THE EFFECTS OF HEPATITIS C INFECTION, TREATMENT, AND POPULATION INTERVENTIONS ON ALL-CAUSE MORTALITY AMONG PEOPLE LIVING WITH HIV

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A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology in the Gillings School of Global Public Health.

Chapel Hill
2018

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ABSTRACT

Alexander Samuel Breskin: The effects of hepatitis C infection, treatment, and population interventions on all-cause mortality among people living with HIV (Under the direction of Daniel Westreich)

Approximately 25% of people living with HIV (PLWH) in the United States are co-infected with hepatitis C virus (HCV), which, if left untreated, causes mortality through decompensated cirrhosis and hepatocellular carcinoma. Direct-acting antiviral (DAA) treatment for HCV can produce sustained HCV virologic response in nearly all PLWH and HCV (PLWH+HCV). However, in the era of effective antiretroviral therapy (ART), the effects of HCV infection, treatment, and population interventions on mortality are not clear for PLWH.

Using data from 3,056 PLWH in the Women’s Interagency HIV Study and Multicenter AIDS Cohort Study from 1994 to 2015, we used the parametric g-formula to estimate the effects of HCV infection and DAA treatment on 10-year all-cause mortality. We also estimated the effects of DAA treatment policies in which different groups are treated with DAAs: all PLWH+HCV, PLWH+HCV who met two existing Medicaid treatment criteria – achieving HIV suppression and having severe fibrosis or cirrhosis, and PLWH+HCV chosen at random with proportions treated equal to those under the Medicaid criteria. All estimates occurred after a hypothetical intervention to have all PLWH initiate ART at baseline, as modern guidelines suggest ART for all PLWH regardless of CD4 cell count.

The estimated 10-year mortality risk difference (RD) for HCV infection was 4.3% (95% CI: 0.4%, 8.9%). The RD for DAA treatment was -3.7% (95%CI: -9.1%, 0.6%). The RD for treating
those with HIV suppression and severe fibrosis or cirrhosis was -1.1% (95% CI: -2.8%, 0.6%). Under this policy, 51% (95% CI: 38%, 59%) of PLWH+HCV would be treated with DAAs. The RD for treating the same proportion of PLWH+HCV chosen at random was -1.9% (95% CI: -4.7%, 0.3%). The population attributable risk difference for treating all PLWH+HCV with direct acting antivirals (DAA) was -0.7% (95% CI: -1.8%, 0.1%).

These results show that HCV is a major cause of mortality among PLWH, and that DAA treatment is effective at reducing mortality in this population. They also suggest that common DAA access criteria may be suboptimal and expanding access to these medications could lead to a substantial survival benefit among PLWH.
In memory of my father, Kenneth Breskin
ACKNOWLEDGEMENTS

First and foremost, I thank my wife, Greta Breskin. This dissertation would not have been possible without her love, support, wit, humor, patience, and intelligence.

I thank my advisor, Dr. Daniel Westreich, whose generosity with his time, knowledge, and resources during my time in this program gave me the freedom to pursue my research interests along with the structure and guidance to develop as an epidemiologist and researcher. Because of Daniel, my time as a doctoral student has been a rich, rewarding experience.

I thank the members of my dissertation committee for their time, patience, and guidance. Drs. Adaora Adimora and Christopher Hurt gave me the clinical perspective necessary to be successful as an epidemiologist, and Drs. Stephen Cole and Michael Hudgens provided me with methodological support and helped me understand complex, cutting-edge epidemiological methods.

I thank Valerie Hudock and Jennifer Moore for helping me with the administrative aspects of this program.

I thank Drs. Jess Edwards and Alex Keil for additional methodological support. They helped me work my way through methodological issues and helped me with many of the computational aspects of this dissertation, likely saving me weeks of running the analysis for this dissertation.

I thank my collaborators from the Women’s Interagency HIV Study and the Multicenter AIDS Cohort Study. Catalina Ramirez, Dr. Andrew Edmonds, and Ruibin Wang helped me navigate the complex data used in this dissertation, and they helped me through the process of obtaining data and submitting manuscripts using these data. Drs. Eric Seaberg, Chloe Thio, and
Phyllis Tien provided me excellent feedback on the manuscripts associated with this dissertation, and ultimately made this research stronger.

I thank everyone involved with the Women’s Interagency HIV Study and the Multicenter AIDS Cohort Study, including the members of the cohorts and the staff who make these studies possible. Their dedication to HIV research is remarkable, and without them our understanding of HIV would not be where it is today.

I thank the many friends I have made in this program. Without you, I would never have made it past the first semester.

Finally, I thank my family for their support throughout my career and education, in particular my mother, Wendy Breskin.

Funding for this study was provided by the National Institutes of Health in a grant from NICHD (DP2-HD-08-4070).
TABLE OF CONTENTS

LIST OF TABLES ........................................................................................................................................... xi
LIST OF FIGURES ............................................................................................................................................ xii
LIST OF ABBREVIATIONS ............................................................................................................................. xiii

CHAPTER 1: INTRODUCTION .......................................................................................................................... 1
  1.1 Hepatitis C Virus (HCV) ......................................................................................................................... 1
  1.2 Human Immunodeficiency Virus (HIV) .................................................................................................... 11
  1.3 HIV/HCV Coinfection ............................................................................................................................. 24

CHAPTER 2: STATEMENT OF SPECIFIC AIMS ........................................................................................... 37
  2.1 Specific aims and justifications ............................................................................................................... 37
  2.2 Rationale ................................................................................................................................................ 39
  2.3 Quantities to estimated ........................................................................................................................... 41

CHAPTER 3: METHODS ................................................................................................................................... 43
  3.1 Description of data sources ..................................................................................................................... 43
  3.2 Variable measurement and operationalization ......................................................................................... 49
  3.3 Notation ............................................................................................................................................... 56
  3.4 The parametric generalized computation algorithm formula ............................................................... 56
  3.5 Inverse probability weighted estimation of marginal structural models .............................................. 70
  3.6 Policy-relevant effect measures .............................................................................................................. 74
  3.7 Estimating hepatitis C infection and treatment effects from observational data ............................... 82
CHAPTER 4: THE EFFECTS OF HEPATITIS C INFECTION AND TREATMENT ON ALL-CAUSE MORTALITY AMONG PEOPLE LIVING WITH HIV .................................................. 84
  4.1 Introduction........................................................................................................ 84
  4.2 Methods............................................................................................................ 85
  4.3 Results............................................................................................................. 90
  4.4 Discussion........................................................................................................ 92
  4.5 Tables and figures .......................................................................................... 96

CHAPTER 5: THE POPULATION INTERVENTION EFFECTS OF HEPATITIS C TREATMENT CRITERIA ON ALL-CAUSE MORTALITY AMONG PEOPLE LIVING WITH HIV .................................................................................. 102
  5.1 Introduction........................................................................................................ 102
  5.2 Methods............................................................................................................ 103
  5.3 Results............................................................................................................. 107
  5.4 Discussion........................................................................................................ 110
  5.5 Tables and figures .......................................................................................... 113

CHAPTER 6: DISCUSSION ....................................................................................... 118
  6.1 Overview .......................................................................................................... 118
  6.2 Study findings .................................................................................................. 119
  6.3 Strengths and limitations ................................................................................. 123
  6.4 Future directions .............................................................................................. 128
  6.5 Figures ............................................................................................................. 131

APPENDIX A: FURTHER DETAILS OF ANALYSIS IN CHAPTER 4 ...................... 132
  A.1 Notation .......................................................................................................... 132
  A.2 Natural course and g-formula equations used in chapter 4 ......................... 133
  A.3 Final models used in chapter 4 ..................................................................... 134
A.4 Estimation of the marginal structural model for chapter 4 ........................................137
A.5 Comparison of observed and modelled natural course in chapter 4 .........................139
A.6 Results of sensitivity analyses for chapter 4 ..........................................................141

APPENDIX B: FURTHER DETAILS OF ANALYSIS IN CHAPTER 5 .................................142

B.1 Notation ..................................................................................................................142
B.2 Natural course and g-formula equations used in chapter 5 ........................................143
B.3 Final models used in chapter 5 ................................................................................144
B.4 Comparison of observed and modelled natural course in chapter 5 ......................149
B.5 Timing of DAA treatment under dynamic interventions in chapter 5 ....................151

REFERENCES .............................................................................................................152
**LIST OF TABLES**

Table 1.1: Prior studies estimating the effect of HCV coinfection on mortality among people living with HIV in the ART era..........................................................35

Table 1.2: Prior studies estimating the effect of HCV sustained virologic response on mortality among people living with HIV and HCV in the ART era.............36

Table 4.1: Study population at baseline, Women’s Interagency HIV Study and Multicenter AIDS Cohort Study, 1994-2015............................................................96

Table 4.2: Effects of HCV infection and DAA treatment on 10-year all-cause mortality had all subjects initiated ART at baseline, Women’s Interagency HIV Study and Multicenter AIDS Cohort Study, 1994-2015.............................................98

Table 5.1: Baseline characteristics of eligible study participants stratified by source, Women’s Interagency HIV Study and Multicenter AIDS Cohort Study, 1994-2015.................................................................113

Table 5.2: Effects of DAA treatment criteria on 10-year all-cause among people living with HIV and HCV, Women’s Interagency HIV Study and Multicenter AIDS Cohort Study, 1994 - 2015.................................................................115

Table 5.3: Population intervention effects of DAA treatment criteria on 10-year all-cause mortality among people living with HIV, Women’s Interagency HIV Study and Multicenter AIDS Cohort Study, 1994 - 2015............116

Table A.1: Comparison of observed versus modelled variable distributions under the natural course using models from chapter 4, Women’s Interagency HIV Study and Multicenter AIDS Cohort Study, 1994-2015...............139

Table A.2: Sensitivity analysis results for chapter 4.................................................................141

Table B.1: Comparison of observed versus modelled variable distributions under the natural course using models from chapter 5, Women’s Interagency HIV Study and Multicenter AIDS Cohort Study, 1994-2015...............149
LIST OF FIGURES

Figure 3.1: Causal diagram used to select confounders.................................................................55

Figure 3.2: Causal diagram motivating the g-computation algorithm formula .........................62

Figure 4.1: The effect of HCV infection on 10-year all-cause mortality among PLWH, Women’s Interagency HIV Study and Multicenter AIDS Cohort Study, 1994-2015 ..........................................................99

Figure 4.2: The effect of HCV infection on 10-year all-cause mortality among PLWH and HIV, Women’s Interagency HIV Study and Multicenter AIDS Cohort Study, 1994-2015 ..........................................................100

Figure 4.3: The effect of DAA treatment on 10-year all-cause mortality among PLWH and HIV, Women’s Interagency HIV Study and Multicenter AIDS Cohort Study, 1994-2015 ..........................................................101

Figure 5.1: Effects of DAA treatment criteria on 10-year all-cause mortality among people living with HIV and HCV, the Women’s Interagency HIV Study and Multicenter AIDS Cohort Study, 1994-2015 .........................................................117

Figure 6.1: Simplified causal diagram demonstrating potential lack of conditional exchangeability when estimating HCV treatment effects .........................................................131

Figure A.1: Comparison of observed versus modelled mortality under the natural course using models from chapter 4 ..........................................................140

Figure B.1: Comparison of observed versus modelled mortality under the natural course using models from chapter 5 ..........................................................150

Figure B.2: Timing of DAA treatment under dynamic interventions in chapter 5 ...............151
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>Acquired immune deficiency syndrome</td>
</tr>
<tr>
<td>APEX</td>
<td>Average effect of policy in the exposed</td>
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<tr>
<td>ART</td>
<td>Antiretroviral therapy</td>
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<td>ARV</td>
<td>Antiretroviral drug</td>
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<td>BMI</td>
<td>Body mass index</td>
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<td>DAA</td>
<td>Direct-acting antiviral</td>
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<td>DPEX</td>
<td>Dynamic effect of policy in the exposed</td>
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<tr>
<td>GPEX</td>
<td>Generalized effect of policy in the exposed</td>
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<td>HCV</td>
<td>Hepatitis C virus</td>
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<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>IDU</td>
<td>Injection drug use</td>
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<tr>
<td>INI</td>
<td>Integrase inhibitor</td>
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<tr>
<td>NNRTI</td>
<td>Non-nucleoside reverse transcriptase inhibitor</td>
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<tr>
<td>NRTI</td>
<td>Nucleoside reverse transcriptase inhibitor</td>
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<tr>
<td>PEG-IFN</td>
<td>Pegylated Interferon</td>
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<td>Protease inhibitor</td>
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<tr>
<td>PLWH</td>
<td>Person(s) living with human immunodeficiency virus</td>
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<td>PLWH+HCV</td>
<td>Person(s) living with human immunodeficiency virus and hepatitis C virus</td>
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<td>PWID</td>
<td>Person(s) who inject drugs</td>
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CHAPTER 1: INTRODUCTION

In the following section, key concepts related to hepatitis C virus (HCV) and human immunodeficiency virus (HIV) are highlighted. First, important topics for HCV and HIV are reviewed separately, including their virology, pathogenesis, natural history, epidemiology, and treatment. Next, a thorough overview of HIV/HCV coinfection is presented, including the reasons for the high prevalence of coinfection, the way each virus affects the other, the implications of coinfection for treatment of each disease, and current challenges and unanswered questions.

1.1 Hepatitis C virus

Virology of the hepatitis C virus

Hepatitis C virus (HCV) is a single-stranded, positive-sense RNA virus of the family Flaviviridae (Chevaliez & Pawlotsky 2006). The virus is introduced into a host via contact with infected blood (Liang et al. 2000). After exposure, the virus enters host cells through a combination of receptors referred to as a “receptor complex,” which includes (but is not limited to) the SRB1, CD81, CLDN1, OCLN, EFGR, EphA2, NPC1L1, and LDL receptors (Kim & Chang 2013; Scheel & Rice 2013; Dubuisson & Cosset 2014). Of particular importance are the SRB1 and NPC1L1 receptors, as these are highly expressed in the liver and are likely part of the reason why the virus primarily infects hepatic cells (Dubuisson & Cosset 2014).

Upon entry into the cell, the positive-sense RNA is released and is directly translated by the host into the viral polyprotein. The polyprotein is cleaved by host and viral proteases into 10
proteins, 3 structural - Core, E1, and E2 - and 7 non-structural - NS2, NS3, NS4A, NS4B, NS5A, NS5B, and p7 (Kim & Chang 2013). The structural proteins are used to form the virion itself, with core being a component of the viral capsid and E1 and E2 being proteins that bind to cell receptors and aid the virus in entering the host cell. The non-structural proteins include an RNA-dependent RNA polymerase (NS5B) involved in replicating the viral genome, proteases for processing the viral polyprotein (NS2, NS3, NS4A), and other proteins with various functions. Of these other proteins, the most important is perhaps NS5A, which alters the host cell to increase viral replication efficiency. The NS3/NS4A proteases, NS5A multi-function protein, and NS5B RNA polymerase are the targets of many modern HCV drugs.

The viral genome is reproduced by creating a negative-sense RNA template from the positive-sense RNA, and then using that template to create additional positive-sense strands (Chevaliez & Pawlotsky 2006). These newly created positive-sense strands are then used for further translation into viral protein and for packaging into new virions. Of note, the liver-specific microRNA miR-122 is necessary to facilitate viral replication, further explaining why the liver is the primary target for the virus. (Dubuisson & Cosset 2014). Because of the lack of efficient infectious cell culture systems until 2005 as well as the limitations of most in vitro models (Tariq et al. 2012), many aspects of the pathobiology of HCV remain poorly understood (Scheel & Rice 2013; Hoshida et al. 2014).

HCV does not enter the host cell’s nucleus and does not integrate into the host genome, and thus the virus must continuously replicate (Hoshida et al. 2014). The virus is extremely efficient at replication, with a single person with HCV producing as many as \(10^{12}\) virions per day (Jackowiak et al. 2014). This, along with the lack of proofreading ability of the viral RNA, leads to constant mutation and extraordinary diversity both within and between people with HCV.
HIV shares many of these properties, see Virology of HIV. To date, 7 HCV genotypes (referred to as 1-7) and dozens of subtypes (referred to with letters) have been identified (Jackowiak et al. 2014). Each genotype shares only 70% of its genome with other HCV genotypes, and each subtype shares only 85% of its genome with other subtypes of the same genotype. This rapid mutation leads to HCV existing as a “quasispecies,” with substantial genetic variability within a host (Jackowiak et al. 2014). The extreme diversity of HCV makes it difficult for the host immune response to fully clear the infection and makes vaccine development challenging.

**Pathogenesis of HCV**

HCV is non-cytopathic, and instead damages the host through indirect mechanisms (Irshad et al. 2013; Hoshida et al. 2014). HCV triggers relatively weak humoral and cellular immune responses to infection. Due to the high mutation rate within a host, the humoral response is typically unable to completely neutralize the virus (Liang et al. 2000). The cellular immune response is characterized by a weak T-cell response, which often fails to control the virus and instead leads to chronic inflammation, hepatocellular injury, and fibrosis (Liang et al. 2000; Hoshida et al. 2014). Additionally, a complex interaction between HCV and lipoproteins may shield the virus from the host immune response (Dubuisson & Cosset 2014).

Fibrosis is a response to liver injury that results in the increased production and deposition of extracellular matrix (in lay terms, the formation of scar tissue), which in turn diminishes liver function and increases the risk of malignant mutations (Hoshida et al. 2014). Liver fibrosis is driven by the activation of hepatic stellate cells, a type of cell found in the liver with poorly understood purpose or function (Hoshida et al. 2014). HCV induces fibrosis by stimulating profibrogenic mediators and inducing the production of inflammatory chemokines and cytokines. Additionally, HCV promotes oxidative stress, insulin resistance, and steatosis, all of which may
lead to fibrosis, though the exact mechanism is not fully understood (Irshad et al. 2013). Because insulin resistance and steatosis are also caused by obesity, weight management is an important aspect of HCV care.

**Natural history of HCV**

HCV is transmitted through contact with infected blood, either directly through inoculation (e.g. through injection drug paraphernalia) or transfusion of contaminated blood products, or indirectly through breakage of a cutaneous or mucosal barrier, as may happen with sexual or perinatal transmission (Liang et al. 2000). HCV remains stable on surfaces for extended periods of time, and as such the sharing of many types of drug paraphernalia beyond needles and syringes, such as spoons, tourniquets, cotton balls, or water glasses, can potentially lead to HCV transmission. HCV transmission through contaminated blood products is virtually non-existent in the United States, as the blood supply has been screened for HCV since 1992 (Centers for Disease Control and Prevention 2016).

Acute infection, which is generally defined as occurring during the initial 6 months after acquisition of the virus, is asymptomatic in most cases (Seeff 2002). Due to the mildness of acute HCV infection, it is challenging to properly characterize the natural history of the disease, as most cases are not identified until their later stages; therefore the onset and duration of disease is usually not determined (Seeff 2002). A large meta-analysis found that approximately 25% of people with HCV spontaneously clear the acute infection without treatment, with the remaining progressing to chronic HCV infection (Micallef et al. 2006). Chronic HCV infection can persist for decades with no symptoms, despite the potential for accumulation of fibrosis related to viral replication in the liver.
Patients who accumulate enough fibrosis to be classified as cirrhotic may succumb to end-stage liver disease, hepatocellular carcinoma (HCC), and other liver-related causes of death. Cirrhosis develops in 10-20% of patients after 20-30 years of chronic infection, but the pace differs substantially from person to person depending on the presence of other risk factors, such as older age at infection, male sex, coinfection with HIV or hepatitis B virus, obesity, heavy drinking, smoking, type 2 diabetes, and hepatic steatosis (Seeff 2002; Hajarizadeh et al. 2013; Westbrook & Dusheiko 2014). Once cirrhosis develops, patients experience a 1-5% annual risk of HCC and a 3-6% annual risk of hepatic decompensation, defined as the failure of normal liver function due to cirrhosis (Westbrook & Dusheiko 2014). Although episodes of hepatic decompensation may be reversible with medical therapy, once a patient has experienced decompensation for the first time, their annual risk of death is 15-20% (Westbrook & Dusheiko 2014).

Epidemiology of HCV

The incidence of HCV and its risk factors are a challenge to investigate, as most acute cases are undiagnosed, and chronic cases are discovered years after infection. For instance, in 2014, out of an estimated 30,500 incident cases of HCV infection in the US, only 2,194 were reported to the CDC (Centers for Disease Control and Prevention 2017d). Therefore, most of the understanding of HCV incidence and risk factors comes from biological knowledge of how the virus operates and from prevalence estimates, and therefore many aspects of the disease are still not fully understood.

The global prevalence of HCV infection is estimated at 2-3%, meaning 130-170 million people are infected worldwide (Hajarizadeh et al. 2013). In the United States, the prevalence has been somewhat stable since HCV was first discovered to be the causative agent of “non-A, non-
B” hepatitis in 1989 (Bukh 2016). Between 1988 and 1994, an estimated 1.3% of adults in the US had chronic HCV based on the National Health and Nutrition Examination Survey (NHANES) (Alter et al. 1999). In a follow-up study from NHANES conducted between 1999 and 2002, the prevalence remained stable at 1.3% (Armstrong et al. 2006). Finally, the most recent NHANES study estimated the prevalence of chronic HCV infection in the United States to be slightly lower at 1.0%, corresponding to 2.7 million chronic cases (Denniston et al. 2014).

The majority of HCV in the US is genotype 1 (primarily 1a, followed by 1b) (comprising 70% of cases), but genotypes 2 and 3 are also prevalent (Scheel & Rice 2013).

The prevalence in the US varies within subpopulations, with the highest prevalence being among 40-49 year-olds, males, and non-Hispanic blacks (Denniston et al. 2014). The epidemic is rapidly evolving, however, with increasing proportions of cases occurring in younger, non-Hispanic white PWID (Suryaprasad et al. 2014). Certain other subpopulations in the US face a substantially increased burden of HCV, for instance people born between 1945 and 1965 (Smith et al. 2012) and people with HIV, as discussed in section 2C: HIV-HCV Coinfection.

The primary mode of HCV transmission in the US is related to injection drug use (IDU) (Klevens et al. 2012). Between 2003 and 2010, an estimated 51.5% of chronic HCV cases had reported ever injecting drugs (Denniston et al. 2014), and in 2009 56% of individuals with acute HCV infections reported IDU (Klevens et al. 2012) (it is important to note that these are likely severe underestimates due to underreporting of IDU (Klevens et al. 2012)). Other behaviors and characteristics that may predispose someone to come into contact with infected blood, such as participating in high risk sexual practices, getting tattoos from unsterilized equipment, perinatal transmission, and working in healthcare settings (especially hemodialysis centers), have a role in HCV transmission in the US (Klevens et al. 2012)
HCV infection remains the leading cause of liver transplantation in the United States (Thuluvath et al. 2010). In 2007, the number of deaths in the US attributed to HCV exceeded those due to HIV for the first time (Ly et al. 2012). In 2014, nearly 20,000 deaths in the United States were attributed in whole or in part to HCV infection (Centers for Disease Control and Prevention 2017d).

Treatment of HCV: historical context

Successful treatment for HCV is defined as achieving a sustained virologic response (SVR), which means a loss of detectable HCV RNA during treatment, and a continued absence for at least 12 weeks after therapy ends (American Association for the Study of Liver Diseases & Infectious Diseases Society of America 2017). SVR is durable in over 95% of patients (Feld & Hoofnagle 2005), and Patients who achieve SVR have improved clinical outcomes (Veldt et al. 2007).

Shortly after HCV was discovered in 1989, interferon-α (IFN) was identified as a moderately effective treatment (Davis et al. 1989; Di Bisceglie et al. 1989). IFN has general antiviral, antiproliferative, and immunomodulatory activity, and it operates to treat HCV through at least two known mechanisms (neither of which acts directly on HCV). First, it induces IFN-stimulated genes, causing a general antiviral state to occur within the cell. Second, it causes memory T-cell to proliferate and prevents their apoptosis, and it causes the stimulation and maturation of natural killer and dendritic cells (Feld & Hoofnagle 2005). Unfortunately, IFN produces moderate to severe side effects, including influenza-like symptoms, gastrointestinal disturbances, neuropsychiatric symptoms, and hematologic abnormalities (Fried 2002). Poor adherence due to side effects, as well as the non-specific antiviral activity of the treatment, lead to a poor response to IFN-based treatment of only 16-20% rate of SVR (Di Bisceglie & Hoofnagle 2002). Also of
note, IFN is substantially less effective for infections by HCV genotype 1, the most commonly found genotype in the US, compared with other genotypes (Jackowiak et al. 2014).

In the late 1990s, it was discovered that the addition of ribavirin to IFN based treatments substantially improved treatment outcomes (Davis et al. 1998; Poynard et al. 1998), leading to SVR rates of 35-40% (Feld & Hoofnagle 2005). Like IFN, ribavirin is a non-specific antiviral agent that directly inhibits viral replication. It is believed that ribavirin acts as a viral mutagen which increases the number of mutations and causes “error catastrophes” that lead to non-viable viral mutants (Feld & Hoofnagle 2005).

In the early 2000s, researchers found that the use of IFN conjugated to polyethylene glycol (PEG-IFN) led to additional improvements in treatment success (Manns et al. 2001), with SVR rates over 50% (Feld & Hoofnagle 2005). PEG-IFN has an improved pharmacokinetic profile and fewer side effects (Feld & Hoofnagle 2005). Unfortunately, due to the lack of efficient cell culture systems and limited in vitro models, PEG-IFN remained the best available treatment for over a decade, leaving the nearly half of treated individuals who did not achieve SVR with no alternatives.

Treatment of HCV: recent developments

After 2005, with the discovery of useful HCV cell culture systems, research accelerated for HCV-specific treatments. In 2011, the first two drugs of a new class, known as direct acting antivirals (DAA), were approved. The first two approved DAAAs, boceprevir and telaprevir, were developed to be used in combination with PEG-IFN and ribavirin (Poordad et al. 2011; Jacobson et al. 2011). Both of these drugs are protease inhibitors, inhibiting the action of the NS3 and NS4A viral proteases (Welsch et al. 2012). Because of the difficulty of treating HCV genotype 1
and the variability of NS3 across genotypes, these drugs were specifically approved for that genotype (Kiser & Flexner 2013). When used in combination with PEG-IFN and ribavirin, these drugs led to SVR rates as high as 75% (Poordad et al. 2011; Jacobson et al. 2013). Though SVR rates were improved substantially, treatment duration remained long (as long as 48 weeks), and the side effect profile was similar to prior treatments.

In 2013, the blockbuster drug sofosbuvir was approved for the treatment of HCV (Gilead Sciences 2013). Sofosbuvir inhibits the HCV RNA-dependent RNA-polymerase, NS5B, which is highly conserved, and thus the drug is effective for all HCV genotypes (Lawitz et al. 2013). The first approved treatments with sofosbuvir included PEGIFN and ribavirin, and achieved SVR rates of over 90% with only 12 weeks of treatment for most HCV genotypes (Jacobson et al. 2013; Lawitz et al. 2013). Though the treatment success rate was excellent, the need for PEGIFN remained a problem. Shortly thereafter, it was discovered that all-oral, interferon-free regimens of sofosbuvir along with second-generation NS3/NS4A protease inhibitors (e.g. simeprevir) and NS5A inhibitors, such as daclatasvir and ledipasvir, resulted in SVR rates up to 99% and minimal side effects with 12 weeks of treatment (Feld et al. 2015; Sulkowski et al. 2014; Lawitz et al. 2014), with highly effective options available for all major genotypes, for patients with previously failed treatment, for patients with advanced liver disease, and for patients with HIV coinfection (American Association for the Study of Liver Diseases & Infectious Diseases Society of America 2017). Additional non-sofosbuvir containing regimens with similar mechanisms of action have since been approved (American Association for the Study of Liver Diseases & Infectious Diseases Society of America 2017).
Current challenges and remaining questions with HCV

Modern DAA therapy is extremely effective and has completely changed the landscape of HCV treatment (Burstow et al. 2017). However, there are several remaining challenges and open questions with regards to HCV treatment. Perhaps first among them regards access to treatment. The list price for sofosbuvir, $1,000 per pill ($84,000 for a course of treatment) (University of Washington 2017), is prohibitively expensive for many people with HCV (Rosenthal & Graham 2016). Even though the price paid by insurers in the United States is typically heavily discounted, with an average discount of 46% off of the list price (Rosenthal & Graham 2016), DAA treatment continues to be restricted by many Medicaid programs. As of October 2017, 30 states restrict DAAs to patients with at least moderate liver fibrosis (12 states restrict to those with severe fibrosis), and 40 states restrict access to patients based on substance use (Ooka et al. 2017), restrictions that are particularly problematic given the ‘treatment as prevention’ paradigm (Trooskin et al. 2015). As of September 2016, 5 states plus Washington, DC restrict treatment among people living with HIV and HCV to those who meet certain HIV treatment goals, such as achieving HIV suppression. These restrictions persist despite guidelines that suggest that nearly all people with HCV be treated (American Association for the Study of Liver Diseases & Infectious Diseases Society of America 2017). The treatment landscape is rapidly evolving, however, as more drugs come to market to increase competition and reduce costs (Nisen 2017), and as legal challenges force insurance companies to drop coverage restrictions (National AIDS Treatment Advocacy Project 2017). Nevertheless, it has been estimated that, even with current discounts, treating all patients with HCV in the US would comprise more than 50% of pharmaceutical expenditures in the country (Iyengar et al. 2016). Given these high costs and the limited access to treatment, understanding which patient populations would benefit from DAA
regimens and whether or not current Medicaid restrictions are optimizing survival benefits is essential for maximizing access to those most in need.

There are many additional open questions with regards to HCV and its treatment, including the possibility of drug-drug interactions, the effectiveness of DAAs in key populations, and the effect of HCV on survival among people with certain common comorbidities. Some of these are discussed in detail in section 2C: HIV-HCV Coinfection.

1.2 Human immunodeficiency virus

Virology of the human immunodeficiency virus

Human immunodeficiency virus (HIV), the causative agent of acquired immunodeficiency syndrome (AIDS), is a retrovirus of the genus lentivirus (Turner & Summers 1999). After transmission via contact with infected bodily fluids, the virus binds to the CD4 receptor and either the CCR5 or CXCR4 coreceptors of host cells, which are primarily found on T cells, but also monocytes, macrophages, dendritic cells, astrocytes, and epithelial cells (Maartens et al. 2014).

The virion contains several elements necessary for replication, including reverse transcriptase, protease, ribonuclease, and integrase (Turner & Summers 1999). Once inside the host cell, the viral reverse transcriptase transcribes the viral RNA into double-stranded DNA (Sierra et al. 2005). The viral integrase then integrates the DNA into the host genome, where it is transcribed by host cell processes in order to produce viral proteins and new copies of viral RNA (Sierra et al. 2005). Finally, the viral protease cleaves the polyproteins and packages them, along with viral RNA, into new virions, which exit and infect new cells (Sierra et al. 2005). Of note, some actions of the viral protease take place after the virion has budded from the host cell.
The HIV genome codes for several structural, functional, and accessory proteins. The Gag polyprotein is cleaved by the viral protease into the four nucleocapsid proteins – MA, CA, NC, and p6. The Pol polyprotein is cleaved into the functional proteins – protease, reverse transcriptase, RNase H, and integrase. Additionally, the HIV genome codes for Env, the envelope protein, and the accessory proteins Tat, Rev, Nef, Vif, Vpr, and Vpu (Turner & Summers 1999; Sierra et al. 2005).

The HIV virus has two subtypes – HIV-1 and HIV-2 (Maartens et al. 2014). HIV-2 is predominantly found in West Africa, and is notable for being less transmissible, having a slower disease progression, and being less susceptible to certain classes of antiretroviral medications. HIV-1 is the type found in the vast majority of cases globally and will thus be the focus of the rest of this work. There are four HIV-1 subgroups, each corresponding to distinct zoonotic transmission events – M, N, O, and P. The majority of cases worldwide are group M; N, O, and P are only found in West Africa (Maartens et al. 2014). Each subgroup’s genome differs from the others’ by at least 30%, while subtypes within the subgroups differ by 15-20% (Levy 2009). Like HCV, HIV exhibits a very high rate of mutation, and many strains can coexist within an individual. This is largely due to efficient replication - $10^9$ virions are typically produced within a person with HIV every day (Ho et al. 1995) - and the high error rate of HIV reverse transcriptase (Stebbing & Moyle 2003). The large degree of heterogeneity has important consequences for immune system evasion and treatment resistance (Turner & Summers 1999).

**Pathogenesis of HIV**

The primary mechanism by which HIV causes morbidity and mortality is by destruction of CD4 T-cells (Levy 2009; Lucas & Nelson 2015). HIV primarily destroys T-cells via two mechanisms – apoptosis of infected, activated cells, and pyroptosis of bystander non-infected
cells (Lucas & Nelson 2015). The CD4 cells of the gastrointestinal tract are the first to be destroyed, and these usually do not recover even after successful HIV therapy (Levy 2009; Lucas & Nelson 2015). The progressive exhaustion of CD4 cells leaves the host vulnerable to opportunistic infections, which ultimately lead to severe morbidity and death (Maartens et al. 2014). Besides CD4 cell destruction, the destruction of astrocytes and renal epithelial cells also directly lead to neurocognitive disorder and nephropathy (Maartens et al. 2014).

The host immune system mounts a potent response to HIV infection. The innate immune response is mediated by natural killer cells which identify and destroy cells that do not display major histocompatibility complex due to being infected by the virus (Levy 2009; Maartens et al. 2014). The cellular immune response, which begins within hours or days of infection, involves CD8 T-cells killing HIV-infected cells (Maartens et al. 2014). Lastly, the humoral immune response involving HIV neutralizing antibodies arises within weeks of infection (Maartens et al. 2014). Because of the high mutation rate of HIV, the immune response quickly selects for immune resistant strains, and is ultimately unable to completely clear the virus (Maartens et al. 2014).

The strong and lasting immune response to HIV often causes persistent immune activation and inflammation via several mechanisms (Maartens et al. 2014; Lucas & Nelson 2015). First, HIV triggers Toll-like receptors that induce pro-inflammatory cytokine production. Second, due to the depletion of CD4 cells from the gut, microbial translocation often occurs, leading to an immune response to the translocated bacteria. Third, CD4 cell destruction by pyroptosis is highly inflammatory, as the process releases inflammatory chemokines and cytokines (Lucas & Nelson 2015).
Natural history of HIV infection

HIV is transmitted via exposure to infected bodily fluids such as blood or semen. Common routes of exposure are mother to child transmission, condomless sexual intercourse, injection drug use, blood transfusion, accidental inoculation, or organ transplants (Maartens et al. 2014; Lucas & Nelson 2015). The risk of infection after exposure is directly correlated with the viral load of the person with HIV (Maartens et al. 2014), which has important implications for treatment as prevention.

The initial, acute infection causes symptoms in approximately 50% of cases, and includes an illness characterized by fever, lymphadenopathy (swollen glands), pharyngitis (sore throat), GI upset, and other flu-like symptoms (Lucas & Nelson 2015) (the proportion of people with acute HIV experiencing symptoms is likely much higher, but only a fraction of such individuals seek care for their symptoms). This acute phase is characterized by an extremely high viral load, which increases the risk of transmission 20-fold (Hollingsworth et al. 2008). The immune response is able to slow down the viral replication, but is not able to eliminate the virus (Maartens et al. 2014). The next phase is characterized by a drop in viral load to a ‘setpoint,’ followed by a partial recovery of CD4 cells (Maartens et al. 2014; Lucas & Nelson 2015). At this stage, the virus can persist for years in a latent state in resting memory T-cells where the virus has been integrated into the host genome (Maartens et al. 2014), with a median incubation period of approximately 10 years without treatment (Bacchetti & Moss 1989). This ‘reservoir’ of infected cells is a major impediment of HIV cure efforts.

Without treatment, the supply of CD4 cells is gradually exhausted (Maartens et al. 2014; Lucas & Nelson 2015). The immune system becomes depleted to the point of dysfunction, at which point the patient is said to have AIDS. AIDS is defined as a CD4 cell count of less than
200 cells per mm$^3$ or the presence of an AIDS-defining illness, such as Pneumocystis pneumonia, cytomegalovirus retinitis, or certain cancers (US Department of Health and Human Services 2017). Before effective treatments were available and early in the HIV epidemic, people living with HIV (PLWH) had a median survival time of 1 year after diagnosis with an AIDS-defining illness (Lee et al. 2001). Just prior to the discovery of combination antiretroviral therapy, this median survival time had improved to nearly 2 years (Lee et al. 2001).

Besides the gradual destruction of the immune system, HIV also causes chronic immune activation (see Pathogenesis of HIV). This chronic inflammatory state exists in many patients even after successful HIV treatment, and is associated with mortality and several chronic diseases, including cardiovascular disease, cancer, neurological disease, liver disease, chronic obstructive pulmonary disease, neurocognitive disorders, and osteopenia/osteoporosis (Lucas & Nelson 2015).

The most important prognostic factor for HIV infection is viral load (Mellors et al. 1996), and as such the goal of treatment is to reduce the viral load to undetectable levels (See Treatment of HIV). Other factors can also lead to a worse prognosis, including (but not limited to): older age, lower nadir CD4 cell count, higher viral setpoint, coinfection with herpesviruses or viral hepatitis, and increased immune activation (Lucas & Nelson 2015).

Since the introduction and widespread adoption of effective combination antiretroviral therapy (ART) in Western countries, the natural history of HIV has changed dramatically. HIV is now managed as a chronic disease, and much of the focus of HIV care is now on managing HIV-related comorbidities (Deeks et al. 2013). The outlook for PLWH has also greatly improved. For instance, between 1993 and 1995, prior to the introduction of ART, the risk of mortality 12 months after beginning treatment for HIV was 15.8% in a large Canadian cohort (Lima et al.
2007). Between 2002 and 2004, well into the ART era, the risk in that same cohort had decreased to 6.1\% (Lima et al. 2007). Additionally, PLWH can now achieve lifespans beginning to approach those of the general population (Samji et al. 2013; Nakagawa et al. 2013; Marcus et al. 2016). Between 1996 and 1997, in the early ART era, a 20-year-old with HIV was expected to live an additional 19 years; by 2011, that figure had increased to 53 years (Marcus et al. 2016). AIDS as a cause of death decreased substantially pre- and post- ART as well, from 78\% of deaths in between 1988 and 1995 to 15\% between 2005 and 2010 (Weber et al. 2013). This decrease in AIDS as a cause of death has corresponded to an increase in the proportion of non-AIDS causes of death, rising from 17\% between 1988 and 1995 to 71\% between 2005 and 2010 (Weber et al. 2013). Further implications of HIV treatment are discussed in the section Current challenges and remaining questions of HIV.

Epidemiology of HIV

The World Health Organization estimates that 36.7 million people across the world were living with HIV in 2015 (World Health Organization 2017). The majority of these people (25.5 million) are in Africa. That year, 2 million individuals became newly infected with HIV, of whom 1.4 million were in Africa. Finally, HIV caused 1.1 million deaths in 2015, including 800 thousand in Africa (World Health Organization 2017).

According to the Centers for Disease Control and Prevention, there were 1.2 million PLWH in the United States 2014, of whom 13\% are unaware of their HIV status (Centers for Disease Control and Prevention 2017b). Most diagnosed PLWH in the US are middle-aged; individuals aged 40-59 years make up nearly 50\% of people living with HIV. Non-Hispanic blacks accounted for 42\% of diagnosed people living with HIV in the US, and 24\% of diagnosed PLWH in the US were female. The region with the highest burden of HIV is the South, which
contains 44% of diagnosed HIV cases in the US, followed by the Northeast (25%), West (20%),
and Midwest (12%) (Centers for Disease Control and Prevention 2015a).

In 2015, 40 thousand people in the US were newly infected with HIV (Centers for Disease
Control and Prevention 2015a). The majority (67%) of new cases were men who have sex with
men (MSM), and most of those were among non-Hispanic Blacks. Women made up 19% of new
diagnoses. Among women, 86% of cases were acquired sexually, while 13% were attributed to
injection drug use. Overall, 9% of new cases were at least partially attributed to injection drug
use. Non-Hispanic Blacks accounted for 45% of all new diagnoses, while Hispanics accounted
for 24%. Individuals aged 20-39 made up 61% of new diagnoses (Centers for Disease Control
and Prevention 2015a). In 2014, 12 thousand PLWH died in the United States, with 7 thousand
of those deaths attributed to HIV (Xu et al. 2016).

The HIV epidemic in the United States has been in rapid transition in the last decade as HIV
prevention and treatment have improved. Between 2005 and 2014, there has been an 18%
decline in HIV incidence among White MSM, a 40% decline among women, a 35% decline
among heterosexuals, and a 63% decline among PWID. Unfortunately, not all groups shared in
these improvements. Non-Hispanic Black and Hispanic MSM have experienced increases in
incidence of over 20% in that time period. Overall, between 2005 and 2014, the incidence of
HIV declined by 19% (Centers for Disease Control and Prevention 2015c).

**HIV treatment: historical perspective**

HIV treatment has several goals. The first goal is to suppress HIV RNA replication, as
reflected by the plasma RNA “viral load”. The second is to restore the functionality of the
immune system to the greatest extent possible. The third is to reduce morbidity and prolong life.
The last, and most recent, goal of treatment is to prevent HIV transmission (Panel on Antiretroviral Guidelines for Adults and Adolescents 2018).

For the first six years of the HIV epidemic, there were no approved or known effective treatments for the deadly disease (Vella et al. 2012). HIV care providers focused on managing crises, dealing with opportunistic infections, and providing palliative care (Chu & Selwyn 2011). In 1987, a major breakthrough occurred with the discovery of the first HIV antiretroviral therapy, a nucleoside reverse transcriptase inhibitor (NRTI) called azidothymidine (abbreviated AZT and later renamed zidovudine, ZDV) (Fischl et al. 1987). With treatment, 98% of patients survived for 24 weeks, and only 23% of these patients developed an opportunistic infection (Fischl et al. 1987). Unfortunately, the benefit appeared to be short-lived, as the virus quickly develops resistance to single-agent therapy and thus immune system functional improvements are lost (Fischl et al. 1987). Nevertheless, additional NRTIs were quickly developed, though all faced similar shortcomings (Vella et al. 2012).

It was soon discovered that, due to the high rate at which HIV mutates, monotherapy with any one antiretroviral selected for resistant strains of the virus (Shirasaka et al. 1995; Richman 2001). To combat this resistance, new classes of drugs were developed to be used in combination with NRTIs. The first new drugs developed were the protease inhibitors (PI), the first of which was saquinavir (Vella et al. 2012). Shortly thereafter, nevirapine, the first of the non-nucleoside reverse transcriptase inhibitors (NNRTI), was approved (Vella et al. 2012).

Despite the new classes of drugs, mono- and dual-therapy still did not provide adequate results (Vella et al. 2012). The most important breakthrough in HIV treatment occurred in 1997, when it was first demonstrated that three-drug therapy led to substantially better survival and immune function than prior treatment regimens (Hammer et al. 1997). The use of a potent
combination of three antiretroviral drugs is now referred to as combination antiretroviral therapy (ART). Future trials found that ART led to extremely durable HIV suppression, with one early trial demonstrating effectiveness beyond three years (Gulick et al. 2000).

ART caused a paradigm shift in HIV care. In 1995, just prior to the discovery of ART, the all-cause mortality rate among people with HIV was 29.4 per 100 person-years. In 1997, after ART was introduced, that rate declined to 8.8 per 100 person-years (Palella et al. 1998). Since then, major improvements have been made to ART, such as treatment regimens with easier dosing and better side effect profiles, including the introduction of multiple single tablet, fixed-dose, once-daily regimens (Vella et al. 2012). New drug classes have also been developed. The first entry inhibitor (EI), enfuvirtide, was approved in 2003 as a salvage therapy for patients who had developed resistance to other classes of antiretrovirals (Lalezari et al. 2003). In 2007, the first integrase inhibitor (II), raltegravir, was approved and was shown to have similar efficacy as existing drugs (Lennox et al. 2009).

With early ART regimens, the toxicity of the drugs and the possibility of developing resistance led to clinicians delaying initiation of ART until their patients showed substantial immune system decline, typically when their CD4+ T-Cell count dropped below 200 cells per mm³ (Vella et al. 2012). A debate quickly ensued about when to initiate treatment, especially as treatments became less toxic. Some ideas included starting patients on ART when their CD4+ dropped below the usual threshold, but then stopping when their immune system recovered, a so-called ‘strategic interruption’ (Vella et al. 2012). Unfortunately, this strategy was shown to lead to substantially worse outcomes than simple starting patients on treatment at existing thresholds and staying on treatment (The Strategies for Management of Antiretroviral Therapy (SMART) Study Group 2006). In 2009, the When to Start Consortium found that starting at or above 350
CD4 cells per mm$^3$ led to better treatment outcomes than further delaying treatment (When To Start Consortium 2009). By 2015, the INSIGHT study showed that starting patients immediately after entry into care, regardless of CD4 count, provided the best patient outcomes (The INSIGHT START Study Group 2015), and this is the current guideline for treatment initiation in the United States (Panel on Antiretroviral Guidelines for Adults and Adolescents 2018).

In addition to providing benefit to the patients themselves, early ART initiation has been shown to prevent transmission to others, as viral suppression is the key determinant of infectivity (Panel on Antiretroviral Guidelines for Adults and Adolescents 2018). In 2011, the HPTN 052 trial was stopped three years early when it was found that immediate ART initiation led to a 93% reduction in HIV transmission in serodiscordant couples (Cohen et al. 2016). These results have led to the paradigm of ‘treatment as prevention,’ which is now a cornerstone of HIV control efforts and is being integrated into debates about treatment for other diseases.

**HIV treatment: classes of drugs and current guidelines**

Current guidelines recommend treatment initiation regardless of CD4 cell count, and provide several options for initial ART regimens (Panel on Antiretroviral Guidelines for Adults and Adolescents 2018). There are four main classes of antiretroviral drugs (ARV) that are used in recommended initial ART regimens. Typically, these involve two nucleoside/nucleotide reverse transcriptase inhibitors and either an integrase inhibitor, boosted protease inhibitor, or non-nucleoside reverse transcriptase inhibitor (Panel on Antiretroviral Guidelines for Adults and Adolescents 2018). While other classes of ARVs exist, such as fusion inhibitors and entry inhibitors, these are not included in any recommended treatment regimens (Panel on Antiretroviral Guidelines for Adults and Adolescents 2018).
The first class of ARVs is the nucleoside/nucleotide reverse transcriptase inhibitors (NRTI). NRTIs are analogues of naturally-occurring deoxynucleotides that are used in DNA synthesis (Moyle 2000). Reverse transcriptase cannot distinguish between the NRTIs and deoxynucleotides, and as such the NRTIs compete for incorporation into the DNA strand (Moyle 2000). NRTIs are “chain-terminator” molecules that lack an important 3’-hydroxyl group necessary for DNA elongation, so after they are integrated into the DNA strand, the next deoxynucleotide cannot bond to the DNA chain, halting DNA synthesis (Moyle 2000). Early NRTIs had severe side effect profiles, including neuropathy, myopathy, cardiomyopathy, pancreatitis, hepatitis, lactic acidosis, nephrological toxicity, bone marrow toxicity, and skin toxicity – all thought to be the effect of mitochondrial toxicity (Brinkman et al. 1998). Fortunately modern NRTIs have far fewer side effects and are better tolerated by patients (Vella et al. 2012). Commonly used NRTIs include abacavir (ABC), lamivudine (3TC), tenofovir (TAF or TDF), and emtricitabine (FTC) (Panel on Antiretroviral Guidelines for Adults and Adolescents 2018).

The second class of ARVs used in ART are the protease inhibitors (PI). PIs work by inhibiting the action of the viral protease. By binding to the site where protein cleavage occurs, PIs prevent HIV proteins from being produced, leading to virions that are unfit or inactive (Richman 2001). PIs share a common side effect of inhibiting the CYP450 metabolic system, and thus can be involved in serious drug-drug interactions (Richman 2001). The side effects of early PIs were often pronounced, including insulin resistance, dyslipidemia, and body fat redistribution (Richman 2001). When PIs are used, they are almost always ‘boosted’ with a pharmacokinetic enhancing agent (e.g. cobicistat or ritonavir) to prolong their half-lives in the body (Panel on Antiretroviral Guidelines for Adults and Adolescents 2018). The most commonly
used protease inhibitors are atazanavir and darunavir (Panel on Antiretroviral Guidelines for Adults and Adolescents 2018).

A third class of ARVs is the non-nucleoside reverse transcriptase inhibitors (NNRTIs). Like the NRTIs, these drugs target the reverse transcription step in the viral replication process. Their mechanism, however, is quite different. Rather than mimicking components of viral DNA, NNRTIs bind to the HIV reverse transcriptase and inhibit it from polymerizing DNA (Sluis-Cremer & Tachedjian 2008). NNRTIs tend to induce the CYP450 system, and thus may cause drug-drug interactions (Richman 2001). The most common adverse effects from NNRTIs are skin rashes (Panel on Antiretroviral Guidelines for Adults and Adolescents 2018) and, in the case of efavirenz, neuropsychiatric complications (Apostolova et al. 2015). Efavirenz is the only NNRTI currently recommended for first-line ART initiation, and it is only recommended as part of an ‘alternative’ regimen (Panel on Antiretroviral Guidelines for Adults and Adolescents 2018).

The last, and most recently discovered, class of ARVs is the integrase inhibitors (INI). INIs bind to and inhibit the action of HIV integrase, which is necessary for integrating the HIV DNA into the host cell genome (Mouscadet & Tchertanov 2009). INIs typically have fewer and milder side effect profiles compared with other ARVs (Lennox et al. 2009; Panel on Antiretroviral Guidelines for Adults and Adolescents 2018). The currently recommended INIs for initial ART are dolutegravir, elvitegravir, and raltegravir (Panel on Antiretroviral Guidelines for Adults and Adolescents 2018).
Current challenges and remaining questions of HIV

Perhaps the greatest current challenge with HIV is the lack of curative treatment or an effective vaccine. While there are many promising avenues being explored in that arena, it is important to tackle the challenges that are most pressing for PLWH and care providers today. The next greatest challenge is identifying PLWH and engaging them in care. In 2014, of the 1.1 million people with HIV over 13 years old in the US, 15% were not aware of their status (Centers for Disease Control and Prevention 2017c), corresponding to 166,000 undiagnosed cases. Perhaps more strikingly, only 57% of PLWH in the US were engaged in continuous HIV medical care, and, 58% were virally suppressed (Centers for Disease Control and Prevention 2017c). Because viral suppression is key for patient survival and the prevention of HIV transmission, getting patients engaged in care should be one of the top priorities for this population.

With the great gains in HIV treatment and care that have been made in the last decade have come new considerations for HIV patients and providers. PLWH are now experiencing life expectancies rivaling those of the general population (Samji et al. 2013; Nakagawa et al. 2013). However, the residual inflammation, suboptimal CD4 cell counts, and hypercoagulable state causes chronic diseases to occur at higher frequency (Justice 2010; High et al. 2012) and younger ages (Desquilbet et al. 2007; High et al. 2012) than in the general population. Though the reason for the high rates of these conditions is not fully understood, it is believed to include immune dysfunction and senescence, microbial translocation, chronic inflammation, toxicity from ART, oxidative stress, comorbid diseases such as hepatitis C, and high rates of alcohol, tobacco, and drug use (Desquilbet et al. 2007; Justice 2010; High et al. 2012). Recently, there have been notable increases in cardiovascular disease, malignancies (not limited to those associated with
infections), osteopenia and osteoporosis, liver disease, renal disease, and cognitive decline in this population (High et al. 2012), perhaps reflecting a closer alignment to the conditions impacting the general population. In fact, the most common causes of death among PLWH in the US are non-AIDS-related, and are instead primarily related to hepatic complications, cardiovascular disease, and non-AIDS-defining cancers (Smith et al. 2014).

HIV care providers are now faced with a complex problem. While they still must provide care and treatment for their patients’ HIV infection, they must also often guide and direct care for their patients’ multiple comorbid chronic conditions and manage their polypharmacy (Chu & Selwyn 2011). As such, it is important to elucidate the most severe conditions facing these patients and to identify what patient-level treatments and policy-level interventions may best reduce morbidity and mortality among people with HIV. Additional research is needed to determine how to properly prioritize the conditions to target for prevention and treatment interventions at both the patient and policy levels, and to aid providers in obtaining the best possible evidence to provide the best possible care for their patients.

1.3 HIV/HCV Coinfection

Diseases that travel together

Due to shared transmission routes, HCV is a common coinfection of HIV. Both viruses can be transmitted via contact with infected blood (Sulkowski 2008). The most efficient means of blood to blood transmission is through percutaneous exposure, and therefore injection drug use (IDU) is the primary driver of HIV/HCV coinfection (Sulkowski 2008; Taylor et al. 2012). Typically, those with IDU as a primary risk factor acquire HCV prior to HIV, as HCV is much more likely to be acquired from any given exposure; for instance, in a study of disease
transmission from accidental needle-stick injuries, HCV was ten times more likely to be transmitted than HIV (Kim et al. 2009).

Besides IDU, sexual transmission of HCV has had an increasing role in HIV/HCV coinfection (Danta et al. 2007; Taylor et al. 2012; Breskin et al. 2015). The reason for the increase in sexual transmission is thought to be due to increases in the prevalence and frequency of condomless sex and ‘sero-sorting,’ or choosing perceived HIV sero-concordant sexual partners, since the widespread adoption of effective ART (Taylor et al. 2012). This theory is consistent with reports of high rates of sexually transmitted infections in men who have sex with men with both HIV and HCV (Danta et al. 2007; Breskin et al. 2015). Though HCV does not usually transmit efficiently through sexual contact (Sulkowski 2008), individuals with HIV are more likely to shed the virus through semen. (Taylor et al. 2012), and thus those with sexual practices as a primary risk factor typically acquire HIV prior to HCV (Taylor et al. 2012).

Epidemiology of HIV-HCV coinfection

Globally, 6.2% of PLWH are thought to be coinfected with HCV, corresponding to 2.3 million cases (Platt et al. 2016). The odds of HCV infection among PLWH are 6 times the odds among those without HIV (Platt et al. 2016). Among people who inject drugs (PWID), the picture is much different. The estimated prevalence of HCV among PWID with HIV worldwide is 82.4%, and injectors with HIV have 36 times the odds of HCV infection than PWID without HIV (Platt et al. 2016).

In the United States, HCV infection is much more common among PLWH, largely due to the higher proportion of PLWH with injection drug use as their primary risk factor for infection. Here, 25% of PLWH are coinfected with HCV, meaning approximately 300,000 people have
both diseases (Centers for Disease Control and Prevention 2017a). Similar to the picture
globally, the prevalence of HCV is much higher among PWID with HIV, of whom 75% are
thought to be coinfected (Centers for Disease Control and Prevention 2017a). Due to the high
prevalence of HCV coinfection among PLWH in the United States, the CDC currently
recommends that all PLWH be tested for HCV upon entry into care, regardless of primary
transmission risk factor (Centers for Disease Control and Prevention 2015b). Notably, the
guidance is less clear regarding the screening of individuals already engaged in care (Freiman et
al. 2014).

Coinfection and mortality

Prior to the introduction of effective ART, HCV coinfection did not appear to impact
mortality among people with HIV in the US (Staples et al. 1999; Klein et al. 2003). The high
mortality associated with HIV at the time likely precluded PLWH and HCV (PLWH+HCV)
from experiencing the adverse, prolonged effects of HCV. After ART was introduced, the effect
of HCV coinfection on mortality among PLWH has remained unresolved. A meta-analysis of
studies conducted early in the ART era estimated that the rate of death among PLWH+HCV was
1.4 times the rate of people with HIV alone (Chen et al. 2009). More recently, results from the
Swiss HIV Cohort and Antiretroviral Therapy Cohort Collaboration estimated that HCV
coinfection increases the rate of death among PLWH by a factor of 2 to 3 (Kovari et al. 2015;
May et al. 2015). However, other studies have found that HCV has no effect on mortality in
PLWH (Sułkowski et al. 2002; Scherzer et al. 2017). Of note, no studies have been conducted
estimating the role of HCV on mortality under current HIV treatment guidelines (See Current
challenges and remaining questions with HIV-HCV coinfection).
In particular, HCV has been shown to lead to substantial increases in death from liver-related causes among PLWH. In a study during the early ART era, it was estimated that HCV coinfection increased the rate of liver-related mortality by a factor of twelve in PLWH (Rockstroh et al. 2005). Indeed, liver-related disease, including hepatocellular carcinoma, is the leading non AIDS-related cause of death among PLWH in the Western world, and much of it is attributed to viral hepatitides (Weber et al. 2013; Smith et al. 2014).

How HIV affects HCV

HIV has been shown to lead to a substantially worse prognosis for HCV infection. PLWH+HCV are much less likely to clear their acute HCV infection, and therefore are more likely to progress to chronic disease, compared with people with HCV only (Sulkowski 2008). PLWH+HCV also tend to carry a higher HCV viral load (Sulkowski 2008) and can shed virus through their semen, thus facilitating sexual transmission (Taylor et al. 2012).

PLWH+HCV often experience faster fibrosis progression compared with people with HCV only (Graham et al. 2001). In the early ART era, PLWH+HCV progressed by 0.18 fibrosis units per year, compared with 0.14 in people with HCV only, corresponding to a twelve-year faster progression to cirrhosis in these patients (Benhamou et al. 1999). Notably, PLWH+HCV have been found to have liver fibrosis measurements similar to those of people with HCV only who were nearly 10 years older, suggesting a substantially faster rate of fibrosis progression (Kirk et al. 2013). A meta-analysis conducted in 2001 found that PLWH+HCV had a risk of decompensated liver disease that was six times higher than that in people with HCV only, and a risk of cirrhosis that was twice as high (Graham et al. 2001). A second meta-analysis conducted in 2008 found a similar increase in the risk of cirrhosis, despite advances in and increased uptake of HIV therapy (Thein et al. 2008).
The mechanism by which HIV accelerates the progression of HCV infection is not fully understood but is likely due to several distinct mechanisms. First, it is known that HIV directly promotes fibrosis through hepatocyte apoptosis and activation of hepatic stellate cells (Kim et al. 2009; Liberto et al. 2015). Second, HIV directly dysregulates the immune system through the depletion of CD4 cells, which may allow for higher HCV viral loads (Kim et al. 2009). Third, the chronic inflammatory state caused by HIV infection may accelerate fibrosis (Kim et al. 2009; Liberto et al. 2015). Fourth, the depletion of gastrointestinal lymphoid tissue by HIV may lead to disruption of the epithelium and microbial translocation (Kim et al. 2009). In particular, lipopolysaccharides from gut bacteria may enter the bloodstream and promote inflammation. Fifth, certain adverse side effects of HIV therapy, including insulin resistance, dyslipidemia, and hepatic steatosis, are known risk factors for fibrosis (Kim et al. 2009).

Effective HIV treatment has been shown to partially attenuate the fast HCV progression due to HIV. PLWH+HCV on ART with detectable HIV viral load or suppressed CD4 cell counts had faster fibrosis progression than people with undetectable HIV viral load or normal CD4 cell counts (Bräu et al. 2006). Additionally, PLWH+HCV receiving ART have been shown to have a risk of liver-related mortality one tenth that of untreated PLWH+HCV (Qurishi et al. 2003), and ART has been shown to reduce the rate of hepatic decomposition by 30% (Anderson et al. 2014). Despite the improved fibrosis progression rates from effective HIV treatment, PLWH+HCV on ART still have a rate of cirrhosis that is 1.7 times that of people with HCV only (in the same meta-analysis, untreated PLWH+HCV had 2.5 times the rate of cirrhosis of people with HCV only) (Thein et al. 2008). Another study found that virally suppressed PLWH+HCV had a rate of hepatic decomposition 1.4 times that of people with HCV only (Re et al. 2014). Though HCV
infection may lead to an increased risk of hepatotoxicity from ART, this increased risk is far outweighed by the benefit of HIV control and decreased fibrosis progression (Sułkowski 2008).

HIV has a major impact on the success rate of PEG-INF-based treatment for HCV. The success rate of these treatments were extremely low in PLWH+HCV, with only 14% success among patients with genotype 1 and 73% success among people with other genotypes (Chung et al. 2004). Notably, very few PLWH+HCV were considered eligible for treatment due to poor immune function and other comorbidities (Rauch et al. 2005). Fortunately, modern DAA based HCV treatment appears to be as effective in PLWH+HCV as in people with HCV only, with SVR rates over 90% across patient populations (Molina et al. 2015; Wyles et al. 2015; Naggie et al. 2015; Sogni et al. 2016; Montes et al. 2017).

How HCV affects HIV

The effect of HCV coinfection on the progression of HIV is less clear, and the evidence thus far is equivocal. While some studies have found no effect of HCV on HIV progression to AIDS or response to ART (Staples et al. 1999; Sułkowski et al. 2002; Rockstroh et al. 2005), others have found that HCV leads to double the risk of AIDS-related mortality and hospitalization (Greub et al. 2000; Klein et al. 2003).

Modern HCV treatments may have important adverse drug-drug interactions with some ART regimens and non-HIV-related medications. The NS5B inhibitors, including sofosbuvir, have very few serious drug-drug interactions (El-Sherif et al. 2015; Panel on Antiretroviral Guidelines for Adults and Adolescents 2018). In general, the most serious drug-drug interactions are found in drugs metabolized by CYP3A, and as such these drugs should not be administered together (Panel on Antiretroviral Guidelines for Adults and Adolescents 2018). Common examples of
CYP3A-inducing ARVs are efavirenz, etravirine, and nevirapine, while CYP3A-substrate DAAs include daclatasvir, elbasvir, grazoprevir, paritaprevir, and simeprevir. An additional important drug-drug interaction is between ledipasvir, a substrate of P-glycoprotein, and tenofovir disoproxil fumarate. Co-administration of these drugs may lead to renal injury, especially when used with a boosted PI (Panel on Antiretroviral Guidelines for Adults and Adolescents 2018). Despite the possibility of drug-drug interactions, the large number of ART and DAA choices provide HCV and HIV treatment options for nearly all coinfected patients, though ART regimens and dosing may need to be adjusted if HCV treatment is to be initiated, and monitoring for adverse interactions is warranted (Panel on Antiretroviral Guidelines for Adults and Adolescents 2018). Because of the more immediate effect of HIV on adverse outcomes, treating HIV is considered most urgent, and it is recommended that ART be initiated prior to HCV treatment (Panel on Antiretroviral Guidelines for Adults and Adolescents 2018).

**Current challenges and remaining questions with HIV-HCV coinfection**

There are many open questions and challenges remaining with regard to HIV/HCV coinfection. First, the effect of HCV on mortality among PLWH under current ART regimens and guidelines is unknown, as was highlighted in a recent review article (Klein et al. 2016). The results from our systematic review of the effect of HCV on mortality among PLWH during the ART era are presented in Table 1. Out of a total of 2,174 search results, title and abstract review narrowed the number of relevant studies to 22. Many of these studies suffer from design and methodological flaws that call their results into question. Of note, only one study conducted in the US completed follow-up after 2009 (May et al. 2015), and none of the studies captured the period of modern HIV treatment guidelines which recommend initiation of ART for all patients regardless of CD4 cell count (Panel on Antiretroviral Guidelines for Adults and Adolescents
Additionally, only five studies restricted their samples to patients on ART (Backus et al. 2005; Greub et al. 2000; May et al. 2015; Rancinan et al. 2002; Weis et al. 2006), and none properly dealt with time-varying ART initiation or included ART as a potential effect measure modifier. Among the high-quality studies that appear most applicable to the population of people with HIV in the US, there is no clear consensus as to the effect of HCV on mortality. Five studies found that people with HIV and HCV have 1.4 to 2.4 times the rate of mortality compared with people with HIV only (Greub et al. 2000; May et al. 2015; Rockstroh et al. 2005; Weis et al. 2006; Thornton et al. 2017), while two studies found no effect of HCV on mortality among people with HIV (Sulkowski et al. 2002; Scherzer et al. 2017). A 2009 meta-analysis estimated that PLWH+HCV had 1.4 times the risk of mortality of PLWH alone (Chen et al. 2009). That study, however, combined estimates corresponding to varying lengths of follow-up, and therefore the results are difficult to interpret. Given the lack of consensus among studies, the scarcity of high-quality studies generalizable to the US population of PLWH, and the fact the no studies have been conducted under modern ART guidelines, there is a clear need for more research to determine the effect of HCV on mortality among PLWH.

A second open question with HIV-HCV coinfection is the effect of sustained virologic response following HCV treatment on mortality among PLWH+HCV. To date, there is minimal evidence of the effect of successful HCV treatment on mortality in the DAA era, and there is no evidence specifically for PLWH+HCV (Jakobsen et al. 2017). Two studies have evaluated how DAA treatment impacts mortality in the short term among people with HCV only, and they found that those treated with DAAs had a mortality rate less than half the rate of those who were untreated over one year (Backus et al. 2018) and 18 months (Butt et al. 2017). Unfortunately, these studies specifically excluded PLWH, and the short time-span covered is likely not long
enough to fully uncover the slowly progressing effects of HCV infection. Because those studies specifically excluded PLWH, they cannot be directly compared with our results, as risk factors for and causes of mortality differ between PLWH and the general population. Table 2 presents the results of a brief review of the literature investigating the effect of SVR on mortality in coinfected individuals from pre-DAA era studies. Using a broad search string, only 6 of 183 results were relevant. Of these six studies, three were conducted by the same research group using the same cohort (Berenguer et al. 2009; Berenguer et al. 2012; Berenguer et al. 2014), and five were conducted in Spain (Berenguer et al. 2009; Berenguer et al. 2012; Berenguer et al. 2014; Labarga et al. 2015; Mira et al. 2013). All six studies suffer from design and methodological flaws. First, all of these studies compared coinfected individuals who had achieved SVR to those who did not respond to treatment or who were not treated. Because response to the older PEG-IFN-based treatments used in these studies is poor among people with HIV and HCV, factors related to general overall health and immune function are likely predictors of both treatment initiation, response, and death, and are difficult or impossible to measure and control for in analysis. Second, since five of the studies only included people who had been given treatment, the results may not be well generalizable to the overall population of PLWH+HCV in the US, as most people with HIV and HCV were not eligible for PEG-INF treatment (Rauch et al. 2005). The study that included patients based on coinfection status rather than treatment status (Leone et al. 2016) did not properly account for time-varying confounding and thus the results are possibly biased (Robins 1986). Notably, none of the studies investigated the joint effect of HIV and HCV treatment on mortality. Overall, despite the appearance of a large effect of SVR on mortality, the available evidence is weak, potentially biased, and limited:
further studies are needed in the DAA era in order to properly assess the effect DAA treatment will have on mortality among PLWH+HCV.

One other challenge with respect to HIV/HCV coinfection is that the effect of DAA therapy on SVR is not well-studied in real-world coinfected populations and cohorts. While many randomized trials have been conducted to evaluate the efficacy of DAAs in PLWH+HCV, their restrictive inclusion criteria make them non-generalizable to the actual population of coinfected individuals. A study of the representativeness of coinfected trial populations found that fewer than half of the members of a Canadian cohort of PLWH+HCV would have been eligible for even the least restricted trial, and in almost every other trial fewer than 10% of the cohort would have been eligible (Saeed et al. 2016). The most common reason for exclusion was due to subjects not following the specific ART regimens required by the trial, followed by exclusion due to active drug use (Saeed et al. 2016). Even if the exclusions for ART regimens were not in place, only 25% of the cohort members would have met the inclusion criteria for the majority of the trials (Saeed et al. 2016). The exclusion due to injection drug use is particularly troubling, as PWID are most likely to spread their infection to others and therefore, from a public health perspective, they may be a key population to target for HCV control efforts. Though evidence of the effectiveness of DAAs in real-world populations and cohorts of PLWH+HCV is beginning to accumulate and has shown SVR rates consistently greater than 90% (Hawkins et al. 2016; Sogni et al. 2016; Milazzo et al. 2017; Montes et al. 2017), further studies are needed to understand their effectiveness in other realistic coinfected populations, such as among PWID.

It is clear that additional research is needed to elucidate the role HCV plays among PLWH. Without an understanding of how HCV infection and treatment impact mortality in this population, it is impossible to properly assess the impact and cost-effectiveness of policies aimed
at providing DAAs and potentially curing HCV, and providers are left without the information necessary to prioritize treatments among their patients.
## Table 1.1: Prior studies estimating the effect of HCV coinfection on mortality among people living with HIV in the ART era

<table>
<thead>
<tr>
<th>Study</th>
<th>Years</th>
<th>Source Population</th>
<th>N</th>
<th>Effect Measure</th>
<th>Baseline</th>
<th>Bias¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson et al. 2004</td>
<td>1997 - 2001</td>
<td>Atlanta Veterans Affairs Medical Center</td>
<td>305 HCV+ / 665 HCV-</td>
<td>HR: 2.46 (1.26; 4.2)</td>
<td>73%</td>
<td>T, C, G</td>
</tr>
<tr>
<td>Backus et al. 2005</td>
<td>1997 - 2003</td>
<td>US Department of Veterans Affairs</td>
<td>4,668 HCV+ / 7,548 HCV-</td>
<td>HR: 1.56 (1.42; 1.70)</td>
<td>100%</td>
<td>G</td>
</tr>
<tr>
<td>Bonacini et al. 2004</td>
<td>1992 - 2001</td>
<td>University of Southern California HIV/Hepatitis Clinic</td>
<td>256 HCV+ / 126 HCV-</td>
<td>RR²: 0.78 (0.56; 1.08)</td>
<td>48%</td>
<td>C, O</td>
</tr>
<tr>
<td>Branch et al. 2012</td>
<td>1998 - 2009</td>
<td>Studies of the Ocular Complications of AIDS cohort</td>
<td>337 HCV+ / 1,597 HCV-</td>
<td>HR: 1.50 (1.20; 1.90)</td>
<td>84%</td>
<td>G</td>
</tr>
<tr>
<td>Chen et al. 2016</td>
<td>2012</td>
<td>TREAT Asia HIV Observational Database</td>
<td>794 HCV+ / 4421 HCV-</td>
<td>HR: 1.81 (1.21; 2.72)</td>
<td>15%</td>
<td>M, G</td>
</tr>
<tr>
<td>El-Serag et al. 2005</td>
<td>1996 - 2001</td>
<td>US Department of Veterans Affairs</td>
<td>5,320 HCV+ / 12,761 HCV-</td>
<td>HR: 0.78 (0.70; 0.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erqou et al. 2014</td>
<td>2001 - 2008</td>
<td>ERCHIVES Study (US Veterans with HCV)</td>
<td>525 HCV+ / 2788 HCV-</td>
<td>HR: 1.58 (1.36; 1.84)</td>
<td></td>
<td>C, G</td>
</tr>
<tr>
<td>Fuster et al. 2014</td>
<td>2001 - 2009</td>
<td>Longitudinal Interrelationships of Virus and Ethanol</td>
<td>200 HCV+ / 197 HCV-</td>
<td>HR: 2.55 (1.50; 4.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greub et al. 2000</td>
<td>1996 - 2000</td>
<td>Swiss HIV Cohort Study</td>
<td>1,157 HCV+ / 1,954 HCV-</td>
<td>HR: 1.70 (1.26; 2.30)</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Hung et al. 2005</td>
<td>1994 - 2002</td>
<td>National Taiwan University Hospital</td>
<td>53 HCV+ / 387 HCV-</td>
<td>HR: 0.78 (0.43; 1.43)</td>
<td>85%</td>
<td>T, G</td>
</tr>
<tr>
<td>May et al. 2015</td>
<td>2000 - 2012</td>
<td>Antiretroviral Therapy Cohort Collaboration</td>
<td>4,630 HCV+ / 28,073 HCV-</td>
<td>HR: 2.04 (1.68; 2.76)</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Mayor et al. 2006</td>
<td>1998 - 2003</td>
<td>Puerto Rican Retrovirus Research Center cohort</td>
<td>193 HCV+ / 163 HCV-</td>
<td>HR: 1.17 (0.79; 1.72)</td>
<td>45%</td>
<td>C, M</td>
</tr>
<tr>
<td>Monga et al. 2001</td>
<td>1994 - 1998</td>
<td>Houston Veterans Affairs Medical Center</td>
<td>166 HCV+ / 263 HCV-</td>
<td>RR: 1.67 (0.90; 3.10)</td>
<td></td>
<td>C, G, O</td>
</tr>
<tr>
<td>Rancinan et al. 2002</td>
<td>1995 - 1999</td>
<td>Aquitaine HIV Cohort</td>
<td>576 HCV+ / 419 HCV-</td>
<td>HR: 1.24 (0.78; 1.98)</td>
<td>100%</td>
<td>M, C</td>
</tr>
<tr>
<td>Rezaianzadeh et al. 2012</td>
<td>2001 - 2011</td>
<td>Behavioral consultation center in Shiraz, Iran</td>
<td>1,044 HCV+ / 394 HCV-</td>
<td>HR: 2.12 (1.10; 4.52)</td>
<td>90%</td>
<td>G</td>
</tr>
<tr>
<td>Rockstroh et al. 2005</td>
<td>1995 - 2004</td>
<td>EuroSIDA cohort</td>
<td>1,960 HCV+ / 3,997 HCV-</td>
<td>IRR: 1.41 (1.13; 1.76)</td>
<td>48%</td>
<td></td>
</tr>
<tr>
<td>Scherzer et al. 2017</td>
<td>2000 - 2007</td>
<td>Fat Redistribution and Metabolic Change in HIV</td>
<td>193 HCV+ / 720 HCV-</td>
<td>OR: 0.90 (0.51; 1.59)</td>
<td>88%</td>
<td></td>
</tr>
<tr>
<td>Sulkowski et al. 2002</td>
<td>1995 - 2001</td>
<td>Johns Hopkins HIV cohort</td>
<td>873 HCV+ / 1,082 HCV-</td>
<td>HR: 1.05 (0.85; 1.30)</td>
<td>74%</td>
<td></td>
</tr>
<tr>
<td>Tedaldi et al. 2003</td>
<td>1996 - 2002</td>
<td>HIV Outpatient Study</td>
<td>267 HCV+ / 556 HCV-</td>
<td>HR: 0.91 (0.55; 1.51)</td>
<td>84%</td>
<td>L, C</td>
</tr>
<tr>
<td>Thornton et al. 2017</td>
<td>2004-2011</td>
<td>UK Collaborative HIV Cohort Study</td>
<td>1,404 HCV+ / 22,739 HCV-</td>
<td>IRR: 1.42 (1.15-1.76)</td>
<td>56%</td>
<td></td>
</tr>
<tr>
<td>Weis et al. 2006</td>
<td>1995 - 2004</td>
<td>Danish HIV Cohort Study</td>
<td>443 HCV+ / 2,183 HCV-</td>
<td>IRR: 2.40 (1.90; 3.00)</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

PubMed search string: ((Hepatitis C) OR HCV) AND (HIV OR (Human Immunodeficiency Virus)) AND (Survival OR Mortality OR Death). HR: Hazard ratio; IRR: Incidence rate ratio; RR: Risk ratio; OR: Odds ratio; U: Unknown

¹C: Regression control; R: Restriction; N: No control
²C: Uncontrolled confounding; G: Poor generalizability to US HIV-infected population; T: Improper methods for time-varying confounding; L: Loss to follow-up; M: Missing data; O: Other
³Not directly reported, estimated from crude risks
Table 1.2: Prior studies estimating the effect of HCV sustained virologic response on mortality among people living with HIV and HCV in the ART era

<table>
<thead>
<tr>
<th>Study</th>
<th>Years</th>
<th>Study Population</th>
<th>N</th>
<th>Effect Measure (95% CI)</th>
<th>Baseline ART</th>
<th>Bias^1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berenguer et al. 2009</td>
<td>2000-2005</td>
<td>Spanish AIDS Study Group</td>
<td>218 SVR / 493 no SVR</td>
<td>IRR^2: 0.15 (0.01; 0.76)</td>
<td>84%</td>
<td>C, G</td>
</tr>
<tr>
<td>Berenguer et al. 2012</td>
<td>2000-2008</td>
<td>Spanish AIDS Study Group</td>
<td>626 SVR / 973 no SVR</td>
<td>IRR^2: 0.14 (0.04; 0.30)</td>
<td>79%</td>
<td>C, G</td>
</tr>
<tr>
<td>Berenguer et al. 2014</td>
<td>2000-2008</td>
<td>Spanish AIDS Study Group</td>
<td>274 SVR / 421 no SVR</td>
<td>HR: 0.22 (0.08; 0.60)</td>
<td>81%</td>
<td>C, G</td>
</tr>
<tr>
<td>Labarga et al. 2015</td>
<td>2004-2012</td>
<td>Madrid Hospital Clinic</td>
<td>138 SVR / 389 no SVR</td>
<td>HR: 0.12 (0.03; 0.54)</td>
<td>92%</td>
<td>C, G</td>
</tr>
<tr>
<td>Leone et al. 2016</td>
<td>1997-2012</td>
<td>MASTER HIV Cohort (Italy)</td>
<td>102 SVR / 238 no SVR</td>
<td>HR: 0.85 (0.16; 4.76)</td>
<td>Unknown</td>
<td>T, C</td>
</tr>
<tr>
<td>Mira et al. 2013</td>
<td>2001-2011</td>
<td>10 Hospitals in Spain</td>
<td>43 SVR / 123 no SVR</td>
<td>HR: 0.13 (0.02; 0.93)</td>
<td>96%</td>
<td>C, G</td>
</tr>
</tbody>
</table>

PubMed search string: ((Hepatitis C) OR HCV) AND (HIV OR (Human Immunodeficiency Virus)) AND ((Sustained Virologic Response) OR SVR OR Cure) AND (Survival OR Mortality OR Death)

SVR: Sustained virologic response; IRR: Incidence rate ratio; H: Hazard ratio

^1C: Uncontrolled confounding; G: Poor generalizability to US HIV-infected population; T: Improper methods for time-varying confounding

^2Not directly reported, estimated from reported crude rates
CHAPTER 2: STATEMENT OF SPECIFIC AIMS

2.1 Specific Aims and Justification

To further elucidate the role of HCV infection and DAA treatment on mortality among PLWH, at both the individual and population levels, this work has the following aims:

Aim 1

Estimate the effect of chronic hepatitis C infection and its treatment on 10-year all-cause mortality among PLWH in the Multicenter AIDS Cohort Study and Women’s Interagency HIV Study had they initiated ART upon study entry.

Justification and approach: While HCV is known to substantially impact long-term all-cause mortality in the general population, its effect among PLWH remains unclear. Further, due to the fairly recent development of effective treatment for HCV, no studies have assessed the impact of treating HCV with DAA therapies on all-cause mortality in this population. Additionally, no studies of HCV or DAA treatment on mortality have been conducted in the era of modern HIV treatment guidelines. In this aim, we will use the parametric g-formula to assess the effect on 10-year all-cause mortality of a joint exposure consisting of HCV infection at baseline and ART initiation at study entry, compared with no HCV infection at baseline and ART initiation at study entry. Additionally, we will estimate the effect of treating HCV with DAAs among PLWH+HCV, had they initiated ART upon entry into the study. Because the current standard of care for HIV is to begin ART regardless of CD4 cell count, estimating these effects among patients had they initiated ART at study entry will provide results that are more useful for future
policy decisions, as most patients not receiving treatment for their HIV would likely not receive treatment for HCV.

**Aim 2**

Estimate the effects on 10-year all-cause mortality among PLWH+HCV, as well as the population intervention effects among PLWH in general, of having all PLWH in the MACS and WIHS initiate ART at study entry and treating 1) all PLWH+HCV, 2) PLWH+HCV selected based on their hepatic fibrosis and viral suppression status, and 3) randomly selected proportions of PLWH+HCV, with proportions equal to the proportions treated under the policies in (2).

Justification and approach: Existing Medicaid treatment criteria for DAAs often require patients to meet certain clinical conditions, including progressing to severe liver fibrosis or cirrhosis and achieving HIV suppression. It is currently not known whether or not those policies are optimal for treating PLWH+HCV. In this aim, using the parametric g-formula, we will assess the effect of treating HCV with DAAs in subsets of PLWH+HCV in the WIHS/MACS, and we will compare policies in which treatment is provided based on clinical criteria to policies in which similar proportions of PLWH+HCV are treated at random. Because HIV care providers and policy-makers now have to consider the many comorbidities of HIV that may arise among PLWH long-term, in addition to standard effect estimates restricted to PLWH+HCV, we will also estimate population intervention effects in the population of PLWH more generally which depend on the prevalence of HCV and can thus be compared with similar estimates for other HIV comorbidities.
2.2 Rationale

Hepatitis C (HCV) is a common co-infection of HIV. Of the approximately 40 million PLWH worldwide, an estimated 4-5 million are also have HCV (Alter 2006). This proportion is even higher in the United States, where an estimated 25% of the population of PLWH is coinfectected with HCV (Centers for Disease Control and Prevention 2017a). Since the widespread adoption of combination antiretroviral therapy (ART) in the United States, the prognosis for PLWH has drastically improved, with life expectancies now approaching those of the people without HIV (Nakagawa et al. 2013).

Unfortunately, PLWH and HCV (PLWH+HCV) have experienced more modest gains. The rate of all-cause mortality among PLWH+HCV is estimated to be between 1.7 and 2.5 times the rate among PLWH only (Anderson et al. 2004; Greub et al. 2000), though other studies have found no effect of HCV on all-cause mortality among PLWH (Sulkowski et al. 2002; Scherzer et al. 2017). In addition, PLWH+HCV have increased morbidity due to both their HIV and HCV infections (Greub et al. 2000; Koziel & Peters 2007; Sulkowski & Thomas 2003; Graham et al. 2001; Bambha et al. 2012).

Prior to 2013, treatment for HCV infection involved PEGylated interferon (United States Centers for Disease Control and Prevention 2010). For PLWH+HCV, treatment lasted 48 weeks, and sustained virologic response (SVR) rates were poor (Koziel & Peters 2007). The extremely low effectiveness of these treatments can be attributed to poor efficacy and low compliance because of the common and severe side effects of the medications (Mulhall & Younossi 2005). Fortunately, in 2013, a new class of HCV medications known as direct acting antivirals (DAA) were introduced. These treatments are not only more effective, but they also had substantially fewer side effects and only require a 12 week course of treatment (Afdhal et al. 2014; Jacobson...

DAAs come with a significant cost, however, with the current list price of Sofosbuvir being $84,000 (University of Washington 2017). These treatments are therefore well-suited for viewing through the lens of precision medicine, in which treatments are targeted to populations expected to achieve the greatest benefit. Currently, many state Medicaid programs limit DAA treatment to those who meet certain clinical criteria, such as those who abstained from illicit drugs and alcohol, who have achieved HIV suppression, or who have progressed to severe fibrosis or cirrhosis (Ooka et al. 2017), despite guidelines suggesting that nearly all people with HCV should be treated regardless of clinical factors (American Association for the Study of Liver Diseases & Infectious Diseases Society of America 2017). To date, no studies have been conducted to assess the effect of HCV infection and DAA treatment policies on all-cause mortality among PLWH who receive ART regardless of CD4 cell count, as is recommended by current HIV treatment guidelines (Panel on Antiretroviral Guidelines for Adults and Adolescents 2018).

Randomized controlled trials evaluating the effect of HCV interventions on mortality in this population are infeasible due to the long period between HCV infection and clinical manifestations, as well as because the known effectiveness of modern HCV treatment precludes equipoise. Therefore, to fill these important gaps in the literature, this work uses existing cohort data from the combined Multicenter AIDS Cohort Study (Kaslow et al. 1987) and Women’s Interagency HIV Study (Barkan et al. 1998; Adimora et al. 2018) along with causal inference methodology (Hernán & Robins 2017) to estimate the causal impact on all-cause mortality of HCV infection and various treatment policies under current HIV treatment guidelines. In
addition to average treatment effects, this work will also estimate population intervention effects (Westreich 2017) that contrast the observed mortality in the population of PLWH had all individuals initiated ART immediately with that which would be observed if all PLWH initiated ART immediately and certain subgroups of PLWH+HCV were treated for their HCV.

By taking a ‘patients to policy’ approach (Westreich 2017), the results of this work will provide important evidence for both clinicians and policymakers. Given the many comorbidities that the aging population of PLWH experience, it is necessary to understand the conditions that have the greatest impact on patient and population health. By estimating standard exposure and treatment effects as well as population intervention effects, these results will aid in determining how to prioritize HCV treatment against treatments for other HIV comorbidities and will provide valuable evidence for guiding policies with regards to HCV treatment.

2.3 Quantities to be estimated

As both aims of this work involve the estimation of disease, treatment, and intervention effects, no statistical hypothesis tests will be conducted. The following quantities, in the form of risk differences and risk ratios, will be estimated in this work (each quantity will be estimated after first applying a hypothetical intervention to have all study participants initiate ART at baseline):

Aim 1

1) The effect of baseline chronic HCV on 10-year all-cause mortality among PLWH in the MACS and the WIHS.

2) The effect of baseline chronic HCV on 10-year all-cause mortality among PLWH+HCV in the MACS and the WIHS.
3) The effect of DAA treatment at study entry on 10-year all-cause mortality among PLWH+HCV in the MACS and the WIHS.

Aim 2

1) The effect of treating all PLWH+HCV with DAAs at study entry on 10-year all-cause mortality in the MACS and the WIHS.
2) The effect of treating PLWH+HCV with DAAs after they progress to severe liver fibrosis or cirrhosis on 10-year all-cause mortality in the MACS and the WIHS.
3) The effect of treating PLWH+HCV with DAAs after they achieve HIV suppression on 10-year all-cause mortality in the MACS and the WIHS.
4) The effect of treating PLWH+HCV with DAAs after they progress to severe liver fibrosis or cirrhosis and achieve HIV suppression on 10-year all-cause mortality in the MACS and the WIHS.
5) The effect of treating randomly selected PLWH+HCV with DAAs at baseline, with proportions selected equal to the proportions treated in 2-4, on 10-year all-cause mortality in the MACS and the WIHS.
6) The population intervention effects of each of the above policies, estimated in the entire population of PLWH in the MACS and the WIHS.
CHAPTER 3: METHODS

3.1 Description of data sources

The Multicenter AIDS Cohort Study

The Multicenter Aids Cohort Study (MACS) is an ongoing study of men who have sex with men (MSM) with and without HIV (Kaslow et al. 1987). The MACS began as in 1984 with the goals of describing the natural history of AIDS, determining the biological and behavioral factors that caused AIDS, and collecting biological specimens for further research (Kaslow et al. 1987). After HIV was discovered to be the causative agent of AIDS in 1983 (Barre-Sinoussi et al. 1983; Gallo et al. 1983), the goals of the MACS changed (Kaslow et al. 1987). First, the MACS seeks to identify and evaluate HIV seropositive men in the study, which included determining correlates of seropositivity and describing the natural history of HIV. Second, the study aims to identify and evaluate HIV seroconverters, in particular by determining the factors associated with seroconversion, characterizing the early phases of HIV infection, and determining the relationship between clinical status, viremia, and host immune response. Third, the study seeks to characterize those who did not seroconvert to identify protective factors against infection and determine whether or not HIV infection was possible without seroconversion. Lastly, the MACS aims to design additional studies of HIV prevention and therapy. Since its inception, many additional aims and substudies have been added to the MACS protocols.

The MACS has study sites in four locations across the United States: Baltimore, MD/Washington, DC (Johns Hopkins University); Pittsburgh, PA / Columbus, OH (University
of Pittsburgh); Chicago, IL (Northwestern University); and Los Angeles, CA (University of California – Los Angeles). Any MSM without a diagnosis of AIDS is eligible to participate (Kaslow et al. 1987). Participants are recruited through a variety of mechanisms, including media publicity (including publicity in the gay press), personal connections of gay activists and study participants, promotional events and offerings (e.g. raffles, free medical screening), and clinical contacts with medical practices and studies focusing on MSM (Kaslow et al. 1987). The success of each recruitment effort has differed by study site. In Baltimore, most participants had responded to gay and metropolitan newspaper stories or had been recruited by leaders of the gay community. In Chicago, the greatest success came from recruiting participants from clinics for MSM and from an existing hepatitis B vaccine study. In Los Angeles, most participants came from an existing AIDS cohort, referrals from health professionals, and announcements in the media. Finally, in Pittsburgh, investigators found most participants through recruitment at gay bars and bathhouses.

The initial wave of recruitment occurred between 1984 and 1985 and included 4,954 participants. A second wave recruited 668 additional participants between 1987 and 1990 with the goal of including more black individuals. The third wave occurred between 2001 and 2003 in which 1,350 participants were recruited, with an aim of including more black and Hispanic subjects. Finally, a fourth wave of recruitment began in 2010 with the goal of replacing participants who were lost to follow-up or died. As of October 2013, a total of 7,087 men had been recruited into the study, contributing 61,357 HIV positive person-visits (Multicenter AIDS Cohort Study Group 2017).

MACS study visits occur at baseline and every six months thereafter (Kaslow et al. 1987). The baseline visits have several components, and subsequent visits include a subset of these
components. First, study investigators conduct a face-to-face interview and administer a questionnaire to determine identifying information, demographic data, past medical history, current medical history, risk factors, drug use, and sexual practices. Next, a physician, physician’s assistant, or nurse practitioner performs a complete, standard physical exam on the participant. Lastly, samples are collected for lab tests, for instance (but not limited to) complete blood counts, HIV immunoassays, and lymphocyte phenotyping (for information on specific lab tests and collected information, see Variable measurement and operationalization).

The MACS investigators make great efforts to prevent loss to follow-up (Dudley et al. 1995). Community advisory boards are included in the study planning and design in order to ensure acceptability with the MSM community. Meeting location and hours are chosen in order to best accommodate study participants. At each study visit, the investigators collect several pieces of information that could be used to locate the participants. These include driver’s license and social security numbers, the names and addresses of people who would know how to contact the participant, and the name and contact information for the participant’s health care providers. At the end of each study visit, an appointment is scheduled for the next study visit. Between 2-4 weeks prior to a study visit, a reminder letter is sent to the participant, which is followed by a telephone call two weeks later. If contact cannot be made, investigators continue calling the participant for an additional 45 days or until contact is made. If contact is still not made, and extended search is conducted of named contacts, death certificates and obituaries, AIDS registries, death indices, departments of motor vehicles, consumer information services, and tax and voter rolls. If a participant moves away from a study site, they are able to have study visits at the nearest study site to their new location, and if they are too far away or a full visit is not possible, participants can have laboratory samples collected by their own physician and can be
interviewed by telephone and mailed questionnaires. As of October 2015, 67% of the members of the cohort with HIV who were known to be alive remained in active follow-up (Center for the Analysis and Management of MACS Data 2017).

The Women’s Interagency HIV Study

The Women’s Interagency HIV Study (WIHS) began in 1994 to address the lack of knowledge about HIV among women (Barkan et al. 1998; Adimora et al. 2018). Still ongoing, the WIHS had several initial aims. First, the study aims to describe the spectrum and natural history of HIV among women. Second, the WIHS has the goal of investigating the relationship between virologic and immunologic factors with HIV disease progression in women. Finally, the study seeks to investigate the risk factors that may be related to HIV disease progression, including infectious, treatment-related, endocrine, nutritional, health care utilization, socioeconomic, and behavioral risk factors. As understanding of HIV improved, additional aims and substudies have been added to the WIHS.

The WIHS began with six study sites – Bronx, NY/Manhattan, NY; Washington, DC; San Francisco, CA/Bay Area, CA; Los Angeles, CA/Southern California/Hawaii; and Brooklyn, NY. Later, four additional sites were added – Chapel Hill, NC; Atlanta, GA; Miami, FL; and Birmingham, AL. In order to be eligible for participation in the WIHS, subjects have to be older than 13 years of age, provide informed consent, be willing to be tested for HIV, be able to complete an interview in English or Spanish, be able to travel to and from the clinic site, and be willing and able to provide blood for laboratory analyses (Barkan et al. 1998). People with and without HIV are frequency matched on demographics and key risk factors including age, race/ethnicity, highest education level attained, injection drug use, and total number of sexual partners. Recruitment occurs through several avenues. First, participants are recruited from HIV
primary care clinics, hospital-based programs, and HIV research programs. Second, investigators attend community outreach events and posted notices at community gathering sites and women’s support groups. Third, potential participants are identified at HIV testing sites and drug rehabilitation programs. Finally, participants are able to provide referrals for other potential subjects. In order to encourage participation, remuneration in the form of gift packs, access to bathing facilities, laundry supplies, meals, transportation, and access to dental care may be provided.

The first wave of recruitment occurred between 1994 and 1995, in which 2,623 participants were enlisted for the study (Women’s Interagency HIV Study Group 2017). Additional recruitment waves occurred between 2001 and 2002 (1,143 additional subjects), 2011 and 2012 (371 additional subjects), and 2013 and 2015 (845 additional subjects). As of September 2015, a total of 3,702 participants with HIV had enrolled in the WIHS, contributing 64,931 HIV positive person-visits (Women’s Interagency HIV Study Group 2017).

WIHS study visits are similar to those of the MACS. Study visits occur at baseline and every six months (Barkan et al. 1998). The baseline visit includes several components, of which a subset is included in follow-up visits. First, study investigators administer a structured interview to determine sociodemographic information; medical, health, obstetric, gynecologic, and contraceptive history; substance abuse; sexual behavior; health care utilization; and psychosocial information. Second, participants go through a comprehensive physical and gynecologic exam that includes measurement of vital signs; a test of cognitive function; an evaluation of Karnofsky score; an examination of external and internal genitalia; a cervical vaginal lavage; and colposcopy, biopsy, and dysplasia treatment as indicated. Finally, laboratory specimens are
collected (for information on select laboratory measurements, see Variable measurement and operationalization).

Like the MACS, the WIHS has detailed, extensive protocols to minimize loss to follow-up (Hessol et al. 2001). Community advisory boards are included in the study design phase in order to ensure acceptability among participants. The study utilizes bilingual, female interviewers and staff in order to make the participants feel comfortable, safe and respected. Transportation assistance is offered for women who have difficulty attending study visits, and women who move are able to attend visits at their closest WIHS site. Also, abbreviated interviews are offered to participants who were too ill to attend a study visit or who were incarcerated. In order to encourage participants to attend follow-up visits, monetary compensation is offered. In order to locate women if they are lost, prior to study visit appointments, study investigators send letters and make phone calls to confirm the visits and remind the participants to attend. Additionally, after each visit, participants are asked to fill out a form that provided information on contacts who would know how to reach the subject. If a woman missed a study visit or cannot be located, the investigators used extended searches to find her including visits to clinics and locations where the women were recruited, searches of medical databases and death registries, and checks of county jails and prisons. As of September 2016, of the cohort participants with HIV who were known to be alive, 70% from the first recruitment wave, 79% from the second recruitment wave, 92% from the third recruitment wave, and 96% from the fourth recruitment wave remained in active follow-up (WIHS Data Management and Analysis Center 2017).

Study inclusion/exclusion criteria

The cohort used for this work has relatively minor inclusion/exclusion criteria. First, only participants without a clinical diagnosis of AIDS are included, as these subjects are at high risk
for mortality and are not likely to be candidates for HCV treatment. Second, only participants with no prevalent ART use at baseline are included in to avoid the possibility of selection bias and left truncation bias due to conditioning on survival on ART until entry into the study. Finally, only visits that occurred between October 1, 1994 and September 30, 2015 are (corresponding to WIHS visits 1 through 42 and MACS visits 22 through 63), as these are the dates in which both the WIHS and the MACS were simultaneously operating.

3.2 Variable measurement and operationalization

HIV

In both the MACS and the WIHS, all participants are screened at baseline using enzyme-linked immunosorbent assays (ELISA). For those who screen positive, the diagnosis is confirmed with Western Blot. Those who screen negative are retested at subsequent visits until seroconversion.

HCV

Routine HCV testing was not part of the original MACS protocol. Prospective HCV testing in the MACS began in 2001 (Seaberg et al. 2014). Participants enrolled after 2001 were screened for HCV Ab at baseline. For those reactive to HCV Ab, further tests for HCV RNA were performed. For participants who enrolled prior to 2001, stored blood specimens from within two years of the baseline visit were retrospectively tested for HCV Ab. Those reactive to HCV Ab were tested for HCV RNA using samples from their most recent study visit at the time of screening. Those who tested positive for HCV Ab but negative for HCV RNA at this last study visit had their baseline samples tested for HCV RNA. HCV Ab was tested with 3rd generation Enzyme Immunoassays (ADVIA Centaur HCV assay, Siemens Healthcare Diagnostics,
Tarrytown, NY, USA), and HCV RNA was quantified with quantitative real-time polymerase chain reaction assays (COBAS AmpliPrep COBAS TaqMan HCV assay, Roche Molecular Systems, Pleasanton, CA, USA). Baseline HCV status was determined for 99.3% of MACS participants under this protocol (Seaberg et al. 2014).

Women in the WIHS were screened for HCV Ab at baseline. Those who screened positive were further tested for HCV RNA. HCV Ab testing in the WIHS was conducted using 2nd or 3rd generation Enzyme Immunoassays (Ortho-Diagnostic Systems, Rochester, NY, USA), and HCV RNA was tested for with branched DNA methods (Quantiplex 2.0 branched chain DNA-enhanced label amplification assay, Chiron, Emeryville, CA, USA) and real-time polymerase chain reaction assays (COBAS Amplicor HCV Detection Kit, Roche Diagnostic Systems, Pleasanton, CA).

Baseline HCV status was classified into three levels for this work (Seaberg et al. 2014). Those negative for HCV Ab were considered to have never had HCV (HCV-). Those positive for HCV Ab but negative for HCV RNA were considered to have successfully treated HCV or spontaneously cleared HCV (SVR). Those who were positive for HCV RNA were considered to have chronic HCV infection (HCV+). In this work, comparisons were between the HCV+ group and the combined HCV- and SVR groups.

Antiretroviral therapy

At each study visit, participants are asked to bring lists of any medications and pill bottles for any prescription drugs they used since their last visit. If no documentation is provided, the participant is asked to name any medications they can from memory, and pictures of commonly
used antiretroviral medications are provided. If a previously reported medication is not mentioned, the interviewer specifically asks about that medication.

The definition of antiretroviral therapy (ART) used in this work was guided by the November 2014 US Department of Health and Human Services guidelines (Panel on Antiretroviral Guidelines for Adults and Adolescents 2014). ART was defined as regimens consisting of three or more antiretroviral drugs including at least one protease inhibitor, entry inhibitor, integrase inhibitor, or non-nucleotide reverse transcriptase inhibitor.

Once a participant reported initiating ART, they were considered on ART for the remainder of the study (the intent-to-treat assumption). The intent-to-treat assumption was previously found to correctly classify the ART status of 94% of person-time in the MACS and WIHS (Cole et al. 2003).

In order to isolate more recent ART regimens, ART was split into two variables based on initiation date. ART initiated prior to October 1, 2001 (the first visit following the approval of tenofovir, a component of many modern ART regimens (Panel on Antiretroviral Guidelines for Adults and Adolescents 2018)) was considered early ART, while any ART initiated after that date was considered modern ART. All interventions considered in this work assumed participants initiate specifically modern ART upon entry into the study.

Loss to follow-up

Study participants are considered lost to follow-up at their second consecutive missed study visit and are censored at the moment where they are defined as lost to follow-up.
**Death**

Study coordinators obtained date and cause of death either directly from the National Death Index ([https://www.cdc.gov/nchs/ndi/index.htm](https://www.cdc.gov/nchs/ndi/index.htm)) or through hard copies of death certificates obtained by the study investigators. Participants who were not lost to follow-up and died within 6 months of their $k$th study visit were considered to have died between their $k$th and $k+1$th study visits.

**Potential confounders**

Baseline and time-varying confounders for each aim were identified using a causal diagram (Greenland et al. 1999) constructed prior to data analysis (Figure 3.1). Baseline and follow-up CD4 cell count is evaluated in each study using flow cytometric procedures (Giorgi et al. 1990). Continuous CD4 cell count was included in the models with five-knot restricted cubic splines, with knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles (Harrell 1986).

Baseline and follow-up HIV viral load measurement procedures varied over time in each study as the accuracy of measurements improved. In the MACS, viral load was initially measured using sensitive bDNA signal amplification assays (Chiron, Emoryville, CA, USA), with a lower limit of detection of 500 copies/ml. Next, viral loads were measured with Roche Amplicor RNA kits (Hoffman-Laroche, Nutley, NJ, USA), with lower limits of detection of 400 copies/ml. The MACS currently uses Ultrasensitive RNA polymerase chain reaction assays (Hoffman-LaRoche, Nutley, NJ, USA), with lower limits of detection of 50 copies/ml. The first test to be used in the WIHS was the nucleic acid sequence-based amplification assay (Organon-Teknika, Durham, NC, USA), with a lower limit of detection of 4000 copies/ml. The WIHS currently uses the COBAS AmpliPrep/COBAS TaqMan test (Roche, Pleasonton, CA, USA),
with lower limit of detection of 20 copies/ml. Baseline HIV viral load was included in the models as a single continuous variable, and time-varying HIV Viral load was included as a dichotomous variable representing detectable or undetectable viral load.

Chronic hepatitis B infection was defined as a positive test at baseline for HBV surface antigen (HBsAg). In both studies, HBsAg is tested at baseline using enzyme immunoassays (Abbot Laboratories, Abbot Park, IL, USA).

Age, sex, race/ethnicity, injection drug use (IDU), alcohol use, and smoking are determined from self-administered questionnaires and interview at baseline and follow-up visits. Age was included in the models with five-knot restricted cubic splines with knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles. Sex was represented with an indicator variable for female sex. Race/ethnicity was categorized as non-Hispanic White, non-Hispanic Black, Hispanic, and Other. IDU and smoking were dichotomized as current versus prior/never. Alcohol use was dichotomized as current heavy alcohol use versus no current heavy alcohol use, with heavy alcohol use being defined as consuming more than 7 drinks per week for women and more than 14 drinks per week for men (United States Department of Health and Human Services 2015). BMI is assessed at each study visit, and BMI was categorized as obese (BMI greater than 30 kg/m²) versus non-obese.

Fibrosis is measured with the non-invasive FIB-4 index (Sterling et al. 2006) and AST to Platelet Ratio Index (APRI) (Lin et al. 2011), defined as

\[
FIB4 = \frac{Age \ast AST}{Platelets \ast ALT^2}
\]

and
\[
APRI = \frac{(AST/UL)}{Platelets} \times 100
\]

where AST is aspartate aminotransferase and ALT is alanine aminotransferase, both measured in units/liter, UL is the upper limit of normal for the AST test measured in the same units as AST, age is measured in years, and platelets are measured in units of \(10^9\) per liter (Sterling et al. 2006).

Fibrosis was categorized into 3 groups: \(FIB-4 \geq 3.25 \text{ or }\) AST to Platelet Ratio Index (APRI) \(\geq 1\) was classified as severe fibrosis/cirrhosis, while \(FIB-4 < 1.45 \text{ and }\) APRI < 0.7 (together) was classified as no significant fibrosis. Other combinations were classified as moderate fibrosis. The APRI cutoffs are based on a meta-analysis (Lin et al. 2011) that suggested these perform better at classifying severe fibrosis/cirrhosis and no significant fibrosis than the commonly used cutoffs of 2 and 0.5, respectively. Severe fibrosis/cirrhosis was assumed to be non-reversible.
Figure 3.1: Causal diagram used to select confounders

Baseline: IDU, Alcohol, Smoking, Obesity, Age, Sex, Race/Ethnicity
3.3 Notation

The following notation will be used throughout this section. Individuals will be indexed by \( i \in \{1,2,3, \ldots, n\} \), and time (in visits) will be indexed by \( t \in \{0,1,2,3, \ldots, \tau\} \). Uppercase letters will denote random variables, and lowercase letters and numbers will represent their potential realizations. An overbar (e.g. \( \bar{A}_{it} \)) denotes history, for example \( \bar{A}_{it} = \{A_{i0}, A_{i1}, A_{i2}, \ldots, A_{it}\}, \bar{U}_{it} = \{U_{i0}, U_{i1}, \ldots, U_{it}\}, \) and \( \bar{W}_{it} = \{W_{i0}, W_{i1}, \ldots, W_{it}\} \). Let \( \bar{A}_i = \bar{A}_{i\tau} \). Superscripts, e.g. \( Y_i^a \), on random variables represent potential outcomes, in this case meaning the level of \( Y \) that subject \( i \) would have experienced had, possibly counter to fact, they received treatment level \( a \).

Additionally, \( f_X(x) \) denotes a probability mass function or probability density function for the random variable \( X \) evaluated at \( x \). From here forward, observations will be assumed independent and identically distributed, and subscripts distinguishing individuals will be dropped.

3.4 The generalized parametric computation algorithm formula

The parametric generalized computation algorithm formula (Robins 1986) will be used in both aims of this work. Hereafter, the use of the parametric generalized computation algorithm formula for the estimation of causal effects will be referred to as g-computation, and the formula itself will be referred to as the g-formula. In this section, the goal is to motivate the need for g-computation (or other causal inference methods) and demonstrate how it can be used to estimate causal effects.

Consider a study is to estimate the causal effect of a dichotomous exposure (or treatment) \( A \) measured at times 0,1, \ldots, \( \tau \), with exposure at time \( t \) denoted \( A_t \), on an outcome \( Y \) measured at the end of the study. Measured covariates at time \( t \) are denoted with \( W_t \), and unmeasured covariates with \( U_t \). Assume that \( U_t \) temporally precedes \( W_t \), which temporally precedes \( A_t \). For
simplicity, the discussion that follows will be restricted to static exposure regimes, meaning regimes that consist of setting a subject’s exposure history to a certain value regardless of exposure or covariate history, e.g. \( \tilde{a} = \{a_0, a_1, ..., a_T \} \), though similar results are available for non-static (dynamic) exposure regimes (Young et al. 2011). The set of all possible static exposure regimes is denoted \( \mathcal{A} \), and the set of all possible covariate histories is \( \mathcal{W} \). Common examples of static regimes for a binary exposure are always exposed \( \{1, 1, ..., 1\} \) or never exposed \( \{0, 0, ..., 0\} \). Using counterfactual notation, the average causal effect (ACE) comparing two exposure regimes is defined as \( ACE = E(Y^{\tilde{a}} - Y^{\tilde{a}^*}) = E(Y^{\tilde{a}}) - E(Y^{\tilde{a}^*}) \), for \( \tilde{a} \neq \tilde{a}^* \), which can be interpreted as the difference in the expected value of \( Y \) had the entire population followed regime \( \tilde{a} \) compared with the expected value of \( Y \) had the entire population followed regime \( \tilde{a}^* \). The ACE, which compares the expected values of two unobserved variables, is distinct from the usual associational effect, \( E(Y|\tilde{A} = \tilde{a}) - E(Y|\tilde{A} = \tilde{a}^*) \), which compares the expected outcomes among the subsets of individuals who followed regimes \( \tilde{a} \) and \( \tilde{a}^* \).

To identify the ACE nonparametrically, four conditions are sufficient to link the observed data to the potential outcomes (Robins 1986):

1) Consistency

\[
Y = \sum_{\tilde{a} \in \mathcal{A}} I(\tilde{A} = \tilde{a}) Y^{\tilde{a}}
\]

where \( I(x) \) is the indicator function that takes the value 1 if \( x \) is true and 0 otherwise.

The potential outcome for a subject under their observed exposure history is equal to their observed outcome. Threats to consistency typically come from two sources: interference between
subjects and relevant variation in the versions of exposure (Cole & Frangakis 2009; VanderWeele 2009).

2) Conditional exchangeability

\[ Y^\bar{a} \perp A_t | \{ \bar{A}_{t-1}, \bar{W}_t \}, \forall \bar{a} \in \bar{A} \]

where \( \bar{A} \) are the exposure regimes to be compared. Each potential outcome is statistically independent of the observed exposure at a given time conditional on exposure history and the history of a set of covariates \( W \). Threats to conditional exchangeability typically arise from uncontrolled confounding and selection bias (Hernán & Robins 2017).

3) Positivity

If \( f_{\bar{A}_{t-1},\bar{W}_t}(\bar{a}_{t-1}, \bar{w}_t) > 0 \), then \( f_{A_t|\bar{A}_{t-1},\bar{W}_t}(a_t|\bar{a}_{t-1}, \bar{w}_t) > 0 \), \( \forall \bar{a} \in \bar{A} \)

At every time \( t \), there are individuals following each exposure history to be compared in every stratum defined by observed combinations of exposure history and covariate history. Violations of positivity can be either random (by chance nobody with a certain exposure level is observed in a strata of past treatment and covariates) or deterministic (it is not possible for someone with certain past exposure and covariates to have a certain exposure level, for example men cannot be exposed to hysterectomy) (Westreich & Cole 2010).

4) No measurement error (Edwards et al. 2015)

Under these four conditions, \( E(Y^\bar{a}) \) can be identified nonparametrically from the observed data as follows:
\[ E(Y^{\bar{a}}) \]

\[ = \sum_{w_0 \in \mathcal{W}_0} E(Y^{\bar{a}}|W_0 = w_0) f_{w_0}(w_0) \text{ (law of total probability)} \]

\[ = \sum_{w_0 \in \mathcal{W}_0} E(Y^{\bar{a}}|A_0 = a_0, W_0 = w_0) f_{w_0}(w_0) \text{ (exchangeability)} \]

\[ = \sum_{w_0 \in \mathcal{W}_0} \sum_{w_1 \in \mathcal{W}_1} E(Y^{\bar{a}}|A_0 = a_0, W_1 = w_1, W_0 = w_0) f_{w_1|w_0,A_0}(w_1|a_0,w_0) f_{w_0}(w_0) \text{ (law of total probability)} \]

\[ = \sum_{w_0 \in \mathcal{W}_0} \sum_{w_1 \in \mathcal{W}_1} E(Y^{\bar{a}}|A_1 = a_1, A_0 = a_0, W_1 = w_1, W_0 = w_0) f_{w_1|w_0,A_0}(w_1|a_0,w_0) f_{w_0}(w_0) \text{ (exchangeability)} \]

... (iterate until time \( \tau \))

\[ = \sum_{\bar{w} \in \mathcal{W}} E(Y^{\bar{a}}|A = \bar{a}, \bar{W} = \bar{w}) \prod_{t=0}^{\tau} f_{w_t|w_{t-1},\bar{a}_{t-1}}(w_t|\bar{w}_{t-1}, \bar{a}_{t-1}) \]

\[ = \sum_{\bar{w} \in \mathcal{W}} E(Y|\bar{A} = \bar{a}, \bar{W} = \bar{w}) \prod_{t=0}^{\tau} f_{w_t|w_{t-1},\bar{a}_{t-1}}(w_t|\bar{w}_{t-1}, \bar{a}_{t-1}) \text{ (positivity and consistency)} \]

In summary,

\[ E(Y^{\bar{a}}) = \sum_{\bar{w} \in \mathcal{W}} E(Y|\bar{A} = \bar{a}, \bar{W} = \bar{w}) \prod_{t=0}^{\tau} f_{w_t|w_{t-1},\bar{a}_{t-1}}(w_t|\bar{w}_{t-1}, \bar{a}_{t-1}) \]  \hspace{1cm} (1)

Equation (1) is the non-parametric g-formula (Robins 1986), which only includes expectations and distributions of observed variables. If the covariates are continuous, the sum becomes an integral. Intuitively, the g-formula is an extension of standardization. Consider the single time-period case. There, (1) becomes

\[ E(Y^{\bar{a}}) = \sum_{w \in \mathcal{W}} E(Y|\bar{A} = \bar{a}, \bar{W} = \bar{w}) \prod_{t=0}^{\tau} f_{w_t|w_{t-1},\bar{a}_{t-1}}(w_t|\bar{w}_{t-1}, \bar{a}_{t-1}) \]

which is exactly the formula for direct standardization.
In the setting of a well-designed and properly executed randomized controlled trial with no loss to follow-up and perfect compliance, it is reasonable to expect conditions (1) - (3) to be met by design. In non-experimental settings or in less ideal experiments, however, the conditions cannot as easily be assumed to hold, and care must be taken to evaluate whether each condition is reasonable. G-computation is particularly useful for analyzing observational studies in settings where randomized controlled trials are either infeasible or unethical.

The causal diagram (Greenland et al. 1999) in Figure 3.2 represents a two time-period study like the one above, and will be used to motivate the need for methods beyond ‘standard’ statistical methods to estimate the causal effects of time-varying exposure. According to the diagram, to d-separate \( A_0 \) from \( Y \), it is sufficient to control for \( W_0 \). Similarly, to d-separate \( A_1 \) from \( Y \), it is sufficient to control for \( W_1, A_0 \) and \( W_0 \). \( W_1 \), however, is on the causal pathway \( A_0 \rightarrow W_1 \rightarrow Y \), so controlling for \( W_1 \) will block an open causal pathway for the exposure of interest, leading to bias. Additionally, controlling for \( W_1 \) opens the non-causal pathways \( A_0 \rightarrow W_1 \leftarrow U_1 \rightarrow Y \) and \( A_0 \rightarrow W_1 \leftarrow U_1 \leftarrow U_0 \rightarrow Y \), which may cause additional bias. It is therefore clear that standard statistical methods, such as multivariable regression analysis, will lead to biased effect estimates in scenarios in which there is time-varying confounding affected by prior exposure. As shown above, however, g-computation is capable of estimating the effects in such scenarios without bias.

Because of the high-dimensionality (large number of variables and time-points) of the data in typical applications, it is often not possible to nonparametrically identify causal effects. Instead, each component of the g-formula can be estimated using parametric or semiparametric models (Robins 1986). The use of parametric or semiparametric models adds a fifth identification condition:

60
5) Properly specified models

In this work, to assess model specification, the modelled and observed natural course were compared on their survival curves, the proportion of people censored and lost to follow-up, the proportion of person-time on ART, the proportion of subjects with chronic HCV at baseline, the proportion of person-time with suppressed viral load, the average CD4 cell count at last visit, and the proportion of person-time with each time-varying covariate category. If the models differed substantially from the observed natural course, a two-step procedure was used to improve model fit. First, interaction terms were added to the models in the following order until the values are aligned: ART/HCV, ART/Time, HCV/Time, HCV/ART/Time, ART/covariates, HCV/covariates, covariates/covariates. Second, to improve parsimony, spline terms were removed and variable categories collapsed until the models displayed misalignment.

One undesirable property of parametric g-computation is the g-null paradox (Robins & Wasserman 1997). The g-null paradox states that, if the sharp null hypothesis holds, meaning $Y^{\bar{a}} = Y^{\bar{a}^*}$ for every $\bar{a}, \bar{a}^*$, then, under certain assumptions, model misspecification is guaranteed if typical parametric models are used (e.g. linear and logistic regression) without additional precautions. Because the exposures/treatments in this work (HCV, ART) almost certainly have an effect on the outcome (death), the sharp null hypothesis is not likely to hold and the g-null paradox should not be a major concern.
Figure 3.2: Causal diagram motivating the g-computation algorithm formula
G-computation and survival analysis

To use g-computation, it is necessary to estimate two separate quantities: the conditional probability of the outcome conditional on exposure and covariate history, and the probability mass or density function of the covariates conditional on past exposure and covariate histories. Well-established methods have been developed to estimate the former quantity in the presence of censoring (loss to follow-up and unequal follow-up time between subjects), such as the product-limit estimator (Kaplan & Meier 1958).

Risk estimation in this context falls under the rubric of survival analysis. In survival analysis, instead of simply being interested in the probability of the outcome, we are instead interested in the time to the outcome. Let the time that some individual experiences the outcome of interest be denoted $T$, and the potential time the individual would experience the outcome had they had exposure history $\bar{a}$ be $T^{\bar{a}}$. A participant is administratively censored if their event time $T$ is larger than the endpoint of the study, $\tau$. Participants lost to follow-up are censored at the time the definition for loss to follow-up is met (not necessarily at their last missed visit). Let $C_t = 1$ if a participant is censored by time $t$, otherwise $C_t = 0$. The survival probability at time $t$ (denoted $S_t$), the probability of not experiencing the outcome by $t$, is $P(T > t)$, and the risk is $R_t = 1 - P(T > k)$. The discrete-time hazard, which is the probability of experiencing the outcome at time $t$ conditional on not having experienced the outcome prior to $t$, is $h_t = P(T = t|T > t - 1)$. Finally, let $Y_t = 0$ if $T > t$, otherwise $Y_t = 1$. With this notation, $S_t = P(Y_t = 0), R_t = P(Y_t = 1) = 1 - S_t$, and $h_t = P(Y_t = 1|Y_{t-1} = 0)$.

The product limit method was used to estimate survival probabilities:
$$\bar{P}_t(Y_{t+1} = 1) = \bar{R}_{t+1} = 1 - \prod_{k=0}^{t} \left( 1 - \bar{P}_k(Y_{k+1} = 1|Y_k = 0) \right)$$

$$= \sum_{k=0}^{t} \left[ \bar{P}_r(Y_{k+1} = 1|Y_k = 0) \prod_{m=0}^{k} \bar{P}_r(Y_m = 0|Y_{m-1} = 0) \right]$$

(2)

In words, the estimated survival probability by time $t + 1$ is the product of 1 minus the estimated discrete-time hazard at each time up to $t + 1$. Estimating the survival probability and thus the risk reduces to estimating the discrete-time hazard at each time.

Recall that individuals in the study may be censored if they are lost to follow-up or if they are administratively censored. To validly estimate the survival probability in the presence of such censoring, it is necessary to assume that censoring is noninformative or independent, which means $\bar{C}_t \perp T|\bar{A}_{t-1}, \bar{W}_{t-1}$. In words, this means that censoring history at $t$ is independent of event time conditional on covariate and exposure history. Hereafter, the potential outcomes $Y_t^{\overline{a}}$ will always include a second intervention to prevent subject-specific censoring and loss to follow-up, so $Y_t^{\overline{a}} = Y_t^{\overline{a}, \overline{c}_t=\overline{0}}$.

In this setting, g-computation can be implemented as follows. First, use survival methods to estimate the probability of the outcome conditional on exposure and covariate history and remaining uncensored. Second, standardize over the distribution of covariate history conditional on exposure history and remaining uncensored. To estimate the former quantity, it is sufficient to estimate the time-varying discrete-time hazard function, as shown above. The time-varying discrete-time hazard was modelled parametrically using logistic regression with parameters estimated with maximum likelihood. Under the assumption that the discrete-time hazard is small at each time-point, the parameters from the logistic model will approximate those from a discrete-time hazard model.
To estimate the probability distribution of covariate history conditional on exposure history and remaining uncensored, the distribution of the covariates can be factored in two steps (in the following formulas, conditioning on exposure history and remaining uncensored is omitted for brevity, though the concepts remain the same). First,

$$f_{\bar{w}_t | \ldots} = \prod_{k=0}^{t} f_{\bar{w}_k | \bar{w}_{k-1}, \ldots}$$ (3)

which in words means that the probability distribution of covariate history by time $t$ is equal to the product of the conditional distributions of covariates at each time point conditional on covariate history up to that time point. Second,

$$f_{\bar{w}_l | \ldots} = \prod_{l=1}^{m} f_{\bar{w}_l | \bar{w}_{-l}, \ldots}$$ (4)

where $W_{l,t}$ is the $l$th covariate at time $t$, and $W_{-l,t}$ is the vector of all covariates indexed less than $l$ at time $t$. This means that the conditional distribution of covariates at time $k$ is equal to the product of the distributions of each individual covariate conditional on the other covariates at time $k$ that are prior to that covariate. From (3) and (4), the distribution of the covariate history can be factored into the product of the conditional distributions of the individual covariates at each time conditional on prior covariate history, thus obviating the need for multivariate modelling. These distributions were estimated using parametric models: logistic regression for binary covariates and linear regression for continuous covariates, with parameters estimated by maximum likelihood.

Combining the estimator from (2) with the results from (3) and (4), the g-formula in the survival context takes the form (adapted from Westreich et al. 2012)
where

\[ f(w_k | \tilde{A}_{k-1}, \tilde{W}_{k-1} = \tilde{w}_{k-1}, \tilde{Y}_k = \tilde{c}_k = 0) = \prod_{l=1}^{m} f(w_{l:k} | w_{-l:k}, \tilde{A}_{k-1}, \tilde{w}_{k-1}, \tilde{Y}_k, \tilde{c}_k (w_{l:k} | w_{-l:k}, \tilde{a}_{k-1}, \tilde{w}_k, 0, 0) \]

Note that the independent censoring assumption allows for conditioning on \( \tilde{c}_k = 0 \). By replacing the probabilities and distributions in (5) with their respective estimates from properly specified models, we can obtain a valid estimate \( \hat{E}(Y_{t+1}) \). Confidence intervals and standard errors of the estimate are obtained with the nonparametric bootstrap (Efron & Tibshirani 1986).

The natural course

Because all of the components of the g-formula are estimated from the data, it is advisable to perform tests to check for proper model specification. One such model check is to compare their results to the so-called natural course, which is the observed cumulative incidence function in the study. While alignment with the natural course is neither necessary nor sufficient for valid effect estimation, it does provide a degree of confidence in the model specification. To estimate the natural course, it is sufficient to estimate the joint distribution of the data and sum over exposure and covariate histories as follows (Westreich et al. 2012)

\[ E(Y_{t+1}) = \sum_{k=0}^{t} \sum_{w_k \in W_k} \sum_{\tilde{a}_k \in A_k} \left\{ \left[ \frac{1}{m} \left( 1 - \Pr(Y_{t+1} = 1 | \tilde{A}_k = \tilde{a}_k, \tilde{W}_k = \tilde{w}_k, \tilde{Y}_k = \tilde{c}_k = 0) \right) \right] \prod_{m=0}^{k} f(w_m | \tilde{A}_{m-1} = \tilde{a}_{m-1}, \tilde{W}_{m-1} = \tilde{w}_{m-1}, \tilde{Y}_{m-1} = \tilde{c}_{m-1} = 0) \times \prod_{m=0}^{k} f(A_m = a_m | \tilde{A}_{m-1} = \tilde{a}_{m-1}, \tilde{W}_{m-1} = \tilde{w}_{m-1}, \tilde{Y}_{m-1} = \tilde{c}_{m-1} = 0) \right\} \]
which requires additional models for the censoring and exposure processes.

As an aside, note that (6) and (7) allow for another interpretation of the g-formula: a modification to the distribution of the data in which the distributions of the exposure and censoring histories are replaced with a degenerate distribution taking value 1 at the exposure and censoring histories of interest (Robins & Hernán 2009).

**G-computation in practice**

Due to the large number of covariates and time points, it may not be possible to sum over all possible covariate histories needed for g-computation. Instead, Monte Carlo simulation can be used as follows (adapted from (Taubman et al. 2009; Westreich et al. 2012; Keil et al. 2014)):

1) Using the entire study sample, use maximum likelihood to estimate the parameters of models for

   a. The density of covariates at time $k$ conditional on covariate history, exposure history, and not experiencing the outcome and remaining uncensored through time $k$

   b. The discrete-time hazard of the outcome by visit $k + 1$ conditional on covariate history, exposure history, and remaining uncensored through time $k$.

   c. *If estimating the natural course additionally estimate models for the following, otherwise continue to (2)*

      i. *The probability of exposure at time $k$ conditional on covariate history, exposure history, remaining uncensored through time $k$, and not experiencing the outcome and remaining uncensored by time $k.*
ii. The probability of remaining uncensored through time \( k + 1 \) conditional on covariate history, exposure history, not experiencing the outcome and remaining uncensored by time \( k \).

2) Randomly select with replacement a large sample (in this case, \( n=50,000 \)) of the participants in the study.

3) For each subject in the sample:
   a. Set time \( k \) to 0. Assign the subjects their baseline covariates (values at \( k = 0 \)) from the input data and set baseline exposure to the exposure level of interest.
      i. If estimating the natural course, rather than assigning exposure at this step, use the observed value of baseline exposure.
   b. Estimate the discrete-time hazard of the outcome by time \( k + 1 \) conditional on previously assigned covariates and exposure history through time \( k \) and remaining uncensored through time \( k \) using the parameters estimated in 1b.
      i. If estimating the natural course, also estimate the probability that the subject was lost to follow-up at time \( k + 1 \) conditional on previously assigned covariate and exposure history through time \( k \) and remaining uncensored through time \( k \) using the estimated parameters for the model in 1cii. Draw a Bernoulli variable with this probability. If this variable, which represents loss to follow-up, takes the value 1, record the subject as lost to follow-up, and proceed to the next subject.
c. Increment \( k \) by 1. For each subject draw covariates for time \( k \) with probabilities conditional on previously assigned covariate and exposure history through \( k - 1 \) and remaining uncensored and free of the outcome through time \( k \) using the parameters estimated in step 1a. Set exposure to the value for time \( k \) from the exposure regime of interest.

   i. *If estimating the natural course, rather than setting exposure, draw a value of exposure for time \( k \) from the estimated parameters for the model in 1ci conditional on previously assigned covariate and exposure history through \( k - 1 \) and remaining uncensored and free of the outcome through time \( k \).*

d. Repeat 3b-3c for that subject until \( k = t \), that is, until the end of follow-up.

e. Use the estimated discrete-time hazards from each time point in the product-limit estimator to estimate the probability of survival to time \( t \) for that subject

   i. *If estimating the natural course, weight each subject by the cumulative probability of remaining uncensored by time \( t \).*

4) Average the predicted survival probabilities across subjects, use 1 minus that average as an estimate of the risk of the outcome by \( t \) under the assigned exposure regime.

5) Repeat step 3-4 for each exposure regime of interest.

   a. Compare across exposure regimes of interest to estimate causal contrasts.

6) Estimate standard errors and confidence intervals with the non-parametric bootstrap (Efron & Tibshirani 1986). For this work, 1000 bootstrap samples were used.
Intuitively, this algorithm works by creating datasets based on modified data distributions in which exposure takes on each exposure regime of interest with probability 1. The survival probability estimated in this dataset is an estimate of the potential survival probability under the assigned exposure regime. When the algorithm is used for the natural course, a dataset is generated using the unmodified data distribution. If the models are properly specified, the survival probabilities and features of the covariate densities from this dataset should be the same as in the original data.

3.5 Inverse probability weighted estimation of marginal structural models

The use of g-computation is one of several methods for estimating causal effects. One alternative, for instance, is the nonparametric inverse probability weighted estimator. For a time-fixed exposure and binary outcome, it is straightforward to derive the nonparametric inverse probability weighted estimator starting from the nonparametric g-formula estimator as follows:

\[
E(Y^a) = \sum_{w \in W} \frac{Pr(Y = 1|A = a, W = w) \cdot Pr(W = w)}{\sum_{i=1}^{n} I(A_i = a, W_i = w)}
\]

\[
= \sum_{w \in W} \frac{\sum_{i=1}^{n} I(Y_i = 1, A_i = a, W_i = w) \cdot \sum_{i=1}^{n} I(W_i = w)}{\sum_{i=1}^{n} I(A_i = a, W_i = w) \cdot n}
\]

\[
= \frac{1}{n} \sum_{w \in W} \frac{\sum_{i=1}^{n} I(Y_i = 1, A_i = a, W_i = w)}{\sum_{i=1}^{n} I(A_i = a, W_i = w) / \sum_{i=1}^{n} I(W_i = w)}
\]

\[
= \frac{1}{n} \sum_{i=1}^{n} \sum_{w \in W} \frac{Y_i I(A_i = a, W_i = w)}{Pr(A_i = a|W_i = w)} = \frac{1}{n} \sum_{i=1}^{n} \frac{Y_i I(A_i = a)}{Pr(A_i = a|W_i = w_i)}
\]

Perhaps the most widely used method (more widely used than g-computation) for estimating the causal effects of time-varying exposure regimes is the estimation of marginal structural
models (MSM) with inverse probability weighted (IPW) estimating equations (Robins et al. 2000).

A MSM is a model of the form

\[ E(Y_t^a) = g(\bar{a}, t; \theta) \]

which is *marginal* because it models the marginal distribution of the potential outcomes and is *structural* because it is a model for the potential outcomes (Robins et al. 2000). The IPW estimating equations estimation of MSMs involves two steps. First, construct weights for each individual of the form

\[ sw_t = sw_t^A \ast sw_t^C, \]

where

\[ sw_t^A = \frac{\prod_{k=0}^{t} P(A_k = a_k | \bar{A}_{k-1} = \bar{a}_{k-1})}{\prod_{k=0}^{t} P(A_k = a_k | \bar{A}_{k-1} = \bar{a}_{k-1}, \bar{W}_k = \bar{w}_k)} \]

and

\[ sw_t^C = \frac{\prod_{k=0}^{t} P(C_k = 0 | \bar{A}_{k-1} = \bar{a}_{k-1,i}, \bar{C}_{k-1} = 0)}{\prod_{k=0}^{t} P(C_k = 0 | \bar{C}_{k-1} = 0, \bar{A}_{k-1} = \bar{a}_{k-1,i}, \bar{W}_k = \bar{w}_k)} \]

where each of the probabilities needed for the weights can be estimated with properly specified parametric, semiparametric, or nonparametric models.

Second, estimate the parameters of the model

\[ E(Y_t | \bar{A} = \bar{a}) = h(\bar{a}, t; \gamma) \]

using the uncensored subjects with each subject weighted by their estimated weight \( \hat{sw}_t \). If the models for the weights are properly specified, then the estimated parameters \( \hat{\gamma} \) are valid estimates of the parameters \( \theta \) (Robins et al. 2000).
Intuitively, IPW estimation of MSMs works by creating a pseudo-population in which the
groups subjects who had each exposure regime, as well as the censored and uncensored groups,
are unconditionally exchangeable (Cole & Hernán 2008). The exposure weights $sw_t^A$ standardize
the distribution of the covariates among each group to be the same as the distribution of the
covariates in the entire study population. Similarly, the censoring weights $sw_t^C$ standardize the
distribution of the covariates in the uncensored in a given exposure group to be the same as that
entire group. Another way to conceptualize this is that after weighting, each uncensored
exposure regime group represents a copy of the entire population (scaled down to the size of that
particular uncensored exposure group) had they been set to that exposure regime and been
prevented from being censored. Because the exposure regime groups and the censored and
uncensored are exchangeable in the pseudo-population, association in the pseudo-population can
be interpreted as causation, and the parameters from conditional models will estimate the
parameters from MSMs.

IPW estimation of MSMs can be used in the survival context as well. Such estimation can
proceed in four steps (adapted from Westreich et al. 2010)

1) Estimate the time-varying weights $sw_t$ for each individual at each time, as described
above.

2) Nonparametrically estimate the discrete-time hazards for each exposure regime at each
time $k$ in the uncensored population weighted by $sw_k$ using the Kaplan-Meier estimator
(Kaplan & Meier 1958)

$$Pr(Y_{k+1} = 1 | \bar{Y}_k = \bar{C}_k = 0, \bar{A}_k = \bar{a}_k) = \frac{d_{k,\bar{a}}}{r_{k,\bar{a}}}$$
where

\[ d_{k,\bar{a}} = \sum_{i=1}^{n} s w_{i,k} \times Y_{i,k+1} \times I(\tilde{A}_{i,k} = \bar{a}_{k}, \tilde{C}_{i,k} = \bar{Y}_{i,k} = 0) \]

And

\[ r_{k,\bar{a}} = \sum_{i=1}^{n} s w_{i,k} \times I(\tilde{A}_{i,k} = \bar{a}_{k}, \tilde{C}_{i,k} = \bar{Y}_{i,k} = 0) \]

Note that instead of conditioning on the entire exposure history, practical applications often condition on only the \( k \) most recent exposures (Westreich et al. 2010). In such a case, the estimator is no longer nonparametric, and the structural model must be properly specified for valid estimation (Breskin et al. 2018).

3) Estimate the distribution of the potential outcomes at \( t + 1 \) as

\[ \bar{P}_r(Y_{t+1}^\bar{a} = 0) = S_{t+1}^\bar{a} = \prod_{k=0}^{t} (1 - \bar{P}_r(Y_{k+1} = 1|\bar{Y}_k = \bar{C}_k = 0, \bar{A}_k = \bar{a}_k)) \]

4) Use the nonparametric bootstrap to estimate standard errors and confidence intervals (Efron & Tibshirani 1986).

Because the models that need to be specified for IPW estimation of MSMs (structural model, exposure model, censoring model) are orthogonal to the models that need to be specified for g-computation (outcome model, covariates model), obtaining similar results from both methods adds reassurance that the models for each method may be properly specified. Of note, IPW estimation of MSMs is not subject to the g-null paradox.
Many other methods exist for the estimation of the distribution of potential outcomes, such as g-estimation of structural nested models (Robins 1999), augmented inverse probability weighted estimators (Bang & Robins 2005), and targeted maximum likelihood estimators (van der Laan & Rubin 2006). Though these estimators have many desirable properties such as double robustness and semiparametric efficiency, they were not used in this work.

3.6 Policy-relevant effect measures

Commonly used effect measures, such as the risk difference and risk ratio, are not ideal for comparing interventions for different conditions. These measures do not take into account the effectiveness of the intervention, the proportion of the population to which the intervention would apply, nor the prevalence of the exposure in the population. Different effect measures, such as the population intervention effects (Hubbard & Van Der Laan 2008; Westreich 2014; Westreich 2017), may be better suited for such purposes. Unlike standard effect measures, which compare an entire population being exposed to the same population being unexposed, these policy-relevant effects compare the observed experience (natural course) of the population to that which would occur under an intervention applied to some subset of the population. Because these effects may take into account the effectiveness of the intervention, the proportion intervened upon, and the prevalence of exposure, they can be used to compare the effects of interventions for different conditions or different policies for treating a single condition.

For simplicity, we present results for a baseline treatment and exposure, though these results can be extended for time-varying treatments and exposures. We present results definitions and results specific to the difference scale, though these effects can be defined on any scale of interest. Note that many of the relationships described here do not hold on other scales. The
fundamental quantity underlying these policy-relevant effects is the *average effect of policy among the exposed* (APEX), defined as:

\[
APEX = E[Y|H = 1] - E[Y^{D=1,H=1}|H = 1]
\]

where \(H, D, Y\), and \(Y^{D=d,H=h}\) are binary random variables, with \(H\) equal to 1 if a person was observed to have the exposure (i.e. hepatitis C infection at baseline), \(D\) equal to 1 if a person received treatment (i.e. DAA), \(Y\) equal to 1 if a person experienced the event (i.e. death by 10 years), and \(Y^{D=d,H=h}\) equal to 1 if the person would have experienced the outcome of interest if, possibly counter to fact, they had received treatment level \(d\) and had exposure level \(h\). We assume that treatment has no effect on people who are not exposed, so \(Y^{D=1,H=0} = Y^{D=0,H=0}\).

Hereafter we will refer to the potential outcome under no exposure, regardless of treatment, as \(Y^{H=0}\). The APEX thus contrasts the observed outcomes among people with exposure to the outcome that would be expected if all people with the exposure received treatment.

When the treatment is 100% effective, works instantaneously (or nearly so), completely eliminates the effect of exposure, and has no side effects, treatment becomes the same as erasing exposure \(Y^{D=1,H=1} = Y^{H=0}\). The APEX can then be expressed as:

\[
APEX = E[Y|H = 1] - E[Y^{H=0}|H = 1]
\]

If treatment is unsuccessful, we assume treatment has no impact on the outcome among the exposed (it has no effect on the exposure and has no side effects), and thus \(Y^{D=1,H=1}\) can take on one of two forms, either \(Y^{D=1,H=1} = Y^{H=0}\) (treatment was successful) or \(Y^{D=1,H=1} = Y^{D=0,H=1}\) (treatment was unsuccessful). We define \(R = I[Y^{D=1,H=1} = Y^{H=0}]\) as an indicator of successful treatment, where \(I\) is the indicator function. Assuming that treatment success is independent of
the values of \( Y_{D=1,H=1} = 1 \) and \( Y_{H=0} \) (though not \( \{ Y_{D=1,H=1}, Y_{H=0} \} \)) among the exposed (e.g. treatment success is essentially random), the APEX is then:

\[
APEX = E[Y|H = 1] - E[Y_{D=1,H=1} = 1|H = 1]
\]

\[
= E[Y|H = 1] - E[R \times Y_{H=0} + (1 - R) \times Y_{D=0,H=1}|H = 1]
\]

\[
= E[Y|H = 1] - (E[Y_{H=0}|H = 1] \times Pr(R = 1|H = 1)) + E[Y_{D=0,H=1}|H = 1] \times (1 - Pr(R = 1|H = 1))
\]

In the present study, we assume that no individuals received treatment at baseline (as nearly all of the study period predates the introduction of DAAs), so by causal consistency:

\[
E[Y|H = 1] = E[Y_{D=0,H=1}|D = 0, H = 1] \times Pr(D = 0|H = 1) + E[Y_{D=1,H=1}|D = 1, H = 1] \times Pr(D = 1|H = 1)
\]

\[
= [Y_{D=0,H=1}|D = 0, H = 1]
\]

\[
= [Y_{D=0,H=1}|H = 1]
\]

We then have:

\[
APEX = (E[Y|H = 1] - E[Y_{H=0}|H = 1]) \times Pr(R = 1|H = 1)
\]

In words, this means that the APEX is equal to the APEX under perfectly effective treatment times the probability that treatment is effective among the exposed.

In contrast to the APEX, which is only estimated among those with exposure, the population attributable risk difference is estimated among the entire population of interest (Westreich 2017). The population attributable risk difference compares the risk in the entire population to the risk if all of the exposed were treated with a treatment that is 100% effective. The population attributable risk difference can be defined as:

Population Attributable Risk Difference

\[
= E[Y] - (E[Y_{D=1,H=1}|H = 1] \times Pr(H = 1) + E[Y|H = 0] \times Pr(H = 0))
\]
\[ E[Y] = \left( E[Y|H = 1] \times Pr(H = 1) + E[Y|H = 0] \times Pr(H = 0) \right) \]

\[ = (E[Y|H = 1] \times Pr(H = 1) + E[Y|H = 0] \times Pr(H = 0)) \]

\[ - \left( E[Y|H = 1] \times Pr(H = 1) + E[Y|H = 0] \times Pr(H = 0) \right) \]

\[ = Pr(H = 1) \times (E[Y|H = 1] - E[Y|H = 1]) \]

\[ = Pr(H = 1) \times APEX \]

Often, interest lies in the effect of policies under which people receive treatment based on their covariate values, referred to as the *dynamic effect of policy in the exposed* (DPEX). The DPEX compares the risk of the outcome among the exposed to the risk had certain exposed individuals been treated based on the values of their covariates. For a baseline exposure and treatment, the DPEX is:

\[
\text{DPEX} = E[Y|H = 1] - \left( \sum_{g \in G} (E[Y|H = 1, G = g, H = 1]) \times Pr(G = g|H = 1) \right) \\
+ \left( \sum_{g \in G} (E[Y|G = g, H = 1]) \times Pr(G = g|H = 1) \right) \\
- \left( \sum_{g \in G} (E[Y|H = 1, G = g, H = 1]) \times Pr(R = 1|G = g, H = 1) \right) \\
+ E(Y|G = g, H = 1) \times (1 - Pr(R = 1|G = g, H = 1)) \times Pr(G = g|H = 1) \\
+ \left( \sum_{g \in G} (E[Y|G = g, H = 1]) \times Pr(G = g|H = 1) \right) \]
\[
\sum_{g \in G} E[Y|G = g, H = 1] \times \text{Pr}(G = g|H = 1)
\]

\[
- \sum_{g \in G} (E[Y^{H=0}|G = g, H = 1] \times \text{Pr}(R = 1|G = g, H = 1)) \times \text{Pr}(G = g|H = 1)
\]

\[
= 1 + E(Y|G = g, H = 1) \times (1 - \text{Pr}(R = 1|G = g, H = 1)) \times \text{Pr}(G = g|H = 1)
\]

\[
= \sum_{g \in G} \text{Pr}(G = g|H = 1) \times \text{Pr}(R = 1|G = g, H = 1) \times (E[Y|G = g, H = 1] - E[Y^{H=0}|G = g, H = 1])
\]

\[
= \sum_{g \in G} \text{Pr}(G = g|H = 1) \times APEX_g
\]

where subgroups are defined by \(g, G\) is the set of subgroups that receive treatment under the given policy, \(APEX_g\) is the APEX in subgroup \(g\).

Similar to the population intervention effect, the dynamic intervention risk difference compares the risk in the entire population of interest to the risk in the entire population if certain exposed individuals were treated based on the values of their covariates (Westreich 2017). For instance, the difference in the 10-year risk of mortality observed in the entire population of PLWH and the risk in that population if all of those coinfected with HCV with severe fibrosis/cirrhosis are treated with DAAs is an example of a dynamic intervention risk difference.

The dynamic intervention risk difference is:

Dynamic intervention risk difference

\[
E[Y] - \left( E[Y|H = 0] \times \text{Pr}(H = 0) \right)
\]

\[
+ \sum_{g \in G} (E[Y^{G=1,H=1}|G = g, H = 1]) \times \text{Pr}(G = g|H = 1)
\]

\[
+ \sum_{g \in G} (E[Y|G = g, H = 1]) \times \text{Pr}(G = g|H = 1) \times \text{Pr}(H = 1)
\]
\[
= \Pr(H = 1) \times \left( E[Y|H = 1] - \left( \sum_{g \in G} E[Y^D = 1, H = 1|G = g, H = 1] \times \Pr(G = g|H = 1) \right) \right)
+ \sum_{g \not\in G} E[Y|G = g, H = 1] \times \Pr(G = g|H = 1)) \right)\right)
= \Pr(H = 1) \times DPEX
\]

Finally, one may be interested in the effect of treating randomly selected exposed individuals at baseline. Such effects are referred to as the generalized effect of policy in the exposed (GPEX), defined as:

\[
GPEX
= E[Y|H = 1] - (p \times E[Y^D = 1, H = 1|H = 1] + (1 - p) \times E[Y|H = 1])
= E[Y|H = 1] - (p \times E[Y^H = 0|H = 1] + (1 - p) \times E[Y|H = 1])
= p \times (E[Y|H = 1] - (E[Y^H = 0|H = 1] \times \Pr(R = 1|H = 1) + E[Y|H = 1] \times (1 - \Pr(R = 1|H = 1))
= p \times \Pr(R = 1|H = 1) \times (E[Y|H = 1] - E[Y^H = 0|H = 1])
= p \times APEX
\]

where \( p \) is the proportion of the exposed who are treated.

Again, a population intervention analog of the GPEX exists, and is known as the generalized intervention risk difference (Westreich 2017). The generalized intervention risk difference compares the risk in the entire population to the risk if randomly selected exposed individuals receive treatment. The generalized intervention risk difference is:

\[
Generalized\ \text{intervention risk difference}
\]
\[ \begin{align*}
  & = E[Y] - (E[Y|H = 0] \times Pr[H = 0] + (p \times E[Y^{D=1,H=1}|H = 1] + (1 - p) \times E[Y|H = 1]) \times Pr(H = 1)) \\
  & = Pr(H = 1) \times (E[Y|H = 1] - (p \times E[Y^{D=1}|H = 1] + (1 - p) \times E[Y|H = 1])) \\
  & = Pr(H = 1) \times GPE
\end{align*} \]

Estimation of these effects can be accomplished with modifications to the \( g \)-computation estimation procedure, as follows:

1) Using the entire study sample, use maximum likelihood to estimate the parameters of models for

   a. The density of time-varying covariates at time \( k \) conditional on covariate history, exposure history, and not experiencing the outcome and remaining uncensored through time \( k \)

   b. The discrete-time hazard of the outcome by visit \( k + 1 \) conditional on covariate history, exposure history, and remaining uncensored through time \( k \).

2) Randomly select with replacement a large sample (in this case, \( n=50,000 \)) of the participants in the study \textit{with exposure} at baseline

3) For each subject in the sample

   a. Set time \( k \) to 0. Assign the subjects their baseline covariates (values at \( k = 0 \)) from the input data and set baseline exposure to the exposure level of interest if the conditions for intervention are met

   b. Estimate the discrete-time hazard of the outcome by time \( k + 1 \) conditional on previously assigned covariates and exposure history through time \( k \) and remaining uncensored through time \( k \) using the parameters estimated in 1b.
c. Increment \( k \) by 1 For each subject draw covariates for time \( k \) with probabilities conditional on previously assigned covariate and exposure history through \( k - 1 \) and remaining uncensored and free of the outcome through time \( k \) using the parameters estimated in step 1a. Set exposure to the value for time \( k \) from the exposure regime of interest if the conditions for intervention are met.

d. Repeat 3b-3c for that subject until \( k = t \), that is, until the end of follow-up.

4) Use the estimated discrete-time hazards from each time point in the product-limit estimator to estimate the probability of survival to time \( t \) for that subject.

5) Average the predicted survival probabilities across subjects, use 1 minus that average as an estimate of the risk of the outcome by \( t \) under the assigned exposure regime.

6) Repeat step 3-4 for each intervention of interest.

7) Estimate the effect measure

   a. For the APEX, simply take the difference of the estimates from each intervention.

   b. For the GPEX, multiply the difference of the estimates by the proportion treated.

   c. For the population intervention analogs of the effects, multiply the APEX, GPEX, or DPEX by the prevalence of exposure in the population.

8) Estimate standard errors and confidence intervals with the non-parametric bootstrap (Efron & Tibshirani 1986).
a. When using the bootstrap for the generalized effects, randomly assign treatment within the simulation and skip step 6b. This captures the variability due to the random treatment selection process.

It may be useful to cast these policy-relevant effects as a public health analog of precision medicine (Collins & Varmus 2015). Rather than tailoring individual treatments to patients based on their individual characteristics to maximize the benefit to the patient, these effects tailor policy-level interventions to target those members of the population who are most likely to benefit from the policy. Such targeted interventions may improve the effectiveness, both in terms of outcomes and cost, compared with interventions that are targeted to an entire population. Incorporating cost-effectiveness measures into the estimation of these effects is a natural next step to connect the fields of epidemiology and health policy, and will connect research from ‘bench to bedside, and from bedside to policy.’

### 3.7 Estimating hepatitis C infection and treatment effects from observational data

Under certain assumptions, the effects of HCV infection and DAA treatment can be estimated separately without data on DAA usage. Consider Figure 3.2. For the effect of HCV infection, the variable $HCV_{Acquisition}$ is the exposure of interest. For this exposure, fibrosis lies on the causal pathway between exposure and outcome, and therefore should not be accounted for in the analysis as it is a mediator of the effect of HCV infection on mortality.

For the effect of HCV treatment, the exposure is $HCV_0$. Here, accounting for fibrosis blocks confounding pathways, and therefore should be accounted for in the analysis. Intuitively, this holds baseline fibrosis constant, so that an individual’s liver damage is not immediately reversed after HCV treatment, as would happen with actual DAA treatment. In contrast, when fibrosis is
not accounted for, toggling baseline HCV status also toggles baseline fibrosis, thus emulating what would happen if subjects acquired or never acquired HCV. Assuming HCV primarily impacts mortality through pathways that involve liver damage, and that curing HCV with DAAs has no effect besides halting HCV’s effect on liver damage, this method allows for the estimation of the effect of treatment without actually having data on patients treated with DAAs. Stated differently, under the assumption that an individual without HCV with a given degree of liver fibrosis at baseline has the same risk of mortality as a similar individual after successful treatment of their HCV infection (conditional on confounders), the survival experience of HCV-uninfected PLWH can serve as a proxy for the experience PLWH+HCV would have had if they were treated with DAAs. Technically, PLWH without HCV infection are assumed to be conditionally exchangeable (Hernán & Robins 2017) with treated PLWH+HCV given baseline fibrosis and confounders. Additionally, it is assumed that someone with a given set of baseline characteristics has the same risk of mortality whether they never had HCV or were successfully treated for HCV. A thorough discussion of these assumptions is provided in Chapter 6.
CHAPTER 4: THE EFFECTS OF HEPATITIS C INFECTION AND TREATMENT ON ALL-CAUSE MORTALITY AMONG PEOPLE LIVING WITH HIV

4.1 Introduction

With modern antiretroviral therapy (ART), life expectancies for people living with HIV (PLWH) are approaching those of HIV seronegative individuals (Samji et al. 2013). While AIDS-related causes of death continue to decline (Smith et al. 2014), liver-related complications have emerged as a major source of mortality, largely driven by co-infection with viral hepatitides (Weber et al. 2013).

In the United States (US), an estimated 25% of PLWH are co-infected with HCV (Centers for Disease Control and Prevention 2017a). However, the effect of HCV on mortality among PLWH remains unclear. In the era of effective and less toxic ART, studies estimated that all-cause mortality rates are up to two-fold higher among individuals with HIV/HCV co-infection (Anderson et al. 2004; May et al. 2015), but others found more modest effects (Thornton et al. 2017; Scherzer et al. 2017). Most studies investigating the role of HCV co-infection on mortality among PLWH were conducted prior to ART guidelines recommending treatment for all PLWH regardless of CD4 cell count (Panel on Antiretroviral Guidelines for Adults and Adolescents 2018). These studies also pre-date direct acting antiviral (DAA) medications, which are capable of reliably producing sustained HCV virologic response (SVR) in more than 97% of individuals (Afdhal et al. 2014), irrespective of HIV status (Milazzo et al. 2017).
Though DAA treatment is considered curative, it may not fully reverse the effects of HCV infection, and thus infection and treatment effects may differ (Westreich 2014). Although data are accumulating that DAAs reduce complications of HCV infection (van der Meer & Berenguer 2016; Ioannou et al. 2017) and improve survival (Butt et al. 2017; Backus et al. 2018), treatment does not immediately reverse liver fibrosis. Therefore, mortality risk may remain elevated in successfully treated individuals.

Without estimates of the long-term impacts of HCV co-infection and DAA treatment on mortality in those initiating modern ART, it is difficult for clinicians and policy-makers to properly prioritize HCV care among PLWH. We thus separately estimated the long-term effects of HCV infection and DAA treatment on all-cause mortality among PLWH under modern guidelines suggesting ART initiation regardless of CD4 cell count. Because DAAs are a recent development, there is insufficient person-time to directly estimate their effects on long-term mortality. We thus used a novel application of the parametric g-formula (Robins 1986) in which HCV-uninfected PLWH serve as proxies for DAA-treated PLWH+HCV with the same degree of liver fibrosis.

4.2 Methods

Study sample

Data came from the Women’s Interagency HIV Study (WIHS) (Barkan et al. 1998; Adimora et al. 2018) and the Multicenter AIDS Cohort Study (MACS) (Kaslow et al. 1987). Briefly, the WIHS and MACS are ongoing US-based cohort studies of HIV-infected and -uninfected women and men who have sex with men, respectively. MACS began in 1984, with additional recruitment waves in 1987, 2001, and 2010 at four urban locations. WIHS began in 1994 at six
urban locations, with additional recruitment waves in 2001, 2011, and 2013, eventually expanding to 10 urban and suburban sites. In both studies, laboratory procedures, clinical examinations, and structured interviews are conducted at entry and every six months thereafter. Information collected through interview includes self-reported medication use along with demographic, socioeconomic, and behavioral characteristics. The laboratory procedures included measures of, in particular, CD4 cell count, HIV RNA, HCV Ab and RNA, and non-invasive markers of liver fibrosis.

Individuals included in our cohort were HIV-infected at study entry or seroconverted during follow-up. Visits occurring after the opening of WIHS recruitment (October 1, 1994) were included. All participants were ART-naïve and without an AIDS diagnosis prior to their first eligible study visit. Follow-up began at the first eligible study visit after HIV diagnosis and continued until the first of: loss to follow-up, death, 10 years after the first eligible visit, or September 30, 2015. A participant was considered lost to follow-up at the time of their second missed study visit. Time was discretized into 6-month intervals, corresponding to the approximate interval between planned study visits.

Definitions

In both studies, HCV Ab was assessed at baseline by enzyme immunoassay. Specimens with reactive Ab results underwent HCV RNA testing by real-time polymerase chain reaction assays. Those with detectable HCV RNA were considered to have chronic HCV (HCV+).

The definition of ART was guided by the November 2014 US Department of Health and Human Services guidelines (Panel on Antiretroviral Guidelines for Adults and Adolescents 2014). Once a participant reported initiating ART, they were assumed to remain on it for the
duration of the study (the intent-to-treat assumption). ART was split into two variables based on time of initiation. ART initiated prior to October 1, 2001 (when tenofovir, a key component of many modern ART regimens (Panel on Antiretroviral Guidelines for Adults and Adolescents 2018), was approved) was considered early ART, while ART initiated after that date was considered modern ART.

Ascertainment of death

Both studies perform death registry searches to obtain information on the mortality of participants. Date and cause of death are obtained either directly from the National Death Index (https://www.cdc.gov/nchs/ndi/index.htm) or through copies of death certificates obtained by study investigators.

Confounders

Confounders were chosen using a causal diagram (Greenland et al. 1999) constructed prior to data analysis. Time-fixed confounders included age, sex, race and ethnicity, injection drug use (IDU), heavy alcohol use, and smoking status. Time-varying confounders included CD4 cell count and HIV RNA. For the effect of DAA treatment (but not HCV infection, see the statistical analysis section), hepatic fibrosis was also included as a time-fixed confounder after categorization into 3 levels: FIB-4 (Sterling et al. 2006) $\geq 3.25$ or AST to Platelet Ratio Index (APRI) (Lin et al. 2011) $\geq 1$ was classified as cirrhosis, while FIB-4 $< 1.45$ and APRI $< 0.7$ (together) was classified as no significant fibrosis. Other combinations were classified as non-cirrhotic fibrosis. We chose APRI cutoffs based on a meta-analysis (Lin et al. 2011) that suggested the improved performance of these cutoffs for classification of cirrhosis and no
significant fibrosis than the commonly used cutoffs of 2 and 0.5, respectively. Further details on variable measurement and operationalization are in Chapter 3.

**Statistical analysis**

The parametric g-computation algorithm formula (hereafter referred to as the g-formula) (Robins 1986) was used to estimate the causal effects in this study. We estimated the effects on 10-year all-cause mortality of: 1) chronic HCV infection among all PLWH, 2) chronic HCV infection among PLWH+HCV, and 3) DAA treatment among PLWH+HCV. Pooled logistic regression was used to model the discrete-time hazard of mortality conditional on ART, HCV status, and confounders. Pooled logistic and linear regressions were used to model the conditional distributions of the time-varying confounders. Using these models, the time-varying confounder histories and survival curves were simulated for an enlarged resampled set of the observed population under each HCV scenario (Westreich et al. 2012; Murray et al. 2017). Each effect was estimated after first setting each person to initiate modern ART at study entry. Confidence intervals were estimated using the nonparametric bootstrap with 1000 samples. Full details of the g-formula estimation procedure are in the Chapter 3.

Multiple imputation was used to handle missing data (Allison 2001) (the amount missing for each variable is presented in Table 4.1, and ranged from none to 30% missing (baseline fibrosis)). We assumed a multivariate normal imputation model, which is robust to non-normality in many settings (Allison 2001). Missing time-varying covariates were carried forward from the most recent measurement. The ‘Boot MI’ algorithm was used to incorporate multiple imputation into the bootstrap (Schomaker & Heumann 2018), with 20 imputed datasets per bootstrap sample.
To assess the fit of parametric models, the natural course was simulated in one imputed dataset and the distributions of key variables were compared to those observed in the data.

Though most of the period covered in this study predates DAAs, it is still possible to estimate the effect of DAAs using data available from the MACS and WIHS. These effects were estimated under the assumption that an individual without HCV with a given degree of liver fibrosis at baseline has the same risk of mortality as a similar individual after successful treatment of their HCV infection (conditional on confounders). Intuitively, the survival experience of HCV-uninfected PLWH served as a proxy for the experience PLWH+HCV would have had if they were treated with DAAs. Technically, PLWH without HCV infection were assumed to be conditionally exchangeable (Hernán & Robins 2017) with treated PLWH+HCV given baseline fibrosis and confounders.

Therefore, baseline fibrosis was included as a confounder to estimate the effect of DAA treatment. In contrast, fibrosis was not included when estimating the effect of HCV infection, because fibrosis is the primary mechanism through which HCV causes mortality. Rather than assuming all PLWH+HCV would achieve SVR with DAAs, a beta-Bernoulli random variable was used to determine DAA treatment success, with average treatment effectiveness of 0.96 and 95% of the distribution falling between 0.93 and 0.98 (Naggie et al. 2015).

**Sensitivity analyses**

First, the effect of HCV infection was estimated with a marginal structural model fit with inverse probability weighted estimating equations (Robins et al. 2000). The models needed for this method are distinct from those needed for the g-formula, so concordance between the results
provides confidence in the model specifications. Further details of the MSM are provided in the Chapter 3 and Appendix A.

Second, subjects may have been enrolled long after HCV acquisition and time of HCV acquisition is unknown in this study. As such, subjects with prolonged infection have more advanced liver fibrosis on average than those with recently acquired infections, and there is also a possibility of selection bias. To provide an estimate less impacted by such biases, we estimated the effect of HCV infection restricted to participants without significant fibrosis, as these individuals are more likely to have recently acquired HCV.

Third, to address possible confounding by hepatitis B virus (HBV) co-infection, we conducted each of the analyses restricted to those negative for HBsAg at baseline. We used restriction (rather than standardization or adjustment) due to the small number of HBV/HCV co-infected individuals in the study population leading to issues of non-positivity (Westreich & Cole 2010).

4.3 Results

Study sample

Overall, 3,056 people were eligible for the study, of whom 543 (18%) had HCV at baseline. The study population was 58% female (85% of those with HCV were female). The median follow-up time was 7.5 years (interquartile range: 2, 10). PLWH+HCV had more advanced liver fibrosis by FIB-4 and APRI and lower median CD4 cell counts; they were also more likely to inject drugs, use alcohol heavily, and smoke at baseline than those without HCV. ART was initiated by 63% of study participants during follow-up. Of those initiating ART, 32% did so after October 1, 2001 (constituting modern ART). Additional characteristics of the study
population are presented in Table 4.1 (the characteristics of the populations from the MACS and WIHS are presented separately in Table 5.1), and the modelled and observed natural course are presented in Table A.1 and Figure A.1.

Estimated effects of HCV infection and DAA treatment

All of the estimated effects occur after intervening to have all PLWH initiate modern ART at study entry. The 10-year risk difference (RD) for all-cause mortality comparing all PLWH having HCV to none having HCV was 4.3% (95% confidence interval [CI]: 0.4%, 8.9%), and the risk ratio (RR) was 1.4 (95% CI: 1.0, 1.9) (Table 4.2; Figure 4.1). We also estimated the effect of HCV infection specifically among PLWH+HCV (in contrast to among all PLWH as above). The 10-year RD comparing all-cause mortality among PLWH with observed HCV to that expected had they not had HCV was 5.3% (95% CI: 0.6%, 10.5%) and the RR was 1.4 (95% CI: 1.0; 1.8) (Table 4.2; Figure 4.2).

The 10-year RD for all-cause mortality comparing all PLWH+HCV being treated with DAAs to none being treated was -3.8% (95% CI: -9.2%, 0.9%), corresponding to a RR of 0.8 (95% CI: 0.6, 1.1) (Table 4.2; Figure 4.3).

Sensitivity Analyses

The estimated effect of HCV infection from the marginal structural model was similar to that from the g-formula, but the CI was wider (RD: 4.1%; 95% CI: -7.4%, 25.0% compared to 4.3%; 95% CI: 0.4%, 8.9%). After restricting to those without significant fibrosis, the estimated effects of HCV infection among all PLWH and among PLWH+HCV were attenuated (RD: 3.7% and 4.1%, compared with 4.3% and 5.3%, respectively). When restricted to those without HBV co-infection, the effects of HCV infection among all PLWH and among PLWH+HCV, as well as
the effect of DAA treatment, were stronger (RD: 4.9%, 6.1%, and -4.5%, compared with 4.3%, 5.3%, and -3.8%, respectively) (Table A.2).

4.4 Discussion

In the modern ART era, it is imperative to identify interventions that alleviate the sources of mortality that most impact PLWH. Using causal inference methods, we estimated the effects of HCV infection and DAA treatment on mortality risk among PLWH after initiating modern ART according to current guidelines. Our results suggest that successful interventions to prevent and treat HCV would likely yield mortality benefits in this population. Our estimated RD for HCV co-infection among all PLWH corresponds to a number needed to harm (NNH, defined as $\frac{1}{|RD|}$) of 23, meaning that if 23 PLWH initiated ART at study entry and had HCV, we would expect one additional death over 10-years compared with none of them having HCV. Our estimated risk difference for DAA treatment corresponds to a number needed to treat (NNT) of 26, so we would expect one fewer death over 10 years if 26 PLWH+HCV initiated ART at study entry and were treated with DAAs compared with only initiating ART. The estimated beneficial effect of DAA treatment among PLWH+HCV was smaller than the harmful effect of HCV infection in the same population, likely due to the time necessary for liver fibrosis to revert after SVR.

Our results provide evidence of the effect of HCV infection and DAA treatment among PLWH. We estimated effects after ART initiation at study enrollment, providing evidence that is useful for clinicians and policy-makers to properly prioritize HCV prevention and DAA treatment after patients enter care for HIV. By using data from large, long-running observational cohorts, we could estimate effects on 10-year all-cause mortality, a time-frame that captures the slow, progressive nature of HCV. These cohorts also had data on liver fibrosis which, along with
modern causal inference methodology, allowed us to separately estimate the effects of HCV infection and a well-defined DAA treatment intervention (Westreich 2014).

The risk ratio attributable to HCV infection that we estimated is similar to the pooled risk ratio of 1.35 reported by a 2009 meta-analysis (Chen et al. 2009). Despite the numerical similarity, our results carry a different interpretation. Most notably, all prior studies accounted for ART use either with regression adjustment or by restricting their study populations to those who had initiated ART, thus providing estimates that are conditional on observed ART. Our estimates can instead be interpreted as the effect of HCV infection after an intervention had been applied so that all study participants initiate modern ART upon study enrollment, regardless of what ART use was actually observed.

Our estimated effect of HCV treatment is smaller than previous estimates among PLWH from the pegylated interferon (PEG-IFN) era, where hazard ratios for mortality comparing those who achieved SVR on PEG-IFN plus ribavirin to those who did not achieve SVR or were not treated ranged from 0.12 (Labarga et al. 2015) to 0.22 (Berenguer et al. 2014). As PEG-IFN is more toxic than DAAs among PLWH+HCV (Koziel & Peters 2007), those who were successfully treated with a PEG-IFN plus ribavirin regimen were likely selected for treatment based upon ability to tolerate the drugs, and thus were likely healthier than those who would have been successfully treated with DAAs as well as those for whom PEG-IFN plus ribavirin treatment was not attempted or was not successful. Therefore, these prior results are likely overestimates for the effect of DAAs. Our estimated DAA treatment effect is also smaller than the hazard ratios of 0.43 and 0.44 reported in short-term studies in the general population of the effect of DAA treatment (Butt et al. 2017) and the effect of SVR after DAA treatment (Backus et al. 2018), respectively. Because those studies specifically excluded PLWH, they cannot be
directly compared with our results, as risk factors for and causes of mortality differ between PLWH and the general population.

Our inferences are subject to limitations. First, there are likely confounders not accounted for in our analyses. For instance, for HCV treatment, we assumed that those without HCV could serve as proxies for those who were treated for HCV. However, HCV uninfected individuals with moderate-to-severe fibrosis (or cirrhosis) likely had underlying factors causing their liver damage. Some of these were measured and controlled for in the analysis, but others likely remain, meaning the proxies may have had a higher mortality risk than co-infected individuals who achieved SVR. Therefore, we likely provide a conservative estimate of the effect of HCV treatment. After restricting to PLWH without HBV co-infection, HCV infection and DAA treatment had somewhat stronger estimated effects on mortality. However, the similarity of the estimates, along with the rarity of HBV in our study and the fact that the distribution of HBV was similar between those with and without HCV, imply that meaningful confounding by HBV is unlikely. Second, we did not account for the possibility of fibrosis reversion after successful DAA treatment (van der Meer & Berenguer 2016). Reversion should reduce mortality after HCV treatment, further suggesting that our estimated treatment effect is conservative. We likewise did not account for reinfection after successful treatment or for incident infections after baseline.

Third, our estimates may be biased if the models for mortality or the time-varying confounders are misspecified. Though we used several methods to assess the fit of the outcome and confounder models, the possibility of model misspecification remains. Due to the large amount of missing data, our results may also be particularly sensitive to misspecification of the imputation models. Lastly, our study sample is historical, as it combines studies of men and
women beginning in the mid-1990’s. As such, our results may not be immediately applicable to the current population of PLWH in the US (Lesko et al. 2016).

Likely violations of our assumptions would suggest that our results are underestimates of the true effect of DAA treatment among people with HIV. Given our effect estimates for HCV infection and treatment, we believe HIV care providers should make strong efforts to prevent and treat HCV in their patients, and that policy-makers and insurers should expand access to DAAs and prioritize HCV interventions for PLWH. As person-time accrues in the DAA era, future studies should directly estimate the effect of DAAs on long-term mortality among PLWH+HCV.
Table 4.1: Study population at baseline, Women’s Interagency HIV Study and Multicenter AIDS Cohort Study, 1994-2015

<table>
<thead>
<tr>
<th></th>
<th>Total (N=3056)</th>
<th>HCV+ (N=543)</th>
<th>HCV- (N=2411)</th>
<th>Missing HCV (N=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (Median, IQR)</strong></td>
<td>38 (32; 44)</td>
<td>40 (35; 44)</td>
<td>37 (31; 43)</td>
<td>40 (33; 49)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (Non-Hispanic)</td>
<td>1113 (36.4)</td>
<td>109 (20.1)</td>
<td>980 (40.7)</td>
<td>24 (23.5)</td>
</tr>
<tr>
<td>African American</td>
<td>1339 (43.8)</td>
<td>321 (59.1)</td>
<td>957 (39.7)</td>
<td>61 (59.8)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>529 (17.3)</td>
<td>107 (19.7)</td>
<td>409 (17.0)</td>
<td>13 (12.7)</td>
</tr>
<tr>
<td>Other</td>
<td>74 (2.4)</td>
<td>6 (1.1)</td>
<td>64 (2.7)</td>
<td>4 (3.9)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (0)</td>
<td>0 (0)</td>
<td>1 (0)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Female Sex</strong></td>
<td>1777 (58.1)</td>
<td>460 (84.7)</td>
<td>1231 (51.1)</td>
<td>86 (84.3)</td>
</tr>
<tr>
<td><strong>CD4 count (median, IQR)</strong></td>
<td>417 (258; 607)</td>
<td>379 (217; 586)</td>
<td>422 (271; 606)</td>
<td>471 (333; 685)</td>
</tr>
<tr>
<td>Missing</td>
<td>169 (16)</td>
<td>16 (16)</td>
<td>139 (14)</td>
<td>14</td>
</tr>
<tr>
<td><strong>Detectable HIV Viral Load</strong></td>
<td>2393 (95.1)</td>
<td>487 (95.5)</td>
<td>1829 (95.0)</td>
<td>77 (93.9)</td>
</tr>
<tr>
<td>Missing</td>
<td>539 (33)</td>
<td>486 (20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IDU</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>2313 (76.5)</td>
<td>102 (19.0)</td>
<td>2156 (90.4)</td>
<td>55 (53.9)</td>
</tr>
<tr>
<td>Former</td>
<td>491 (16.2)</td>
<td>300 (55.8)</td>
<td>162 (6.8)</td>
<td>29 (28.4)</td>
</tr>
<tr>
<td>Current</td>
<td>220 (7.3)</td>
<td>136 (25.3)</td>
<td>66 (2.8)</td>
<td>18 (17.6)</td>
</tr>
<tr>
<td>Missing</td>
<td>32 (5)</td>
<td>27 (5)</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td><strong>Heavy Alcohol Use</strong></td>
<td>377 (12.7)</td>
<td>102 (19.4)</td>
<td>252 (10.7)</td>
<td>23 (23.0)</td>
</tr>
<tr>
<td>Missing</td>
<td>77 (18)</td>
<td>57 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Abbreviations: HCV, hepatitis C virus; IQR, interquartile range; IDU, injection drug use; HBsAg, hepatitis B surface antigen; ART, antiretroviral therapy

---

- **Never**
  - 918
  - 30.4
  - 58
  - 10.8
  - 837
  - 35.2
  - 23
  - 22.8

- **Former**
  - 693
  - 23.0
  - 77
  - 14.4
  - 601
  - 25.2
  - 15
  - 14.9

- **Current**
  - 1406
  - 46.6
  - 400
  - 74.8
  - 943
  - 39.6
  - 63
  - 62.4

- **Missing**
  - 39
  - 8
  - 30
  - 1

- **BMI > 30 kg/m²**
  - 617
  - 22.2
  - 105
  - 20.8
  - 482
  - 22.1
  - 30
  - 32.6

- **HBsAg Positive**
  - 130
  - 4.4
  - 17
  - 3.2
  - 109
  - 4.6
  - 4
  - 7.0

- **Missing**
  - 103
  - 4
  - 54
  - 45

```text
Fibrosis Status
```

- No significant fibrosis
  - 1621
  - 76.2
  - 225
  - 49.0
  - 1362
  - 84.6
  - 34
  - 56.7

- Non-cirrhotic fibrosis
  - 304
  - 14.3
  - 127
  - 27.7
  - 162
  - 10.1
  - 15
  - 25.0

- Cirrhosis
  - 203
  - 9.5
  - 107
  - 23.3
  - 85
  - 5.3
  - 11
  - 18.3

- Missing
  - 928
  - 84
  - 802
  - 42

### ART

- Initiated pre-October 2001
  - 1296
  - 42.4
  - 229
  - 42.2
  - 1034
  - 42.9
  - 33
  - 32.4

- Initiated post-October 2001
  - 613
  - 20.1
  - 52
  - 9.6
  - 537
  - 22.3
  - 24
  - 23.5

---

Abbreviations: HCV, hepatitis C virus; IQR, interquartile range; IDU, injection drug use; HBsAg, hepatitis B surface antigen; ART, antiretroviral therapy

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- **a**Lower limit of detection varied over time, and ranged from 500 copies/ml to 20 copies/ml
- **b**Defined as more than 7 drinks per week for women and more than 14 drinks per week for men (United States Department of Health and Human Services 2015)
- **c**Cirrhosis defined as FIB-4 $\geq 3.25$ or AST to Platelet Ratio Index APRI $\geq 1$; no significant fibrosis defined as FIB-4 < 1.45 and APRI < 0.7; other combinations were classified as non-cirrhotic fibrosis.
Table 4.2: Effects of HCV infection and DAA treatment on 10-year all-cause mortality had all subjects initiated ART at baseline, Women’s Interagency HIV Study and Multicenter AIDS Cohort Study, 1994-2015

<table>
<thead>
<tr>
<th>Effect</th>
<th>Population</th>
<th>Exposure/Treatment</th>
<th>Riska (95% CI)</th>
<th>Risk Differencea (95% CI)</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV Infection</td>
<td>All PLWH</td>
<td>HCV+</td>
<td>14.69 (8.10, 24.36)</td>
<td>4.34 (0.42, 8.92%)</td>
<td>1.42 (1.04, 1.86)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HCV-</td>
<td>10.35 (6.04, 17.60)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>HCV Infection</td>
<td>Only PLWH+HCV</td>
<td>HCV+</td>
<td>18.56 (10.67, 30.34)</td>
<td>5.29 (0.57, 10.47)</td>
<td>1.40 (1.04, 1.81)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HCV-</td>
<td>13.27 (8.36, 22.08)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>HCV Treatment</td>
<td>Only PLWH+HCV</td>
<td>All HCV treated</td>
<td>14.88 (9.17, 24.39)</td>
<td>-3.80 (-9.22%, 0.89)</td>
<td>0.80 (0.61, 1.06)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No HCV treated</td>
<td>18.68 (10.81, 30.54)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
</tbody>
</table>

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; HCV, hepatitis C virus

aExpressed as percent
Figure 4.1: The effect of HCV infection on 10-year all-cause mortality among PLWH, Women’s Interagency HIV Study and Multicenter AIDS Cohort Study, 1994-2015.

Solid line is the risk for HCV+, dashed line is risk for HCV-
Figure 4.2: The effect of HCV infection on 10-year all-cause mortality among PLWH and HIV, Women’s Interagency HIV Study and Multicenter AIDS Cohort Study, 1994-2015.

Solid line is the risk for HCV+, dashed line is risk for HCV-
Figure 4.3: The effect of DAA treatment on 10-year all-cause mortality among PLWH and HIV, Women’s Interagency HIV Study and Multicenter AIDS Cohort Study, 1994-2015.

Solid line is the risk no HCV treated with DAAs, dashed line is all HCV treated with DAAs
CHAPTER 5: THE POPULATION INTERVENTION EFFECTS OF HEPATITIS C TREATMENT POLICIES ON ALL-CAUSE MORTALITY AMONG PEOPLE LIVING WITH HIV

5.1 Background

The prognosis for persons living with HIV (PLWH) has markedly improved with antiretroviral therapy (ART) (Samji et al. 2013). Given the many comorbidities now associated with HIV, understanding the impact of interventions for each condition is essential for allocating patient, clinician, and public resources. Among causes of death that predominate in the ART-era, liver-related complications have emerged as a major culprit, with mortality largely attributable to hepatitis C virus (HCV) co-infection (Weber et al. 2013). Fortunately, the advent of direct acting antiviral (DAA) treatments has changed the landscape for people with HIV-HCV co-infection dramatically; sustained HCV virologic response (SVR) is achievable in >97% of individuals (Afdhal et al. 2014) irrespective of HIV status (Milazzo et al. 2017).

These treatments, however, come at a high financial cost to the healthcare system. To limit expenditures, payers have restricted DAA treatment to those who meet certain criteria. As of October 2017, 30 Medicaid programs restricted DAA treatment based on liver fibrosis, with 12 limiting access to only those beneficiaries at or nearing cirrhosis (National Viral Hepatitis Roundtable & Harvard Law School Center for Health Law and Policy Innovation 2017). Additionally, 40 programs required patients to be free of alcohol or illicit drugs (National Viral Hepatitis Roundtable & Harvard Law School Center for Health Law and Policy Innovation 2017). Achievement of HIV clinical benchmarks for persons with HIV-HCV co-infection, such
as achieving CD4 count targets or HIV suppression, has been used as a restriction for DAA treatment in 5 states plus Washington, DC (Ooka et al. 2017). These restrictions persist despite treatment guidelines recommending DAA treatment for nearly all patients with HCV regardless of such factors (American Association for the Study of Liver Diseases & Infectious Diseases Society of America 2017). Because these policies are rapidly evolving as the cost of DAAs falls (Kapadia et al. 2017), evidence is needed to properly evaluate how such restrictions impact mortality – especially for people with HIV-HCV co-infection whose risk for progression of liver disease exceeds that of HCV monoinfected individuals (Kirk et al. 2013).

The goal of our analysis was to evaluate the impact of DAA restrictions on 10-year, all-cause mortality among PLWH at two levels. First, we estimated the effects of various restrictive DAA treatment policies on mortality among HIV-HCV co-infected persons to determine how much mortality could be averted by expanding access to DAAs. Second, we estimated the population-level impact of these criteria on mortality among the entire population of PLWH. These estimates take into account the prevalence of HCV among PLWH, and thus will aid in comparing HCV treatment with interventions for other comorbidities among PLWH. Together, these results will provide important information that may be used by policymakers when setting future HIV and HCV policies.

5.2 Methods

Study Sample

cities. WIHS opened in 1994 in six US cities and added additional participants in 2001, 2011, and 2013; it now represents 10 urban and suburban locations. In both cohorts, participants attend visits every 6 months for laboratory testing and specimen storage, clinical examinations, and interviews. Information collected at these visits includes medication use; sociodemographic and behavioral characteristics; CD4 cell count and HIV RNA; and HCV antibody and RNA. Additionally, scores assessing liver fibrosis (FIB-4 (Sterling et al. 2006) and AST to platelet ratio index (APRI) (Lin et al. 2011)) are calculated for all cohort members.

Eligibility for this analysis required documentation of HIV infection at cohort entry or HIV seroconversion during follow-up (with inclusion beginning at the visit corresponding to HIV diagnosis). Only visits after the start of WIHS recruitment (October 1, 1994) were included. All participants were required to be ART-naïve and free of an AIDS diagnosis at their first eligible visit. Follow-up lasted until the first of: loss to follow-up (the date of a participant’s second missed study visit), death, 10 years after the first eligible visit, or September 30, 2015.

Definitions

The presence of antibody (Ab) against HCV was tested at baseline in both studies by enzyme immunoassay. Reactive specimens underwent HCV RNA testing by nucleic acid amplification; those with detectable HCV RNA were considered to have active, chronic HCV infection. Participants who lacked HCV RNA tests but had reactive HCV Ab were considered missing HCV.

The definition of ART was guided by the November 2014 US Department of Health and Human Services guidelines (Panel on Antiretroviral Guidelines for Adults and Adolescents 2014). Any three-drug regimen including at least one protease inhibitor, entry inhibitor, integrase
inhibitor, or non-nucleoside reverse transcriptase inhibitor was considered ART. Once a participant initiated ART, they were assumed to remain on it for the remainder of follow-up (in a previous analysis, this assumption correctly classified 94% of person-time in MACS and WIHS (Cole et al. 2003)). ART initiated after October 1, 2001 (the first visit following the approval of tenofovir, a component of many current ART regimens (Panel on Antiretroviral Guidelines for Adults and Adolescents 2018)) was considered “modern ART.” Each effect in this study was estimated after applying a hypothetical intervention to have all participants initiate modern ART at entry, as HIV treatment guidelines recommend that all PLWH receive ART (Panel on Antiretroviral Guidelines for Adults and Adolescents 2018).

Date and cause of death are obtained either directly through periodic searches of the National Death Index or through copies of death certificates obtained by study investigators.

Confounders

Confounders for the ART-on-mortality and HCV-on-mortality relationships were chosen using a causal diagram (Greenland et al. 1999) constructed prior to analysis. Baseline confounders were age, sex, race and ethnicity, CD4 cell count, HIV RNA, injection drug use (IDU), heavy alcohol use (defined as >7 drinks per week for women and >14 drinks per week for men (United States Department of Health and Human Services 2015)), smoking, obesity, and liver fibrosis. Time-varying confounders for the ART-on-mortality relationship included CD4 cell count, HIV RNA, IDU, heavy alcohol use, smoking, obesity, and liver fibrosis. Fibrosis was categorized into 3 levels: $\text{FIB-4} \geq 3.25$ or $\text{APRI} \geq 1$ was classified as severe fibrosis/cirrhosis, while $\text{FIB-4} < 1.45$ and $\text{APRI} < 0.7$ (together) was classified as no significant fibrosis. Other combinations were considered moderate fibrosis. The APRI cutoffs were guided by a meta-analysis (Lin et al. 2011) that suggested these perform better than commonly used cutoffs of 2
and 0.5, respectively. Details on variable measurement and operationalization are in the Chapter 3.

**Statistical analysis**

We compared the difference between the risk of 10-year, all-cause mortality among HIV-HCV co-infected persons and the risk under different DAA access policies, including treating i) all HIV-HCV co-infected persons, ii) HIV-HCV co-infected persons who meet certain preconditions (achieving HIV suppression, progressing to severe fibrosis or cirrhosis, or both), and iii) treating the same proportion of HIV-HCV co-infected persons as in (ii) chosen randomly without clinical restrictions. Additionally, we estimated the population intervention analogs of the above three effects (Hubbard & Van Der Laan 2008; Westreich 2014; Westreich 2017). Such population-level effects compare mortality among all PLWH to mortality in that population had HIV-HCV co-infected persons been treated according to each of the previously described criteria. All of these effects are defined in detail in Chapter 3.

The above effects cannot be directly estimated with existing data, as insufficient person-time has accrued in the DAA era to estimate long-term effects. Instead, we used data collected prior to the DAA era along with strong assumptions to estimate the effects in this study. Each effect was estimated by assuming that an HCV-uninfected person has the same risk of mortality as an HCV-infected person after successful treatment of their HCV infection, assuming they both have similar degrees of liver fibrosis and are of similar age, race and ethnicity, sex, smoking status, etc. Technically, those without HCV infection were assumed to be conditionally exchangeable (Hernán & Robins 2017) with successfully treated co-infected individuals given baseline fibrosis and confounders.
We estimated these values using the parametric g-computation algorithm formula (hereafter referred to as the g-formula) (Robins 1986). The g-formula simulates the impact of interventions in cohort data by conducting microsimulations within a single cohort (Westreich et al. 2012; Keil et al. 2014). We used regressions pooled over time to model the distributions of mortality and the time-varying confounders. Using these models, we simulated the time-varying confounder histories and survival curves under each HCV intervention. We assumed that DAAs had an average effectiveness of 96% (Naggie et al. 2015). Confidence limits were estimated using the nonparametric bootstrap percentile method with 1000 samples (Efron & Tibshirani 1986). Full details of the g-formula estimation procedure are in the Chapter 3.

We used multiple imputation to handle missing data with a multivariate normal imputation model (Allison 2001). The proportion missing for each variable ranged from 0% to 30% (for fibrosis, specifically). Missing time-varying covariates were carried forward from the most recent measurement. We incorporated multiple imputation into the bootstrap with the ‘Boot MI’ algorithm (Schomaker & Heumann 2018), with 20 imputed datasets per bootstrap sample.

5.3 Results

Study sample

A total of 3,056 PLWH were included in the study (1,777 women, 1,279 men). The prevalence of HCV was 18% (27% among women; 7% among men). Follow-up lasted a median of 7.5 years (interquartile range: 2, 10). Those with HIV-HCV co-infection were generally older; more likely to be female; had lower CD4 cell counts; were more likely to use injection drugs, drink heavily, or smoke; and had worse fibrosis at baseline (Table 5.1). ART was prescribed to 63% of participants, 32% of whom initiated a modern ART regimen. The observed and modelled distributions of key variables were similar (Figure B.1, Table B.1).
Estimated effects of DAA access criteria

The risk difference (RD) comparing 10-year all-cause mortality risk among co-infected persons who were not treated for HCV to what would be expected if all were treated with DAAs was -3.7% (95% confidence interval (CI): -9.1%, 0.6%) (Table 5.2).

If only those co-infected persons with undetectable HIV RNA received DAAs, mortality risk would be reduced by -1.9% (95% CI: -5.2%, 0.5%). Under this criterion, 90% (95% CI: 84%, 93%) of co-infected persons would be treated with DAAs. The effect of treating the same proportion of co-infected persons at baseline without regard for HIV viral suppression (that is, the effect of choosing 90% of co-infected persons at baseline to receive treatment) was an expected mortality risk reduction of -3.3% (95% CI: -8.2%, 0.5%) (Table 5.2 and Figure 5.1).

Only providing DAAs to co-infected persons with severe fibrosis/cirrhosis would be expected to reduce the risk of mortality by -1.6% (95% CI: -4.7%, 0.8%), and 60% (95% CI: 45%, 70%) of co-infected persons would receive treatment. If the same proportion of co-infected persons were randomly selected for treatment at baseline, mortality risk would be reduced by -2.2% (95%: -5.6%, 0.3%) (Table 5.2 and Figure 5.1).

Finally, by only treating co-infected persons with severe fibrosis/cirrhosis and undetectable HIV viral load, the risk of mortality would be expected to decline by -1.1% (95% CI: -2.8%, 0.6%), and 51% (95% CI: 38%, 59%) of co-infected persons would be treated. By treating the same proportion of co-infected persons at baseline without these restrictions, mortality would be expected to decline by -1.9% (95% CI: -4.7%, 0.3%). (Table 5.2 and Figure 5.1). The timing of DAA treatments under each set of treatment criteria are presented in Figure B.2.
Estimated population intervention effects of DAA access criteria

The RD comparing the 10-year all-cause mortality risk in the entire population of PLWH to the risk in the entire population that would be expected if all co-infected persons received DAAs was -0.7% (95% CI: -1.8%, 0.1%) (Table 5.3).

If only co-infected persons with undetectable HIV RNA received DAAs, the mortality risk among all PLWH would be expected to be reduced by -0.4% (95% CI: -1.0%, 0.1%). Under this criterion, 90% (the same proportion reported in the previous section) of co-infected persons received DAAs. The effect of treating the same proportion of co-infected persons randomly at baseline was an expected -0.6% (95% CI: -1.6%, 0.1%) decrease in mortality among all PLWH (Table 5.3).

Treating only co-infected persons with severe fibrosis/cirrhosis with DAAs would lead to an expected -0.3% (95% CI: -0.8%, 0.2%) reduction in mortality among all PLWH, and 60% of co-infected persons would be treated. Treating the same proportion of co-infected persons at baseline without fibrosis restrictions would reduce mortality among all PLWH by -0.4% (95% CI: -1.1%, 0.1%) (Table 5.3).

Finally, the effect of treating only co-infected persons with severe fibrosis/cirrhosis and undetectable HIV RNA was an estimated -0.2% (95% CI: -0.5%, 0.1%) reduction in mortality risk among all PLWH, and 51% of co-infected persons would be treated. If the same proportion of co-infected persons were treated without these restrictions, the mortality risk among all PLWH would decrease by -0.4% (95% CI: -0.9%, 0.1%) (Table 5.3).
5.4 Discussion

We found that use of common eligibility criteria for treating people with HIV/HCV co-infection with DAAs consistently yield a smaller decline in 10-year, all-cause mortality than treating a similar proportion of persons at random upon diagnosis of HCV infection, without any eligibility criteria. Treating people upon diagnosis would require providing treatments earlier than under the criteria we investigated and could therefore entail higher upfront costs (Figure B.2). However, the additional mortality benefit of earlier treatment is substantial. To state this another way: consider the most restrictive policy we investigated, providing treatment to those who achieve HIV suppression and progress to severe fibrosis or cirrhosis, which led to treatment of 51% of co-infected persons on average. We could achieve the same mortality benefit by treating only 28% of co-infected persons at diagnosis chosen randomly, nearly cutting in half the proportion treated.

The worse mortality outcomes conferred by restrictive eligibility criteria are not surprising: these criteria were developed based on financial considerations, in contrast to evidence-based HCV treatment guidelines that recommend treating nearly all persons with HCV (American Association for the Study of Liver Diseases & Infectious Diseases Society of America 2017). By only treating co-infected individuals who have severe fibrosis/cirrhosis, we may be intervening too late in the HCV disease process. At that stage of liver damage, the increased risk of adverse outcomes due to liver fibrosis and cirrhosis may attenuate the benefit of DAA treatment, thus reducing the effect of such an intervention.

These findings suggest that setting treatment access policies with only short-term cost-containment in mind can cause patients unnecessary harm. Lives may have been saved if careful consideration had been used to set DAA treatment policies. These restrictive policies were likely
well-intentioned, as deferring treatment may have been in anticipation of market-driven DAA price reductions which would allow wider access in the future. However, such considerations are somewhat obviated by the large mortality reduction we estimated for treating patients at baseline without consideration of clinical factors. Survival could be further improved by using methods that have been developed to optimize treatment allocation (Athey 2017). Such methods, along with guidance from clinicians and care-providers, should be used when considering future policies to prevent unnecessary mortality.

Our study is subject to several limitations. First, because our study mostly predates the DAA era, all of our effect estimates rely on the assumption that PLWH without HCV had the same mortality experience that similar people with HIV-HCV co-infection would have had with successful DAA treatment. We controlled for several risk factors for fibrosis, such as alcohol use, injection drug use, and obesity, but other risk factors probably remain. The presence of such factors would mean that our effects underestimate the true effects. On the other hand, we also assumed that all effects of HCV on mortality besides fibrosis are eliminated by successful DAA treatment and that DAAs have no side effects impacting mortality. Second, we did not model incident HCV infections or reinfection (and subsequent retreatment) after successful treatment. Third, all of our results rely on the correct model specifications. While our models were able to re-create the observed distributions of several key variables with fidelity, this does not guarantee proper model specification. Lastly, our study sample was included MSM and women in roughly even proportions, with data dating back to 1994. Our results therefore may not generalize to the current population of PLWH in the United States (Lesko et al. 2016). One particular caution is that the applicability of the population intervention effects is contingent on the prevalence of
HCV in the population of interest; care must be taken to adjust these values for potential differences in the HCV prevalence observed in real-world populations.

Even with these limitations, our results provide valuable evidence that can aid policymakers in setting DAA policies for people living with HIV/HCV, as well as in prioritizing interventions to reduce mortality among PLWH in general. Because it takes years for HCV to impact mortality, there has been insufficient time in the DAA-era to estimate the true impact of HCV treatment criteria. Until more person-time accumulates in this era, estimates that rely on strong assumptions, like those we present, are needed to properly evaluate treatment policies.

The population intervention effects we estimated consider not only the effect of successful HCV treatment, but also the proportion of PLWH who would be intervened upon. As such, these estimates can be compared with similar estimates for other conditions in this population and can thus be used to properly compare interventions for different HIV comorbidities. Similar effects should be estimated for other conditions impacting PLWH to optimally allocate limited public health resources.

DAA access in the US is rapidly evolving. Though many DAA restrictions requiring patients to meet clinical pre-conditions are being updated (Kapadia et al. 2017), as of October 2017 the majority of Medicaid programs still limit treatment to those with at least moderate liver fibrosis (National Viral Hepatitis Roundtable & Harvard Law School Center for Health Law and Policy Innovation 2017). Policymakers in those states may wish to consider our results when setting future DAA access policies. As we proceed further into the DAA era, studies should directly evaluate the impact of HCV treatment policies among people living with HIV-HCV co-infection to optimize the delivery of DAAs in this population.
Table 5.1: Baseline characteristics of eligible study participants stratified by source, Women’s Interagency HIV Study and Multicenter AIDS Cohort Study, 1994-2015

<table>
<thead>
<tr>
<th></th>
<th>Women's Interagency HIV Study</th>
<th>Multicenter AIDS Cohort Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HCV+ n=460</td>
<td>HCV- n=1231</td>
</tr>
<tr>
<td>Age (Median, IQR)</td>
<td>40 (35; 44)</td>
<td>34 (29; 40)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (Non-Hispanic)</td>
<td>74 (16.1%)</td>
<td>178 (14.5%)</td>
</tr>
<tr>
<td>African American</td>
<td>281 (61.1%)</td>
<td>710 (57.7%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>99 (21.5%)</td>
<td>293 (23.8%)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (1.3%)</td>
<td>49 (4.0%)</td>
</tr>
<tr>
<td>Missing</td>
<td>0 (1.3%)</td>
<td>1 (0.0%)</td>
</tr>
<tr>
<td>CD4 count (median, IQR)</td>
<td>373 (213; 575)</td>
<td>410 (262; 609)</td>
</tr>
<tr>
<td>Missing</td>
<td>13 (2.3%)</td>
<td>36 (2.7%)</td>
</tr>
<tr>
<td>Detectible Viral Load</td>
<td>428 (95.3%)</td>
<td>1137 (94.3%)</td>
</tr>
<tr>
<td>Missing</td>
<td>11 (2.3%)</td>
<td>25 (2.1%)</td>
</tr>
<tr>
<td>IDU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>61 (13.3%)</td>
<td>1096 (89.1%)</td>
</tr>
<tr>
<td>Former</td>
<td>293 (63.7%)</td>
<td>106 (8.6%)</td>
</tr>
<tr>
<td>Current</td>
<td>106 (23.0%)</td>
<td>28 (2.3%)</td>
</tr>
<tr>
<td>Missing</td>
<td>0 (0.0%)</td>
<td>1 (0.0%)</td>
</tr>
<tr>
<td>Heavy Alcohol Use</td>
<td>93 (20.8%)</td>
<td>143 (11.9%)</td>
</tr>
<tr>
<td>Missing</td>
<td>12 (2.6%)</td>
<td>28 (2.3%)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Never</td>
<td>47</td>
<td>10.3%</td>
</tr>
<tr>
<td>Former</td>
<td>58</td>
<td>12.7%</td>
</tr>
<tr>
<td>Current</td>
<td>353</td>
<td>77.1%</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Obese</td>
<td>97</td>
<td>22.6%</td>
</tr>
<tr>
<td>Missing</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>HBsAg Positive</td>
<td>12</td>
<td>2.6%</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Fibrosis Status&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No significant fibrosis</td>
<td>211</td>
<td>51.2%</td>
</tr>
<tr>
<td>Moderate fibrosis</td>
<td>112</td>
<td>27.2%</td>
</tr>
<tr>
<td>Severe fibrosis/Cirrhosis</td>
<td>89</td>
<td>21.6%</td>
</tr>
<tr>
<td>Missing</td>
<td>48</td>
<td>64</td>
</tr>
<tr>
<td>ART</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiated pre-October 2001</td>
<td>212</td>
<td>46.1%</td>
</tr>
<tr>
<td>Initiated post-October 2001</td>
<td>33</td>
<td>7.2%</td>
</tr>
</tbody>
</table>

Abbreviations: HCV, hepatitis C virus; IQR, interquartile range; IDU, injection drug use; HBsAg, hepatitis B virus surface antigen; ART, antiretroviral therapy

102 Participants had missing HCV status

<sup>a</sup>Lower limit of detection varied over time, and ranged from 500 copies/ml to 20 copies/ml

<sup>b</sup>Defined as more than 7 drinks per week for women and more than 14 drinks per week for men (United States Department of Health and Human Services 2015)

<sup>c</sup>Cirrhosis defined as FIB-4 ≥ 3.25 or AST to Platelet Ratio Index APRI ≥ 1; no significant fibrosis defined as FIB-4 < 1.45 and APRI < 0.7; other combinations were classified as non-cirrhotic fibrosis
Table 5.2: Effects of DAA treatment criteria on 10-year all-cause among people living with HIV and HCV, Women’s Interagency HIV Study and Multicenter AIDS Cohort Study, 1994 – 2015

<table>
<thead>
<tr>
<th>Policy</th>
<th>% Treated&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Risk difference&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Treat same % at random&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Intervention</td>
<td>0</td>
<td>Ref</td>
<td>Ref</td>
<td>-</td>
</tr>
<tr>
<td>All HCV Treated</td>
<td>100</td>
<td>-3.7 (-9.1, 0.6)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Only HIV suppressed treated&lt;sup&gt;c&lt;/sup&gt;</td>
<td>89.6 (84.3, 93.0)</td>
<td>-1.9 (-5.2, 0.5)</td>
<td>-3.3 (-8.1, 0.5)</td>
<td>-1.4 (-3.6, 0.3)</td>
</tr>
<tr>
<td>Only severe fibrosis treated&lt;sup&gt;c&lt;/sup&gt;</td>
<td>59.9 (44.3, 69.4)</td>
<td>-1.6 (-4.7, 0.8)</td>
<td>-2.2 (-5.6, 0.3)</td>
<td>-0.6 (-1.4, 0.0)</td>
</tr>
<tr>
<td>Only HIV suppressed and cirrhosis treated</td>
<td>51.0 (37.9, 59.1)</td>
<td>-1.1 (-2.8, 0.6)</td>
<td>-1.9 (-4.7, 0.3)</td>
<td>-0.8 (-2.4, 0.1)</td>
</tr>
</tbody>
</table>

Abbreviations: DAA, direct-acting antiviral; PLWH, people living with HIV; ART, antiretroviral therapy; HCV, hepatitis C virus

<sup>a</sup>Percent of all people living with HIV-HCV co-infection treated with DAAs.

<sup>b</sup>Expressed as percent, comparing stated scenario to a reference group of no one treated for HCV.

<sup>c</sup>Includes those who meet the criteria at baseline as well as those who progress to meet it during follow-up.
Table 5.3: Population intervention effects of DAA treatment criteria on 10-year all-cause mortality among people living with HIV, Women’s Interagency HIV Study and Multicenter AIDS Cohort Study, 1994 – 2015

<table>
<thead>
<tr>
<th>Policy</th>
<th>% Treated&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Risk Difference&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Treat Same % at Random&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Intervention</td>
<td>0</td>
<td>Ref</td>
<td>Ref</td>
<td>-</td>
</tr>
<tr>
<td>All HCV Treated</td>
<td>100</td>
<td>-0.7 (-1.8; 0.1)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Only HIV suppressed treated&lt;sup&gt;c&lt;/sup&gt;</td>
<td>89.6 (84.3, 93.0)</td>
<td>-0.4 (-1.0, 0.1)</td>
<td>-0.6 (-1.6, 0.1)</td>
<td>-0.3 (-0.7, 0.1)</td>
</tr>
<tr>
<td>Only severe fibrosis treated&lt;sup&gt;c&lt;/sup&gt;</td>
<td>59.9 (44.3, 69.4)</td>
<td>-0.3 (-0.9, 0.2)</td>
<td>-0.4 (-1.1, 0.1)</td>
<td>-0.1 (-0.3, 0.0)</td>
</tr>
<tr>
<td>Only HIV suppressed and cirrhosis treated</td>
<td>51.0 (37.9, 59.1)</td>
<td>-0.2 (-0.5, 0.1)</td>
<td>-0.4 (-0.9, 0.1)</td>
<td>-0.2 (-0.4, 0.0)</td>
</tr>
</tbody>
</table>

Abbreviations: DAA, direct-acting antiviral; PLWH, people living with HIV; ART, antiretroviral therapy; HCV, hepatitis C virus

<sup>a</sup>Percent of all people living with HIV-HCV co-infection treated with DAAs.

<sup>b</sup>Expressed as percent, comparing stated scenario to a reference group of no one treated for HCV.

<sup>c</sup>Includes those who meet the criteria at baseline as well as those who progress to meet it during follow-up.
Figure 5.1: Effects of DAA treatment criteria on 10-year all-cause mortality among people living with HIV and HCV, the Women’s Interagency HIV Study and Multicenter AIDS Cohort Study, 1994-2015

Triangle is the effect of treating those who achieve HIV viral suppression. Diamond is the effect of treating those progress to severe fibrosis/cirrhosis. Square is the effect of treating those who both achieve HIV viral suppression and progress to severe fibrosis/cirrhosis. Circles are the effects of treating the same proportion without regard for clinical factors. Effects falling in the green region are superior to treating without regard for clinical factors, and effects falling in the red region are inferior to treating without regard for clinical factors.
CHAPTER 6: DISCUSSION

6.1 Overview

As PLWH begin to achieve life expectancies rivalling those of HIV-uninfected individuals (Samji et al. 2013), non-AIDS related comorbidities are taking center stage in the provision of care for this population. In this work, we explored the role of one such comorbidity, HCV infection, and its treatment on 10-year all-cause mortality among PLWH. Additionally, we formally defined effect measures that may be of interest to patients, clinicians, and policy-makers; provide conditions under which they can be estimated from observational data, even in the absence of actual treatment data; and provide expressions and algorithms for their estimation.

We estimated several effect measures that may inform treatment and policy decisions, including the effect of HCV infection on 10-year all-cause mortality among all PLWH and among PLWH+HCV, the effect of DAA treatment among PLWH+HCV, and the effects of DAA treatment policies in which subgroups of PLWH+HCV are treated with DAAs, either chosen at random or based on clinical criteria used by certain Medicaid programs to determine treatment eligibility. All of the effects were estimated after first applying a hypothetical intervention in which all study participants initiate ART at baseline, making the results particular relevant in the era of modern ART guidelines suggesting ART initiation for all PLWH, regardless of CD4 cell count.

The results from Aim 1 may be of particular interest to patients and clinicians. The effect of HCV infection on all-cause mortality gives an estimate of the increased risk PLWH may face if they have HCV coinfection, and the effect of DAA treatment provides an estimate of how
mortality would be impacted among PLWH+HCV if their HCV coinfection is treated. Given the robustness of the effect of HCV infection in a sensitivity analysis in which only those with no or mild fibrosis were included, this effect may also be reasonably used to inform clinicians as to the reduction in all-cause mortality that may be achieved if HCV is prevented in PLWH.

The estimates in Aim 2 may be used to inform population-level interventions and policies for PLWH. By comparing interventions based on Medicaid reimbursement criteria to interventions in which the same proportion of PLWH+HCV are treated at random, we provide information that can be used to determine whether or not these Medicaid criteria are efficient and provide an estimate of how much additional benefit could be had by changing or loosening these restrictions. The estimated population intervention effects incorporate information on the prevalence of HCV coinfection and the proportion of PLWH+HCV who would be treated, so these estimates may be compared with similar estimates for other comorbidities, thus aiding in determining which interventions on which conditions would lead to the greatest benefit in this population.

6.2 Study findings

In Chapter 3, we described two methods for estimating causal effects – the parametric generalized computation algorithm formula (the g-formula) (Robins 1986) and the estimation of marginal structural models using inverse probability of treatment weighted estimating equations (Robins et al. 2000). We then demonstrated how these methods can be used to estimate the average effect of a policy among the exposed (APEX), the generalized effect of a policy among the exposed (GPEX), and the dynamic effect of a policy among the exposed (DPEX), as well as corresponding population intervention effects. Under certain conditions, we showed that the APEX is equivalent to the average effect of exposure in the exposed (ATT), thus allowing for the
estimation of the APEX without data on treatment. Using this methodological framework, it is possible to predict the long-term impact of hypothetical or recently developed treatments using cohort data that precedes the introduction of these new therapies. Evidence can then be provided to guide treatment decisions and policies far sooner than would be possible if investigators had to wait for adequate person-time to accrue after treatment introduction. We further showed how the GPEX, DPEX, and population intervention effects can be estimated by scaling the APEX and provided an algorithm for estimating each of these parameters.

In Chapter 4, we estimated the effects of HCV infection and treatment among PLWH. We found that HCV leads to a substantial increase in the 10-year risk of all-cause mortality in PLWH, and that DAA treatment is effective at reducing the 10-year risk of all-cause mortality among PLWH+HCV. The results were robust to sensitivity analyses for the functional forms of the models used in the analysis, the set of confounders accounted for in the analysis, and the degree of liver fibrosis among study participants.

Though our estimated effect of HCV infection among PLWH was similar to the pooled effect from a 2009 meta-analysis (Chen et al. 2009), our analysis permits a different interpretation. First, the meta-analysis pooled results from studies of varying duration, thus precluding a clear interpretation of the results. Second, studies included in the meta-analysis accounted for ART either through stratification or restriction. In contrast, we applied a hypothetical intervention to have all participants initiate ART at study entry. The meta-analysis results are thus interpreted as conditional on observed ART use, whereas ours are interpreted as occurring after providing ART to the entire population, regardless of observed use, and thus are more applicable to the current era in which all PLWH are recommended to be on ART, regardless of CD4 count.
Our estimated effect of DAA treatment was substantially smaller in magnitude than the results from past studies of HCV treatment among PLWH. Nearly all previous studies were conducted prior to the introduction of DAAs, and instead compared PLWH+HCV who achieved HCV SVR with PEG-IFN to those who did not achieve SVR or did not receive treatment. As PEG-IFN is much more poorly tolerated than DAAs among PLWH, those who successfully achieved SVR using PEG-IFN are likely to differ on risk factors for mortality compared with those who did not achieve SVR or who did not receive treatment, so unmeasured and uncontrolled confounding may be a serious issue in prior studies.

To date, only two studies have estimated the effect of DAAs on mortality, and both found DAAs to have a much larger effect on mortality than our results suggest. Both of these studies were of short duration (under 18 months), and both excluded PLWH. As the risk of mortality differs substantially between PLWH and HIV-uninfected people, the results of those studies cannot be directly compared to our results. Additionally, those studies were likely too short in duration to capture the full effect of HCV, a slow, progressive disease.

In Chapter 5, we estimated the effects of interventions to provide DAA treatment to subsets of the population of PLWH+HCV chosen according to criteria used by some state Medicaid programs to determine treatment eligibility. We also estimated the effect of randomly treating proportions of PLWH+HCV at baseline, with the proportions selected to equal those who would receive therapy under the Medicaid criteria. In addition to standard effect estimates, we estimated the population intervention effects of these interventions, which account for the prevalence of HCV among PLWH and can thus be compared to similar estimates for interventions on other HIV comorbidities. To our knowledge, this was the first study to estimate these effects. We found that interventions in which PLWH+HCV are able to access treatment
only if they meet certain clinical criteria (such as progression to severe fibrosis or cirrhosis and/or achieving HIV suppression), were substantially less effective at reducing mortality than treating an identical proportion of PLWH+HCV chosen at random. Our results suggest that these Medicaid criteria are inefficient, and that mortality could be prevented among PLWH without increasing the total number of people treated with DAAs, though the number of people treated immediately would increase (as would upfront costs). However, our estimates show that treating 27% of PLWH+HCV at baseline would lead to the same 10-year all-cause mortality risk as the most restrictive policy we investigated (i.e. treating only those co-infected individuals who achieve HIV suppression and progress to severe fibrosis or cirrhosis). This is almost half the proportion treated under the restrictive policy. As such, it may be possible to make improvements to DAA treatment policies without increasing present costs. These results also show that expanding access so that all PLWH+HCV receive DAAs would substantially reduce mortality. Our findings support the HCV treatment guidelines recommended by the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America, which suggest DAA treatment for nearly all people living with HCV regardless of clinical factors (American Association for the Study of Liver Diseases & Infectious Diseases Society of America 2017). As such, policy-makers should consider these results when setting future HCV treatment policies for PLWH+HCV.

More generally, the results from Chapter 5 highlight the fact that policies based on cost-containment are often suboptimal, and that lives can be saved by considering evidence when choosing treatment allocation strategies. Though such policies are often well-intentioned, particularly in anticipation of future price decreases that would allow broader access at a later date, when lives are at stake it is necessary to take greater care when setting policy. The fact that
we found that simply allocating treatment at random was more effective than allocating based on commonly used clinical criteria shows how poorly such policies perform in practice.

6.3 Strengths and limitations

This work resulted in a valuable contribution to the literature for both HIV and HCV. Using data from 1994 to 2015, this was the longest study of HIV/HCV coinfection to date. The study period allowed for the study of long-term outcomes, such as 10-year all-cause mortality, which is important given the increased lifespan of PLWH and the slow, progressive nature of HCV infection. This work was also the first study to look at mortality due to HCV among PLWH under modern ART guidelines. Because current HIV treatment guidelines advise all people with HIV to receive ART regardless of their CD4 cell count, the effects estimated here represent realistic treatment scenarios and are more immediately applicable to the current population of PLWH.

The dataset and analytic approach for this work also add to its unique strength. Because the data include information on liver function, it was possible to estimate the effects of both HCV infection and its treatment, making the results pertinent for informing both prevention and treatment strategies. The analytic methods we used produced estimates of the effects of well-defined interventions, and thus allowed us to separately explore the role HCV infection and treatment have on mortality among PLWH under modern HIV treatment guidelines. We additionally were able to estimate the reduction in mortality that one would expect under different DAA access policies in this population. Despite the population under study having not actually fully existed in the modern ART era nor the era of DAA treatment, the carefully considered assumptions applied in this work allow for the estimation of causal effects under
hypothetical interventions that ensure ART initiation at baseline for all study participants and that effectively treat HCV.

In addition to “usual” causal effects, this work estimated policy-relevant effects which have yet to be explored for this topic. These estimates provide information necessary to understand the impact of HCV interventions and treatment policies applied to the population of PLWH as a whole. By estimating both traditional treatment effects and population intervention effects, these results aid patients, care providers, and policy-makers in properly prioritizing HCV interventions against interventions for other HIV comorbidities and help to determine the best way to implement such interventions.

To evaluate the impact of chronic HCV infection and its treatment in the population of PLWH, this work used a longitudinal cohort design using existing data from two long-running, ongoing HIV cohort studies. Ideally, randomized controlled trials, including pragmatic trials (Roland & Torgerson 1998), are used to evaluate the causal effect of a treatment or intervention. A randomized controlled trial of HCV treatment in this population to explore its effect on all-cause mortality would be prohibitively expensive, time-consuming, and ethically problematic because of the long period between HCV infection and its clinical manifestations, as well as because of the known efficacy of HCV therapy in this population.

Thus, the observational cohort study design using existing data is well-suited for this topic for several reasons. Because the cohort study is not designed specifically to test an intervention in the study population, broad inclusion and exclusion criteria can be used allowing important subgroups to be represented. This may allow for the results to be better generalized or transported to relevant target populations (Lesko et al. 2017). Additionally, the cohort study collects rich data on many characteristics of the study subjects, allowing the same data set to be
used to evaluate multiple interventions. In this case, the effects of both HCV infection and treatment were evaluated. Further, because the study data were already available, the timing from analysis to results was not delayed due to the collection of new data. Lastly, as this study did involve collecting new data from cohort members or applying an intervention, the cost was minimal and there was no need for clinical equipoise. Under the causal identification assumptions, the results of this cohort study should mimic those of a well-conducted randomized controlled trial (Hernán et al. 2008).

Unfortunately, there are “costs” that are incurred by not conducting a randomized controlled trial. First among them is the need to address the causal identification conditions in the analysis phase of the study, rather than the design phase. In order for the methods used in this work to produce unbiased estimates of causal effects, then consistency, conditional exchangeability, positivity, elimination of measurement error, and proper model specification must all hold. As these conditions (except positivity) cannot generally be assessed, a reasonable justification for assuming each of them to hold is necessary.

In order for consistency to hold, the observed outcome for individuals must be equal to the outcome that they would have if an intervention set them to have their observed exposure. Consistency is typically violated due to interference or relevant treatment variation. In the case of HCV and HIV, interference is unlikely, as the exposure or treatment status of others should not impact the outcome of a given individual. In order to validly assume treatment variation irrelevance holds, it should be sufficient to assume that the effect of prior HCV is fully mediated by the baseline characteristics of study participants, and that successful HCV treatment or spontaneous clearance have no effect on mortality besides its effect on HCV. In other words, for those without baseline chronic HCV, given a participant’s baseline variables, it was assumed that
it does not matter whether the participant never had HCV, spontaneously cleared HCV, or had successful HCV treatment (in this cohort, the two latter situations are likely to be relatively rare, as people with HIV and HCV have poor clearance and successful treatment rates with older HCV treatments). For those with baseline chronic HCV, it was assumed that the duration of HCV prior to study entry does not impact mortality besides its impact on baseline variables. While it is reasonable to assume that the primary pathway through which HCV impacts mortality is through progressive liver fibrosis and that successful DAA treatment halts HCV-related fibrosis progression, there may be other effects of HCV that do not get eliminated by treatment, thus violating the assumption of consistency.

In this work, the greatest concern for exchangeability is the fact that people with HCV may systematically differ from those without HCV in unknown ways. For instance, after controlling for baseline demographic, behavioral, and health-related variables, those with advanced liver fibrosis who do not drink alcohol and do not have HCV likely have another underlying health condition causing their fibrosis, such as non-alcoholic fatty liver disease. Though controlling for variables such as heavy alcohol use and obesity status may mitigate these issues, residual confounding is likely. Such confounding would be expected to lead to bias towards the null of the estimates, as the group without HCV will have higher mortality. An example of how such confounding may operate is displayed in the simplified causal diagram in Figure 6.1. Conditional exchangeability for ART is perhaps less of a concern, as the primary factors used for ART treatment decisions prior to the current guidelines are accounted for in this study.

Positivity may pose a problem in this work as many confounders will be included in the model, leading to potentially sparse data. The models used for g-computation extrapolate over
the variable combinations that exhibit non-positivity, but such extrapolation must be carefully considered as it may not be valid to do so.

Measurement error may enter the work in a few ways. First, information was only collected at six-month intervals, and thus measurement error could be introduced due to course measurement with respect to time. Such measurement error would lead to residual confounding and would be a threat to conditional exchangeability. Also, all of the laboratory measurements used in the work may be subject to both random error and systematic error. The data collected through questionnaires may be subject to recall bias and bias due to the sensitive nature of some of the questions, which may lead to underreporting of some variables, such as injection drug use. HCV status may also be subject to misclassification. Because only baseline HCV is included as an exposure, it is possible that some subjects clear HCV during the study, either spontaneously or through treatment. This is not an issue for this work, as the effect of baseline HCV can be interpreted as including observed clearance and treatment patterns. Some subjects may also acquire HCV during the study period. Such misclassification would bias the estimates toward the null. Finally, liver fibrosis was measured indirectly, and such measurements do not have perfect sensitivity or specificity for liver fibrosis, assuming liver biopsy as a reference or “gold” standard.

Finally, model specification may be an issue, as the many variables that will be included in the models may impact the outcome in complex and unpredictable ways. By using flexible modelling techniques, such as the use of splines for continuous variables and including product terms, the models are hopefully able to approximate the true relationships. By checking the natural course against the observed data and using methods that require orthogonal models as a
sensitivity analysis, some confidence can be had that the models were correctly specified, though whether or not they were is ultimately unverifiable.

Besides these identification conditions, there are several other threats to the validity of the results in this work. In order for multiple imputation to produce valid results in the presence of missing data, missingness must be at random, and the functional form of the imputation models must be properly specified. In order for the effects of HCV treatment to be identified from the observed data, the assumptions that (given measured baseline characteristics) HCV primarily impacts mortality through liver fibrosis progression and HCV treatment primarily impacts mortality by halting this progression must hold. Based on the current understanding of HCV and its treatment, this assumption is not unrealistic. Finally, the population used for this work is likely not representative of any populations of PLWH in the United States which are of direct clinical interest, and as such these results are not trivially transportable to any population that would realistically be the target of HCV interventions (Westreich et al. 2017).

Even with these limitations and untestable assumptions, this work provides valuable information that adds to the literature and will ultimately contribute to the evidence base for updating HIV and HCV care policies and guidelines. The sensitivity analyses that were conducted systematically evaluated many of the threats to validity that this work may face, thus providing additional confidence in the results and a deeper understanding of possible sources of bias. The innovative study design, analytical methods, and effects to be estimated make this work a powerful and unique contribution to the HIV and HCV literature.

6.4 Future directions

There are several directions that future research on HCV infection and treatment among PLWH could take. First, as person-time accumulates in the DAA era, studies that directly
estimate the effect of DAA treatment on mortality among PLWH+HCV should be conducted. If properly conducted, such studies will not require the same strong assumptions required for the results of this work to be valid, and thus may provide stronger evidence of the effect of HCV treatment on all-cause mortality in this population.

Second, the results of this study and future studies should be transported to other key populations of PLWH, such as the population of PLWH alive in the US, or the population of newly diagnosed PLWH. The population studied in this work was historical and was created by combining the populations of PLWH from two cohort studies. By transporting the results to more relevant populations, the results will be even more informative for guiding clinical practice and policy.

Third, cost-effectiveness measures should be estimated for the interventions in Chapter 5. While the estimates in Chapter 5 provide valuable evidence for policy-makers, they do not account for the cost of the interventions, nor do they account for the quality of life among PLWH under each intervention. Additionally, as treatment is delayed under certain DAA treatment policies, it will be important to account for the time value of money, so that costs incurred after baseline are discounted. Incorporating cost-effectiveness into these estimates will aid policy-making in three ways. First, it will provide estimates that are relevant in a resource-constrained environment and will allow for policies to be adopted that optimally balance the benefit of an intervention with its cost. Second, it will aid in determining the timing of expenditures under each treatment policy, thus helping insurers and public health agencies in forecasting future expenditures. Finally, it will allow policy-makers to understand what mortality reduction they could achieve if DAA costs were reduced or budgets were increased, thus providing evidence that can be used in negotiations with pharmaceutical manufacturers and funding organizations.
Fourth, further exploration of optimal DAA treatment policies should be undertaken. While we were able to show that treating people at random performed better than treating based on commonly used clinical criteria, gains can almost certainly be had by targeting treatment to those most likely to benefit. Advances in statistical and epidemiological methodology now allow us to estimate optimal treatment allocation policies (Athey 2017). These methods should be implemented in the context of DAA treatment to maximize the benefit in the population of PLWH+HCV.

Lastly, population intervention effects should be estimated for other conditions that commonly affect PLWH, such as type 2 diabetes, cardiovascular disease, chronic kidney disease, non-viral liver diseases, and non-AIDS-related cancer. In isolation, the effects estimated in Chapter 5 are only useful for comparison with other DAA interventions. With similar estimates for other conditions, interventions can be compared head-to-head, and conditions and treatments can be prioritized against one another in specific populations. Such comparisons will take into account the effect of the condition on mortality, the effectiveness of the treatments, the prevalence of the conditions, and the proportion of people who would receive treatment, and will thus allow for the proper allocation of time and resources to best benefit PLWH.
Figure 6.1: Simplified causal diagram demonstrating potential lack of conditional exchangeability when estimating HCV treatment effects
APPENDIX A: FURTHER DETAILS OF ANALYSIS IN CHAPTER 4

A.1 Notation

The following notation will be used throughout this section. Individuals will be indexed by \( i \in \{1, 2, 3, \ldots, n\} \), and time (in visits) will be indexed by \( t \in \{0, 1, 2, 3, \ldots, \tau\} \). Uppercase letters will denote random variables, and lowercase letters and numbers will represent their potential realizations. \( Y_{k+1,i} \) is 1 if subject \( i \) died between times \( k \) and \( k + 1 \). \( A_{1,k} = 1 \) if subject \( i \) initiated ART between time \( k - 1 \) and \( k \) with \( k \) prior to October 1, 2001; with \( k \) on or after October 1, 2001 \( A_{1,k} = 2 \). \( H_i = 1 \) if subject \( i \) had chronic HCV at baseline, \( C_{k,i} \) is 1 if subject \( i \) was lost to follow-up at time \( k \), and \( W_{k,i} \) is a vector of covariate values at time \( k \) for subject \( i \). Because the MACS and WIHS visits occur at regular semi-annual intervals, the time index represents visits since baseline, with 10-years being represented by the 20\(^{th} \) visit. Mortality and loss to follow-up were thus estimated over 6-month intervals rather than continuously. An overbar (e.g. \( \tilde{A}_{t,i} \)) denotes history, for example \( \tilde{A}_{t,i} = \{A_{0,i}, A_{1,i}, A_{2,i}, \ldots, A_{t,i}\} \). Superscripts on random variables represent potential outcomes, e.g. \( Y_{i}^{a} \) indicates the level of \( Y \) that subject \( i \) would have experienced had, possibly counter to fact, they received treatment level \( A = a \). Finally, \( f_X(x) \) denotes a probability mass function or probability density function for the random variable \( X \) evaluated at \( x \). From here forward, observations will be assumed independent and identically distributed, and subscripts distinguishing individuals will be dropped. Hereafter, the use of the parametric generalized computation algorithm formula for the estimation of causal effects will be referred to as g-computation, and the formula itself will be referred to as the g-formula.

A.2 Natural course and g-formula equations used in chapter 4

The natural course distribution for this study can be represented as:
Under the conditions of causal consistency (treatment variation irrelevance) (VanderWeele 2009; Cole & Frangakis 2009), conditional exchangeability (Hernán & Robins 2017), positivity (Westreich & Cole 2010), no measurement error (Edwards et al. 2015), and properly specified models, the causal effect of setting HCV and ART to particular values and preventing loss to follow-up can be estimated by replacing the last three quantities with degenerate distributions taking value 1 at the exposure and loss to follow-up regimes of interest. The corresponding g-formula is thus:

\[
E(Y_{t+1} = 1|A_k = \tilde{a}_k, H = h, \overline{W}_k = \overline{w}_k, \overline{Y}_k = \overline{c}_k = 0) \times \prod_k \left[ f(W_m|A_m = \tilde{a}_m, H = h, \overline{W}_{m-1} = \overline{w}_{m-1}, \overline{Y}_{m-1} = \overline{c}_{m-1} = 0) \times \right. \\
\left. \Pr(Y_m = 0|A_{m-1} = \tilde{a}_{m-1}, H = h, \overline{W}_{m-1} = \overline{w}_{m-1}, \overline{Y}_{m-1} = \overline{c}_{m-1} = 0) \times \Pr(C_m = 0|A_{m-1} = \tilde{a}_{m-1}, H = h, \overline{W}_{m-1} = \overline{w}_{m-1}, \overline{Y}_{m-1} = \overline{c}_{m-1} = 0) \times \right. \\
\left. \Pr(\overline{A}_m = \overline{a}_m|\overline{A}_{1,m-1} = \overline{a}_{1,m-1}, H = h, \overline{W}_{m-1} = \overline{w}_{m-1}, \overline{Y}_{m-1} = \overline{c}_{m-1} = 0) \times \Pr(H = h|W_0 = w_0) \right] \\
\times \prod_{k=0}^{t} \sum_{\overline{w}_k \in \mathcal{W}_k} \sum_{\overline{a}_k \in \mathcal{A}_k} \sum_{h \in \mathcal{H}} \Pr(Y_{t+1} = 1|A_k = \overline{a}_k, H = h, \overline{W}_k = \overline{w}_k, \overline{Y}_k = \overline{c}_k = 0) \times \prod_k \left[ f(W_m|A_m = \overline{a}_m, H = h, \overline{W}_{m-1} = \overline{w}_{m-1}, \overline{Y}_{m-1} = \overline{c}_{m-1} = 0) \times \right. \\
\left. \Pr(Y_m = 0|A_{m-1} = \overline{a}_{m-1}, H = h, \overline{W}_{m-1} = \overline{w}_{m-1}, \overline{Y}_{m-1} = \overline{c}_{m-1} = 0) \times \right. \\
\left. \Pr(C_m = 0|A_{m-1} = \overline{a}_{m-1}, H = h, \overline{W}_{m-1} = \overline{w}_{m-1}, \overline{Y}_{m-1} = \overline{c}_{m-1} = 0) \times \right. \\
\left. \Pr(\overline{A}_m = \overline{a}_m|\overline{A}_{1,m-1} = \overline{a}_{1,m-1}, H = h, \overline{W}_{m-1} = \overline{w}_{m-1}, \overline{Y}_{m-1} = \overline{c}_{m-1} = 0) \times \Pr(H = h|W_0 = w_0) \right]
\]
A.3 Final models used in chapter 4

The first component estimated, the time-varying hazard of death, was modelled as:

\[
\Pr(Y_{k+1} = 1 | \bar{A}_k = \bar{a}_k, H = h, \bar{W}_k = \bar{w}_k, \bar{Y}_k = \bar{c}_k = 0) = \expit(\alpha_0 + \alpha_1 a_{e,k} + \alpha_2 a_{l,k} + \alpha_3(a_{e,k-1} + a_{l,k-1}) + \alpha_4 h + \alpha_5 CD4_0
\]

\[+ \alpha_6 CD4_{0,1} + \alpha_7 CD4_{0,2} + \alpha_8 CD4_{0,3} + \alpha_9 VL_0 + \alpha_{10} IDU + \alpha_{11} Smoke
\]

\[+ \alpha_{12} Alcohol + \alpha_{13} Obese + \alpha_{14} Sex + \alpha_{15} Race_{black} + \alpha_{16} Race_{Hispanic}
\]

\[+ \alpha_{17} Race_{other} + \alpha_{18} Age + \alpha_{19} Age^1 + \alpha_{20} Age^2 + \alpha_{21} Age^3 + \alpha_{22} k + \alpha_{23} k^1
\]

\[+ \alpha_{24} k^2 + \alpha_{25} k^3 + \alpha_{26} CD4_k + \alpha_{27} CD4^1_k + \alpha_{28} CD4^2_k + \alpha_{29} CD4^3_k + \alpha_{30} DVL_k
\]

\[+ \alpha_{31} CD4_{k-1} + \alpha_{32} CD4^1_{k-1} + \alpha_{33} CD4^2_{k-1} + \alpha_{34} CD4^3_{k-1} + \alpha_{35} DVL_{k-1}
\]

\[+ \alpha_{36} (a_{e,k} + a_{l,k}) h + \alpha_{37} (a_{e,k} + a_{l,k}) k + \alpha_{38} h k)
\]

where \(a_{e,k} = 1\) if \(a_k = 1\), \(a_{l,k} = 1\) if \(a_k = 2\), \(VL_k\) is the viral load at time \(k\) (set to lower limit of detection if undetectable), \(DVL_k = 1\) if HIV virus was detectable at time \(k\), \(Z^s\) is the \(s\) spline term for variable \(Z\), and \(\expit(\cdot) = \frac{\exp(\cdot)}{1+\exp(\cdot)}\) is the inverse logit function.
Time-varying detectable viral load was modelled as:

\[
Pr(VL_k = 1|\tilde{A}_k = \tilde{a}_k, H = h, \tilde{W}_{k-1} = \tilde{w}_{k-1}, \tilde{Y}_k = \tilde{C}_k = 0) = \exp(\beta_0 + \beta_1 a_{e,k} + \beta_2 a_{l,k} + \beta_3 (a_{e,k-1} + a_{l,k-1}) + \beta_4 h + \beta_5 CD4_0
\]
\[
+ \beta_6 CD4_{0,1} + \beta_7 CD4_{0,2} + \beta_8 CD4_{0,3} + \beta_9 VL_0 + \beta_{10} IDU + \beta_{11} Smoke
\]
\[
+ \beta_{12} Alcohol + \beta_{13} Obese + \beta_{14} Sex + \beta_{15} Race_{black} + \beta_{16} Race_{Hispanic}
\]
\[
+ \beta_{17} Race_{other} + \beta_{18} Age + \beta_{19} Age^1 + \beta_{20} Age^2 + \beta_{21} Age^3 + \beta_{22} k + \beta_{23} k^1
\]
\[
+ \beta_{24} k^2 + \beta_{25} k^3 + \beta_{26} CD4_{k-1} + \beta_{27} CD4^1_{k-1} + \beta_{28} CD4^2_{k-1} + \beta_{29} CD4^3_{k-1}
\]
\[
+ \beta_{30} DVL_{k-1} + \beta_{31} CD4_{k-2} + \beta_{32} CD4^1_{k-2} + \beta_{33} CD4^2_{k-2} + \beta_{34} CD4^3_{k-2}
\]
\[
+ \beta_{35} DVL_{k-2} + \beta_{36} (a_{e,k} + a_{l,k}) h + \beta_{37} (a_{e,k} + a_{l,k}) k + \beta_{38} h k
\]

Finally, time-varying CD4+ T-cell count was modelled as:

\[
CD4_k = \gamma_0 + \gamma_1 a_{e,k} + \gamma_2 a_{l,k} + \beta_3 (a_{e,k-1} + a_{l,k-1}) + \gamma_4 h + \gamma_5 CD4_0 + \gamma_6 CD4_{0,1} + \gamma_7 CD4_{0,2}
\]
\[
+ \gamma_8 CD4_{0,3} + \gamma_9 VL_0 + \gamma_{10} IDU + \gamma_{11} Smoke + \gamma_{12} Alcohol + \gamma_{13} Obese
\]
\[
+ \gamma_{14} Sex + \gamma_{15} Race_{black} + \gamma_{16} Race_{Hispanic} + \gamma_{17} Race_{other} + \gamma_{18} Age
\]
\[
+ \gamma_{19} Age^1 + \gamma_{20} Age^2 + \gamma_{21} Age^3 + \gamma_{22} k + \gamma_{23} k^1 + \gamma_{24} k^2 + \gamma_{25} k^3
\]
\[
+ \gamma_{26} CD4_{k-1} + \gamma_{27} CD4^1_{k-1} + \gamma_{28} CD4^2_{k-1} + \gamma_{29} CD4^3_{k-1} + \gamma_{30} DVL_{k-1}
\]
\[
+ \gamma_{31} CD4_{k-2} + \gamma_{32} CD4^1_{k-2} + \gamma_{33} CD4^2_{k-2} + \gamma_{34} CD4^3_{k-2} + \gamma_{35} DVL_{k-2}
\]
\[
+ \gamma_{36} (a_{e,k} + a_{l,k}) h + \gamma_{37} (a_{e,k} + a_{l,k}) k + \gamma_{38} h k + \varepsilon
\]

where \(\varepsilon \sim N(0, \sigma^2)\).

For the natural course, ART initiation, baseline HCV status, and loss to follow-up were modelled as follows:
\[ Pr(A_k \neq 0 | \tilde{A}_{k-1} = 0, H = h, \tilde{W}_{k-1} = \tilde{W}_{k-1}, \tilde{Y}_k = \tilde{C}_k = 0) \]
\[ = \expit(\delta_0 + \delta_1 h + \delta_2 CD_0 + \delta_3 CD_{0,1} + \delta_4 CD_{0,2} + \delta_5 CD_{0,3} + \delta_6 VL_0 \]
\[ + \delta_7 IDU + \delta_8 Smoke + \delta_9 Alcohol + \delta_{10} Obese + \delta_{11} Sex + \delta_{12} Race_{black} \]
\[ + \delta_{13} Race_{Hispanic} + \delta_{14} Race_{other} + \delta_{15} Age + \delta_{16} Age_1 + \delta_{17} Age_2 + \delta_{18} Age_3 \]
\[ + \delta_{19} k + \delta_{20} k^1 + \delta_{25} k^2 + \delta_{27} CD_4_k + \delta_{28} CD_4_{k-1} + \delta_{29} CD_4_{k-1} \]
\[ + \delta_{30} CD_4^3_k - \delta_{31} DVL_{k-1} + \delta_{32} CD_4_{k-2} + \delta_{33} CD_4^1_{k-2} + \delta_{34} CD_4^2_{k-2} \]
\[ + \delta_{35} CD_4^3_{k-2} + \delta_{36} DVL_{k-2} + \delta_{37} hk) \]

\[ Pr(H = 1 | W_0 = w_0) \]
\[ = \expit(\zeta_0 + \zeta_1 CD_0 + \zeta_2 CD_{0,1} + \zeta_3 CD_{0,2} + \zeta_4 CD_{0,3} + \zeta_5 VL_0 + \zeta_6 IDU \]
\[ + \zeta_7 Smoke + \zeta_8 Alcohol + \zeta_9 Obese + \zeta_{10} Sex + \zeta_{11} Race_{black} \]
\[ + \zeta_{12} Race_{Hispanic} + \zeta_{13} Race_{other} + \zeta_{14} Age + \zeta_{15} Age^2 + \zeta_{16} Age^3 + \zeta_{17} Age^4 \)

\[ Pr(C_k = 1 | \tilde{A}_{k-1} = \tilde{a}_{k-1}, H = h, \tilde{W}_{k-1} = \tilde{W}_{k-1}, \tilde{Y}_k = \tilde{C}_{k-1} = 0) \]
\[ = \expit(\eta_0 + \eta_1 a_{e,k-1} + \eta_2 a_{l,k-1} + \eta_3 (a_{e,k-2} + a_{l,k-2}) + \eta_4 h + \eta_5 CD_0 \]
\[ + \eta_6 CD_{0,1} + \eta_7 CD_{0,2} + \eta_8 CD_{0,3} + \eta_9 VL_0 + \eta_{10} IDU + \eta_{11} Smoke \]
\[ + \eta_{12} Alcohol + \eta_{13} Obese + \eta_{14} Sex + \eta_{15} Race_{black} + \eta_{16} Race_{Hispanic} \]
\[ + \eta_{17} Race_{other} + \eta_{18} Age + \eta_{19} Age^1 + \eta_{20} Age^2 + \eta_{21} Age^3 + \eta_{22} k + \eta_{23} k^1 \]
\[ + \eta_{24} k^2 + \eta_{25} k^3 + \eta_{26} CD_{4,k-1} + \eta_{27} CD_4^1_{k-1} + \eta_{28} CD_4^2_{k-1} + \eta_{29} CD_4^3_{k-1} \]
\[ + \eta_{30} DVL_{k-1} + \eta_{31} CD_4_{k-2} + \eta_{32} CD_4^1_{k-2} + \eta_{33} CD_4^2_{k-2} + \eta_{34} CD_4^3_{k-2} \]
\[ + \eta_{35} DVL_{k-2} + \eta_{36} (a_{e,k-1} + a_{l,k-1}) h + \eta_{37} (a_{e,k-1} + a_{l,k-1}) k + \eta_{38} hk) \]

136
When modelling the natural course, if ART was initiated prior to October 1, 2001 then $A_{1,k}$ was set to 1, and if it was initiated after that date $A_{1,k}$ was set to 2. Note that the intent to treat assumption implies $Pr(A_k = 1|A_{k-1} = 1, A_2 = a_2, \bar{W}_{k-1} = \bar{w}_{k-1}, \bar{Y}_k = \bar{c}_k = 0) = 1$.

To estimate the effect of HCV treatment, three modifications were made to the above procedure. First, baseline fibrosis status entered all of the above models with two dummy variables representing fibrosis/no cirrhosis and cirrhosis. Second, a modification was made to step 2 of the g-computation procedure. Rather than sampling from the entire study population, only those with chronic HCV at baseline were sampled to represent the covariate distribution among those who would be intervened upon. Lastly, because treatment is not 100% effective, rather than simply comparing $H = 1$ to $H = 0$, a random variable was drawn to determine treatment success. First, a beta random variable, $P$, with parameters chosen to represent the average effectiveness and reasonable uncertainty of effectiveness was drawn (in this case, we chose the average effectiveness to be 0.96, with 95% of the distribution falling between 0.93 and 0.98 (Naggie et al. 2015)). Second, a Bernoulli random variable, $B$ was drawn with parameter $P$. Those with $B = 1$ had $H$ set to 0, while the others remained with $H = 1$.

### A.4 Estimation of the marginal structural model for chapter 4

In this study, the models for censoring, HCV, and ART from the natural course estimation were used to construct the denominators of the weights. For the numerators of the weights, only the time on study and prior exposure history was conditioned on to allow us to estimate effects that were marginal over baseline covariates at each time. The estimated weights for ART history, censoring history, and HCV status were multiplied together to produce the final weight for each subject at each time. Because of exceptionally large weights and influential outliers that led to unstable results, five subjects were excluded from the MSM analysis. The MSM for the risk of
death under ART and HCV interventions was estimated using the inverse-probability weighted
Kaplan-Meier survival curve method on the ‘time on treatment’ time scale as follows (Westreich et al. 2010):

A MSM for the discrete-time hazard was specified as

\[
\Pr \left( Y_{k+1} = 1 \mid \bar{Y}_k = \bar{a}, H = h \right) = \frac{d_{k,a,h}}{r_{k,a,h}} = f(\bar{a}, h; \beta_k)
\]

The MSM was then estimated in the weighted population by

\[
\tilde{Pr}(Y_{k+1} = 1 \mid \bar{Y}_k = \bar{C}_k = 0, \bar{A}_k = \bar{a}_k, H = h) = \frac{d_{k,a,h}}{r_{k,a,h}}
\]

where

\[
d_{k,a,h} = \sum_{i=1}^{n} s w_i * Y_{i,k+1} * I(A_i = a_k, H = h, \bar{C}_i = \bar{Y}_i = 0)
\]

and

\[
r_{k,a,h} = \sum_{i=1}^{n} s w_i * I(A_i = a_k, H = h, \bar{C}_i = \bar{Y}_i = 0)
\]

Because the time scale is time on treatment, \( k \) indexes the time since entering the study for times prior to ART initiation, and time since initiating ART for times after ART initiation. With properly specified weights, \( \tilde{Pr}(Y_{k+1} = 1 \mid \bar{Y}_k = \bar{C}_k = 0, \bar{A}_k = \bar{a}_k, H = h) \) is a valid estimate of an analogously specified model for \( Pr( Y_{k+1} = 1 \mid Y_{k+1} = 1, \bar{C}_k = \bar{a}, \bar{A}_k = \bar{a}_k, \bar{Y}_k = \bar{Y}_k = 0) \). The risk of mortality at time \( k + 1 \) under a given ART and HCV regime is thus

\[
\tilde{Pr}(Y_{t+1} = 1) = R_{t+1} = 1 - \prod_{k=0}^{t}(1 - \tilde{Pr}(Y_{k+1} = 1 \mid \bar{Y}_k = \bar{C}_k = 0, \bar{A}_k = \bar{a}_k, H = h))
\]
A.5 Comparison of observed and modelled natural course in chapter 4

Table A.1: Comparison of observed versus modelled variable distributions under the natural course using models from chapter 4, Women’s Interagency HIV Study and Multicenter AIDS Cohort Study, 1994-2015

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>% Subjects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV+</td>
<td>18.79</td>
<td>18.53</td>
</tr>
<tr>
<td>Censored</td>
<td>51.23</td>
<td>51.10</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>34.66</td>
<td>34.78</td>
</tr>
<tr>
<td><strong>% Person-Time</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ART</td>
<td>53.54</td>
<td>54.09</td>
</tr>
<tr>
<td>Detectible Viral Load</td>
<td>70.45</td>
<td>70.56</td>
</tr>
<tr>
<td><strong>Average value</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4(^+) T-Cell Count</td>
<td>479.64</td>
<td>503.50</td>
</tr>
<tr>
<td><strong>Kaplan-Meier Estimate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-year All-Cause Mortality(^a)</td>
<td>19.90</td>
<td>19.84</td>
</tr>
</tbody>
</table>

Abbreviations: HCV, hepatitis C virus; ART, antiretroviral therapy
\(^a\)Risk, expressed as percent
Figure A.1: Comparison of observed versus modelled mortality under the natural course using models from chapter 4.

Grey lines are cumulative incidence curves from 200 bootstrap samples from the observed data. Blue line is the modelled cumulative incidence curve.
A.6 Results of sensitivity analyses for chapter 4

Table A.2: Sensitivity analysis results for chapter 4

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Effect</th>
<th>Population</th>
<th>Exposure/Treatment</th>
<th>Risk Difference&lt;sup&gt;a&lt;/sup&gt; (95% CI)</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marginal Structural Model&lt;sup&gt;b&lt;/sup&gt;</td>
<td>HCV Infection</td>
<td>HIV+</td>
<td>HCV+</td>
<td>4.14% (-7.35%; 25.01%)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.48 (0.35; 4.78)&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>None/Mild Fibrosis Only</td>
<td>HCV Infection</td>
<td>HIV+</td>
<td>HCV+</td>
<td>3.66% (-0.23%; 12.15%)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.48 (0.96; 2.48)&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>HCV Infection</td>
<td>HCV+</td>
<td>HCV+</td>
<td>4.10% (-0.27%; 12.60%)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1.45 (0.97; 2.45)&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td>No HBV&lt;sup&gt;c&lt;/sup&gt;</td>
<td>HCV Infection</td>
<td>HIV+</td>
<td>HCV+</td>
<td>4.92% (0.78%; 10.27%)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.48 (1.08; 1.99)&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>HCV Infection</td>
<td>HCV+</td>
<td>HCV+</td>
<td>6.11% (1.11%; 12.04%)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1.46 (1.08; 1.93)&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>HCV Treatment</td>
<td>HCV+</td>
<td>All treated</td>
<td>-4.52% (-10.34%; 0.58%)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>0.77 (0.57; 1.04)&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>None treated</td>
<td></td>
<td>Ref</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; HBV, hepatitis B virus

<sup>a</sup>Expressed as percent

<sup>b</sup>Excludes 5 individuals with extreme weights. Time scale is time on treatment.

<sup>c</sup>HBV defined as a positive test for hepatitis B surface antigen at baseline

Main results for comparison: <sup>d</sup>4.34 (0.42, 8.92%); <sup>e</sup>5.29 (0.57, 10.47); <sup>f</sup>-3.80 (-9.22%, 0.89); <sup>g</sup>1.42 (1.04, 1.86); <sup>h</sup>1.40 (1.04, 1.81); <sup>i</sup>0.80 (0.61, 1.06)
APPENDIX B: FURTHER DETAILS OF ANALYSIS IN CHAPTER 5

B.1 Notation

The following notation will be used throughout this section. Individuals will be indexed by \( i \in \{1,2,3,\ldots,n\} \), and time (in visits) will be indexed by \( t \in \{0,1,2,3,\ldots,\tau\} \). Uppercase letters will denote random variables, and lowercase letters and numbers will represent their potential realizations. \( Y_{k+1,i} \) is 1 if subject \( i \) died between times \( k \) and \( k + 1 \). \( A_{k,i} = 1 \) if subject \( i \) initiated ART between time \( k - 1 \) and \( k \) prior to October 1, 2001; \( A_{k,i} = 2 \) with \( k \) on or after October 1, 2001. \( H_{k,i} = 1 \) if subject \( i \) had chronic HCV at time \( k \), \( D_{k,i} = 1 \) if subject \( i \) received DAAs at time \( k \), \( C_{k,i} = 1 \) if subject \( i \) was lost to follow-up at time \( k \), and \( W_{k,i} \) is a vector of covariate values for subject \( i \) at time \( k \). Because the MACS and WIHS visits occur at regular semi-annual intervals, the time index represents visits since baseline, with 10-years being represented by the 20\textsuperscript{th} visit. Mortality and loss to follow-up were thus estimated over 6-month intervals rather than continuously. An overbar (e.g. \( \tilde{C}_{t,i} \)) denotes history, for example \( \tilde{C}_{t,i} = \{C_{0,i},C_{1,i},C_{2,i},\ldots,C_{t,i}\} \). Superscripts on random variables represent potential outcomes, e.g. \( Y^{A=a}_i \) indicates the level of \( Y \) that subject \( i \) would have experienced had, possibly counter to fact, they received treatment level \( A = a \). Finally, \( f_X(x) \) denotes a probability mass function or probability density function for the random variable \( X \) evaluated at \( x \). From here forward, observations will be assumed independent and identically distributed, and subscripts distinguishing individuals will be dropped. Hereafter, the use of the parametric generalized computation algorithm formula for the estimation of causal effects will be referred to as \( g \)-computation, and the formula itself will be referred to as the \( g \)-formula.

B.2 Natural course and \( g \)-formula equations used in chapter 5.

The natural course distribution for this study can be represented as:
\[ E(Y_{t+1}) = \sum_{k=0}^{t} \sum_{w_1 \in \mathcal{W}_1} \sum_{\tilde{w}_1 \in \mathcal{W}_1} \sum_{n_1 \in \mathcal{N}_1} \prod_{m=0}^{k} \frac{\Pr(Y_{t+1} = 1|\tilde{A}_k = \tilde{a}_k, \tilde{H}_k = \tilde{h}_k, \tilde{W}_k = \tilde{w}_k, \tilde{Y}_k = \tilde{c}_k = 0) \times}{f(W_m|A_m = \tilde{a}_m, H_m = \tilde{h}_m, W_m = \tilde{w}_m, Y_m = \tilde{c}_m = 0) \times} \prod_{m=0}^{k} \frac{\Pr(Y_m = 0|\tilde{A}_{m-1} = \tilde{a}_{m-1}, \tilde{H}_{m-1} = \tilde{h}_{m-1}, \tilde{W}_{m-1} = \tilde{w}_{m-1}, \tilde{Y}_{m-1} = \tilde{c}_{m-1} = 0) \times}{\Pr(C_m = 0|\tilde{A}_{m-1} = \tilde{a}_{m-1}, \tilde{H}_{m-1} = \tilde{h}_{m-1}, \tilde{W}_{m-1} = \tilde{w}_{m-1}, \tilde{Y}_{m-1} = \tilde{c}_{m-1} = 0) \times} \prod_{m=0}^{k} \frac{\Pr(A_m = a_m|\tilde{A}_{m-1} = \tilde{a}_{m-1}, \tilde{H}_{m-1} = \tilde{h}_{m-1}, \tilde{W}_{m-1} = \tilde{w}_{m-1}, \tilde{Y}_{m-1} = \tilde{c}_{m-1} = 0) \times}{\Pr(H_m = h_m|\tilde{A}_{m-1} = \tilde{a}_{m-1}, \tilde{H}_{m-1} = \tilde{h}_{m-1}, \tilde{W}_{m-1} = \tilde{w}_{m-1}, \tilde{Y}_{m-1} = \tilde{c}_{m-1} = 0) \times} \prod_{m=0}^{k} \frac{\Pr(H_m = h_m|\tilde{A}_{m-1} = \tilde{a}_{m-1}, \tilde{H}_{m-1} = \tilde{h}_{m-1}, \tilde{W}_{m-1} = \tilde{w}_{m-1}, \tilde{Y}_{m-1} = \tilde{c}_{m-1} = 0) \times}{\Pr(H_m = h_m|A_m = a_m, H_m = h_m, W_m = w_m, Y_m = c_m = 0)} \]
B.3 Final models used in chapter 5

The first component estimated, the time-varying hazard of death, was modelled as:

\[ Pr(Y_{k+1} = 1 | A_1 = \overline{a}_1, \overline{H}_k = \overline{h}_k, \overline{W}_k = \overline{w}_k, \overline{Y}_k = \overline{c}_k = 0) = \expit(\alpha_0 + \alpha_1 a_{e,k} + \alpha_2 a_{l,k} + \alpha_3 (a_{e,k-1} + a_{l,k-1}) + \alpha_4 h_k + \alpha_5 CD_4 \nonumber \\
+ \alpha_6 CD_{4_0} + \alpha_7 CD_{4_0.2} + \alpha_8 CD_{4_0.3} + \alpha_9 VL_0 + \alpha_10 IDU_0 + \alpha_11 Smoke_0 \\
+ \alpha_12 Alcohol_0 + \alpha_13 Obese_0 + \alpha_14 Sex + \alpha_15 Race_{black} + \alpha_16 Race_{Hispanic} \\
+ \alpha_17 Race_{other} + \alpha_18 Age + \alpha_19 Age^1 + \alpha_20 Age^2 + \alpha_21 Age^3 + \alpha_22 k + \alpha_23 k^1 \\
+ \alpha_24 k^2 + \alpha_25 k^3 + \alpha_26 CD_{4_k} + \alpha_27 CD_{4_k^1} + \alpha_28 CD_{4_k^2} + \alpha_29 CD_{4_k^3} + \alpha_30 DV_L_k \\
+ \alpha_31 CD_{4_{k-1}} + \alpha_32 CD_{4_{k-1}^1} + \alpha_33 CD_{4_{k-1}^2} + \alpha_34 CD_{4_{k-1}^3} + \alpha_35 DV_L_{k-1} \\
+ \alpha_36(a_{e,k} + a_{l,k})h_k + \alpha_37(a_{e,k} + a_{l,k})k + \alpha_38 h_k k + \alpha_39 NoFi_b_0 + \alpha_40 Fi_b_0 \\
+ \alpha_41 Cir_k + \alpha_42 IDU_k + \alpha_43 Smoke_k + \alpha_44 Alcohol_k + \alpha_45 Obese_k) \]

where \(a_{e,k} = 1\) if \(a_k = 1\), \(a_{l,k} = 1\) if \(a_k = 2\), \(VL_k\) is the viral load at time \(k\) (set to lower limit of detection if undetectable), \(DV_L_k = 1\) if HIV virus was detectable at time \(k\), \(NoFi_b_k = 1\) if the person had no significant fibrosis at time \(k\), \(Fi_b_k = 1\) if a person had moderate fibrosis at time \(k\), \(Cir_k = 1\) if a person had severe fibrosis/cirrhosis at time \(k\), \(Z^s\) is the \(s\) spline term for variable \(Z\), and \(\expit(\cdot) = \frac{\exp(\cdot)}{1 + \exp(\cdot)}\) is the inverse logit function.

Time-varying detectable viral load was modelled as:
\[ \Pr(VL_k = 1|A_k = \bar{a}_k, H_{k-1} = \bar{h}_{k-1}, W_{k-1} = \bar{w}_{k-1}, \bar{Y}_k = \bar{C}_k = 0) \]
\[ = \expit(\beta_0 + \beta_1 a_{e,k} + \beta_2 a_{l,k} + \beta_3 (a_{e,k-1} + a_{l,k-1}) + \beta_4 h_{k-1} + \beta_5 CD4_0 + \beta_6 CD4_{0,1} + \beta_7 CD4_{0,2} + \beta_8 CD4_{0,3} + \beta_9 VL_0 + \beta_{10} IDU_0 + \beta_{11} Smoke_0 + \beta_{12} Alcohol_0 + \beta_{13} Obese_0 + \beta_{14} Sex + \beta_{15} Race_{black} + \beta_{16} Race_{Hispanic} + \beta_{17} Race_{other} + \beta_{18} Age + \beta_{19} Age^1 + \beta_{20} Age^2 + \beta_{21} Age^3 + \beta_{22} k + \beta_{23} k^1 + \beta_{24} k^2 + \beta_{25} k^3 + \beta_{26} CD4_{k-1} + \beta_{27} CD4^1_{k-1} + \beta_{28} CD4^2_{k-1} + \beta_{29} CD4^3_{k-1} + \beta_{30} DVL_{k-1} + \beta_{31} CD4_{k-2} + \beta_{32} CD4^1_{k-2} + \beta_{33} CD4^2_{k-2} + \beta_{34} CD4^3_{k-2} + \beta_{35} DVL_{k-2} + \beta_{36} (a_{e,k} + a_{l,k})h_{k-1} + \beta_{37} (a_{e,k} + a_{l,k})k + \beta_{38} h_{k-1}k + \beta_{39} NoFib_0 + \beta_{40} Fib_0 + \beta_{41} Cir_{k-1} + \beta_{42} IDU_{k-1} + \beta_{43} Smoke_{k-1} + \beta_{44} Alcohol_{k-1} + \beta_{45} Obese_{k-1} ) \]
where $\epsilon \sim N(0, \sigma^2)$.

Finally, time-varying severe fibrosis/cirrhosis was modelled as:

$$ Pr(C\text{ir}_k = 1|\bar{A}_k = \bar{a}_k, H_{k-1} = \bar{h}_{k-1}, \bar{W}_{k-1} = \bar{w}_{k-1}, \bar{Y}_k = \bar{C}_k = 0) $$

$$ = \exp\left(\theta_0 + \theta_1 a_{e,k} + \theta_2 a_{l,k} + \theta_3 (a_{e,k-1} + a_{l,k-1}) + \theta_4 h_{k-1} + \theta_5 CD4_0 + \theta_6 CD4_{0,1} + \theta_7 CD4_{0,2} + \theta_8 CD4_{0,3} + \theta_9 VL_0 + \theta_{10} IDU_0 + \theta_{11} Smoke_0 + \theta_{12} Alcohol_0 + \theta_{13} Obese_0 + \theta_{14} Sex + \theta_{15} Race_{black} + \theta_{16} Race_{Hispanic} + \theta_{17} Race_{other} + \theta_{18} Age + \theta_{19} Age^1 + \theta_{20} Age^2 + \theta_{21} Age^3 + \theta_{22} k + \theta_{23} k^1 + \theta_{24} k^2 + \theta_{25} k^3 + \theta_{26} CD4_{k-1} + \theta_{27} CD4_{1,k-1} + \theta_{28} CD4^2_{k-1} + \theta_{29} CD4^3_{k-1} + \theta_{30} DLk_{k-1} + \theta_{31} CD4_{k-2} + \theta_{32} CD4^1_{k-2} + \theta_{33} CD4^2_{k-2} + \theta_{34} CD4^3_{k-2} + \theta_{35} NoFib_0 + \theta_{36} Fib_0 + \theta_{37} IDU_{k-1} + \theta_{38} Smoke_{k-1} + \theta_{39} Alcohol_{k-1} + \theta_{40} Obese_{k-1} \right) $$

We assumed that once someone has cirrhosis, it does not reverse, so $Pr(C\text{ir}_k = 1|C\text{ir}_{k-1} = 1) = 1$.

For the natural course, ART initiation, baseline HCV status, and loss to follow-up were modelled as follows:
\[ Pr(A_k \neq 0 | \bar{A}_{k-1} = 0, \bar{H}_{k-1} = \bar{h}_{k-1}, \bar{W}_{k-1} = \bar{w}_{k-1}, \bar{Y}_k = \bar{c}_k = 0) \]

\[ = \expit(\delta_0 + \delta_1 h_{k-1} + \delta_2 CD4_0 + \delta_3 CD4_{0,1} + \delta_4 CD4_{0,2} + \delta_5 CD4_{0,3} + \delta_6 VL_0 \\
+ \delta_7 DU_0 + \delta_8 Smoke_0 + \delta_9 Alcohol_0 + \delta_{10} Obese_0 + \delta_{11} Sex + \delta_{12} Race_{black} \\
+ \delta_{13} Race_{Hispanic} + \delta_{14} Race_{other} + \delta_{15} Age + \delta_{16} Age_1 + \delta_{17} Age_2 + \delta_{18} Age_3 \\
+ \delta_{19} k + \delta_{20} k^1 + \delta_{25} k^2 + \delta_{26} k^3 + \delta_{27} CD4_k + \delta_{28} CD4_{k-1}^1 + \delta_{29} CD4_{k-1}^2 \\
+ \delta_{30} CD4_{k-1}^3 + \delta_{31} DVL_{k-1} + \delta_{32} CD4_{k-2} + \delta_{33} CD4_{k-2}^1 + \delta_{34} CD4_{k-2}^2 \\
+ \delta_{35} CD4_{k-2}^3 + \delta_{36} DVL_{k-2} + \delta_{37} h_{k-1} k + \delta_{39} NoFib_0 + \delta_{40} Fib_0 + \delta_{41} Cir_{k-1} \\
+ \delta_{42} DU_{k-1} + \delta_{43} Smoke_{k-1} + \delta_{44} Alcohol_{k-1} + \delta_{45} Obese_{k-1} ) \]

\[ Pr(H_0 = 1 | W_0 = w_0) \]

\[ = \expit(\zeta_0 + \zeta_1 CD4_0 + \zeta_2 CD4_{0,1} + \zeta_3 CD4_{0,2} + \zeta_4 CD4_{0,3} + \zeta_5 VL_0 + \zeta_6 DU_0 \\
+ \zeta_7 Smoke_0 + \zeta_8 Alcohol_0 + \zeta_9 Obese_0 + \zeta_{10} Sex + \zeta_{11} Race_{black} \\
+ \zeta_{12} Race_{Hispanic} + \zeta_{13} Race_{other} + \zeta_{14} Age + \zeta_{15} Age^2 + \zeta_{16} Age^3 + \zeta_{17} Age^4 \\
+ \zeta_{18} NoFib_0 + \zeta_{19} Fib_0 ) \]
\[ Pr(C_k = 1|A_{k-1} = \tilde{a}_{k-1}, H_{k-1} = \tilde{h}_{k-1}, \overline{W}_{k-1} = \overline{w}_{k-1}, \overline{Y}_k = \overline{\tilde{c}}_{k-1} = 0) \]

\[
= \expit(\eta_0 + \eta_1 a_{e,k-1} + \eta_2 a_{t,k-1} + \eta_3 (a_{e,k-2} + a_{t,k-2}) + \eta_4 h_{k-1} + \eta_5 CD4_0 + \eta_6 CD4_{0.1} + \eta_7 CD4_{0.2} + \eta_8 CD4_{0.3} + \eta_9 VL_0 + \eta_{10} IDU_0 + \eta_{11} Smoke_0 + \eta_{12} Alcohol_0 + \eta_{13} Obese_0 + \eta_{14} Sex + \eta_{15} Race_{\text{black}} + \eta_{16} Race_{\text{Hispanic}} + \eta_{17} Race_{\text{other}} + \eta_{18} Age + \eta_{19} Age^1 + \eta_{20} Age^2 + \eta_{21} Age^3 + \eta_{22} k + \eta_{23} k^1 + \eta_{24} k^2 + \eta_{25} k^3 + \eta_{26} CD4_{k-1} + \eta_{27} CD4_{k-1}^1 + \eta_{28} CD4_{k-1}^2 + \eta_{29} CD4_{k-1}^3 + \eta_{30} DV\_L_{k-1} + \eta_{31} CD4_{k-2} + \eta_{32} CD4_{k-2}^1 + \eta_{33} CD4_{k-2}^2 + \eta_{34} CD4_{k-2}^3 + \eta_{35} DV\_L_{k-2} + \eta_{36} (a_{e,k-1} + a_{t,k-1}) h_{k-1} + \eta_{37} (a_{e,k-2} + a_{t,k-2}) k + \eta_{38} h_{k-1} k + \eta_{39} No\_Fib_0 + \eta_{40} Fib_0 + \eta_{41} Cir_{k-1} + \eta_{42} IDU_{k-1} + \eta_{43} Smoke_{k-1} + \eta_{44} Alcohol_{k-1} + \eta_{45} Obese_{k-1})
\]

When modelling the natural course, if ART was initiated prior to October 1, 2001 then \( a_k \) was set to 1, and if it was initiated after that date \( a_k \) was set to 2. Note that the intent to treat assumption implies \( Pr(A_k = 1|A_{k-1} = 1, H_{k-1} = \tilde{h}, \overline{W}_{k-1} = \overline{w}_{k-1}, \overline{Y}_k = \overline{\tilde{c}}_k = 0) = 1. \) We additionally assumed no incident HCV infections and that no HCV infections would be resolved without intervention, so

\[ Pr(H_m = h|\tilde{A}_{m-1} = \tilde{a}_{m-1}, \tilde{H}_{m-1} = \tilde{h}_{m-1}, \overline{W}_{m-1} = \overline{w}_{m-1}, \overline{Y}_m = \overline{\tilde{c}}_m = 0) = 1 \) if \( H_0 = h. \)

Treatment success was determined with a beta-Bernoulli distributed random variable. First, a beta random variable, \( P \), with parameters chosen to represent the average effectiveness and reasonable uncertainty of effectiveness was drawn (in this case, we chose the average effectiveness to be 0.96, with 95% of the distribution falling between 0.93 and 0.98 (Naggie et al. 2015)). Second, a Bernoulli random variable, \( B \) was drawn with parameter \( P \). Those with \( B = 1 \) had \( A_2 \) set to 0, while the others remained with \( A_2 = 1. \)
### B.4 Comparison of observed and modelled natural course in chapter 5

Table B.1: Comparison of observed versus modelled variable distributions under the natural course using models from chapter 5, Women’s Interagency HIV Study and Multicenter AIDS Cohort Study, 1994-2015

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>% Subjects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV</td>
<td>19.02</td>
<td>18.79</td>
</tr>
<tr>
<td>Censored</td>
<td>51.23</td>
<td>51.03</td>
</tr>
<tr>
<td>LTFU</td>
<td>34.66</td>
<td>35.10</td>
</tr>
<tr>
<td><strong>% Person-Time</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ART</td>
<td>53.54</td>
<td>54.03</td>
</tr>
<tr>
<td>Detectible viral load</td>
<td>70.37</td>
<td>70.39</td>
</tr>
<tr>
<td>Injection drug use</td>
<td>3.30</td>
<td>3.48</td>
</tr>
<tr>
<td>Smoke</td>
<td>41.42</td>
<td>41.63</td>
</tr>
<tr>
<td>Drink</td>
<td>8.98</td>
<td>9.22</td>
</tr>
<tr>
<td>Obese</td>
<td>24.17</td>
<td>24.56</td>
</tr>
<tr>
<td>Severe fibrosis/Cirrhosis</td>
<td>23.24</td>
<td>22.11</td>
</tr>
<tr>
<td><strong>Average value</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 Count</td>
<td>479.64</td>
<td>503.90</td>
</tr>
<tr>
<td><strong>Kaplan-Meier Estimate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-year All-Cause Mortality(a)</td>
<td>19.90</td>
<td>19.67</td>
</tr>
</tbody>
</table>

Abbreviations: HCV, hepatitis C virus; ART, antiretroviral therapy

\(a\)Risk, expressed as percent
Figure B.1: Comparison of observed versus modelled mortality under the natural course using models from chapter 5.

Grey lines are cumulative incidence curves from 200 bootstrap samples from the observed data. Blue line is the modelled cumulative incidence curve.
B.5 Timing of DAA treatment under dynamic interventions in chapter 5

Figure B.2: Timing of DAA treatment under dynamic interventions in chapter 5

Solid line is treating those with suppressed HIV viral load. Short dashed line is treating those with severe fibrosis/cirrhosis. Long dashed line is treating those with suppressed HIV viral load and severe fibrosis/cirrhosis.
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