

THE POPULATION LEVEL IMPACT OF HIV TREATMENT IN THE TEST-AND-TREAT
ERA

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ABSTRACT

Catherine R. Lesko: The Population Level Impact of HIV Treatment in the Test-and-Treat Era
(Under the direction of Stephen R. Cole)

Antiretroviral therapy (ART) reduces mortality and prevents secondary transmission of HIV. Treatment guidelines now recommend initiating ART immediately following HIV diagnosis. The impact of this test-and-treat strategy on survival among HIV-infected persons in the United States (US) is unknown. First, published estimates of the effect of ART have been based on cohorts that are not representative of this target population. Second, evidence as to whether racial/ethnic/sex disparities in survival persist following ART initiation is mixed.

In this dissertation, I estimated 5-year mortality risks for ART initiators versus non-initiators among 12,547 patients in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) using the complement of weighted Kaplan-Meier survival functions. I subsequently standardized estimates to persons diagnosed with HIV in the US between 2009 and 2011, enumerated using national surveillance data from the Centers for Disease Control and Prevention. Furthermore, I calculated the 10-year all-cause mortality risk among 10,017 ART initiators, stratified by race/ethnicity and sex, from weighted Kaplan-Meier survival functions.

The 5-year mortality among ART initiators in the CNICS was 10.6% (95% CI: 9.3%, 11.9%) compared to 28.3% (95% CI: 19.1%, 37.5%) among non-initiators. ART initiation lowered 5-year mortality by -19.1% (95% CI: -30.5%, -7.8%) among recently HIV-diagnosed persons in the US. This effect was similar to the effect of ART estimated in the CNICS (risk difference: -17.7%, 95% CI: -27.0%, -8.4%). The overall 10-year mortality risk among ART

initiators was 20.2% (95% confidence interval (CI): 19.2%, 21.3%). Black men and women experienced standardized 10-year all-cause mortality risks that were 7.2% (95% CI: 4.3%, 10.1%) and 7.9% (95% CI: 3.9%, 12.0%) larger than white men. White women, Hispanic men, and Hispanic women all had lower 10-year mortality than white men.

ART initiation substantially lowers mortality among persons in the CNICS and this benefit is expected to be similar among persons recently diagnosed with HIV in the US. However, survival following ART initiation differs by race/ethnicity. Effective interventions are needed to ensure that the goal of the National HIV/AIDS Strategy to overcome health disparities becomes a reality.

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LIST OF ABBREVIATIONS

ART	Antiretroviral therapy
CFAR	Centers for AIDS Research
CI	Confidence Interval
CNICS	CFAR Network of Integrated Clinical Systems
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRSA	Health Resources and Services Administration
IDU	Injection drug user
IDSA	Infectious Disease Society of America
IQR	Interquartile Range
MACS	Multicenter AIDS Cohort Study
mL	Milliliter
MSM	Men who have sex with men
NIH	National Institutes of Health
NNRTI	Non-Nucleoside Reverse Transcription Inhibitor
NRTI	Nucleoside Reverse Transcription Inhibitor
RD	Risk Difference
RNA	Ribonucleic Acid
RR	Risk Ratio
US	United States
VACS-VC	Veterans Aging Cohort Study – Virtual Cohort

WIHS Women's Interagency HIV Study

CHAPTER 1: SPECIFIC AIMS

Initiation of combination antiretroviral therapy (ART) by those infected with HIV improves survival and reduces HIV transmission.¹⁻³ Following confirmation of the transmission-prevention benefits of ART, treatment guidelines were recently updated to recommend ART for all HIV infected individuals, regardless of clinical status.⁴ The expected effect of this new policy on survival among persons recently diagnosed with HIV in the United States (US) is poorly quantified because existing estimates of the effect of ART have been based on cohorts that are not representative of this target population.⁵⁻⁷ Namely, cohorts have been primarily European (and receiving care under a different health care system) and have excluded persons with AIDS at baseline, despite the fact that 26% of persons diagnosed with HIV in the US receive a diagnosis of AIDS simultaneously or within 3 months of their HIV diagnosis.⁸ Additionally, differences in the age, race, sex, and risk group distribution between clinical cohorts and persons recently HIV-diagnosed in the US may result in different estimates of the population effect of ART, to the extent that heterogeneity in the effect of ART is associated with these characteristics. Furthermore, while disparities in survival among HIV infected people in the ART era are well documented,⁹⁻¹² they may be associated with simultaneous disparities in access to ART.^{13,14} Reducing disparities in outcomes among HIV-infected persons is a key goal of the National HIV/AIDS Strategy, yet it is unclear whether disparities arise following ART initiation or whether disparities in survival are simply persisting across the care continuum, having arisen

in earlier stages.¹⁵⁻¹⁹ Understanding the potential population level impact of HIV treatment in the test-and-treat era is the overall goal of this thesis.

The specific aims of this dissertation are to:

- 1) describe the effect of ART initiation (versus not) on the 5-year risk of all-cause mortality in Center for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort and generalize this estimate to persons recently diagnosed with HIV in the US; and
- 2) describe differences in the 10-year risk of all-cause mortality following initiation of ART in the CNICS clinical cohort by race/ethnicity and sex.

CHAPTER 2: BACKGROUND

2.1. Significance

Effective combination antiretroviral therapy (henceforth ART) improves survival among HIV-infected persons. After the introduction of ART (compared with mono- or dual-therapy) in 1997, mortality among HIV-infected persons fell sharply compared to pre-1997 and continued falling as more people were prescribed ART and regimens continued to improve.²⁰ Controlling for the health status of patients initiating ART, ART was estimated to reduce the mortality rate by 62%,²¹ although early observational estimates of the effect of ART were biased by time-varying confounding. Improvements in epidemiologic methods (specifically, the development and application of marginal structural models) led to improved estimates of the relative reduction in the mortality due to ART: an 86% relative reduction in the mortality hazard for ART compared to no treatment [hazard ratio (HR)=0.14 (95% Confidence Interval (CI): 0.07, 0.29)] in the Swiss HIV Cohort Study;²² a 52% relative reduction in the mortality hazard in a collaboration of 12 cohort studies from Europe and the US [HR=0.57 (95% CI: 0.49, 0.67) at 1 year after ART initiation, and HR=0.21 (95% CI: 0.14, 0.31) at 5 years after ART initiation];³ and a 46% relative reduction in the hazard of AIDS or death among US participants in the Multicenter AIDS Cohort Study (MACS) and Women's Interagency HIV Study (WIHS) (HR=0.54; 95% CI: 0.38, 0.78).²³

Differences in the effect estimates of ART may be attributable to differences in the health care systems in which the cohorts received care, as well as to differences in patient demographics

and baseline clinical characteristics that modify the effect ART on mortality.³ None of these existing estimates of the effect of ART are based on studies that reflect the demographics, clinical status and treatment experiences of the current US HIV-infected population, however. Clinical cohorts tend to be disproportionately white and male, when compared with the demographics of the US HIV-infected population (Table 2.1). The Swiss HIV Cohort Study²² participants HIV-CAUSAL Collaboration³ participants are predominantly European and differ from the US HIV-infected population on demographics and treatment experience. Men in the MACS and women in the WIHS are demographically distinct from the US HIV-infected population.²³ None of the three existing studies included persons with AIDS at baseline, despite the fact that 26% of all persons newly diagnosed with HIV in the US receive an AIDS diagnosis within 3 months of their HIV diagnosis.²⁴

Assuming effect heterogeneity of ART on survival, published estimates of the effect of ART on mortality reduction are not directly generalizable to the US population. The most recent estimates of the effect of ART on survival may be internally valid estimates (equal to the true effect of ART on mortality within the source population for the study), but even under these ideal circumstances, none of them may equal the average treatment effect that would have been observed if we had estimated the effect of ART in the target population, i.e., the persons recently diagnosed with HIV in the US. Results obtained in one sample may not generalize to another target population due to differences in the distribution of effect modifiers in the sample and target population (results may also be due to differences in treatment-versions or interference patterns between the study sample and target population).^{6,7} Reweighting of an estimate of effect from a study sample to match the distribution of effect modifiers in a specified target population

yields an estimate of effect for the target population.⁵ This is a semiparametric extension of direct standardization.

Table 2.1. Characteristics of cohorts used in prior estimates of the effect of antiretroviral therapy on mortality, persons enrolled in the Center for AIDS Research Network of Integrated Clinical Systems (CNICS) during 1998-2012, and persons diagnosed with HIV in the United States, 2009-2011

	Cole et. al., <i>AJE</i> , 2003 ^a	Sterne et. al., <i>Lancet</i> , 2005 ^b	HIV-CAUSAL Collaboration,	CNICS Study Sample at	HIV-diagnosed in the US, 2009-
Total N	1,498	3,245	62,760	12,457	128,945
Race/ethnicity					
White	561 (37)			5,539 (44)	36,635 (28)
African-American				4,789 (38)	60,516 (47)
Hispanic				1,635 (13)	26,079 (20)
Other				584 (5)	5,715 (4)
Sex					
Male	506 (44)	2,144 (66)	(74)	10,265 (82)	100,819 (78)
Female	992 (66)	1,101 (34)	(26)	2,282 (18)	28,126 (22)
Age					
Median age (IQR)	39 (33, 44)			38 (31, 45)	
18-24 years		720 (22) ^f	30,990 (49) ^g	980 (8)	25,535 (20)
25-34 years				3,731 (30)	35,625 (28)
35-44 years		1,699 (52) ^h	25,743 (41) ⁱ	4,766 (38)	31,153 (24)
45-54 years		575 (18) ^j		2,471 (20)	25,030 (19)
Hx of AIDS at	0 (0)	0 (0)	0 (0)	2,343 (19)	32,896 (26)
IDU (incl. MSM)		1,114 (34)	7,964 (13)	2,343 (19)	10,429 (8)
MSM (incl. IDU)		926 (29)	24,342 (39)	7,509 (60)	81,907 (64)
MSM & IDU				903 (7)	4,105 (3)
Baseline VL					
Median (IQR), log ₁₀	4.5 (4.0, 5.0)		4.5	4.5 (3.5, 5.1)	
≤400	422 (28)	427 (13)		2,037 (14)	
401-10,000	272 (18)	1,232 (38)		3,297 (22)	
>10,000	804 (54)	1,586 (48)		9,661 (64)	
Baseline CD4					
Median (IQR)	395 (257, 560)		390	338 (142, 542)	
<200	258 (17)		518 (16)	4,724 (32)	(32)
200-350	373 (25)		772 (24)	3,026 (20)	(39)
>350	867 (58)		1,955 (60)	7,245 (48)	(28)

^a Only 60% of persons were mono-therapy or combination ART naïve at baseline and all were AIDS free.

^b Only 68% of persons were mono-therapy or dual-therapy naïve at baseline and all were AIDS free.

^c The HIV-CAUSAL collaboration comprises 12 prospective cohort studies from 5 European countries (UK, France, Netherlands, Spain, Switzerland) and the US (VACS-VC).

^d Includes ART-naïve (no documented mono- or dual-therapy, and detectable baseline viral load) patients who established care, defined as attending at least 2 clinical care visits, at a CNICS site between 1 January 1998 and 30 December 2011. Excludes patients with missing race/ethnicity or transmission risk category.

^e US newly HIV-diagnosed population includes individuals age 13-18, whereas CNICS eligibility criteria include age ≥ 18 years. Adolescents are expected to make up a very small proportion of the US newly HIV-diagnosed population and thus the influence on generalization should be minimal.

^f 15-29 years

^g <35 years

^h 30-39 years

ⁱ 35-50 years

^j 40-49 years

^k >50 years

✓ ^l Estimated from persons newly HIV-diagnosed in 2011 in 18 states (Delaware, Iowa, Indiana, Kentucky, Missouri, Nebraska, New York State (excluding New York City), North Dakota, San Francisco, South Carolina, West Virginia, Wyoming) and DC where CD4 cell counts are reportable; 26% of newly diagnosed individuals had no CD4 count performed and reported within 3 months of diagnosis.

The US HIV epidemic is characterized by racial and ethnic disparities. The HIV epidemic has evolved dramatically since it first emerged in 1981. Whereas it was once considered a disease of white men who have sex with men (MSM), today African-American and Hispanic men and women are disproportionately impacted.^{25,26} In 2010, as in previous years, HIV was one of the top five causes of death among African American men and women age 25-44.²⁷ The HIV care continuum is a convenient framework describing patients' progress from HIV infection to treatment and viral suppression, and is used frequently for situational awareness of the HIV epidemic.^{28,29} About 64% of the HIV-infected US population is lost somewhere along the HIV care continuum prior to being prescribed therapy^{28,30} and losses are non-differential with respect to race, ethnicity, sex, and risk group, making the population presenting for HIV treatment different from the HIV-infected population.^{13,31-33} Minorities are more likely to be diagnosed later in the course of their infection, more likely to experience delays in entering HIV care following diagnosis, and less likely to receive ART once in care.^{13,15,31,32,34-39}

Evidence of demographic disparities in survival following ART initiation is mixed. Racial disparities in survival after ART initiation are difficult to disentangle from disparities in survival that have existed since the pre-ART era.^{9,40} The idea that the survival benefits of ART may not be equally experienced by all is supported by studies that reported reductions in mortality rates in the era of effective combination ART that were less dramatic among HIV-infected black or Hispanic persons compared to white persons.^{9,41-43} However, other studies found no modification of the effect of treatment era by race.⁴⁴ In the era of effective combination ART, survival after HIV diagnosis continues to be lower for black persons compared to white persons.⁴⁵ Differential access to care and ART, rather than differential survival after ART initiation, has been postulated as a mediator of the association between race

and mortality. In support of this theory, researchers found no association between race and mortality among members of several cohorts with presumed equal access to care (i.e., the WIHS, persons continuously insured by Kaiser Permanente of Northern California who started ART, veterans, and patients initiating ART at a CD4 cell count >350 cells/ μ L).^{17,46-48} However, other studies have shown racial disparities of varying magnitude in survival regardless of access to care.^{49,50}

The evidence for disparities in survival associated with Hispanic ethnicity is weaker. Prior to the introduction of ART, the few studies that included survival estimates stratified by ethnicity reported no differences among Hispanic and white patients.⁹ Most studies that have been conducted among HIV-infected patients with equal access to care and among HIV-infected patients who started ART have found no association between Hispanic ethnicity and mortality rate.^{17,46,50} However, among participants in the WIHS on continuous ART, Hispanics had a higher, but imprecisely estimated, relative hazard of AIDS-related death compared to whites (HR=1.56, 95% CI: 0.88, 2.77).⁴⁹

Gender disparities in survival after ART initiation have been described less frequently. Perhaps because two of the three studies that mention investigating disparities by sex found no sex differences in survival due to ART use.^{23,51} However, in one pooled analysis of US and European cohorts, the relative hazard of death associated with ART initiation was 0.32 (95% CI: 0.21, 0.50) among women, but only 0.52 (95% CI: 0.44, 0.62) among men.³

2.2. Innovation

This is the first study to estimate the effect of ART on survival standardized to the US population. Thus far, estimates of the effect of ART have come from clinical cohorts that do not

reflect the heterogeneity of the US HIV-infected population or routine clinical care as delivered in the US. No existing studies of the effect of ART on mortality have included persons who had an AIDS diagnosis at baseline,^{3,22,23} despite the fact that 26% of persons newly diagnosed with HIV from 2009-2011 were diagnosed with AIDS within 3 months of their HIV diagnosis date.⁸ Two of the three estimates of the effect of ART on mortality were based on HIV-positive cohorts that were entirely²² or predominantly European.³ Two of the three estimates have been based on cohorts that included HIV-infected patients in the US, however neither of the US-based cohorts had been representative samples; one estimate included patients from the VACS-VC³ and one estimate was based on participants in the MACS and the WIHS.²³ The diversity of the CNICS cohort allows for estimation of stratified estimates of the effect of ART on mortality to reveal effect heterogeneity. Further, it is possible to estimate inverse probability of sampling weights for persons in the CNICS to generalize results to the US population since the probability of being sampled will be greater than 0 for persons of minority race/ethnicity and gender.

To my knowledge, this is the first attempt to generalize an estimate of effect from an observational cohort to a target population other than the source population where the probabilities of selection into the sample are unknown. In all epidemiologic investigations, there is a target population to whom we would like to make inference, a source population from whom the study sample is drawn, and a study sample in whom we measure exposure, outcome, and covariates and estimate an effect.⁵² Inverse probability of exposure weighting is an established method for generating an internally valid causal effect in an observational study, i.e., of estimating the effect for the source population from the study sample when the treatment was not randomized.⁵³ Inverse probability of exposure weights have previously been applied specifically to the estimation of the causal effect of ART from observational data using marginal structural

models.^{3,23} Generalizability weights, or inverse probability of sampling weights, can be used to generalize an estimate of effect from a source population to a specific target population. So far, such inverse probability of sampling weights have only been applied to generalize an estimate from a randomized controlled trial to a specific target population⁵ or to generalize an estimate from an observational study to a target population where the sampling weights were known.⁵⁴ This is the first observational study that would simultaneously address internal and external validity, combining both sets of estimated weights.

This dissertation adds to the literature on HIV outcomes among persons who have initiated ART. Examining disparities within the care continuum framework is useful for identifying specific interventions to improve HIV outcomes overall. Only three prior cohorts have been examined with a focus specifically on the survival of HIV-infected persons who have initiated ART: the WIHS,^{46,49} the Flexible Initial Retrovirus Suppressive Therapies (FIRST) clinical trial;⁵⁰ and a cohort of HIV-positive enrollees in Kaiser Permanente Northern California who initiated ART and were followed until they died, until disenrollment or until administrative censoring.¹⁷ None of these cohorts are representative of all HIV-infected persons in the US. No men are included in the WIHS, yet men make up over 80% of HIV-infected persons in the US. The level of surveillance in the FIRST trial does not match the level of surveillance in routine clinical care. Finally, only a minority of HIV-infected patients, even in care, have private insurance; 31% of HIV-infected persons in care in 1996 had private insurance⁵⁵ and that proportion dropped to 16% from 2006-2012.⁵⁶

Finally, the size and diversity of the CNICS cohort allows for the description of heterogeneity in treatment outcomes between demographic groups that are underrepresented in smaller observational cohorts. The only information that exists about survival for HIV-infected

Hispanic persons comes from public health surveillance⁹ or administrative data,⁵⁷ neither of which include treatment information to be able to distinguish disparities arising prior to initiating ART from disparities arising after initiating ART.

CHAPTER 3: DESCRIPTION OF THE DATA SOURCE

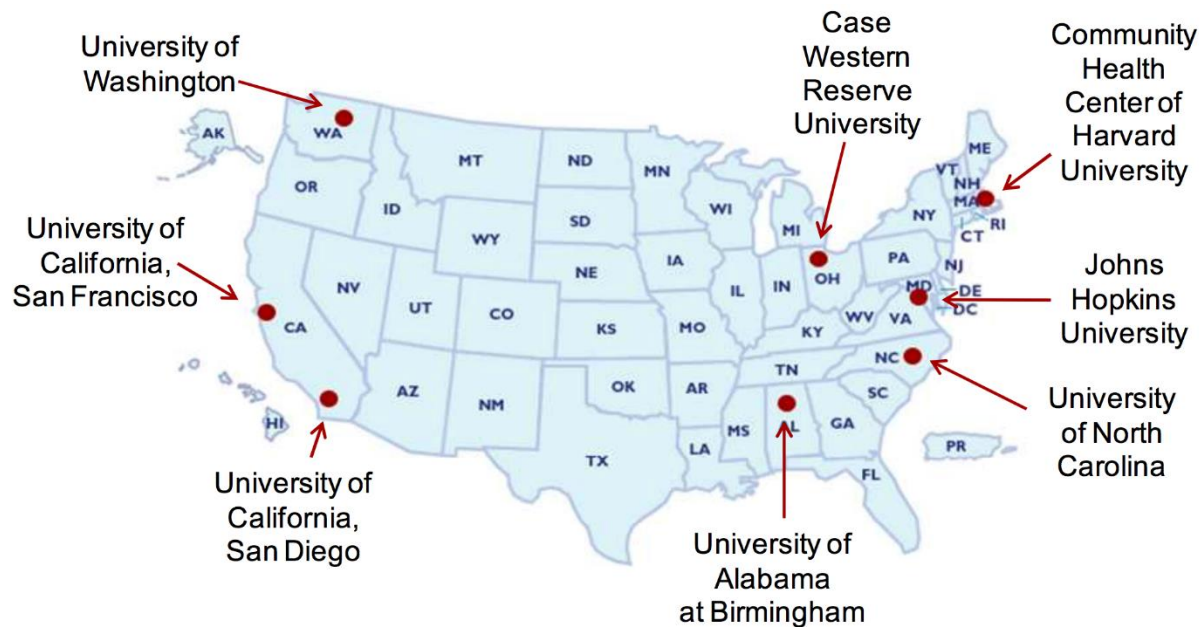
3.1. Centers for AIDS Research Network of Integrated Clinical Systems

Both aims of this study were accomplished using data from the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS).⁵⁸ The CFAR network was established by the National Institutes of Health (NIH) to provide administrative and research support to AIDS research projects that might not otherwise be readily undertaken using traditional funding mechanisms. CNICS is a clinic-based research network developed to support population-based HIV research. Of 19 CFARs, located in academic and research institutions across the US, four were initially chosen to participate in CNICS when it was first funded in September 2006 through the NIH (R24 AI067039): Case Western Reserve University, Cleveland, Ohio; University of Alabama, Birmingham, AL; University of California, San Francisco, CA; and University of Washington, Seattle, WA. Four additional sites were later added: University of California, San Diego, CA; Fenway Community Health Center of Harvard University, Boston, MA; and Johns Hopkins University, Baltimore, MD (Figure 3.1). All sites have institutional review board approval. To further protect patient privacy, CNICS obtained a Certificate of Confidentiality from the NIH, CFAR sites submit data stripped of personal identifiers, and all data are submitted by secure, encrypted FTP to the CNICS data repository.⁵⁸ High quality epidemiologic studies have been based on data from individual CNICS clinics,^{59,60} CNICS as a stand-alone cohort,⁶¹⁻⁶³ and on data from larger collaborations to which CNICS

contributes, namely the North American AIDS Cohort Collaboration on Research and Design.⁶⁴⁻

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Figure 3.1. Centers for AIDS Research Network of Integrated Systems Sites



Source: <http://www.uab.edu/cnics/cnics-sites>

The CNICS data are collected from electronic medical records at each of the sites. This may include both structured queries against an electronic database (e.g., for laboratory results) and manual abstraction of data from clinical notes or other non-standardized fields in the medical chart (e.g., for clinical diagnoses). While each site collects information differently, the CNICS consortium has established standards for terminology, formatting, data verification, and quality assurance procedures. The CNICS data repository contains detailed information on patient demographics [year of birth, sex, race and ethnicity categorized according to US Federal Health Resource and Services (HRSA) standards], risk factors for HIV transmission [categorized

according to the US Centers for Disease Control and Prevention (CDC) classification], laboratory measures (including results of CD4 T cell counts, and plasma HIV-1 RNA levels), antiretroviral treatment data, diagnosis data (AIDS-defining diagnoses defined by the CDC 1993 case definition), and mortality data. Laboratory test results are uploaded directly from Clinical Laboratory Systems at each site. Medication data are entered into the electronic medical record by clinicians or prescription data are uploaded directly from pharmacy dispensing systems and verified through medical record review. Historical data on prior antiretroviral treatment and prior AIDS diagnoses are collected upon enrollment into the cohort.⁵⁸ Data validation occurs both within individual CNICS sites prior to transmission of the data and at the centralized CNICS data repository, both at the time of submission and after data are uploaded into the CNICS repository.⁵⁸

The CNICS cohort includes HIV infected patients 18 years of age and older who initiated primary care (defined as attending at least two primary care visits) at any of eight CNICS sites after 1 January 1995. For these analyses, I included patients who enrolled in care at a CNICS site between 1 January 1998 and 31 December 2011, when patient follow up was administratively censored for analysis (patient follow up from one site was administratively censored on 15 September 2010). Between 1,300 and 2,000 patients have enrolled in CNICS each year since 1998, and before any additional exclusions, the CNICS cohort for these analyses included 23,543 patients.

3.1.1. Exposure Assessment

Specific Aim 1: Medication data are entered into the electronic medical record by clinicians or prescription data are uploaded directly from pharmacy dispensing systems and

verified through medical record review. The effective combination ART initiation date was defined as the first day on which a patient was prescribed three or more antiretroviral medications, each for at least 30 days.

Analyses of the Multicenter AIDS Cohort Study (MACS) data define ART as 1) use of two or more nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs) in combination with at least one protease inhibitor (PI) or one non- nucleoside (or nucleotide) reverse transcriptase inhibitors (NNRTI); 2) use of one NRTI in combination with at least one PI and at least one NNRTI; 3) a regimen containing ritonavir and saquinavir in combination with one NRTI and no NNRTIs; or 4) an abacavir-containing regimen of three or more NRTIs in the absence of both PIs and non-NRTIs. Analyses of the Women's Interagency HIV Study (WIHS) definition for ART is any 3-drug regimen, one of which is a PI, a NNRTI, one of the NRTIs abacavir or tenofovir, an INSTI (raltegravir), or an entry inhibitor (maraviroc or enfuvirtide). The 3+ drug definition of ART used in these analyses is a simpler definition than the ART definition used by the MACS or the WIHS, but there is considerable overlap between all three. While there is the potential that the simpler 3+ drug definition may classify some individuals as on ART who would not meet the ART definition for MACS or WIHS (potentially less than perfect specificity), 3+ drug regimens that do not meet the MACS or WIHS definition are rare, and all individuals meeting the definition of ART for MACS or WIHS would be classified as on ART under the 3+ drug definition (perfect sensitivity). The 3+ drug definition is a definition that has been used before and I am trusting that physicians that prescribe at least 3 antiretroviral drugs will have prescribed a recommended regimen.

ART use is highly prevalent among CNICS patients, with approximately 1,200 to 1,400 patients initiating a regimen containing at least 3 drugs each year. Overall, 77% of CNICS

patients initiated ART at some point prior to enrollment in CNICS or during follow-up, the probability of initiating ART by 10 years following CNICS enrollment went up to 90% when patients were censored at drop out, defined as going 1 year without having a CD4 cell count or viral load measurement (Figure 3.2). The most common initial regimen in 1998 was a triple nucleoside reverse transcriptase inhibitor (NRTI) regimen. By the end of the study period, the most common initial regimens were boosted protease inhibitor (PI) regimens and non-nucleoside reverse transcriptase inhibitor (NNRTI) regimens (Figure 3.3).

Figure 3.2. Proportion of all CNICS patients initiating ART by time since enrollment, 1998-2011, a) censoring at end of administrative follow-up only, and b) censoring patients after 1 year with no laboratory measurements (drop out)

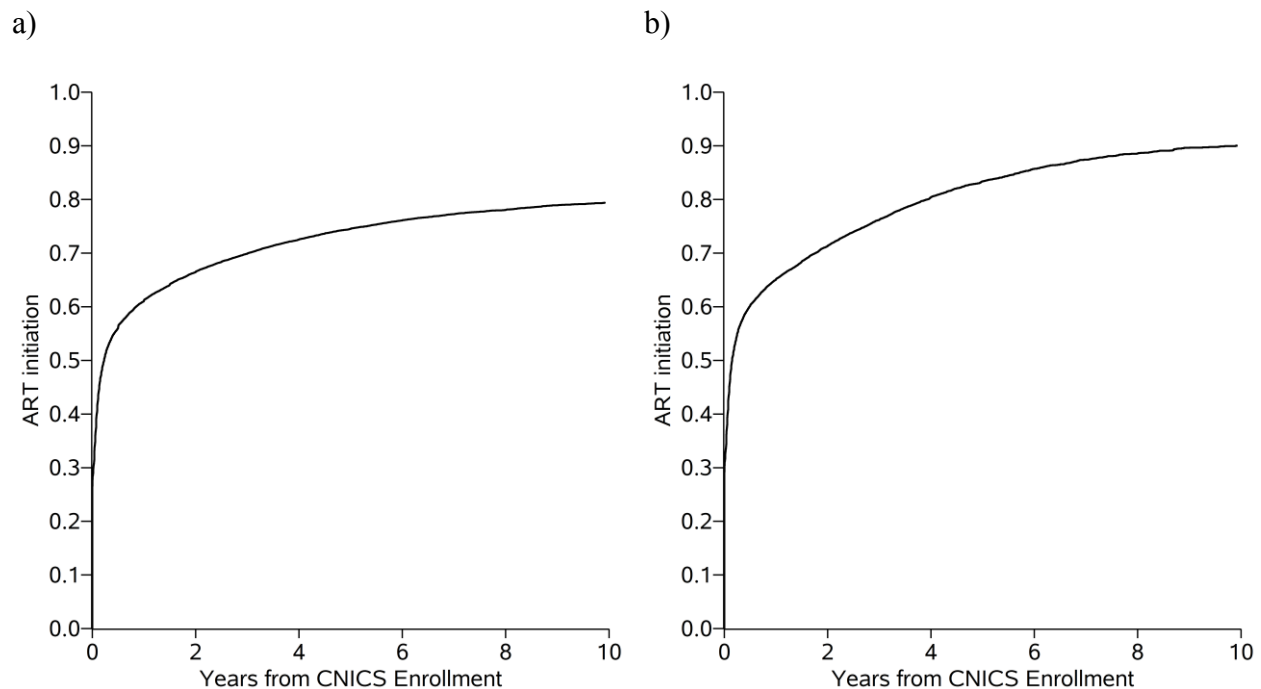
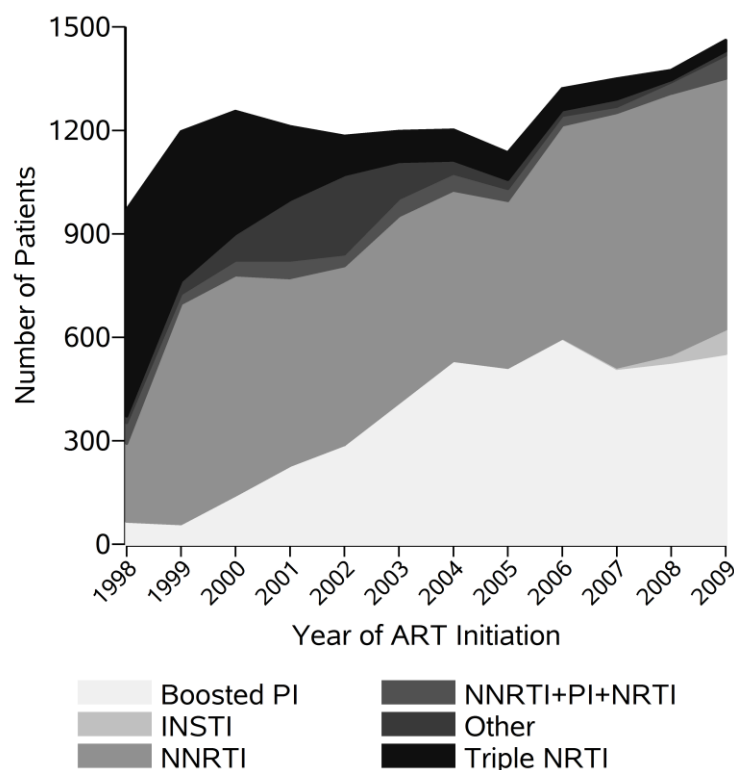


Figure 3.3. Initial ART regimens for CNICS patients initiating ART by year of enrollment, 1998-2011



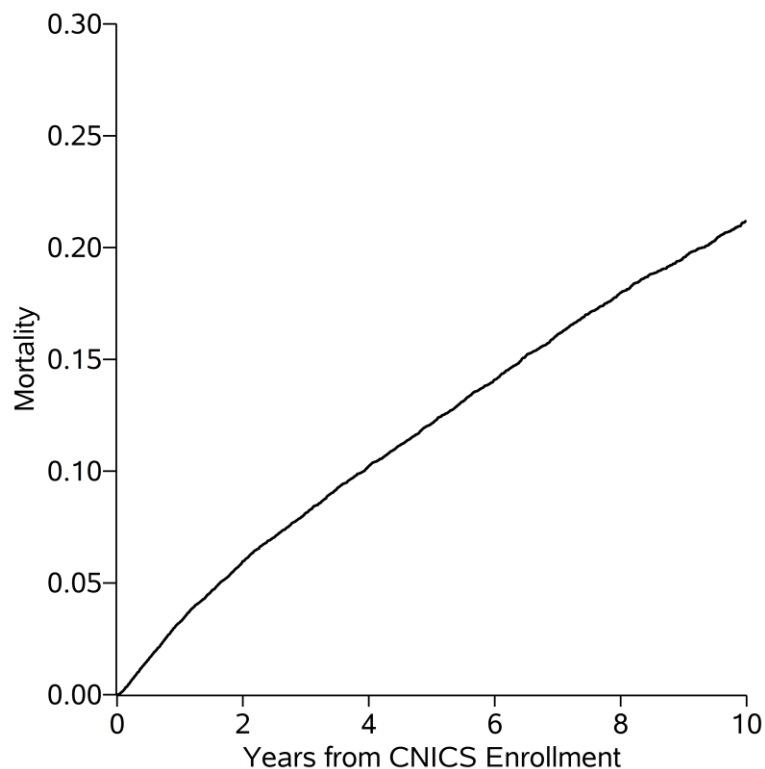
Specific Aim 2: In Specific Aim 2, the main stratification factor of interest was the cross-classification of race/ethnicity and sex. Race and ethnicity were categorized according to US Federal Health Resource and Services Administration standards. For all aims of this study, race and ethnicity were combined into one variable, with patients classified as Hispanic, (non-Hispanic) black, white, or other race. Sex was defined based on birth sex, or present sex if birth sex was missing. Two CNICS sites do not collect birth sex. Birth sex was not missing for any patients at sites that collect it. The proportion of patients for whom birth sex was not equal to present sex ranged from 0.32% to 2.6% in sites that collected both.

The majority of CNICS patients are male (82%) and white (45%), followed by black (37%) and Hispanic (13%).

3.1.2. Outcome Assessment

The outcome for both aims of this study was total mortality. Mortality information was obtained from clinic sources, death certificates, and regular queries to the Social Security Death Index. Different sites follow different query schedules, with the typical query schedule being every 6 months. As of December 31, 2011 (or September 1, 2010 at one clinic), 3,366 patients were known to have died since initiating care in the CNICS cohort (Figure 3.4). Among patients known to have died, the median time from CNICS initiation to death was 2.9 years (IQR: 1.1 – 5.4 years).

Figure 3.4. Crude mortality among all CNICS patients by time since enrollment, 1998-2011



3.1.3. Covariates

- Age was defined at the time of origin for each specific aim: at CNICS enrollment for Specific Aim 1 and at ART initiation for Specific Aim 2. In all instances, age was calculated from mid-year of the reported birth year to the relevant origin date for each of the aims.
- Calendar date of CNICS enrollment was recorded as the date of the second HIV primary care visit at a CNICS site. Patients must attend at least 2 HIV primary care visits before they are enrolled in the CNICS cohort, therefore the date of HIV primary care initiation is not the same as the date of CNICS enrollment. Thus patients who die before attending a second HIV primary care visit and patients who are not retained in care until they can attend a second HIV primary care visit are excluded from these analyses and no information is available to conduct sensitivity analyses to determine the potential impact that exclusion may have on the final results of this study.
- CD4 cell count was reported by the laboratory in cells/mm³. CD4 percent was also reported by CNICS laboratories but was not used in these analyses. CD4 cell count was not available in only 0.5% of all instances where a CNICS patient had a CD4 laboratory assessment.
- HIV-1 RNA viral load was reported by the laboratory in copies/mL and transformed to units of log₁₀ copies/mL. The limit of detection was dependent upon the assays used at each of the CNICS sites and changed over time. For this analysis, HIV-1 RNA values that were below the limit of detection were assigned a value equal to the limit of detection for the assay (i.e., a result of “<50 copies/mL” was assigned a value of 50).
- Antiretroviral therapy naivety was defined as no evidence of prior exposure to mono or dual therapy. If the earliest date of exposure to any antiretroviral drug matched the earliest date of exposure to at least three antiretroviral drugs, the patient was classified as ART naïve.

- AIDS-diagnoses were made at the CNICS site (57%), reported by the patient without outside documentation (18%), or were collected from outside documentation (19%). The remaining 5% of AIDS-defining diagnoses were from unknown sources. If the diagnosis date was missing the day of the month, the diagnosis was assigned to the middle of the month. If the diagnosis date was missing both the day and month, it was assigned to July 1 of the year in which it occurred. Diagnoses that were missing the year were not assigned to the patient.
- Male-to-male sexual contact and injection drug use were collected as part of risk factor data that was not assigned a date of initiation or cessation. Patients for whom injection drug use was ever recorded were assigned injection drug use as a time-independent covariate. Patients for whom male-to-male sexual contact was ever recorded were assigned male-to-male sexual contact as a time-independent covariate. Fifty-eight percent of patients report male-to-male sexual contact and 18% report a history of injection drug use.
- Diagnoses of hepatitis C virus (HCV) infection were made at the CNICS site (67%), reported by the patient without outside documentation (14%), or were collected from outside documentation (15%). The remaining 4% of AIDS-defining diagnoses were from unknown sources. If the diagnosis date was missing the day of the month, the diagnosis was assigned to the middle of the month. If the diagnosis date was missing both the day and month, it was assigned to July 1 of the year in which it occurred. Diagnoses that were missing the year were not assigned to the patient.

3.2. United States Public Health Surveillance for HIV

HIV surveillance in the US is coordinated by the Division of HIV/AIDS Prevention in the CDC. In 1985, many state and local health departments began requiring (through administrative

rules) hospitals, laboratories, and physicians to any evidence of HIV infection in a person in their jurisdiction. It was not until 2008 that all states, the District of Columbia, and 6 US-dependent areas (American Samoa, Guam, Northern Mariana Islands, Puerto Rico, Republic of Palau, and the US Virgin Islands) required confidential, name-based reporting of all HIV infection. State and local jurisdictions investigate and confirm reports of HIV infection, and then transmit de-identified case reports to the CDC using a standard surveillance form. The surveillance form includes information on patient demographics (e.g., sex, race/ethnicity, age) and transmission risk category. When available, initial immune status (i.e., CD4 cell count) and viral load are also collected and reported to the CDC. Some jurisdictions additionally require reporting of all (or a subset of) CD4 cell count and viral load laboratory tests results for HIV-infected persons, which they use to monitor HIV disease progression. Treatment and other clinical data for all HIV-infected persons are not generally available to public health surveillance.

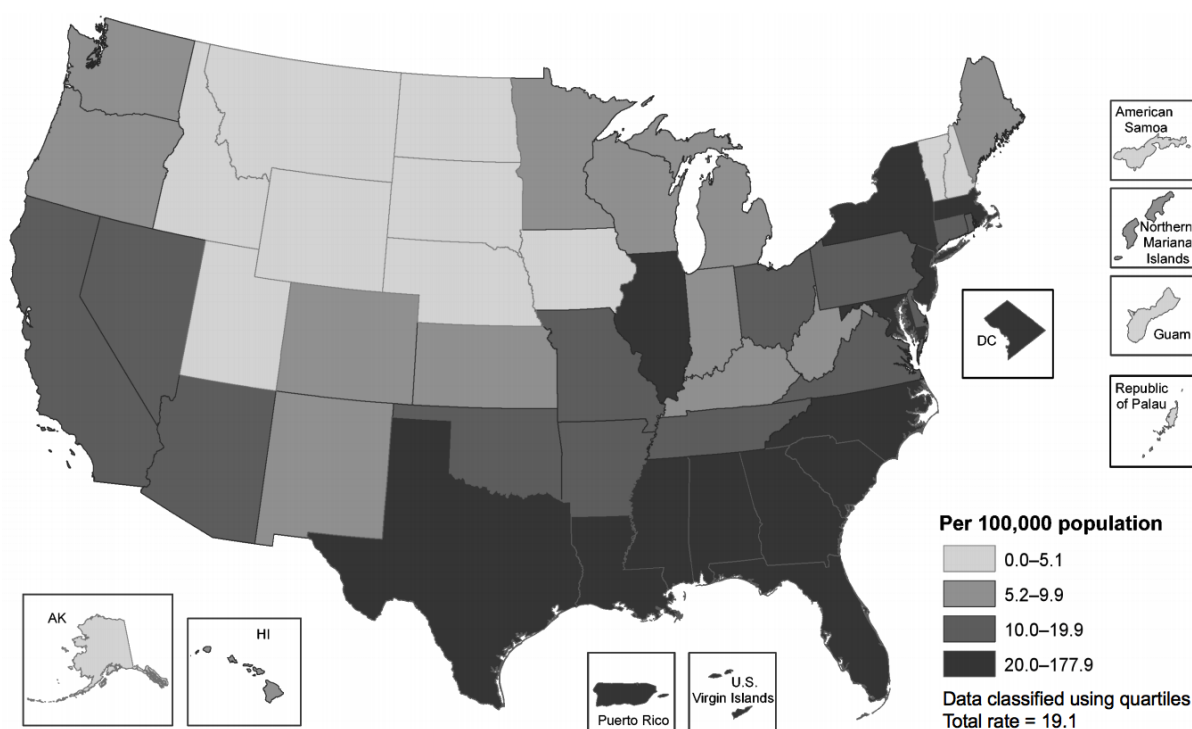
The CDC collects HIV infection case reports from the states, the District of Columbia, and the 6 dependent areas and does a crude check for duplicate reports. Duplicate cases (persons who have previously been HIV-diagnosed in another jurisdiction) are identified through the Routine Interstate Duplicate Review. CDC uses Soundex code generated by the patient's last name, birth date and sex to compare newly reported HIV cases with previously reported cases. CDC alerts the local public health agencies of possible duplicates and the agencies resolve the duplicates using identifiable information.⁶⁷

After waiting for case reporting to be acceptably complete, the CDC analyzes and disseminates data on HIV infection for the US. CDC reports both unadjusted and adjusted data. The unadjusted data is exactly what is reported through the date of analysis. The adjustment to the data is an attempt to delays in reporting (of diagnoses and deaths) and missing transmission

risk category. The adjustments do not attempt to account for incomplete reporting. Adjustments for delays in reporting are based on stratum-specific reporting-delay distributions, which are calculated using a modified semiparametric life-table statistical procedure.⁶⁸ CDC recommends that adjusted data be used in planning, resource allocation, and program evaluation.⁶⁹

The target population for Specific Aim 1 includes all persons over 18 years of age diagnosed with HIV between 1 January 2009 and 31 December 2011 in any of the 50 states, District of Columbia, or 6 US-dependent areas. The target population included 128,945 patients (Figure 3.5).

Figure 3.5. Rates of diagnoses of HIV infection among adults and adolescents, 2011, United States and 6 US-dependent areas



Source: http://www.cdc.gov/hiv/pdf/statistics_2011_HIV_Surveillance_Report_vol_23.pdf

3.2.1. Covariates

For the purposes of surveillance, CDC defines transmission risk category as the most likely mode of HIV transmission.⁸ It is created using a hierarchical decision tree using all risk factor information reported by the patient. Transmission risk category is assigned as follows:

- 1) Male-to-male sexual contact and injection drug use
- 2) Male-to-male sexual contact (alone): includes men who had sexual contact with other men, and men who had sexual contact with both men and women, regardless of their stated sexual identity
- 3) Injection drug use (alone): includes persons who received an injection, either self-administered or given by another person, of a drug that was not prescribed by a physician for that person
- 4) Heterosexual contact: includes persons who had heterosexual contact with a person known to have, or to be at high risk for (e.g., an injection drug user or a man who has sex with men), HIV infection

Race and ethnicity are collected according to the Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity laid out by the Office of Management and Budget in the *Federal Register* for 30 October 1997.⁷⁰

AIDS diagnoses became reportable in 1981, using the same surveillance system described above for HIV diagnoses. By 1986, all 50 states, the District of Columbia, and 6 US-dependent areas had implemented AIDS case reporting. For the purposes of surveillance currently, AIDS is defined as documentation of an AIDS-defining condition (appendix 1) or either a CD4 cell count of <200 cells/ μ L or a CD4 percentage of total lymphocytes of <14. Documentation of an AIDS-defining condition supersedes a CD4 count or percentage that would

not, by itself, be the basis for a stage 3 (i.e., AIDS) classification. For the purposes of Specific Aim 1, AIDS at ‘baseline’ was defined as having an AIDS diagnosis date within 3 months of the HIV diagnosis date reported to HIV surveillance.

3.2.2. Limitations

Not all HIV diagnoses are included in the HIV surveillance data. Some states still offer anonymous HIV testing and positive test results are not included in surveillance data if no personal identifiers are available to allow for deduplication of case reports. Nationally, as of about 2006-2007, completeness of HIV case ascertainment was estimated at between 72% and 95%.^{71,72}

Additionally, because confidential, name-based reporting was not fully implemented across all state and local jurisdictions until 2008, some persons reported as newly HIV diagnosed may actually have been previously diagnosed. If their previous diagnosis was not reported, or reported anonymously under older, code-based systems, any subsequent HIV test will appear to be a new diagnosis without proper investigation by state or local public health officials.

Finally, the HIV diagnosis date reported to surveillance may not be entirely accurate. The year of the HIV diagnosis date reported to surveillance and the HIV diagnosis date reported by the patient in an interview differed in 56% of date pairs nationally, with the self-reported date likely to be the earlier date in 30% of the date pairs.⁷³ In North Carolina, the year of the HIV diagnosis date self-reported by the patient matched the year of the HIV diagnosis date recorded in the medical record and the year of the HIV diagnosis date reported to HIV surveillance in only 67% of cases and 51% of cases, respectively, where both dates were available. The self-reported

date most likely to be the earliest date of the three and the date reported to surveillance was most likely to be the latest date.⁷⁴

CHAPTER 4: METHODS

4.1. Specific Aim 1

4.1.1. Study Sample

The study sample for Specific Aim 1 included ART-naïve patients who initiated care at a CNICS site between 1 January 1998 and 30 December 2011 (or 15 September 2010 for patients at one site). ART naivety was defined as no evidence of prior exposure to mono or dual therapy; patients whose earliest date of exposure to any antiretroviral drug precluded the earliest date of exposure to at least three antiretroviral drugs were excluded from the analysis. Furthermore, patients with missing race/ethnicity were excluded, as were patients classified as intersex, and patients missing data on transmission risk factors.

The target population for Specific Aim 1, to which the estimate of the effect of ART was generalized, was all persons newly diagnosed with HIV in the US between 2008 and 2011. This population was diagnosed after the National HIV/AIDS Strategy was released, and was antiretroviral naïve as we entered an era in which the standard has shifted to providing treatment earlier in the clinical course of infection. The number of HIV-diagnosed persons in categories defined by race/ethnicity, sex, age group, transmission risk and AIDS diagnosis within 3 months of HIV diagnosis was provided by the CDC, Division of HIV/AIDS Prevention, and accounts for delays in reporting new infections.⁸ The marginal distribution of these characteristics is shown in Table 2.1.

The main exposure of interest, ART initiation, was defined as described in detail above, namely initiation of at least 3 antiretroviral drugs on the same day, for at least 30 days. I controlled for confounding due to the following baseline covariates: race/ethnicity; sex; age at CNICS initiation; calendar date of CNICS initiation; CD4 cell count (cells/mm³) and HIV-1 RNA viral load (log₁₀ copies/ml) at CNICS initiation or up to 6 months prior to CNICS initiation; history of injection drug use; history of male-to-male sexual contact; and study site. I further controlled for confounding due to the following time-varying confounder-mediators: history of diagnosis of any AIDS-defining condition; most recent CD4 cell count and viral load measurement; and ART use.

Time-varying covariates, including CD4 cell count, viral load, AIDS diagnosis and hepatitis C virus infection, were updated whenever a patient was seen, with intervals determined by medical providers and by patients' care seeking behavior. Laboratory values were carried forward in time from the most recent observed value until new values were reported. Time since CNICS enrollment was categorized by month to create weights to control time-varying confounding. Time-varying covariates were assigned to the month in which they occurred. To preserve temporality, if a viral load measurement or an AIDS diagnosis occurred in the same month as, but more than 7 days after, ART initiation, the viral load measurement or AIDS diagnosis was assigned to the following month. If there was more than one CD4 cell count or viral load measurement in a particular month (after reassignment of viral load values), the values of all the measurements for that month were averaged.

4.1.2. Statistical Analysis

Survival time was measured in days from CNICS enrollment to death. Patients were administratively censored on 31 December 2011 (or 15 September 2010 for patients at one site to ensure data completeness) or at 5 years of follow up. For patients missing baseline CD4 cell count or HIV-1 RNA viral load, follow up began on the earliest date that both of those measurements became available. This approach is akin to allowing late entries in survival analysis,⁷⁵ and assumes late entries are non-informative.⁷⁶

To mimic an intent-to-treat analysis, once patients initiated ART, they were assumed to remain on treatment for the rest of their time on study. Patients were censored if they initiated any ART medications in a month without initiating three or more drugs (i.e., if they initiated mono- or dual-therapy). Patients who did not have any contact with the CNICS clinic (including therapy initiation or laboratory tests) over a 12-month period were censored 12 months after their last contact. Once patients were censored, they were not allowed to reenter the analysis.

I estimated mortality risks, risk differences, and risk ratios using the complement of the weighted Kaplan-Meier survival function⁷⁷ and described the relative hazard of mortality associated with ART use using a marginal structural Cox proportional hazards model, estimated using inverse-probability weights and using Efron's approximation for tied death times.⁷⁸ Weighting of the Kaplan-Meier survival function is accomplished using inverse probability weighting and is a semiparametric extension of nonparametric direct standardization to the total study population. I controlled for confounding and potentially informative loss-to-clinic in the estimate of effect in the CNICS with weights that were the product of: 1) stabilized inverse probability of treatment weights^{79,80}; and 2) stabilized inverse probability of censoring weights.⁸¹

I standardized estimates to the target population by applying weights that are the product of the previous two weights and scaled inverse probability of sampling weights.^{5,7}

Treatment weights (W_{ij}^X) and censoring weights (W_{ij}^C) were estimated using pooled logistic models, with time defined by months since CNICS enrollment. The inverse probability of treatment weights were defined as:

$$w_{ij}^T = \frac{\prod_{k=0}^j P(X_k = x_{ik} | \bar{X}_{(k-1)} = \bar{x}_{(k-1)i}, \bar{C}_k = 0)}{\prod_{k=0}^j P(X_k = x_{ik} | \bar{X}_{(k-1)} = \bar{x}_{(k-1)i}, \bar{L}_k = \bar{l}_{ki}, V = v_i, \bar{C}_k = 0)}$$

Where X_k is an indicator of treatment in month k ; j denotes the number of whole months since the start of follow-up; and k indexes j so that the weights are specific to the person-month in which they are applied. $\bar{X}_{(k-1)}$ is the history of exposure through month $k-1$, with $\bar{X}_{(-1)}$ defined to be 0. $\bar{L}_k$ is the history of measured time-varying confounders through month k . V is the vector of time-fixed confounders measured at baseline. The inverse probability of censoring weights were defined as:

$$w_{ij}^C = \begin{cases} \frac{\prod_{k=0}^j P(C_k = 0 | \bar{C}_{(k-1)} = 0, \bar{X}_{(k-1)} = \bar{x}_{(k-1)i})}{\prod_{k=0}^j P(C_k = 0 | \bar{C}_{(k-1)} = 0, \bar{X}_{(k-1)} = \bar{x}_{(k-1)i}, \bar{L}_k = \bar{l}_{ki}, V = v_i)}, & C_{ij} = 0 \\ 0, & C_{ij} = 1 \end{cases}$$

Where C_k is an indicator of censoring in month k , j again denotes the number of whole months since the start of follow-up; and k again indexes j so that the weights are specific to the person-

month in which they are applied. $\bar{C}_{(-1)}$ is 0 by definition. X_k , $\bar{X}_{(k-1)}$, $\bar{L}_k$ and V are defined as above.

Inverse probability of sampling weights were defined:

$$w_i^S = \begin{cases} \frac{P(S_i = 1)}{P(S_i = 1|V = v_i)}, & S_i = 1 \\ 0, & S_i = 0 \end{cases}$$

Where S is an indicator of inclusion in the CNICS cohort and V is the vector of time-fixed confounders measured at baseline.

I estimated the denominator of the inverse probability of sampling weights using a logistic regression model for the probability of being in the CNICS cohort based on the joint distribution of baseline covariates in the target population. The model included all second-order interactions. I scaled the weights by the marginal probability of being in the CNICS cohort. To correctly estimate the marginal probability of inclusion in the CNICS, I combined data from the CNICS and the target population, then weighted recently HIV-diagnosed persons (assumed to be a random sample of size m , of a hypothetical, arbitrarily large target population of size N) by $1/[m/(N-n)]$, where n is the size of the study sample. I set N to be 1.1 million; the choice of N did not influence the results. Persons in the CNICS received a weight of 1.

I multiplied all three estimated weights together and then applied the weights to a Cox proportional hazards model for the effect of ART on all-cause mortality. I used the same weights to estimate absolute and relative 5-year mortality from the inverse function of standardized survival curves.^{80,82} I explored changes in the estimates of effect after truncating the weights to reduce the effect of extreme outliers (<0.1 or >10).

The identifying assumptions necessary to conclude that the resultant estimated effect is internally valid include: 1) conditional exchangeability (no unmeasured causes of both the exposure and the outcome);⁸³ 2) positive probability of treatment within every level of covariates (positivity);⁸⁴ 3) treatment variation irrelevance;⁸⁵ 4) no interference (when one person's outcome is affected by another's exposure);⁸⁶ 5) no measurement error;⁸⁷ and 6) correct models specification. These assumptions have been well described.^{79,83,88}

The generalizability assumptions necessary to conclude that the estimated effect is externally valid parallel the identifying assumptions for internal validity: 1) no unmeasured causes of both selection into the sample and the outcome; 2) non-zero probability of being included in the study sample; 3) treatment variation irrelevance or similar versions of treatment in the sample and the target;⁶ 4) no measurement error; 5) no interference or similar patterns of interference in the sample and the target;^{6,86} and 6) correct models specification.^{5,89,90} Under these assumptions, weighting creates a pseudo-population in which the exposure is independent of measured confounders, censoring is independent of exposure and measured confounders, and the distribution of measured effect-modifiers matches that in the target population.

I calculated 95% confidence intervals (CI) using a standard error estimated by the standard deviation from 200 nonparametric bootstrap random samples drawn from the study sample and the target population with replacement.⁹¹ All analyses were carried out using SAS 9.3 (Cary, NC).

4.1.3. Power

Statistical power calculations for marginal structural models have not been developed. The precision for any survival model is dependent upon the number of events and, for weighted

survival models, on the variability in the weights. Prior applications of marginal structural models have been undertaken in smaller cohorts.^{23,92,93} Over 5 years of follow up, there were 918 deaths among 12,457 patients in the study sample, and approximately 32% of the person-time was exposed to ART. With an expected hazard ratio of 0.5, the crude rate ratio under the proposed scenario would have an approximate variance of $[1/(0.32*918) + 1/(0.68*918)] = 0.0050$ and an expected 95% confidence interval of 0.36, 0.64. The power for the naïve analysis was >99%.⁹⁴ Incorporation of weights into the model inflates the variance. In prior applications of marginal structural models, the variance inflation factor has ranged from 1.1 to 2.0.^{23,95-98} A conservative assumption that the variance inflation factor could have been as high as 4, yielded an expected 95% confidence interval in the weighted model of 0.22, 0.78. This was associated with a power of 94%. The precision was expected to be lower for subgroup estimates, but the precision for the overall estimate suggested that I would have enough precision and statistical power to accomplish this aim. Details for the power calculation employed here are available in Appendix B.

4.2. Specific Aim 2

4.2.1. Study Population

The study population for Specific Aim 2 included patients who initiated a first combination ART regimen between 1 January 1998 and 30 December 2011 (or 15 September 2010 for patients at one site). The origin was the date of ART initiation, defined as the first date when data indicated the patient was on 3 or more different antiretroviral drugs.

The cross-classification of race/ethnicity and sex was the exposure of interest. Race and ethnicity are categorized according to US Federal Health Resource and Services Administration standards. Race and ethnicity were combined into one variable, with patients classified as Hispanic, black, white, or other race. Sex was defined based on birth sex, or present sex if birth sex is missing.

Race/ethnicity/sex specific survival curves were standardized to the distribution of the following covariates in the entire study population: age at ART initiation; calendar date of ART initiation; CD4 cell count (cells/mm³) most proximal to ART initiation measured between 6 months prior to 14 days after ART initiation; HIV-1 RNA viral load (log₁₀ copies/ml most proximal to ART initiation measured between 6 months prior to 14 days after ART initiation; antiretroviral therapy naivety (i.e., no evidence of prior exposure to mono or dual therapy); prior diagnosis of any AIDS-defining condition at ART initiation; injection drug use; history of hepatitis C virus (HCV) infection; and study site.

4.2.2. Statistical Analysis

Patients with missing race/ethnicity or patients with race/ethnicity other than white, black, or Hispanic were excluded, because the proportion of patients classified as other race was small, and interpretation of any results for this group would be difficult, given their heterogeneity. I additionally excluded patients classified as intersex, and patients missing data on the other covariates listed above. Characteristics of the study population was described using percentages or medians and quartiles, as appropriate.

Survival time was measured in days from ART initiation until death or administrative censoring on 31 December 2011 or at 10 years of follow up to maintain adequate sized risk sets

(patients from one site were administratively censored on 15 September 2010 to ensure data completeness). I estimated the 10-year mortality risk using the complement of the Kaplan-Meier survival function⁷⁷ standardized to the total study sample at the start of follow up.^{79,80} This is again a semiparametric extension of nonparametric direct standardization using inverse probability weights.⁹⁹ I estimated the denominator of the weights for race/ethnicity and sex categories using polytomous logistic regression, conditional on all measured covariates listed above, using restricted quadratic splines (with 4 knots located at the 5th, 35th, 65th and 95th quantiles) to flexibly model all continuous covariates.¹⁰⁰ Model fit was evaluated using a Hosmer-Lemeshow goodness-of-fit test for generalized logistic regression.¹⁰¹ I stabilized the weights using the site-specific distribution of race/ethnicity and sex.

I calculated crude and standardized absolute and relative difference in mortality risk at 10 years by race/ethnicity and sex categories. I calculated the relative hazard of mortality by race/ethnicity and sex categories with a Cox regression model¹⁰² using Efron's approximation for tied death times.⁷⁸ I calculated Confidence Intervals using a standard error estimated by the standard deviation from 200 nonparametric bootstrap samples.⁹¹ I assessed the proportional hazards assumptions by visual inspection of a plot of the log cumulative hazard by time, as well as with a statistical test of the product terms for race and sex categories with time. Because unstabilized weights were poorly behaved, stabilizing by the site-specific distribution of race/ethnicity and sex was necessary. To examine the potential effects of residual confounding by site, in a supplementary analysis, I calculated site-stratified hazard ratios.

To assess whether the magnitude of disparities in survival have changed over time, I stratified follow-up time into early and late calendar periods, varying the cut point from 2002 to 2008 by increments of 2 years, and then tested the significance of interactions between time

period and race/ethnicity and sex in a Cox model. To assess how disparities observed in the CNICS compared with survival disparities seen in the US general population, I present age- and calendar time-standardized mortality rates for the general population, which I calculated from vital statistics data downloaded from CDC WONDER.¹⁰³ To assess possible hypotheses about mechanisms for disparities in survival, I calculated the proportion of patients retained in care (no gaps in laboratory monitoring >1 year within 2 years of therapy initiation) and the proportion of patients who achieved and maintained viral suppression (defined as <400 copies/mL) at 1 year after therapy initiation, stratified by race/ethnicity and sex. Patients who died within the first 2 years of follow-up without experiencing a gap in laboratory monitoring were considered retained in care. Patients who died before achieving viral suppression (1%) were considered not virally suppressed. All analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC).

4.2.3. Rationale

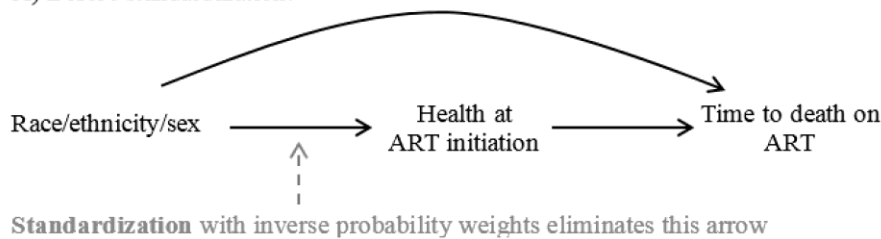
Standardization:

One might question the decision to standardize estimates at all, noting that there should be no confounding in the crude estimate (Figure 4.1.A). The argument against standardizing the estimate of association would be that: 1) I am not claiming to estimate a causal effect; or 2) a confounder is not something affected by the exposure and the covariates that I selected are typically thought of as being downstream from race (i.e., age at ART initiation may reflect differences in HIV incidence and in care seeking patterns among different racial/ethnic/sex subgroups). However, in this instance, interest is in heterogeneity in survival after ART initiation, and thus I have chosen to minimize variation in survival due to disparities before ART

is initiated. Differences in disease stage at ART initiation and subsequent ART use and adherence have been documented by race and ethnicity^{13,15,31,50} and by sex.^{15,34} Differences in disease stage at ART initiation should be controlled for in analyses seeking to estimate the effect of ART because they reflect differential access to care prior to exposure (Figure 4.1.B).¹⁰⁴

Figure 4.1. Directed Acyclic Graph for the 'effect' of race/ethnicity/sex on mortality among treated, HIV-infected persons

A) Before standardization:



B) After standardization:



Decision to not censor:

Censoring patients when they stop treatment or leave the cohort estimates the association of race/ethnicity and sex with mortality conditional on remaining on treatment. If the association between a patient's decision to stop ART or leave the CNICS cohort and his or her potential outcome is confounded, conditioning on remaining on treatment and in the cohort will result in a confounded estimate of the association of race/ethnicity and sex with mortality. Likewise, differences in adherence have been explored as a possible explanation for disparities in

mortality,¹⁸ and some studies support this hypothesis. Adjusting for time varying CD4, viral suppression, ART status and adherence negated observed racial/ethnic differences in hazard of death in a clinical trial⁵⁰ and in an observational cohort.¹⁵ While such ad-hoc attempts at mediation analysis are potentially useful for hypothesis generation, noted problems with collider stratification bias in mediation analysis precluded us from exploring them in this study. I instead estimated the total association of race/ethnicity with mortality after ART initiation.

4.2.4. Power

Given the sample size, I had 80% power to detect a 10-year risk difference of 6.4% comparing black patients to white patients, a risk difference of 13.4% comparing Hispanic patients to white patients, and a risk difference of 7.8% comparing women to men.⁹⁴

CHAPTER 5: RESULTS. THE EFFECT OF ANTIRETROVIRAL THERAPY ON ALL-CAUSE MORTALITY IN THE CNICS, GENERALIZED TO PERSONS DIAGNOSED WITH HIV IN THE UNITED STATES, 2009-2011

The magnitude of the survival benefit of ART among recently diagnosed persons in the US is unclear because existing estimates are derived from cohorts that differ substantially in terms of clinical status, race/ethnicity, age, transmission group and access to care.^{3,22,23} Furthermore, the effect of ART appears to be heterogeneous across these same patient characteristics that differ between previously studied cohorts and recently HIV-diagnosed persons in the US.^{6,89} The objective of this aim was to estimate anticipated reduction in 5-year, all-cause mortality if all persons recently HIV-diagnosed in the US from 2009 to 2011 (the target population) had been prescribed ART immediately after diagnosis versus if treatment had been delayed. To accomplish this, I first described the effect of ART on survival in the CNICS clinical cohort, which is somewhat representative of, but not identical to, the target population. I then explored the impact of this residual non-representativeness by describing subgroup effects in the CNICS and presenting an overall estimate of the effect of ART reweighted to match the target population. A detailed description of the methods is available in section 4.1 of this document.

5.1. Results

Overall, 12,457 patients in the CNICS met the inclusion criteria, most of whom were male and of white race (Table 5.1). The median age at CNICS initiation was 38 years old. The median CD4 cell count and viral load were 304 cells/ μ L and 46,276 copies/mL, respectively.

Nearly one fifth of CNICS patients had a history of an AIDS-defining illness at enrollment (18.7%). Injection drug use (18.7%) and hepatitis C virus co-infection were also common (14.0%).

Patients were followed for a median of 32 months [Interquartile Range (IQR): 17, 60]. During 437,892 person-months of follow-up, 8,703 patients (69%) initiated ART, 5,390 patients (43%) were lost to clinic, and 918 patients died. Overall, 5-year mortality in the cohort was 11.3% (95% CI: 10.5%, 12.0%).

Predictors of ART initiation and censoring are listed in Table 5.2. Treatment and censoring weights were well-behaved and weight models using different functional forms of covariates yielded similar results for the effect of ART on survival.

In the CNICS cohort, after accounting for time-fixed and time-varying confounding, ART lowered the absolute risk of mortality by -17.7% (95% CI: -27.0%, -8.4%; Table 5.4). The hazard ratio (HR) for all-cause mortality in the CNICS due to ART was 0.33 (95% CI: 0.25, 0.43). The effect of ART on survival varied across subgroups of patients, although most subgroup effects were not statistically significantly different. The risk difference (RD) for mortality due to ART use was -14.4% (95% CI: -23.2%, -5.7%) among patients with no reported history of injection drug use, compared to -18.1% (95% CI: -31.8%, -4.4%) among patients with a history of injection drug use. ART was strongly protective against 5-year mortality for patients with lower CD4 cell counts at baseline and less protective as baseline CD4 increased [RD=-29.3% (95% CI: -43.4%, -15.2%) for those with baseline CD4 $\leq$ 200 cells/mm³ versus RD=-2.5% (95% CI: -6.0%, 1.0%) for those with baseline CD4 >500 cells/mm³]. ART was also more strongly protective for patients with a prior AIDS diagnosis [RD=-22.8% (95% CI: -38.3%, -7.3%)] than for those with no prior AIDS diagnosis [RD=-13.4% (95% CI: -21.3%, -5.5%)].

Finally, among white patients, the RD for AIDS initiation was -17.3% (95% CI: -28.9%, -5.8%), compared to -11.3% (95% CI: -20.4%, -2.2%) among black patients and -10.1% (95% CI: -21.8%, 1.6%) among Hispanic or Latino patients (Table 5.3).

Compared to CNICS patients, more people diagnosed with HIV in the US during 2009 through 2011 were women, Hispanic or Latino, or black. More recently HIV-diagnosed persons were diagnosed at younger or older age compared to CNICS patients at enrollment. More CNICS patients were diagnosed with AIDS at baseline and fewer had a history of injection drug use (Table 5.1). All covariates in the sampling model were strong predictors of inclusion in the CNICS (Table 5.2). Inverse probability of sampling weights were well-behaved.

The effects estimated after standardizing to persons recently HIV diagnosed in the US using inverse probability of sampling weights were similar to those estimated in the CNICS. The estimated RD in the US was -19.1% (95% CI: -30.5%, -7.8%) and the HR was 0.32 (95% CI: 0.23, 0.45) (Table 5.4).

5.2. Discussion

ART initiation substantially decreased 5-year mortality among patients in the CNICS. The effect of ART on mortality was heterogeneous across subgroups of patients defined by patient characteristics that were also predictors of inclusion in the CNICS. Despite the effect heterogeneity and differences between the study sample and the target population, the magnitude of the survival benefits of ART among recently HIV-diagnosed persons in the US were similar to those seen in the CNICS.

Despite different study samples and inclusion criteria, the hazard ratio due to ART estimated in the CNICS is consistent with previously published estimates which have ranged

from 0.14 to 0.54.^{3,22,23} This analysis improves on previous studies estimating the effect of ART by presenting cumulative incidence curves and absolute differences in risk, in addition to hazard ratios, which are arguably more useful to policy makers for planning.^{105,106} Furthermore, in this analysis I estimated the effect of ART on death alone, as opposed to the effect of ART on time to AIDS or death (this was also true in the most recent study).³ In the ART era, the risk of mortality following AIDS diagnosis is significantly reduced¹⁰⁷ making death a more relevant clinical outcome. I excluded patients who were not ART naïve, consistent with current treatment standards.¹⁰⁸ Finally, I included people with an AIDS diagnosis at baseline, in line with the reality that many patients are diagnosed with AIDS and HIV almost concurrently and will not have the opportunity to start ART before they are diagnosed with AIDS.²⁴

I was interested in estimating the effect of ART on all-cause mortality among recently HIV-diagnosed persons in the US. For an estimate from a study sample to directly generalize to a specific target population in expectation, either the study sample must be a random sample of the target population or those covariates that predict selection into the study sample must not also be causes of the outcome^{89,90} (in addition to assuming no interference⁸⁶ and similar versions of treatment or treatment variation irrelevance).⁶ Because it was not logistically or financially feasible to randomly sample from the target population, I conducted the analysis in the CNICS. The CNICS cohort is similar to the target population on many structural factors, including the health care delivery system and social context. However, CNICS patients characteristics are still not identical to the characteristics of persons in the target population. We do not, as of yet, have a good understanding of the degree to which non-representativeness and non-significant departures from effect homogeneity across multiple subgroups may interact to produce changes in the final standardized estimate for the target population. Therefore, rather than relegating

considerations of external validity of the results to a thought exercise in the discussion of this manuscript, I applied a formal correction for non-random sampling into the study sample (inverse probability weights for sampling). This formal assessment of generalizability provides confidence in the generalizability of any research in the CNICS that uses mortality as an outcome. The assumptions required for using these methods are detailed further in section 7.1 of this document.

I believe these results are unlikely to be to have been meaningfully affected by measurement and selection bias. CNICS relies on pharmacy or physician notes in the medical record to indicate initiation of ART drugs. ART is not accessible to patients outside the clinical setting, so the specificity of this measurement should be very high. Some patient records indicated very short courses of therapy, leading to uncertainty as to whether or not therapy had actually been initiated. Applying different windows of minimal ART use (0-30 days) to define ART initiation did not meaningfully change the results. I assumed that once patients initiated ART, they remained on ART. I could not assess ART discontinuation rates in the CNICS because discontinuation dates have not yet been constructed across the entire study period. However, in other studies, ART discontinuation was rare.^{22,23} Furthermore, using all-cause mortality as an endpoint reduces the probability of outcome measurement error because there is nearly complete ascertainment of outcomes. Finally, prior analyses have shown that, despite high rates of loss-to-clinic, the effect of loss-to-clinic on mortality is minimal in the CNICS and inverse probability of censoring weighting of persons who are retained in the clinic is sufficient to reconstruct the crude mortality curves.¹⁰⁹

When generalizing the estimate from CNICS to persons newly diagnosed with HIV in the US, I may not have controlled for all causes of selection into the sample and of the outcome.

CD4 cell count and viral load at baseline were associated with the risk of all-cause mortality, but neither were available in the national surveillance data for all persons at the time they were HIV-diagnosed. Not all HIV-infected persons have laboratory tests drawn immediately proximate to their diagnosis, and not all states currently collect prognostic laboratory results through HIV surveillance. Furthermore, even if prognostic laboratory measurements were somehow available for all newly diagnosed persons (e.g., if prognostic laboratory values were measured on all blood samples used to confirm HIV diagnosis), if those persons don't immediately enter HIV care, the values of those measurements may worsen and not be comparable to the baseline CD4 cell counts and viral loads observed in CNICS patients at CNICS enrollment. Failing to account for differences in the distribution of CD4 cell count and viral load at baseline between the CNICS and target population may be a source of residual bias in the generalized effect estimate.¹¹⁰ However, sensitivity analyses indicated that even modest shifts in the average CD4 or viral load of patients in the target population as compared to CNICS failed to appreciably alter the estimated effect of ART (Table 5.5). Treatment versions may differ between the CNICS and the target population as CNICS patients are all treated in academic medical centers, which may influence patient adherence and quality of care.¹¹¹ There was a positive probability of inclusion in the CNICS in nearly all strata of covariates, owing to the diversity of the CNICS cohort, which was reflected in the stability of the inverse probability of sampling weights. Finally, generalizability may be threatened in the presence of interference;⁸⁶ however, interference is likely negligible for this exposure-outcome relationship.

In this study, I showed that ART reduced mortality in a cohort that is geographically and clinically representative of persons recently diagnosed with HIV in the US. The estimates obtained in the cohort and in the formal generalization to the target population of recently HIV-

diagnosed persons in the US were similar. Furthermore, by including persons with prior AIDS diagnosis at baseline, and by excluding people with prior exposure to dual- or mono-therapy, the estimated effect is pertinent to current standards of clinical care. Although there was some heterogeneity in the effect of ART across sub-populations and differences in the distribution of those sub-populations between the CNICS and the target population, this heterogeneity did not change the overall estimate of the effect of ART among persons recently diagnosed with HIV in the US after appropriate weighting.

Table 5.1. Characteristics of persons enrolled in the Center for AIDS Research Network of Integrated Clinical Systems (CNICS) during 1998-2012, and persons diagnosed with HIV in the United States during 2009-2011

	CNICS Study Sample at Enrollment	Recently HIV-Diagnosed Persons in the United States, 2009-2011
Total N	12,457	128,945
Sex		
Male	10,265 (82)	100,819 (78)
Female	2,282 (18)	28,126 (22)
Age		
Median age (IQR)	38 (31, 45)	
18-24 years	980 (8)	25,535 (20)
25-34 years	3,731 (30)	35,625 (28)
35-44 years	4,766 (38)	31,153 (24)
45-54 years	2,471 (20)	25,030 (19)
≥55 years	599 (5)	11,602 (9)
Race/ethnicity		
White	5,539 (44)	36,635 (28)
Black	4,789 (38)	60,516 (47)
Hispanic	1,635 (13)	26,079 (20)
Other	584 (5)	5,715 (4)
History of AIDS at baseline	2,343 (19)	32,896 (26)
HIV risk category		
History of injection drug use only	1,440 (12)	6,324 (5)
Male-to-male sexual contact only	6,606 (53)	77,802 (60)
Injection drug use and male-to-male sexual contact	903 (7)	4,105 (3)

*Abbreviations: CNICS, Centers for AIDS Research Network of Integrated Clinical Systems; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; IQR, interquartile range.

Table 5.2. Characteristics associated with initiation of 3+ antiretroviral medications (ART), censoring, and CNICS enrollment for 12,547 HIV-positive patients receiving care at CNICS sites, 1998-2011

	ART Initiation		Censoring		CNICS Enrollment	
	Hazard Ratio	95% Confidence Interval	Hazard Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
Male sex	0.97	0.90, 1.04	1.19	1.10, 1.30	1.45	1.36, 1.54
Age at CNICS enrollment						
18-24 years					0.27	0.26, 0.30
25-34 years					0.71	0.68, 0.75
35-44 years					1.	
45-54 years					0.61	0.58, 0.65
≥55 years					0.32	0.29, 0.35
Race/ethnicity						
White	1.		1.		1.	
Black	0.88	0.83, 0.93	0.94	0.88, 1.01	0.55	0.53, 0.57
Hispanic	0.86	0.80, 0.92	1.00	0.92, 1.09	0.41	0.38, 0.43
Other	0.96	0.85, 1.07	1.04	0.91, 1.18	0.69	0.64, 0.72
Calendar year of CNICS enrollment, per year	1.08	0.07, 1.09	1.02	1.01, 1.03		
Prior AIDS diagnosis	1.19	1.11, 1.26	0.88	0.82, 0.95	0.59	0.57, 0.62
Injection drug use	0.68	0.63, 0.73	0.96	0.88, 1.04	2.17	2.06, 2.30
Male-to-male sexual contact	1.11	1.05, 1.19	0.89	0.82, 0.96	0.68	0.64, 0.72
Hepatitis C virus infection	0.93	0.86, 1.00	0.92	0.84, 1.00		
ART use	NA		0.34	0.32, 0.37	NA	

*Abbreviations: ART, antiretroviral therapy; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; CNICS, Center for AIDS Research Network of Integrated Clinical Systems

Table 5.3. Modification of the effect of 3+ antiretroviral medications (ART) on all-cause mortality for 12,547 HIV-positive patients receiving care at CNICS sites, 1998-2011

	ART Exposed, 5-year Mortality Risk, %	ART Unexposed, 5-year Mortality Risk, %	Risk Difference, % (95% CI)	Risk Ratio (95% CI)	Hazard Ratio (95% CI)
Overall	10.6 (9.3, 11.9)	28.3 (19.1, 37.5)	-17.7 (-27.0, -8.4)	0.37 (0.26, 0.53)	0.33 (0.25, 0.43)
Sex					
Male	10.1 (8.7, 11.5)	20.6 (15.2, 26.0)	-10.5 (-16.1, -4.8)	0.49 (0.36, 0.67)	0.35 (0.27, 0.45)
Female	11.8 (9.7, 14.0)	29.1 (13.1, 45.1)	-17.3 (-33.5, -1.1)	0.41 (0.23, 0.71)	0.41 (0.26, 0.64)
Age at CNICS start					
18-24 years	2.6 (0.7, 4.5)	1.5 (0.0, 9.4)	1.2 (-7.0, 9.4)	1.79 (0.27, 12.03)	1.77 (0.00, 1140.12)
25-34 years	6.7 (5.3, 8.2)	22.1 (10.2, 34.0)	-15.3 (-27.4, -3.3)	0.31 (0.16, 0.58)	0.38 (0.21, 0.66)
35-44 years	10.9 (8.5, 13.2)	18.1 (12.4, 23.8)	-7.2 (-13.2, -1.2)	0.60 (0.41, 0.87)	0.43 (0.32, 0.57)
45-54 years	15.6 (12.3, 19.0)	44.7 (25.1, 64.2)	-29.0 (-48.8, -9.2)	0.35 (0.21, 0.59)	0.24 (0.16, 0.37)
≥55 years	12.2 (15.1, 27.3)	33.5 (17.2, 49.8)	-12.3 (-30.0, 5.4)	0.63 (0.35, 1.14)	0.38 (0.18, 0.78)
Race/ethnicity					
White	8.2 (6.6, 9.8)	25.5 (14.2, 36.9)	-17.3 (-28.9, -5.8)	0.32 (0.19, 0.53)	0.26 (0.18, 0.38)
Black	14.4 (11.9, 16.9)	25.7 (16.7, 34.6)	-11.3 (-20.4, -2.2)	0.56 (0.38, 0.82)	0.44 (0.33, 0.58)
Hispanic	6.1 (4.3, 7.9)	16.2 (4.5, 27.7)	-10.1 (-21.8, 1.6)	0.38 (0.15, 0.92)	0.37 (0.19, 0.72)
Other	11.5 (4.9, 18.1)	22.9 (1.7, 44.1)	-11.4 (-33.8, 10.9)	0.50 (0.15, 1.62)	0.74 (0.35, 1.57)
Baseline CD4 count					
≤200 cells/mm ³	17.2 (15.6, 18.9)	46.5 (32.7, 60.4)	-29.3 (-43.4, -15.2)	0.37 (0.27, 0.52)	0.26 (0.21, 0.33)
201-350 cells/mm ³	7.6 (5.6, 9.5)	17.7 (5.1, 30.2)	-10.1 (-22.8, 2.5)	0.43 (0.21, 0.89)	0.42 (0.26, 0.68)
351-500 cells/mm ³	5.5 (2.0, 6.8)	12.6 (0.5, 24.7)	-7.1 (-19.4, 5.1)	0.44 (0.14, 1.32)	0.51 (0.26, 0.99)
>500 cells/mm ³	4.4 (2.0, 6.8)	6.9 (4.6, 9.2)	-2.5 (-6.0, 1.0)	0.64 (0.32, 1.28)	0.71 (0.37, 1.37)

Table 5.3. (Continued) Modification of the effect of 3+ antiretroviral medications (ART) on all-cause mortality for 12,547 HIV-positive patients receiving care at CNICS sites, 1998-2011

	ART Exposed, 5-year Mortality Risk, %	ART Unexposed, 5-year Mortality Risk, %	Risk Difference, % (95% CI)	Risk Ratio (95% CI)	Hazard Ratio (95% CI)
Baseline viral load					
<10,000 copies/mL	5.2 (3.2, 7.2)	10.6 (5.5, 15.7)	-5.4 (-10.8, -0.1)	0.49 (0.26, 0.90)	0.55 (0.31, 0.98)
10,000-99,999 copies/mL	9.6 (7.8, 11.4)	23.7 (12.2, 35.3)	-14.1 (-26.2, -2.1)	0.40 (0.22, 0.73)	0.50 (0.35, 0.72)
≥100,000	13.8 (12.1, 15.6)	42.5 (26.1, 58.9)	-28.7 (-45.3, -12.1)	0.35 (0.21, 0.51)	0.20 (0.15, 0.26)
AIDS at baseline					
Yes	20.7 (17.9, 23.5)	47.5 (27.9, 59.1)	-22.8 (-38.3, -7.3)	0.48 (0.32, 0.70)	0.39 (0.30, 0.54)
No	7.6 (6.4, 8.7)	20.9 (13.2, 28.7)	-13.4 (-21.3, -5.5)	0.36 (0.24, 0.54)	0.28 (0.20, 0.40)
Injection drug use					
Yes	20.4 (15.6, 25.2)	38.5 (25.4, 51.6)	-18.1 (-31.8, -4.4)	0.53 (0.35, 0.81)	0.49 (0.34, 0.72)
No	7.8 (7.0, 8.7)	22.3 (13.7, 30.9)	-14.4 (-23.2, -5.7)	0.35 (0.23, 0.53)	0.30 (0.23, 0.40)
MSM					
Yes	7.0 (5.6, 8.4)	15.0 (9.3, 20.7)	-8.0 (-13.9, -2.0)	0.47 (0.30, 0.72)	0.32 (0.23, 0.45)
No	15.1 (12.7, 17.4)	32.1 (22.1, 42.1)	-17.1 (-27.4, -6.7)	0.47 (0.33, 0.66)	0.39 (0.29, 0.51)

*Abbreviations: ART, antiretroviral therapy; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; CNICS, Center for AIDS Research Network of Integrated Clinical Systems; MSM, male-to-male sexual contact

Table 5.4. Effect of 3+ antiretroviral medications (ART) on all-cause mortality for: 1) persons enrolled in the Center for AIDS Research Network of Integrated Clinical Systems (CNICS) during 1998-2012; and 2) persons diagnosed with HIV in the United States during 2009-2011

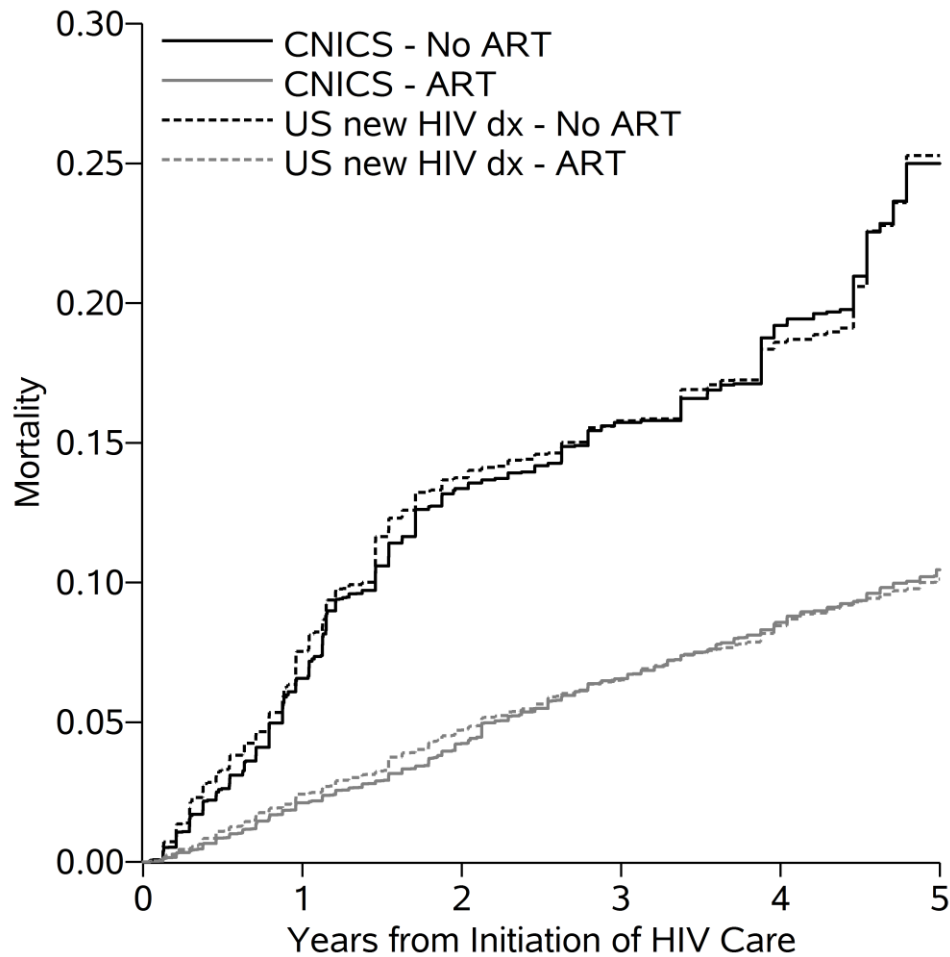
	5-year Mortality Risk, % (95% Confidence Interval)	Risk Difference, % (95% Confidence Interval)	Risk Ratio (95% Confidence Interval)	Hazard Ratio (95% Confidence Interval)
CNICS sample				
Crude				
No ART	12.1 (10.0, 14.3)	0.	1.	1.
ART	11.3 (10.4, 12.1)	-0.9 (-3.2, 1.5)	0.93 (0.76, 1.13)	1.01 (0.87, 1.17)
Weighted				
No ART	28.3 (19.1, 37.5)	0.	1.	1.
ART	10.6 (9.3, 11.9)	-17.7 (-27.0, -8.4)	0.37 (0.26, 0.53)	0.33 (0.25, 0.43)
HIV-diagnosed, United States				
No ART	29.5 (18.2, 40.8)	0.	1.	1.
ART	10.4 (9.2, 11.6)	-19.1 (-30.5, -7.8)	0.35 (0.23, 0.53)	0.32 (0.23, 0.45)

*Abbreviations: ART, antiretroviral therapy

Table 5.5. Sensitivity analysis examining hazard ratios for 3+ antiretroviral medications (ART) on all-cause mortality among persons diagnosed with HIV in the United States during 2009-2011 (target population) assuming different distributions of CD4 cell count and viral load in the target (unmeasured) as compared to the CNICS study sample

CD4 Cell Count in Target is on Average...	Viral Load in the Target is on Average...		
	10,000 Lower Than the Sample for Patients with a Predicted Viral Load >100,000	Equal to Sample	10,000 Higher Than the Sample
200 cells/mL higher than the sample	0.45 (0.28, 0.71)	0.38 (0.23, 0.63)	0.40 (0.25, 0.65)
100 cells/mL higher than the sample	0.40 (0.27, 0.60)	0.35 (0.24, 0.50)	0.35 (0.24, 0.53)
50 cells/mL higher than the sample	0.37 (0.25, 0.55)	0.35 (0.25, 0.49)	0.34 (0.23, 0.49)
Equal to sample	0.35 (0.24, 0.52)	0.34 (0.24, 0.47)	0.32 (0.22, 0.46)
50 cells/mL lower than the sample	0.33 (0.23, 0.48)	0.32 (0.23, 0.45)	0.30 (0.21, 0.43)
100 cells/mL lower than the sample	0.31 (0.22, 0.45)	0.30 (0.21, 0.42)	0.29 (0.20, 0.41)
200 cells/mL lower than the sample	0.34 (0.23, 0.50)	0.33 (0.22, 0.50)	0.32 (0.21, 0.47)

Figure 5.1. 5-year all-cause mortality under two potential interventions: always treat versus never treat with 3+ antiretroviral medications (ART) among: 1) persons enrolled in the Center for AIDS Research Network of Integrated Clinical Systems (CNICS) during 1998-2012; and 2) persons diagnosed with HIV in the United States during 2009-2011



CHAPTER 6: RESULTS. TEN-YEAR SURVIVAL BY RACE/ETHNICITY AND SEX AMONG TREATED, HIV-INFECTED ADULTS IN THE UNITED STATES

HIV/AIDS is a social malady as well as an infectious disease, with infection and morbidity most prevalent among vulnerable and underserved groups. Overcoming disparities in morbidity and mortality among people living with HIV is a principal tenet of the US National HIV/AIDS Strategy.¹¹² Implementing strategies to reduce disparities, however, requires knowledge about whether disparities are arising as opposed to persisting across the continuum of HIV care. In this aim, I describe 10-year all-cause mortality after therapy initiation between 1998 and 2011 by race, ethnicity and sex among a sample of adult patients in the US. I present standardized results to estimate disparities arising after therapy initiation, controlling for differences in pre-treatment health status. A detailed description of the methods is available in section 4.2 of this document.

6.1. Results

The median age in the study sample was 40 years (interquartile range (IQR): 33, 46) and the median year of therapy initiation was 2006 (IQR: 2003, 2009). The median baseline CD4 count and viral load were 238 cells/mm³ (IQR: 85, 385) and 4.7 log₁₀ copies/ml (IQR: 3.9, 5.3), respectively (Table 6.1). Most patients (88%) were treatment-naïve, 27% had a prior AIDS-defining condition, 18% had a history of injection drug use and 16% had a history of hepatitis C virus infection. The median time spent in the CNICS prior to initiation of therapy was 68 days (IQR: 21-371 days). The prevalence of a prior AIDS-defining condition at baseline was 22%

among white men, compared with 28% to 34% of persons in all other race/ethnicity and sex groups. Additionally, 30% of white women had a history of injection drug use, compared to only 12% to 19% in all other race/ethnicity and sex groups, with a correspondingly high risk of HCV infection.

Patients were followed for a median of 4.7 years (IQR: 2.2, 8.2). During 51,121 person-years of follow up, 1,224 of the 10,017 patients died. The overall crude 10-year mortality risk was 20.2% (95% CI: 19.2%, 21.3%) and the overall crude mortality rate was 2.39 deaths per 100 person-years (95% CI: 2.26, 2.53). The crude 10-year mortality risk was 27.0% (95% CI: 24.6%, 29.3%) among black men and 25.0% (95% CI: 21.6%, 28.4%) among black women. In contrast, the crude 10-year mortality risk was only 16.8% (95% CI: 15.1%, 18.5%) among white men and 17.5% (95% CI: 12.9%, 22.1%) among white women. Among Hispanic men and women, the crude 10-year mortality risk was 12.5% (95% CI: 9.5%, 15.5%) and 12.0% (95% CI: 4.5%, 19.4%), respectively (Figure 3.1).

Black men and women experienced a standardized 10-year risk of mortality that was 7.2% (95% CI: 4.3%, 10.1%) and 7.9% (95% CI: 3.9%, 12.0%) larger than white men. The standardized 10-year risk of mortality was 4.0% (95% CI: -8.5%, 0.4%) less among white women compared to white men. Among Hispanic men and women, the standardized 10-year risk of mortality was 3.2% (95% CI: -7.1%, 0.8%) and 7.1% (95% CI: -16.1%, 1.9%) less, respectively than the mortality risk among white men. Standardized risk ratios and hazard ratios exhibited a similar pattern (Table 6.2). Stratifying on CNICS site did not substantively change the results, but it slightly attenuated the estimated relative hazard of all-cause mortality for black men and women, and shifted the estimated relative hazard for white women and Hispanic men and women downwards, away from the null (Table 6.6).

Mortality risk followed similar patterns by race/ethnicity, regardless of sex. The standardized 10-year all-cause mortality risk was 8.2% larger for black patients (95% CI: 5.6%, 10.8%) and 2.7% smaller than for Hispanic patients (95% CI: -6.6%, 1.1%) compared to white patients. Mortality risk also followed similar patterns by sex, regardless of race/ethnicity. The standardized 10-year all-cause mortality risk for women was 2.2% larger than men (95% CI: -0.7%, 5.2%).

Disparities in survival did not change significantly over the study period (p-values for interaction between time period and race/ethnicity and sex were 0.14 when the time period was divided into pre- and post-2002, 0.66 for 2004, 0.75 for 2006, and 0.43 for 2008).

The mortality rate ratio comparing black men with white men in the CNICS was higher than the mortality rate ratio comparing black men with white men in the US general population. The mortality rate ratio comparing black women with white men vastly exceeds the mortality rate ratio comparing black women with white men in the US general population. The relative rate of mortality for Hispanic men and women compared with white men in the CNICS was higher and closer to the null than the relative rate of mortality for Hispanic men and women with white men in the US general population (Table 6.3).

Overall, 66.6% (95% CI: 65.7%, 67.5%) of patients were virally suppressed around 1 year after ART initiation and 75.9% (95% CI: 75.1%, 76.8%) of patients were retained in care at 2 years after ART initiation. There were substantial differences in viral suppression at 1 year post-ART initiation that may point to mechanisms for disparities in survival. Only 59.5% (95% CI: 58.0%, 61.1%) of black patients were virally suppressed at 1 year after ART initiation, compared to 70.9% (95% CI: 69.6%, 72.2%) of white patients and 72.0% (95% CI: 69.7%, 74.3%) of Hispanic patients. Patterns were similar in men and women. There were only minor,

non-significant differences in retention in care at 2 years post-ART initiation by race/ethnicity and sex. Weighting the data to standardize on baseline covariates had little impact on the results (Table 6.4).

6.2. Discussion

There was a markedly higher risk of death from any cause among black men and women compared to other race/ethnicity groups in the CNICS cohort following antiretroviral therapy initiation. Survival by race/ethnicity and sex varies substantially in the general US population due to differences in the prevalence of non-HIV-related conditions like diabetes, hypertension, kidney disease and violence, for example.¹¹³ As a result, by estimating the risk of all-cause mortality, rather than focusing specifically on AIDS-defining illness-associated mortality, I have likely captured differences in the risk of non-AIDS-related causes of death. However, the disparities seen in the CNICS comparing mortality among black persons with white men exceeds the disparities in the US general population comparing black person with white men, especially for black women.¹⁰³ Standardized estimates control for disparities in HIV-related health status prior to therapy initiation;^{13-15,114} the overall lower survival among HIV-infected black persons is only compounded by disparities after therapy initiation as is evident in contrasts of crude mortality risks. Although a thorough mediation analysis is beyond the scope of this study, I observed lower viral suppression at 1-year after therapy initiation among black patients. Other studies have documented greater loss-to-follow-up, more missed visits, and poorer therapy adherence among black patients,^{59,115} which may explain some of the survival disparities observed in this cohort.

The 10-year mortality risk in the CNICS cohort was slightly lower for Hispanic patients compared to non-Hispanic white patients. Although Hispanic men and women in the CNICS tend to experience lower mortality rates than white men, the magnitude of rate ratio is less than the rate ratio comparing Hispanic men and women to white men in the general population.¹⁰³ The survival advantage that Hispanic persons in the general population is still incompletely understood.¹¹⁶ As such, it is difficult to interpret the relative risk of mortality for Hispanics in the CNICS as a survival advantage (since they do better than their white male counterparts) or as a disadvantage (since they do not do as much better as their HIV-uninfected counterparts). This study is one of a few with sufficient size to estimate survival among Hispanic ART initiators. In some settings, Hispanic patients appear to have poorer retention in care¹¹⁷ and lower probability achieving viral suppression³³ as compared to white patients. However, other studies have found no evidence of ethnic disparities for similar outcomes,¹¹⁸ or even a lower hazard of AIDS incidence or death for Hispanic patients with equal access to care.¹⁷ The discrepant results may be due to many factors including: exposure misclassification associated with self-reported ethnicity; geographical differences in structural discrimination and access to care experienced by Hispanics; or the heterogeneity of the Hispanic community, owing to different countries of origin, residency statuses and generations since immigration to the US, among other things.¹¹⁹

Mortality risk observed in the CNICS was similar or slightly higher among women than among men after accounting for differences in baseline covariates (including race/ethnicity). In other cohorts, mortality rates were higher among men than among women¹²⁰ or there were no differences in survival between men and women.⁵¹ While women have been reported to be more likely than men to be retained in care,^{38,118} we observed similar prevalence of gaps in care by two years after therapy initiation. Notably, we found that while black women had poorer survival

than black males, white and Hispanic women generally had better survival than white and Hispanic men, respectively. Few previous studies that have examined survival by sex have simultaneously stratified by race/ethnicity, despite evidence of heterogeneity of HIV death rates within strata of both race/ethnicity and sex.^{43,121}

I estimated all-cause mortality following therapy initiation by race, ethnicity, and sex, standardized to the total cohort at therapy initiation to control for baseline differences in health status. I view race, ethnicity, and sex as markers for unmeasured factors, such as environment, income, social status, social capital, discrimination, structural violence and other phenomena, which may partially or completely explain the demographic disparities I observed.¹²² I did not standardize for these factors because my purpose was not to explain demographic disparities, but rather to document their presence and estimate their magnitude.

Measurement bias is unlikely to explain the strong survival disparities observed in this study. Sex, race, ethnicity and death are likely measured with negligible error. Race and ethnicity are collected differently across sites, but are typically based on self-report and are classified in CNICS using Health Resources and Services Administration standards. Patients were classified as having a single race, which may have oversimplified race in multiracial patients, although the proportion of the US population that is multiracial is relatively low (2.9%, according to the 2010 Census).¹²³ Selection bias is also unlikely to explain the observed results, as the primary outcome, mortality, was ascertained via a national database; patients were not lost to follow-up because administrative censoring was unnecessary (e.g., after prolonged gap in labs or visits). Additionally, nearly all members of the eligible cohort were included in these analyses (only 8% of otherwise eligible subjects were excluded due to missing data).

These findings may or may not generalize to the US population.⁸ The CNICS cohort has proportionately more white patients, fewer young adults, more men and more injection drug users than are HIV-diagnosed and living in the US. Furthermore, CNICS clinics are all associated with academic medical centers, which may not reflect the HIV care provided in non-academic settings. However, the geographic distribution of study sites more closely resembles the US population than studies conducted in any single clinic.

A subsequent investigation into the causes of death would be invaluable to tease out the relative contributions of AIDS-related and non-AIDS-related mortality to the disparity described in this study. At this time, however, cause of death data is not available for all CNICS patients, and the data that is available is generally from the underlying cause of death on the death certificate, which has been shown to have poor specificity.^{124,125}

In summary, I identified elevated and meaningful differences in mortality among black men and women following combination antiretroviral therapy initiation in a large, demographically and geographically diverse cohort. These results serve as a call to action to identify modifiable factors that contribute to these observed differences, so that efficacious interventions may be developed and implemented so that the goal of the National HIV/AIDS Strategy¹¹² to overcome health disparities becomes a reality.

Table 6.1. Characteristics at antiretroviral therapy initiation, 10,017 HIV-infected adults, 1998-2011^a

	Overall	Black men	Black women	White men	White women	Hispanic men	Hispanic women
	<i>n</i> = 10,017	<i>n</i> =2,679	<i>n</i> =1,232	<i>n</i> =4,228	<i>n</i> =457	<i>n</i> = 1,252	<i>n</i> = 169
Age, years	40 (33, 46)	40 (33, 47)	40 (33, 47)	40 (34, 46)	41 (32, 46)	37 (31, 43)	39 (30, 47)
Calendar year	2006 (2003, 2009)	2006 (2002, 2009)	2005 (2002, 2008)	2007 (2003, 2009)	2005 (2003, 2009)	2007 (2004, 2010)	2007 (2004, 2009)
CD4 count, cells/mm ³	238 (85, 385)	196 (44, 343)	210 (64, 348)	276 (126, 428)	256 (114, 407)	226 (77, 364)	217 (91, 324)
Viral load, log ₁₀ copies/ml	4.7 (3.9, 5.3)	4.7 (4.1, 5.3)	4.7 (3.9, 5.3)	4.7 (3.9, 5.3)	4.7 (3.8, 5.3)	4.7 (3.9, 5.3)	4.5 (3.4, 5.0)
Therapy naïve, <i>n</i> (%)	8,787 (88%)	2,364 (88%)	1,030 (84%)	3,724 (88%)	397 (87%)	1,122 (90%)	151 (89%)
AIDS, <i>n</i> (%)	2,735 (27%)	866 (32%)	415 (34%)	912 (22%)	127 (28%)	364 (29%)	51 (30%)
Injection drug use, <i>n</i> (%)	1,758 (18%)	505 (19%)	224 (18%)	715 (17%)	139 (30%)	144 (12%)	31 (18%)
Hepatitis C viral infection, <i>n</i> (%)	1,572 (16%)	516 (19%)	222 (18%)	528 (12%)	133 (29%)	137 (11%)	36 (21%)

Abbreviations: AIDS, acquired immunodeficiency syndrome

^a Median (quartiles) unless noted otherwise

Table 6.2. Standardized^a 10-year mortality risk differences and hazard ratios and by race/ethnicity and sex, 10,017 HIV-infected adults, 1998-2011

	Crude			Standardized			
	No. Deaths	No. Person-years	10-year mortality risk, %	10-year mortality risk, %	Risk difference, % (95% CI)	Risk ratio (95% CI)	Hazard Ratio (95% CI)
Overall	1,224	51,121.1	20.2	20.2	-	-	-
Race/ethnicity/sex							
Black women	207	6,730.0	25	25.8	7.9 (3.9, 12.0)	1.44 (1.21, 1.72)	1.57 (1.32, 1.87)
Black men	458	13,338.4	27	25.2	7.2 (4.3, 10.1)	1.40 (1.23, 1.61)	1.53 (1.33, 1.76)
White men	405	21,792.3	16.8	18	0	1	1
Hispanic men	86	5,924.6	12.5	14.8	-3.2 (-7.1, 0.8)	0.82 (0.63, 1.08)	0.82 (0.64, 1.05)
White women	53	2,482.0	17.5	13.9	-4.0 (-8.5, 0.4)	0.77 (0.57, 1.05)	0.85 (0.61, 1.19)
Hispanic women	15	853.9	12	10.8	-7.1 (-16.1, 1.9)	0.61 (0.26, 1.42)	0.68 (0.37, 1.23)
Race/ethnicity							
White	458	24,274.3	16.9	17.2	0	1	1
Black	665	20,068.4	26.3	25.4	8.2 (5.6, 10.8)	1.48 (1.30, 1.67)	1.29 (1.12, 1.49)
Hispanic	101	6,778.5	12.5	14.5	-2.7 (-6.6, 1.1)	0.84 (0.65, 1.09)	0.75 (0.59, 0.96)
Sex							
Men	949	41,055.3	19.7	19.8	0	1	1
Women	275	10,065.8	22.2	22	2.2 (-0.7, 5.2)	1.11 (0.97, 1.28)	0.95 (0.82, 1.10)

Abbreviations: CI, confidence interval; No., number

^a Standardized for calendar date of therapy initiation, age at therapy initiation, CD4 cell count (cells/mm³) and HIV-1 RNA plasma concentration (viral load) (log₁₀ copies/ml) most proximate to therapy initiation measured between 6 months prior to 14 days after therapy initiation, antiretroviral therapy naivety (i.e., no evidence of prior exposure to mono or dual therapy), prior AIDS diagnosis, history of injection drug use, and history of hepatitis C virus infection; additionally, race/ethnicity risk was standardized for sex and sex risk was standardized for race/ethnicity.

Table 6.3. Crude mortality rate ratios for 10,017 HIV-infected adults in the CNICS, 1998-2011, and age- and calendar time-standardized mortality rates in the US general population based on vital statistics data, 1999-2011

Race/ethnicity/sex	CNICS, 1998-2011				US population, 1999-2011	
	No. Deaths	No. Person-years	Mortality rate per 10,000 person-years	Rate Ratio	Standardized mortality rate*	Rate Ratio
Black women	207	6,730.0	307.6	1.66	45.7	1.05
Black men	458	13,338.4	343.4	1.85	73.9	1.70
White men	405	21,792.3	185.8	1.	43.6	1.
Hispanic men	86	5,924.6	145.2	0.78	27.0	0.62
White women	53	2,482.0	213.5	1.15	25.9	0.59
Hispanic women	15	853.9	175.7	0.95	18.5	0.42

*Directly standardized to match the age group and calendar time distribution of the CNICS data

Table 6.4. Crude and standardized^a probabilities of retention in care at 2 years post-ART initiation and viral suppression at 1 year post-ART initiation, by race/ethnicity and sex, 10,017 HIV-infected adults, 1998-2011

	Crude		Standardized	
	Retention in care 2 years after ART initiation, % (95% CI)	Viral suppression at ~1 year after ART initiation, % (95% CI)	Retention in care 2 years after ART initiation, % (95% CI)	Viral suppression at ~1 year after ART initiation, % (95% CI)
Overall	75.9 (75.1, 76.8)	66.6 (65.7, 67.5)		
Race/ethnicity/sex				
Black women	76.2 (73.8, 78.6)	57.8 (55.0, 60.6)	76.0 (73.6, 78.4)	57.7 (54.9, 60.5)
Black men	75.1 (73.5, 76.7)	60.3 (58.4, 62.2)	75.3 (73.6, 76.9)	60.5 (58.7, 62.4)
White men	76.4 (75.1, 77.7)	72.0 (70.6, 73.3)	76.2 (74.9, 77.5)	71.7 (70.3, 73.1)
Hispanic men	76.2 (73.8, 78.6)	73.1 (70.6, 75.5)	77.0 (74.7, 79.4)	72.3 (69.9, 74.8)
White women	74.0 (69.9, 78.0)	61.3 (56.8, 65.7)	75.2 (71.3, 79.2)	64.3 (59.9, 68.9)
Hispanic women	78.1 (71.9, 84.3)	63.9 (56.2, 71.1)	76.9 (70.5, 83.4)	65.3 (58.0, 72.5)
Race/ethnicity				
White	76.2 (75.0, 77.4)	70.9 (69.6, 72.2)	75.8 (74.6, 77.1)	70.2 (68.9, 71.5)
Black	75.5 (74.1, 76.8)	59.5 (58.0, 61.1)	75.3 (74.0, 76.7)	59.8 (58.2, 61.3)
Hispanic	76.4 (74.2, 78.6)	72.0 (69.7, 74.3)	76.9 (74.7, 79.1)	71.5 (69.2, 73.8)
Sex				
Men	76.0 (75.0, 76.9)	68.3 (67.3, 69.3)	76.1 (75.1, 77.0)	68.1 (67.1, 69.1)
Women	75.8 (73.9, 77.8)	59.2 (56.9, 61.5)	75.2 (73.2, 77.2)	60.0 (57.8, 62.2)

* Retention in care defined as no gaps in laboratory monitoring of ≥ 1 year

^a Standardized for calendar date of therapy initiation, age at therapy initiation, CD4 cell count (cells/mm³) and HIV-1 RNA plasma concentration (viral load) (log₁₀ copies/ml) most proximate to therapy initiation measured between 6 months prior to 14 days after therapy initiation, antiretroviral therapy naivety (i.e., no evidence of prior exposure to mono or dual therapy), prior AIDS diagnosis, history of injection drug use, and history of hepatitis C virus infection; additionally, race/ethnicity risk was standardized for sex and sex risk was standardized for race/ethnicity.

Table 6.5. Characteristics at antiretroviral therapy initiation, 10,017 HIV-infected adults, 1998-2011^a

	Overall <i>n</i> = 10,017	White <i>n</i> =4,685	Black <i>n</i> =3,911	Hispanic <i>n</i> =1,421	Male <i>n</i> =8,159	Female <i>n</i> =1,858
Age, years	40 (33, 46)	40 (34, 46)	40 (33, 47)	37 (31, 44)	40 (33, 46)	40 (33, 47)
Calendar year	2006 (2003, 2009)	2006 (2003, 2009)	2006 (2002, 2009)	2007 (2004, 2010)	2006 (2003, 2009)	2005 (2002, 2008)
CD4 count, cells/mm ³	238 (85, 385)	271 (124, 426)	199 (51, 344)	226 (78, 362)	242 (87, 391)	221 (78, 361)
Viral load, log ₁₀ copies/ml	4.7 (4.0, 5.3)	4.7 (3.9, 5.3)	4.7 (4.0, 5.3)	4.7 (3.9, 5.3)	4.8 (4.0, 5.3)	4.7 (3.9, 5.2)
Therapy naïve, %	8,787 (88%)	4,120 (88%)	3,394 (87%)	1,273 (90%)	7,209 (88%)	1,578 (85%)
AIDS, %	2,735 (27%)	1,039 (22%)	1,281 (33%)	415 (29%)	2,142 (26%)	593 (32%)
Injection drug use, %	1,758 (18%)	854 (18%)	729 (19%)	175 (12%)	1,364 (17%)	394 (21%)
Hepatitis C viral infection, %	1,572 (16%)	661 (14%)	738 (19%)	173 (12%)	1,181 (15%)	391 (21%)

Abbreviations: AIDS, acquired immunodeficiency syndrome

^a Median (quartiles) unless noted otherwise

Table 6.6. Sensitivity analysis, estimates of the relative hazard of all-cause mortality by race/ethnicity and sex, unstratified and stratified on CNICS site, 10,017 HIV-infected adults, 1998-2011

	No. Deaths	No. Person- years	10-year mortality risk, %	Crude Hazard Ratio (95% CI)	Standardized, unstratified by CNICS site (95% CI)	Standardized, stratified by CNICS site (95% CI)
Race/ethnicity/sex						
Black women	207	6,730.0	25	1.66 (1.41, 1.97)	1.57 (1.32, 1.87)	1.18 (0.97, 1.43)
Black men	458	13,338.4	27	1.84 (1.61, 2.11)	1.53 (1.33, 1.76)	1.24 (1.07, 1.45)
White men	405	21,792.3	16.8	1	1	1
Hispanic men	86	5,924.6	12.5	0.78 (0.61, 0.98)	0.82 (0.64, 1.05)	0.74 (0.57, 0.96)
White women	53	2,482.0	17.5	1.15 (0.87, 1.54)	0.85 (0.61, 1.19)	0.72 (0.51, 1.01)
Hispanic women	15	853.9	12	0.94 (0.56, 1.59)	0.68 (0.37, 1.23)	0.59 (0.32, 1.09)

Abbreviations: CI, confidence interval; No., number

a Standardized for age at therapy initiation, calendar year of therapy initiation, therapy naivety, and prior diagnosis of any AIDS-defining condition at therapy initiation

Figure 6.1. Crude all-cause mortality by years from therapy initiation, race/ethnicity and sex, 10,017 HIV-infected adults, 1998-2011

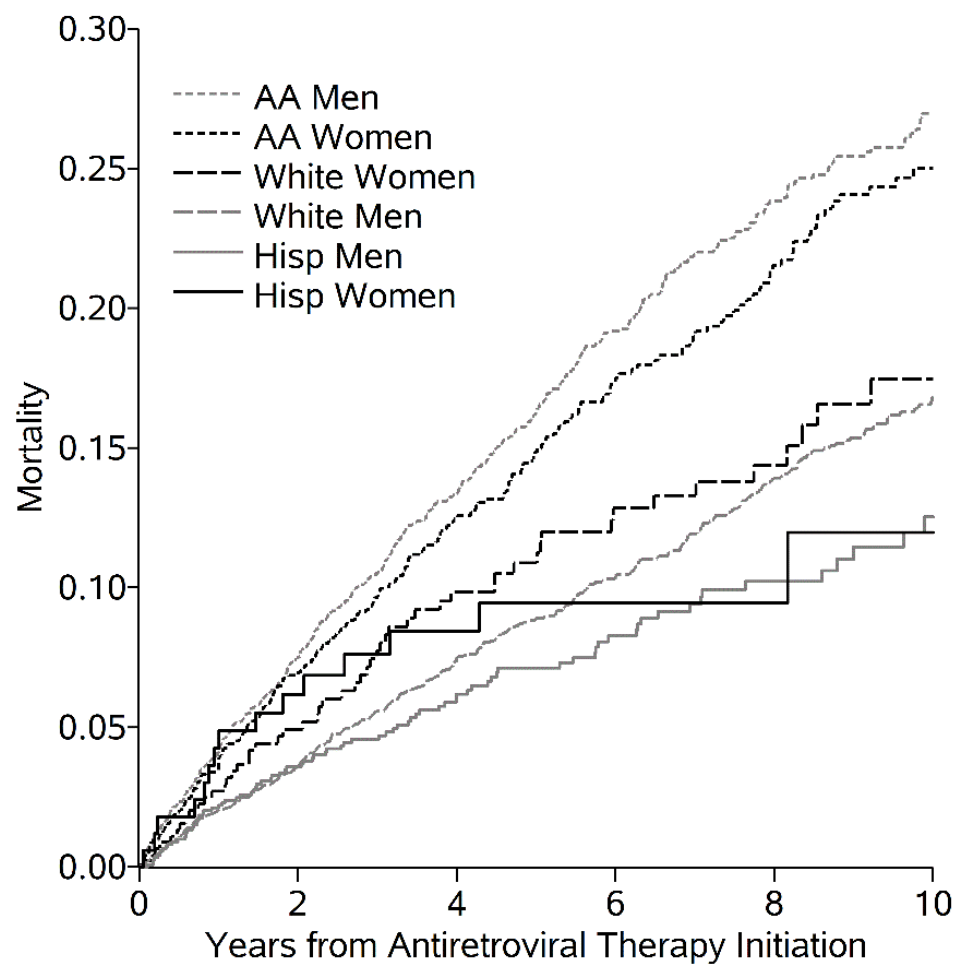
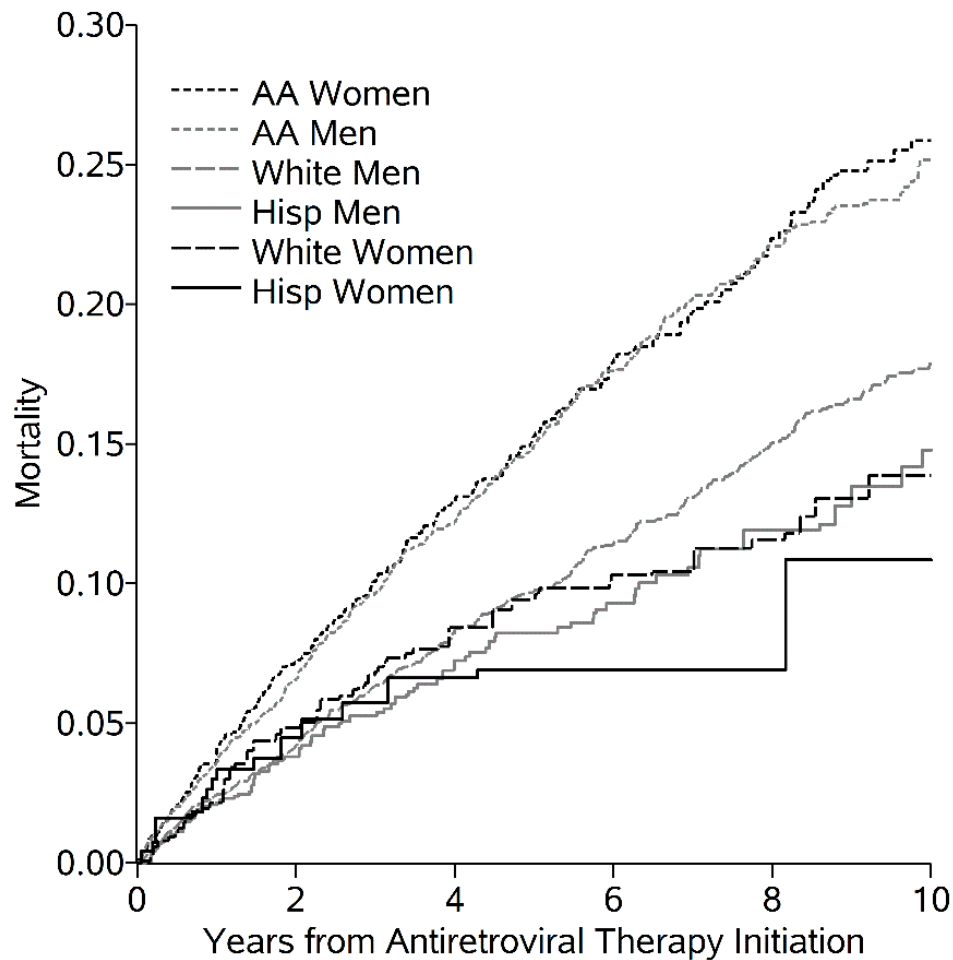
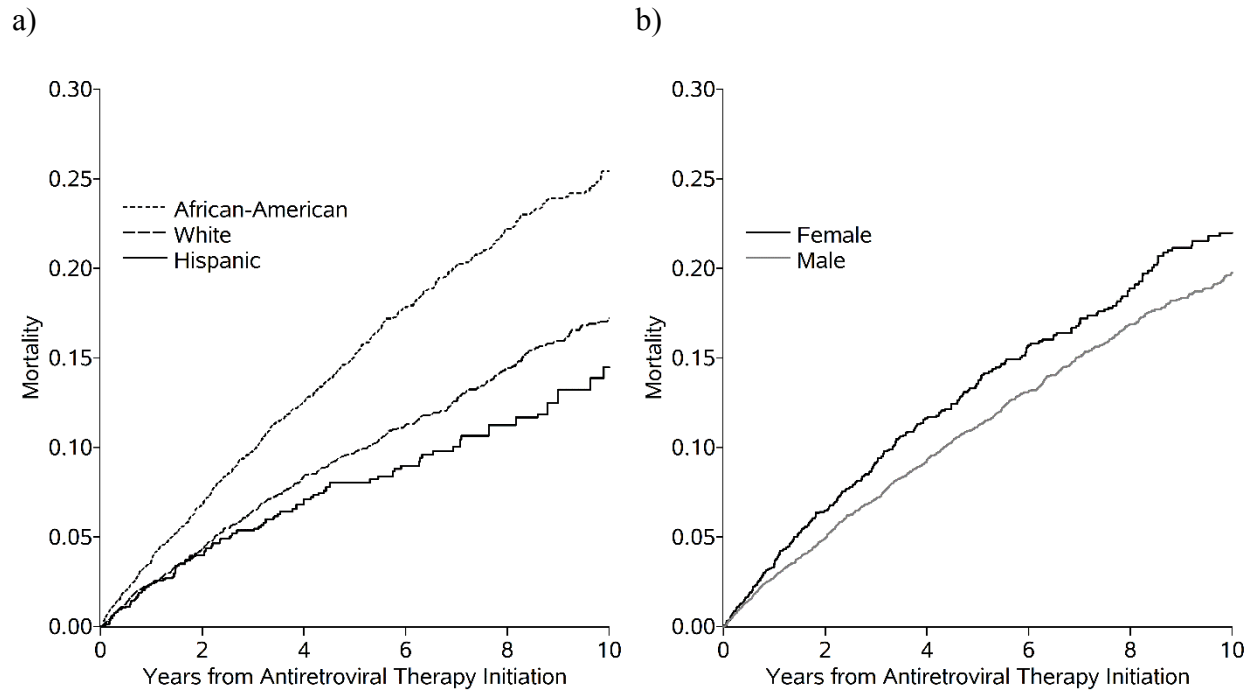


Figure 6.2. Cumulative all-cause mortality standardized^a to total study sample by years from therapy initiation, race/ethnicity and sex, 10,017 HIV-infected adults, 1998-2011



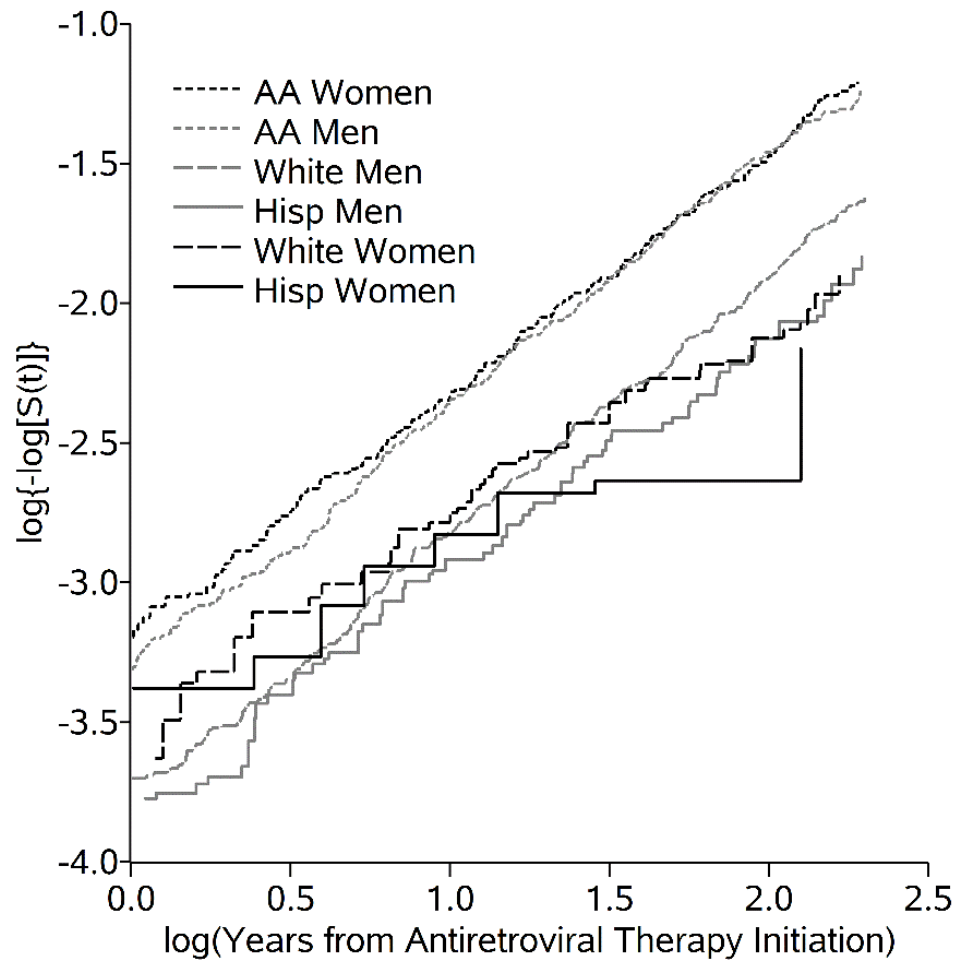
^a Standardized by baseline covariates: age at therapy initiation, CD4 count and viral load, all modeled with restricted quadratic splines (with 4 knots located at the 5th, 35th, 65th and 95th percentiles), antiretroviral therapy naivety, prior diagnosis of any AIDS-defining condition at therapy initiation, injection drug use, and history of hepatitis C virus infection

Figure 6.3. Cumulative all-cause mortality standardized^a to the total study sample by years from therapy initiation and a) race/ethnicity or b) sex, 10,017 HIV-infected adults, 1998-2011



^a Standardized by baseline covariates: sex (a) or race (b), age at therapy initiation, CD4 count and viral load, all modeled with restricted quadratic splines (with 4 knots located at the 5th, 35th, 65th and 95th percentiles), antiretroviral therapy naivety, prior diagnosis of any AIDS-defining condition at therapy initiation, injection drug use, and history of hepatitis C virus infection

Figure 6.4. Log of the cumulative hazard of all-cause mortality standardized^a to the total study sample by years from therapy initiation, race/ethnicity and sex, 10,017 HIV-infected adults, 1998-2011



^a Standardized by baseline covariates: age at therapy initiation, CD4 count and viral load, all modeled with restricted quadratic splines (with 4 knots located at the 5th, 35th, 65th and 95th percentiles), antiretroviral therapy naivety, prior diagnosis of any AIDS-defining condition at therapy initiation, injection drug use, history of hepatitis C virus infection and study site

CHAPTER 7: DISCUSSION

7.1. Generalizability of Effects

Great care is typically taken in epidemiology and public health to study the internal validity of effect estimates, in particular the potentially biasing effects of measurement, confounding and selection. However, the external validity of effect estimates has been understudied and has important implications for health policy and planning. Interventions based on internally valid studies may have unexpected outcomes if those study results are not generalizable to the target population.¹²⁶ The ideal study to estimate the effect of ART on mortality among recently HIV-diagnosed persons in the US would be conducted in a random sample from that population, with subsequent randomized treatment assignment. Randomized treatment assignment is not ethical in this instance, given the documented benefits of ART,¹⁰⁸ and furthermore, accrual of follow-up time required for a prospective study would delay implementation of any intervention thought to be beneficial.

The identifying assumptions necessary to conclude that an estimated effect is internally valid include: 1) conditional exchangeability between treatment arms (no unmeasured causes of both the exposure and the outcome);⁸³ 2) positive probability of treatment within every level of covariates (positivity);⁸⁴ 3) treatment variation irrelevance;⁸⁵ 4) no interference (when one person's outcome is affected by another's exposure);⁸⁶ 5) no measurement error;⁸⁷ and 6) correct models specification. These assumptions have been well described.^{79,83,88} The generalizability assumptions necessary to conclude that an estimated effect is externally valid parallel the

identifying assumptions for internal validity: 1) conditional exchangeability between the selected and those not selected into the sample (no unmeasured causes of both selection into the sample and the outcome); 2) positive probability of being included in the study sample within every level of covariates (positivity); 3) treatment variation irrelevance or similar versions of treatment in the sample and the target;⁶ 4) no interference or similar patterns of interference in the sample and the target;^{6,86} 5) no measurement error; and 6) correct models specification.^{5,89,90} Under these assumptions, weighting creates a pseudo-population in which the exposure is independent of measured confounders, censoring is independent of exposure and measured confounders, and the distribution of effect-modifiers matches that in the target population.

In this dissertation, I demonstrated one method for formally assessing generalizability. There are many potential future directions for research into the generalizability of effects. Specifically, how much of a departure from homogeneity of subgroup effects is tolerable before we need to be concerned about the generalizability of the effect estimate? How vulnerable is the inverse probability weighted estimator for generalizability to the choice of N , the size of the hypothetical target population from which the study sample and the cohort sample used to describe the target are sampled? Is there another estimator that avoids the need for hypothetical N altogether? Furthermore, it may be more useful to contrast the expected 5-year mortality under more realistic interventions, such treat 90% of people immediately following diagnosis versus allow treatment uptake to follow its natural course in the cohort. Such contrasts are possible using the parametric g-formula.¹²⁷ Using the parametric g-formula to accommodate generalizability may be a simple extension in which the datasets for the Monte Carlo simulation are drawn to reflect the baseline characteristics of the target population rather than of the study sample. Furthermore, the parametric g-formula estimator may improve the precision of estimates

over an inverse probability weighted estimator. However, this extension has not yet been evaluated. Finally, while this dissertation has demonstrated (under certain assumptions) the generalizability of the effect of ART on mortality measured in the CNICS to persons recently diagnosed with HIV in the US, there is still a need to test some of those assumptions or to evaluate the generalizability of other effects estimated in the CNICS.

7.2. Disparities

The research question in Specific Aim 2 was descriptive (estimating association) rather than etiologic (estimating causal effects). While I could not identify the causes of disparities, I did document that disparities persist beyond initiation of ART, and are not entirely explained by HIV disease status at ART initiation. By restricting the investigation to persons who had initiated ART I hoped to identify focus areas for future investigation into the etiology of disparities. It is possible that the observed disparities may not be HIV-related at all. Survival by race/ethnicity and sex varies substantially in the general US population due to differences in the prevalence of non-HIV-related conditions like diabetes, hypertension, kidney disease and violence, for example.¹¹³ However, when contrasting inequalities in mortality among the general population and the HIV-positive ART initiators, the inequalities are greater for black HIV-positive ART initiators. Furthermore, the survival benefits seen among Hispanic persons and white women in the general population are not as strong among HIV-positive ART initiators (Table 7.1). The CNICS has recently begun collecting data on Patient Reported Outcomes (PRO) using self-administered surveys. The richness of the data available in the PROs may be a fantastic resource for future studies into modifiable risk factors for mortality that may be targeted to reduce

disparities. Finally, it is relatively easy to nest studies in the CNICS to test the effect of interventions aimed at reducing disparities.

Table 7.1. Death rates among the general population and among HIV-positive ART initiators by race/ethnicity and sex

	Death rates in the general population, age 35-44 (2011). ²⁰		HIV-positive ART initiators in the CNICS	
	Death Rate*	Rate ratio	Death Rate*	Hazard ratio
Black women	208.900	0.93	3,075.8	1.57
Black men	322.200	1.44	3,443.7	1.53
White men	223.700	1.	1,858.5	1.
Hispanic men	141.800	0.63	1,451.6	0.82
White women	136.200	0.61	2,135.4	0.85
Hispanic women	74.100	0.33	1,756.6	0.68

*per 100,000 person-years

There are numerous potential criticisms of health disparities research regarding the interpretation of the coefficient for the race/ethnicity/sex covariate in a regression model.¹²⁸ When considered from the potential outcomes framework, race, ethnicity and sex are problematic exposures as they are not manipulable, and so one cannot imagine any intervention that might produce a potential outcome other than the factual outcome consistent with the race/ethnicity/sex the person was. In a crude model, the coefficient on the race/ethnicity/sex covariate could be interpreted as a simple description of an inequality in outcomes across groups defined by race/ethnicity/sex. The ‘effect’ of race/ethnicity/sex is poorly defined however, even ignoring the aforementioned problem of imagining an intervention on race/ethnicity/sex. One

could imagine asking the questions, “What is the effect of race-based discrimination?” “What is the effect of historical racism?” “What is the effect of gender-based differences in income?” or “What is the effect of genetics more commonly associated with one ethnic group than another?” Questions that might follow from the Specific Aim 2 of this dissertation include, “How much of the inequality in outcomes across groups defined by race/ethnicity/sex could be removed by earlier HIV diagnosis, better retention, or immediate treatment following diagnosis?”

7.3. Conclusions

The overall goal of this dissertation was to improve understanding of the potential population level impact of HIV treatment in the era of test-and-treat. Certainly, the effectiveness of HIV treatment-as-prevention¹²⁹ and the additional individual health benefits that come from initiation of ART earlier in the course of illness provide compelling evidence to endorse the test-and-treat strategy.^{130,131} However, a more detailed understanding of the effects of the strategy, specific to the population in which it will be implemented, is needed to plan appropriately and budget adequately to provide treatment for people over the additional years of life that they can expect from early treatment. In this dissertation, I estimated that immediately treating persons newly diagnosed with HIV in the US from 2009-2011 would reduce the 5-year risk of mortality in this group by two-thirds from nearly 30% if treatment were delayed, to 10%, which would translate to an extra 24,628 persons alive at 5 years post-diagnosis.

The magnitude of the survival benefits of ART among recently HIV-diagnosed persons in the US were similar to those seen in the CNICS. Because it was not logistically or financially feasible to randomly sample from the target population that was of interest (i.e., persons recently diagnosed with HIV in the US), I conducted the main analysis in the CNICS. CNICS patients’

characteristics were not identical to the characteristics of persons in the target population and we do not, as of yet, have a good understanding of the degree to which non-representativeness and non-significant departures from effect homogeneity across multiple subgroups interact to produce changes in the final standardized estimate for the target population. This dissertation therefore used a formal correction for non-random sampling into the study sample (inverse probability of sampling weights). This formal assessment of generalizability provides confidence in the generalizability of any research in the CNICS that uses mortality as an outcome. Further work is needed to quantify the vulnerabilities of results from studies conducted in samples that are not representative of the target population to which interventions will ultimately be applied. In the meantime, cohorts that are not representative samples can bolster claims of external validity by applying inverse probability of sampling weights to their final results. If the joint distribution of the characteristics of the target population is unknown, sensitivity analyses can be undertaken using multiple plausible distributions.

Finally, reducing health disparities is a primary goal of the National HIV/AIDS Strategy.¹¹² Documenting and quantifying disparities in survival is a key first step towards reducing them. In Specific Aim 1, by restricting the investigation to persons who have initiated ART, this study demonstrated that disparities in survival persist and arise anew as persons move through the HIV treatment cascade. Answering this question is important for deciding where to target research and interventions to mitigate disparities.

APPENDIX A. AIDS-DEFINING CONDITIONS (FOR PERSONS ≥ 13 YEARS OF AGE)

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus*
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
- Cytomegalovirus retinitis (with loss of vision)*
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi sarcoma*
- Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex*
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated* or extrapulmonary*
- *Mycobacterium tuberculosis* of any site, pulmonary,* disseminated,* or extrapulmonary*
- *Mycobacterium*, other species or unidentified species, disseminated* or extrapulmonary*

- *Pneumocystis jirovecii* pneumonia*
- Pneumonia, recurrent*
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent
- Toxoplasmosis of brain, onset at age >1 month*
- Wasting syndrome attributed to HIV

*Condition that might be diagnosed presumptively

Available at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5710a2.htm>

APPENDIX B. POWER CALCULATION USING EXPECTED DATA APPROACH

I used the expected data approach to calculate power for Specific Aims 1 and 2. I generated data for the outcome of the study under a range of possibilities for the baseline rate and rate ratio (Specific Aim 1) or the baseline risk and the risk difference (Specific Aim 2) for each comparison of interest, then used that generated data to back-calculate power for each scenario.

In Specific Aim 1, over 5 years of follow up, there were 918 deaths among 12,457 patients in the study sample, and approximately 32% of the person-time was exposed to ART. I calculated the standard error for the risk ratio using the formula:

$$SE(rate\ ratio) = \sqrt{\frac{1}{a} + \frac{1}{b}}$$

Where a is the number of exposed events (assumed to be 0.32×918) and b is the number of unexposed events. I further assumed an expected hazard ratio of 0.5.

In Specific Aim 2, I started with the number of subjects in each stratum of my exposure and calculated the expected number of events over 10 years, assuming a 10-year risk of 10%, 15%, and 20% in the referent group (white or male), and a risk differences ranging from -4% to 30% by 0.05% (to plot smooth power curves). I calculated the standard error for the risk difference in each potential study outcome using the formula:

$$SE(risk\ difference) = \sqrt{\frac{a(N_1 - a)}{N_1^3} + \frac{b(N_0 - b)}{N_0^3}}$$

Where a is the number of expected events in the comparison group, N_1 is the number of patients in the comparison group, b is the number of expected events in the referent group, and N_0 is the number of patients in the referent group.

For both aims, once the expected data has been generated, then power is then the probability that the lower confidence interval from the potential study outcome exceeds zero. This probability is equal to the probability that an observation in a standard normal distribution exceeds $-d$, where $-d$ is the number of standard errors the lower confidence limit is above zero.⁹⁴

$$Power = \Phi \left[\frac{\Theta - 1.96 * SE(\Theta)}{SE(\Theta)} \right]$$

Where $\Phi(.)$ is the cumulative distribution function for a standard normal distribution and Θ is the parameter of interest, that is, the rate ratio for Specific Aim 1 and the risk difference for Specific Aim 2.

Statistical power calculations for marginal structural models have not been developed. The precision for weighted models decreases as the variability in the weights increases. In prior applications of marginal structural models, the variance inflation factor has ranged from 1.1 to 2.0.^{23,95-98} To account for the use of marginal structural models and their influence on the power available to address the specific aims in this dissertation, the variance of potential study outcomes were multiplied by 4, a very conservative assumption about the potential for variance inflation in these analyses.

1. Results: Specific Aim 1

The crude rate ratio under the proposed scenario would have an approximate variance of $[1/(0.32*918) + 1/(0.68*918)] = 0.0050$ and an expected 95% confidence interval of 0.36, 0.64.

The power for the naïve analysis was >99%. A conservative assumption that the variance

inflation factor could have been as high as 4, yielded an expected 95% confidence interval in the weighted model of 0.22, 0.78. This was associated with a power of 94%.

SAS code:

```
data a;
  /*variance for a rate is 1/a+1/b*/
  var=1/(0.32*918)+1/(0.68*918);
  se=sqrt(var);
  lo=0.50-1.96*se;
  hi=0.50+1.96*se;
  z=lo/se;
  p=cdf('normal',z);
run;
proc print data=a noobs;
run;

/*incorporate variance inflation factor*/
data a;
  /*variance for a rate is 1/a+1/b*/
  var=(1/(0.32*918)+1/(0.68*918))*4;
  se=sqrt(var);
  lo=0.50-1.96*se;
  hi=0.50+1.96*se;
  z=lo/se;
  p=cdf('normal',z);
run;
proc print data=a noobs;
run;
```

2. Results: Specific Aim 2

Given the sample size, I had 80% power to detect a 10-year risk difference of 2.2% comparing black patients to white patients, a risk difference of 3.3% comparing Hispanic patients to white patients, and a risk difference of 2.8% comparing women to men. The power

curves for a range of possible outcomes for Specific Aim 2, as well as the SAS code to produce them, are below.

Figure Appendix.1. Power curves for comparing 10-year mortality risk difference for black versus white ART initiators in the CNICS

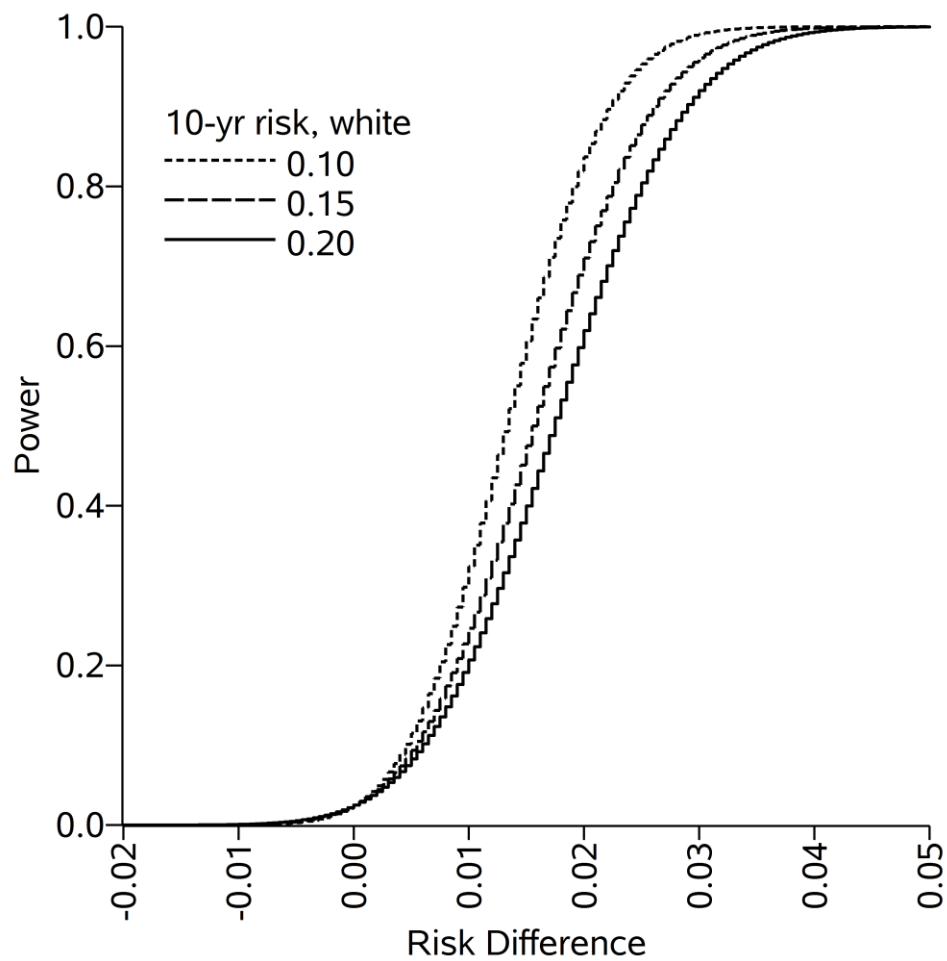


Figure Appendix.2. Power curves for comparing 10-year mortality risk difference for Hispanic versus white ART initiators in the CNICS

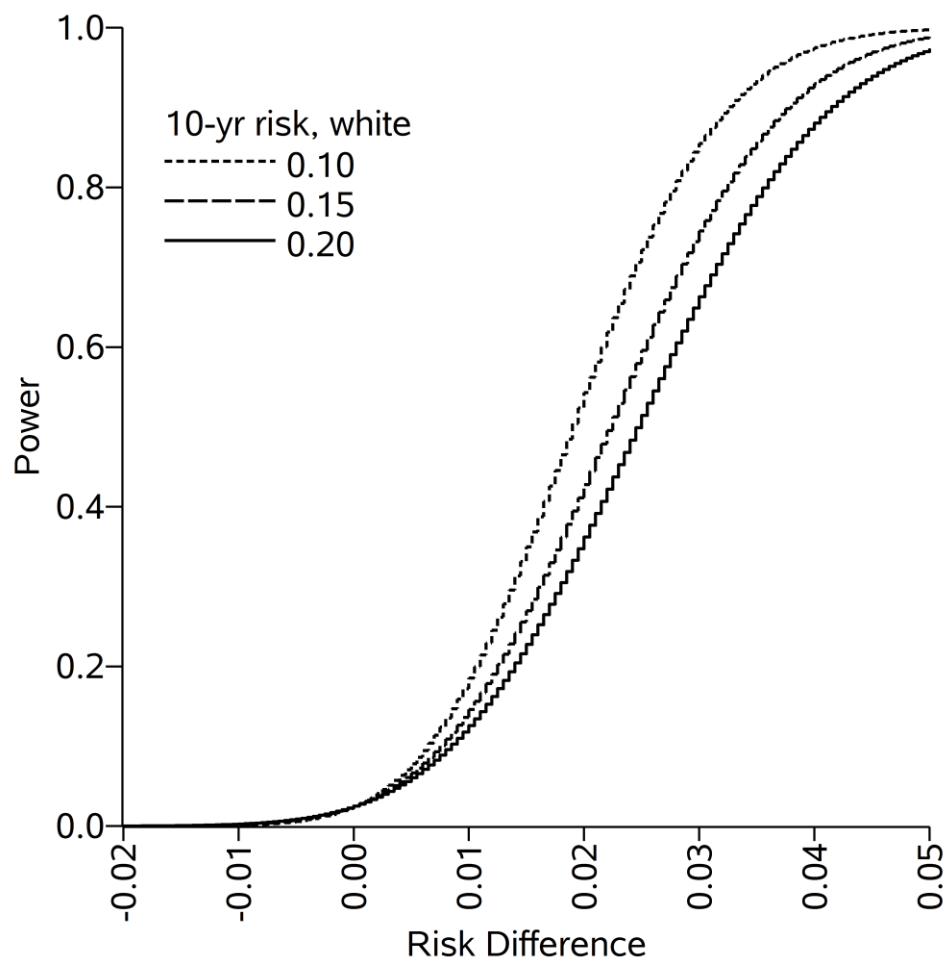
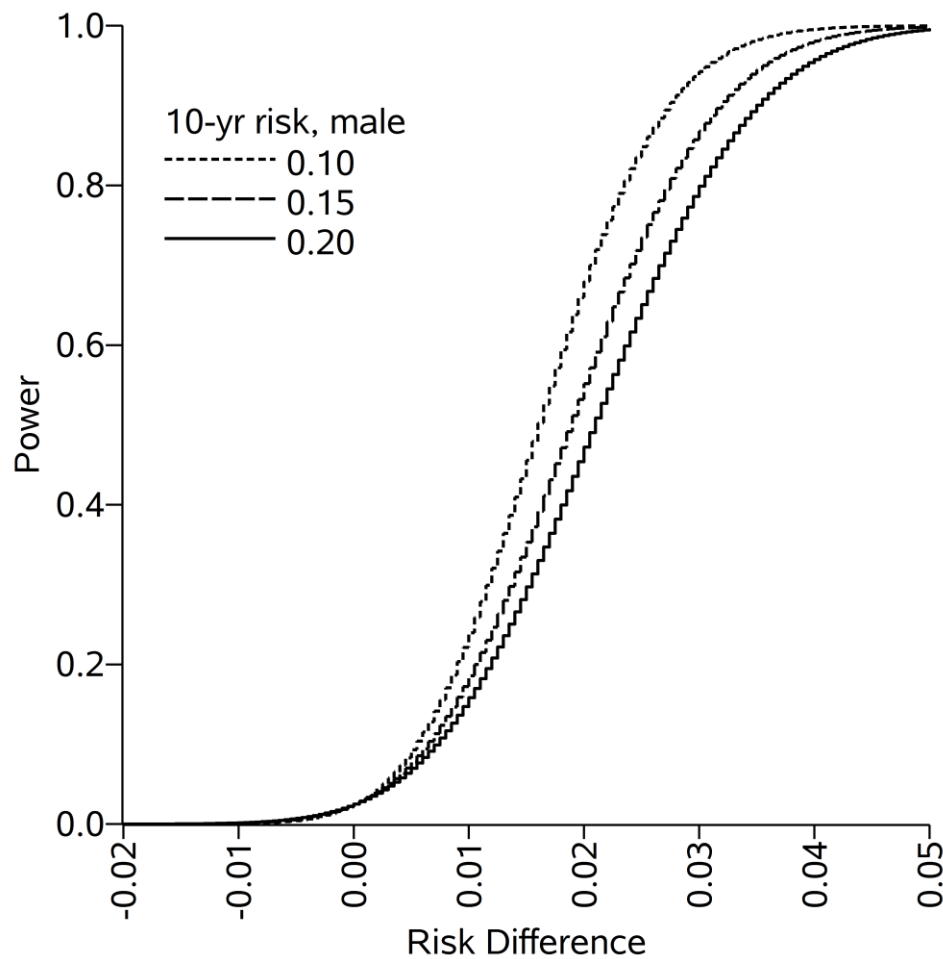


Figure Appendix. 3. Power curves for comparing 10-year mortality risk difference for female versus male ART initiators in the CNICS



SAS Code:

```
data x;
  /*input the estimated number of persons in each exposure group*/
  input white black hisp men women;
cards;
  4685 3911 1421 8159 1858
;;
run;

/*recall formulas for standard error of a risk and of a risk difference
se(risk) = sqrt[R*(1-R)/n];
se(risk difference) = sqrt[(a*(N1-a)/N1^3) + (b*(N0-b)/N0^3)];*/
```

```

data x;
set x;
/*vary the risk in the referent group (white or male) between 10 and 20%*/
do risk = .1 to .2 by .05;
  /*calculate the expected number of events in the referent group*/
  b_white = risk*white;
  b_men = risk*men;
  /*vary the expected risk difference from -4% to 30%*/
  do RD = -.04 to .3 by .0005;
    /*calculate the expected number of events in each comparison group*/
    a_black = (RD+risk)*black;
    a_hisp = (RD+risk)*hisp;
    a_women = (RD+risk/men)*women;
    /*get the standard error for each estimate*/
    se_RD_black = sqrt((a_black*(black-a_black)/(black**3))+
      (b_white*(white-b_white)/(white**3)));
    se_RD_hisp = sqrt((a_hisp*(hisp-a_hisp)/(hisp**3))+
      (b_white*(white-b_white)/(white**3)));
    se_RD_women = sqrt((a_women*(women-a_women)/(women**3))+
      (b_men*(men-b_men)/(men**3)));
    /*convert standard error to power*/
    power_black = cdf('normal',(rd-1.96*se_RD_black)/se_RD_black,0,1);
    power_hisp = cdf('normal',(rd-1.96*se_RD_hisp)/se_RD_hisp,0,1);
    power_women = cdf('normal',(rd-1.96*se_RD_women)/se_RD_women,0,1);
    output;
  end;
end;
run;

/*define general graphics preferences*/
goptions reset=all device=zpng ftext="Albany AMT" htext=12pt gsfname=grafout
gsfmode=replace xmax=4 ymax=4 xpixels=4000 ypixels=4000; *1000dpi;
axis1 label=(angle=90 "Power") order=(0 to 1 by .2) w=8
  major=(w=8 h=18) minor=none offset=(0,0);
axis2 label=("Risk Difference") order=(-0.02 to .05 by .01) value=(angle=90) w=8
  major=(w=8 h=7) minor=none offset=(0,0);
symbol1 c=black v=none i=stepjs w=12 l=22;
symbol2 c=black v=none i=stepjs w=12 l=24;
symbol3 c=black v=none i=stepjs w=12 l=1;
legend1
  noframe
  across=1
  shape=line(120)
  origin=(300,325)
  position=(inside)
  mode=protect

```

```

value=(justify=left " 0.10" " 0.15" " 0.20")
label=(j=1 position=top "10-yr risk, white");

/*plot power for black vs white comparisons – lines for each of 3 baseline risks, x-axis is risk
difference, y-axis is power*/
filename grafout "&dir.\power_black.png";
proc gplot data=x;
  plot power_black*RD=risk/vaxis=axis1 haxis=axis2 legend=legend1 noframe;
run;
quit;

/*plot power for Hispanic vs white comparisons*/
filename grafout "&dir.\power_hisp.png";
proc gplot data=x;
  plot power_hisp*RD=risk/vaxis=axis1 haxis=axis2 legend=legend1 noframe;
run;
quit;

/*plot power for women vs men comparisons*/
legend1
  noframe
  across=1
  shape=line(120)
  origin=(300,325)
  position=(inside)
  mode=protect
  value=(justify=left " 0.10" " 0.15" " 0.20")
  label=(j=1 position=top "10-yr risk, white");
filename grafout "&dir.\power_women.png";
proc gplot data=x;
  plot power_women*RD=risk/vaxis=axis1 haxis=axis2 legend=legend1 noframe;
run;
quit;

/*examine specific values for risk difference associated with specific power values*/
proc print data=x noobs;
  where round(risk,.01)=0.15 and 0.75 <= power_black <= 0.85;
  var rd power_black;
run;

proc print data=x noobs;
  where round(risk,.01)=0.15 and 0.75 <= power_hisp <= 0.85;
  var rd power_hisp;
run;

```

```
proc print data=x noobs;  
  where round(risk,.01)=0.15 and 0.75 <= power_women <= 0.85;  
  var rd power_women;  
run;
```

```
run; quit; run;
```

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