion, what factors would make the conduct of an HIV cure-related study difficult?	(Text)

#### Miscellaneous

If you were to participate in an HIV cure-related study, how would you describe yourself:	A Partner in the Research A Patient A Study Participant An Experimental Subject A Research Subject A Volunteer A "Guinea Pig" Other, Specify_____
Do you think that you can be cured by participating in an HIV cure-related study now or in the near future?	Yes No I don't know
Do you hope that you can be cured by participating in an HIV cure-related study now or in the near future?	Yes No I don't know
How many years do you think it will take to find a cure for HIV?	There is a cure available now Within 5 years 6 – 10 years 11 – 15 years 16 – 20 years 21 - 50 years More than 50 years Never
What does a cure for HIV mean to you (check all that apply)?	No more HIV treatment needed now No more HIV treatment needed ever No risk of transmitting HIV to others

	Negative HIV test HIV completely eliminated from the body There is no risk of opportunistic infection Other, Specify_____
Please share any comment or anecdote about participation in HIV cure-related research	(Text field)

#### Future Contact

Would you be willing to be contacted for an individual interview (about 1 hour)? (If Yes, please provide contact details below)	Yes No
Would you be willing to be contacted for a focus group discussion (about 1 hour)? (If Yes, please provide contact details below).	Yes No

#### (Only if “Yes” above) Contact Information:

Please provide your contact information in order to be contacted regarding participating in an individual interview and/or focus group discussion.

First Name, Last Name:	
Phone: (XXX) XXX-XXXX	
Email:	

#### Prize Drawing and Future Contact

Thank you for completing the survey!

Would you like to be included in a prize drawing of a \$25 gift card (25 survey respondents will be randomly chosen)? If so, please provide your contact information below.

First Name, Last Name (optional):	
Phone: (XXX) XXX-XXXX	
Email:	
Preferred Gift Card (choose one)	VISA™ Target™ Starbucks™

#### THE END

Thank you very much for taking the time to complete this questionnaire. Your assistance is very much appreciated. If you have any questions or concerns, please contact Karine Dubé

([karinedube2003@gmail.com](mailto:karinedube2003@gmail.com)) or Jeff Taylor ([jefftaylorps@gmail.com](mailto:jefftaylorps@gmail.com)).

## **APPENDIX 6: KEY INFORMANT INTERVIEW GUIDES (APPROVED BY UNC IRB)**

[General Introduction for Patients/Participants, Clinicians/Researchers and Policy-Makers/Regulators]

We are implementing a research study looking at factors affecting participation in HIV cure studies in the United States.

The purpose of the key informant interviews is to learn more about how patients/participants, clinicians/researchers and policy-makers/regulators perceive the risks and benefits of HIV cure studies. The key informant interviews will also help understand some of the practical issues affecting HIV cure studies.

We would like to understand the factors that facilitate or hinder participation in HIV cure studies. Around [12 – 15 patients/participants, 6 clinicians/researchers and 6 policy-makers/regulators] will participate in these interviews. The interviews should take between 30 minutes to an hour.

The interviews will be completely confidential. Your name will not be used in any study report, final report or publications. Once the data have been compiled, all identifying information associated with your answers will be removed.

With your permission, we would like to record our interview. This would ensure that none of your important insights are missed. The audiotape will not have any names on it (only an identifier code) and will be kept in a secure location. Tapes and transcriptions will be destroyed at the end of the study. The interview will not be recorded if you prefer. If you prefer it not to be, we will take detailed notes.

Before we begin, do you have any question about the study or the interview?  
May we record the interview?

### **PATIENT/PARTICIPANT INTERVIEW GUIDE (APPROVED BY UNC IRB)**

#### **Introduction**

What motivated you to participate in today's interview?

Can you please tell us more about your history of participating in HIV research?

Have you participated in HIV cure research? (*If so, probe for details.*)

What factors do you think are important to consider when participating in HIV cure research?

#### **Risks and Benefits**

Do you think HIV cure research is a good thing?

What benefits do you think are there to participate in HIV cure studies?

Do you have any concerns about HIV cure research? If so, what are they?

What risks do you think are there to participate in HIV cure studies?

What do you think would be "too much risk" in HIV cure studies?

Are there studies that you would not participate in? Why?

What are some of the burdens to participate in HIV cure research?

What do you consider the safest HIV cure research method? Can you please tell us why?

What do you consider the riskiest HIV cure research method? Can you please tell us why?

### **Barriers and Facilitators**

What do you think are the main motivators to participate in HIV cure studies?

What do you think would motivate someone doing well on HIV treatment to participate in an HIV cure study?

What do you think are the main barriers to participate in HIV cure studies?

### **Programmatic Considerations**

Do people in your community know about HIV cure research? Do you think information about these studies should be promoted in your community?

What do you expect from HIV cure studies?

Would you expect to be cured from early HIV cure studies?

What can be done to facilitate recruitment of patients/participants into HIV cure studies?

What can be done to facilitate retention of patients/participants into HIV cure studies?

What can be done to make sure that HIV cure studies are implemented well?

What can be done to make sure that HIV cure studies are implemented in an ethical way?

What kind of guidance is needed for patients/participants wanting to participate in HIV cure studies?

Do you think any guidance is needed for clinicians/researchers about HIV cure research? If so, please explain.

### **Clinicians/Researchers and Policy-Makers Roles and Responsibilities**

What do you believe is the role of clinicians/researchers in HIV cure studies?

What do you believe is the role of policy-makers (such as institutional review boards) in HIV cure studies?

Is there anything that you consider unethical?

### **Wrap Up and Closing**

Would you like to add anything or make additional comments?

Thank you for taking the time to answer these questions. Your participation in this interview greatly contributes to the research project and to increasing our understanding around the issues affecting participation in HIV cure studies. Your answers will be compiled with the answers of all other interviewees. Please feel free to contact us at anytime if you have any questions about this interview or the research project.

## **CLINICIANS/RESEARCHERS INTERVIEW GUIDE (APPROVED BY UNC IRB)**

### **Introduction**

First, thank you so much for your time.

Can you please tell us more about your role in implementing HIV cure research?

What factors are important to consider for patients/participants wanting to participate in HIV cure research?

### **Risks and Benefits**

Why do you think your patients/participants want to join HIV cure research?

Are there studies that you would not recommend your patients/participants to participate in? If

so, what are they?



What are your patients'/participants' concerns about HIV cure research?  
Do your patients/participants incur risks while participating in HIV cure studies? If so, which ones?  
What do you think would constitute "too much risk" in HIV cure studies?  
Do you think treatment interruption should be done? Why or why not?  
What are some of the most significant burdens for your patients/participants to participate in HIV cure research?  
What do you consider the safest HIV cure research method? Why?  
What do you consider the riskiest HIV cure research method? Why?

### **Barriers and Facilitators**

What do you think are the main factors motivating your patients/participants to participate in HIV cure studies?  
What factors have facilitated the implementation of HIV cure studies in the past? (*Probe for anecdotes.*)

What do you think are the main barriers from participating in HIV cure studies for your patients/participants?  
What are the main reasons for why your patients/participants are ineligible for HIV cure studies?  
What factors have made the implementation of HIV cure studies difficult in the past? (*Probe for anecdotes.*)

### **Programmatic Considerations**

What can be done to facilitate the recruitment of patients/participants into HIV cure studies?  
What can be done to facilitate retention of patients/participants into HIV cure studies?  
What can be done to make sure that HIV cure studies are implemented well?  
What can be done to make sure that HIV cure studies are implemented in an ethical way?  
What kind of guidance is needed for patients/participants wanting to participate in HIV cure studies?  
Do your patients/participants think they will be cured from early HIV cure studies?

### **Patients/Participants and Policy-Makers Roles and Responsibilities**

What do you believe is the role of patients/participants concerning HIV cure studies?  
What do you believe is the role of policy-makers (such as institutional review boards) concerning HIV cure studies?

### **Wrap Up and Closing**

Would you like to add anything or make additional comments?

Thank you for taking the time to answer these questions. Your participation in this interview greatly contributes to the research project and to increasing our understanding around the issues affecting participation in HIV cure studies. Your answers will be compiled with the answers of all other interviewees. Please feel free to contact us at anytime if you have any questions about this interview or the research project.

## **POLICY MAKERS/REGULATORS INTERVIEW GUIDE (APPROVED BY UNC IRB)**

### **Introduction**

Can you please tell us more about your role in HIV (cure research)?

What factors are important to consider for patients/participants wanting to participate in HIV cure studies?

### **Risks and Benefits**

Do you think that there are benefits to participate in HIV cure studies? If so, what are they?

What do you consider the safest HIV cure research method? Why?

What are some of the risks to participate in HIV cure studies?

What do you think would constitute “too much risk” in HIV cure studies?

[If regulator] Are there studies that you would not approve?

[If advocate] Are there studies that you would not recommend HIV-positive patients to participate

in? If so, what are they?

What do you consider the riskiest HIV cure research modality? Why?

### **Barriers and Facilitators**

What do you think are the main motivators to participate in HIV cure studies?

What do you think would motivate someone doing well on HIV treatment to participate in an HIV cure study?

What do you think are the main barriers to participate in HIV cure studies?

### **Programmatic Considerations**

What can be done to facilitate the recruitment of patients/participants in HIV cure studies?

What can be done to facilitate retention of patients/participants in HIV cure studies?

What can be done to make sure that HIV cure studies are implemented well?

What can be done to make sure that HIV cure studies are implemented in an ethical way?

What kind of guidance is needed for patients/participants wanting to participate in HIV cure studies?

Do you think guidance is needed for clinicians/researchers about HIV cure research? If so, please explain.

### **Patients/Participants and Clinicians/Researchers’ Roles and Responsibilities**

What do you believe is the role of patients/participants about HIV cure studies?

What do you believe is the role of clinicians/researchers about HIV cure studies?

### **Wrap Up and Closing**

Would you like to add anything or make additional comments?

Thank you for taking the time to answer these questions. Your participation in this interview greatly contributes to the research project and to increasing our understanding around the issues affecting participation in HIV cure studies. Your answers will be compiled with the answers of all other interviewees. Please feel free to contact us at anytime if you have any questions about this interview or the research project.

**ADDENDUM TO INTERVIEW GUIDES: LIST OF POSSIBLE PROBES**

- Can you please expand a little on this?
- Can you please explain what you mean?
- Can you please tell us more?
- Can you please give us some examples?

## APPENDIX 7: GREY LITERATURE REVIEWED AND KEY INFORMANT INTERVIEWS

### GREY LITERATURE REVIEWED

1. Brookshire B. This Study of Hype in Press Releases will Change Journalism. New Work Shows the Inflation of Scientific Results Happens at Many Times in the Press Game. Science News. 19 December 2014. Available at: <https://www.sciencenews.org/blog/scicurious/study-hype-press-releases-will-change-journalism>.
2. Deming D. Regulatory Issues in HIV Cure Research – CUREiculum Module.
3. Eron J. Challenges in Designing Clinical Trials in Cure Research. Presentation at the 7<sup>th</sup> HIV Persistence during Therapy Workshop, Miami, FL, 10 December 2015.
4. Feldstein AC, Glasgow RE. A Practical, Robust Implementation and Sustainability Model (PRISM) for Integrating Research Findings into Practice. The Joint Commission Journal on Quality and Patient Safety 2008; 34(4): 228 – 43.
5. Food and Drug Administration (FDA) The Voice of the Patient Report. HIV Patient-Focused Drug Development and HIV Cure Research. March 2014.
6. FDA. Background for FDA's HIV Patient-Focused Drug Development and HIV Cure Research Public Meeting. June 2013.
7. FDA. HIV Patient-Focused Drug Development and Cure Research. Meeting Slides 14 June 2013.
8. Forum for Collaborative HIV Research, Meeting Proceedings – Regulatory Pathway for HIV Cure Research. 17 June 2014.
9. Forum for Collaborative HIV Research, Working Group #3 Survey Mapping Sub-Group. Proposed Recommendations for HIV Cure Survey Research. June 2014.
10. Forum for Collaborative HIV Research, Working Group #3, Call Notes 20 May 2014.
11. Forum for Collaborative HIV Research, Working Group #3, Call Notes 2 April 2014.
12. Forum for Collaborative HIV Research, Working Group #3, Call Notes 17 March 2014.
13. Forum for Collaborative HIV Research, Working Group #3, Call Notes 27 February 2014.
14. Forum for Collaborative HIV Research, Working Group #3, Call Notes 17 January 2014.
15. Handibode J, Aidarus N, Fisher K. Women in HIV Cure Trials. A Chance to Reverse the Historical Paradigm of Under-Representation of Women in HIV Treatment Trials. Poster presented at the NIH-sponsored workshop on HIV Cure, October 2014, Bethesda, MD, United States.
16. International AIDS Society: Global Scientific Strategy Towards an HIV Cure 2016. Draft Document. 1 December 2015.
17. International AIDS Society (IAS) Psychosocial Working Group Meeting Notes, 21 July 2014.

18. International AIDS Society (IAS) Psychosocial Working Group Meeting Notes, 5 February 2014.
19. Johnston R. Participation of Women in Clinical Studies Pertinent to HIV Cure. Not Dated.
20. Karn, J. Women in HIV Cure Research. Webinar 4 February 2015.
21. Meeting Proceedings, FDA HIV Community Meeting. 24 February 2015.
22. Notes from Call with the U.S. FDA, 4 November 2015.
23. Notes from 2015 Towards an HIV Cure Symposium, Vancouver, Canada, 18 – 19 July 2015.
24. Notes from 2015 Conference on Retroviruses and Opportunistic Infections, Seattle, WA, 21 – 25 February 2015.
25. Notes from 2014 NIH-Sponsored Workshop on HIV Cure, Bethesda, MD, United States, 15 – 17 October 2014.
26. Notes from 2014 NIH-NIHM Meeting on Social, Ethical and Behavioral Issues in HIV Cure Research, 22 – 23 September 2014.
27. Notes from 2014 Towards an HIV Cure Symposium, Melbourne, Australia, 19 – 20 July 2014.
28. Notes from 2014 Meeting on Unintended and Intended Implications of HIV Cure research: A Social and Ethical Analysis. Brocher Foundation, 7—9 May 2014.
29. Project Inform. HIV/AIDS Cure Glossary 2015.
30. Ramaswamy R. Where is Implementation in Implementation Science? Presentation to DrPH Program 13 May 2015.
31. Rennie S. Ethics of HIV Cure Research – CUREiculum Module.

## **KEY INFORMANT INTERVIEWS**

### **Patients-Participants**

1. ID# 101: Key Informant Interview Patient-Participant – Male More Willing, 3 September 2015 at 12 pm ET.
2. ID# 102: Key Informant Interview Patient-Participant – Male More Willing, 17 September 2015 at 4 pm ET.
3. ID# 103: Key Informant Interview Patient-Participant – Male More Willing, 23 September 2015 at 8 pm ET.
4. ID# 104: Key Informant Interview Patient-Participant – Female Less Willing, 23 September 2015 at 9 am ET.
5. ID# 105: Key Informant Interview Patient-Participant – Female More Willing, 26 September 2015 at 12 pm ET.

6. ID# 106: Key Informant Interview Patient-Participant – Male Less Willing, 30 September 2015 at 7 pm ET.
7. ID# 107: Key Informant Interview Patient-Participant – Male More Willing, 3 October 2015 at 2 pm ET.
8. ID# 108: Key Informant Interview Patient-Participant – Female More Willing, 5 October 2015 at 7 pm ET.
9. ID# 109: Key Informant Interview Patient-Participant – Female Less Willing, 6 October 2015 at 8 pm ET.
10. ID# 110: Key Informant Interview Patient-Participant – Female Less Willing, 8 October 2015 at 8 pm ET.
11. ID# 111: Key Informant Interview Patient-Participant – Male More Willing, 9 October 2015 at 9 pm ET.
12. ID# 112: Key Informant Interview Patient-Participant – Male More Willing, 10 October 2015 at 9 am ET.

#### **Clinicians-Researchers**

13. ID# 201: Key Informant Interview Clinician – Researcher, 8 September 2015 at 9 am ET.
14. ID# 202: Key Informant Interview Clinician – Researcher, 8 September 2015 at 4:45 pm ET.
15. ID# 203: Key Informant Interview Clinician – Researcher, 9 September 2015 at 10 am ET.
16. ID# 204: Key Informant Interview Clinician – Researcher, 9 September 2015 at 1 pm ET.
17. ID# 205: Key Informant Interview Clinician – Researcher, 9 September 2015 at 2:15 pm ET.
18. ID# 206: Key Informant Interview Clinician – Researcher, 9 September 2015 at 5 pm ET.
19. ID# 207: Key Informant Interview Clinician – Researcher, 14 September 2015 at 3 pm ET.
20. ID# 208: Key Informant Interview Clinician – Researcher, 14 September 2015 at 4 pm ET.
21. ID# 209: Key Informant Interview Clinician – Researcher, 14 September 2015 at 6 pm ET.
22. ID# 210: Key Informant Interview Clinician – Researcher, 16 September 2015 at 8 am ET.
23. ID# 211: Key Informant Interview Clinician – Researcher, 6 October 2015 at 7 pm ET.

#### **Policy-Makers (Broadly Defined)**

24. ID# 301: Key Informant Interview Policy-Maker, 2 September 2015 at 1 pm ET.
25. ID# 302: Key Informant Interview Policy-Maker, 3 September 2015 at 11 am ET.

26. ID# 303: Key Informant Interview Policy-Maker, 3 September 2015 at 2:30 pm ET.
27. ID# 304: Key Informant Interview Policy-Maker, 3 September 2015 at 4 pm ET.
28. ID# 305: Key Informant Interview Policy-Maker, 7 September 2015 at 11 am ET.
29. ID# 306: Key Informant Interview Policy-Maker, 8 September 2015 at 10 am ET.
30. ID# 307: Key Informant Interview Policy-Maker, 8 September 2015 at 1 pm ET.
31. ID# 308: Key Informant Interview Policy-Maker, 8 September 2015 at 2:30 pm ET.
32. ID# 309: Key Informant Interview Policy-Maker, 8 September 2015 at 3 pm ET.
33. ID# 310: Key Informant Interview Policy-Maker, 9 September 2015 at 4:15 pm ET.
34. ID# 311: Key Informant Interview Policy-Maker, 17 September 2015 at 2:30 pm ET.
35. ID# 312: Key Informant Interview Policy-Maker, 23 September 2015 at 7 pm ET.
36. ID# 313: Key Informant Interview Policy-Maker, 25 September 2015 at 7 pm ET.

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9. Lewin SR (2013) A cure for HIV: where we’ve been, and where we’re headed. *Lancet* 381: 2057–2058. Available: <http://www.ncbi.nlm.nih.gov/pubmed/23769215>. Accessed 29 January 2014.
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