THE EPIDEMIOLOGY OF CLINICAL RETENTION AMONG HIV-INFECTED PERSONS IN NORTH AMERICA

by

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Abstract

Background: Clinical retention is central to the HIV care continuum and a determinant of improved individual- and population-level HIV outcomes. The goals of this dissertation are to improve retention surveillance by quantifying measurement error due to laboratory-measure proxies for encounters and to examine retention disparities by demographic, HIV risk, and geographic characteristics, using data from 2000-2010.

Methods: We analyzed data from the North American AIDS Cohort Collaboration on Research and Design, the largest North American HIV cohort collaboration. Clinical retention was defined using the Institute of Medicine indicator: ≥2 encounters, >90 days apart, within one calendar year. Discordance between laboratory-based and encounter-based retention measures was evaluated using logistic regression with GEE and inverse probability weights for confounder adjustment. Relative times and cumulative incidences of first retention discontinuation after ART initiation by demographic and HIV risk factors were analyzed using weighted Cox regression. Geographic differences were assessed using modified Poisson and logistic regression with GEE and cluster detection methods.

Results: We identified significant retention disparities by measurement method, patient characteristics, and geography, even adjusting for confounders and clinical practice differences. Misclassification of encounter-based retention by laboratory-based measures was 19% overall, which remained stable over time. Among individuals initiating ART, the cumulative incidence of retention discontinuation was 74% and adjusted cause-specific hazard ratios (HR) were lower for females (HR: 0.81, vs. males), but higher for Black (HR: 1.18, vs. non-Black) patients and individuals with injection drug use as HIV
risk (IDU) (HR: 1.35, vs. non-IDU) (p<0.05, each). The South and West (adjusted Risk Ratios [RR]: 0.95 and 0.89, respectively) lagged the Northeast and Midwest (Ref. and RR: 1.03) in improved retention over the study period (p<0.05, each).

**Conclusions:** Clinical retention improved within all groups over time, yet disparities by important characteristics persisted. Agreement between encounter-based and laboratory-based metrics was strong, but laboratory measures were imperfect proxies. Public health interventions to address poor retention in high-risk populations are needed, and more accurate surveillance of care outcomes will be essential in monitoring HIV policy benchmarks if, indeed, we are to continue to make progress toward them.
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Table of Contents

Abstract .............................................................................................................................. ii

Thesis Committee .............................................................................................................. iv

Thesis Readers .................................................................................................................... iv

Acknowledgements ........................................................................................................... v

Table of Contents ........................................................................................................... xiii

List of Tables ................................................................................................................. xvii

List of Figures ............................................................................................................... xviii

Chapter 1. Introduction ................................................................................................... 1

Overview and specific aims ................................................................................................. 2

Background ......................................................................................................................... 5

Retention in Clinical Care: A core indicator of quality care for HIV-1 infected individuals. 5

Significance of clinical retention for improved HIV disease outcomes and review of published research ................................................................. 7

Study Populations and data sources .................................................................................. 10

Conceptual Framework .................................................................................................... 11

Preliminary Studies .......................................................................................................... 13

Data collection for clinical population and eligibility criteria ........................................... 14

Assessment of mediating factors and interactions between patient characteristics and retention outcomes ................................................................. 15

Study variables and definitions ......................................................................................... 15

Overview of this dissertation ............................................................................................ 16

References ......................................................................................................................... 22
Chapter 2. Laboratory measures are imperfect proxies of primary care encounters: implications for quantifying clinical retention among HIV-infected adults in North America ................................................................. 31

Abstract ....................................................................................................................... 32
Background .................................................................................................................. 34
Methods ....................................................................................................................... 35
Population and study design ....................................................................................... 35
Retention measures, factors associated with retention, and follow-up ..................... 37
Statistical models and methods ................................................................................. 38
Results ......................................................................................................................... 39
Discussion .................................................................................................................... 40
Appendix ...................................................................................................................... 51
Retention measures .................................................................................................... 51
Selection of Toeplitz correlation structure in the GEE context ................................. 53
Construction of stabilized inverse probability of selection weights ......................... 60
References .................................................................................................................. 64

Chapter 3. Race, Sex, and HIV Risk Disparities in Loss of Clinical Retention after ART Initiation in North America .................................................................................... 70

Abstract ....................................................................................................................... 71
Background .................................................................................................................. 74
Methods ....................................................................................................................... 75
Population and study design ....................................................................................... 75
Inclusion criteria and variables of interest. ................................................................. 77
Event of interest, competing event, and follow-up ..................................................... 78
Exposures of interest and factors associated with death and discontinuity in retention ...... 78
Statistical Methods .................................................................................................... 79
Results ......................................................................................................................... 81
Discussion ........................................................................................................................................... 83
Appendix .................................................................................................................................................. 112
Assessment of proportional hazards assumption................................................................. 112
Construction of stabilized inverse probability of selection weights........................................ 116
References .............................................................................................................................................. 120

Chapter 4. The geography of HIV clinical retention in the United States: regional trends in the NA-ACCORD ............................................................................................................. 129
Abstract ............................................................................................................................................... 130
Background .......................................................................................................................................... 132
Methods ............................................................................................................................................... 133
Population and study design............................................................................................................. 133
Retention measures, factors associated with retention, and follow-up ..................................... 134
Additional geographic information.............................................................................................. 136
Statistical models and methods ...................................................................................................... 137
Results ............................................................................................................................................... 139
Discussion .......................................................................................................................................... 141
Appendix ............................................................................................................................................... 160
Individual-level Analyses ................................................................................................................. 160
ZCTA-level Analyses ........................................................................................................................ 164
References ........................................................................................................................................... 173

Chapter 5. Conclusion ......................................................................................................................... 184
Summary of key findings .................................................................................................................... 185
Public health importance ..................................................................................................................... 187
Generalizability of results .................................................................................................................. 190
Other strengths and limitations......................................................................................................... 193
Future directions ................................................................................................................................. 196
List of Tables

Chapter 1. Introduction

Table 1-1. Odds Ratios (OR) and 95% Confidence Intervals (95% CI) for factors associated with suboptimal clinical retention among HIV+ patients in the NA-ACCORD, using various modeling approaches, 2000-2008.......................... 21

Chapter 2. Laboratory measures are imperfect proxies of primary care encounters: implications for quantifying clinical retention among HIV-infected adults in North America

Table 2-1. Percent of patients retained in the NA-ACCORD defined by encounters and laboratory measures, and agreement between retention measures......................... 44

Table 2-2. Agreement between ER and LR, and discrimination of ER by LR, estimated from stabilized IPW ................................................................................................. 47

Appendix Table 2-1. Model diagnostics for different correlation structures used to model ER based on LR ................................................................. 59

Chapter 3. Race, Sex, and HIV Risk Disparities in Loss of Clinical Retention after ART Initiation in North America

Table 3-1 a,b,c. Characteristic differences and endpoint distributions among 17,171 ART initiators in the NA-ACCORD................................................................. 88

Table 3-2 a,b. Cause-specific Hazard Ratios (HR) for and median times to (a.) discontinuation of retention and (b.) death before discontinuation, with nadir CD4+ lymphocyte count after ART initiation ................................................. 91

Table 3-3 a,b. Cause-specific Hazard Ratios (HR) for and median times to (a.) discontinuation of retention and (b.) death before discontinuation, with time-varying median CD4+ lymphocyte count after ART initiation .............................................. 91

Chapter 4. The geography of HIV clinical retention in the United States: regional trends in the NA-ACCORD

Table 4-1. Percent of person-years successfully retained (with % person-years contributed) in the NA-ACCORD ................................................................. 147

Table 4-2. Estimated 95% Odds RatiosCI$s from ZCTA-level logistic regression models using GEE with an unstructured working correlation structure...................... 155

Appendix Table 4-1. Comparison of 95% Risk RatiosCI$s from individual-level Poisson regression models using GEE ................................................................. 160
List of Figures

Chapter 1. Introduction

Figure 1-1. Conceptual framework for factors influencing, and influenced by, retention in clinical HIV care and HIV disease progression or death over time ..... 19

Figure 1-2. “Churn” and clinical retention of patients in the NA-ACCORD, 2000-2010.......................................................................................................................... 20

Chapter 2. Laboratory measures are imperfect proxies of primary care encounters: implications for quantifying clinical retention among HIV-infected adults in North America

Figure 2-1. Temporal trends in encounter- and laboratory-based retention measures, and agreement between measures, in the NA-ACCORD, 2000-2010.............. 46

Figure 2-2 a,b. Receiver operating characteristic (ROC) curves quantifying the discrimination of ER by LR.......................................................... 48

Figure 2-3. Odds Ratios and 95% Confidence Intervals for probability of ER conditioned on LR with interactions by subpopulations of concern for suboptimal retention. .................................................................................. 48

Appendix Figure 2-1. Conceptual framework for continuity and retention in clinical care over time by calendar periods ......................................................... 52

Appendix Figure 2-2. Lorelogram of encounter-based retention (ER) for 10,628 individuals with observations present over the entire 11-year study period........ 57

Appendix Figure 2-3 a,b,c,d. Lower diagonals of the empirical (a.) Exchangeable, (b.) AR1, (c.) Unstructured, and (d.) Toeplitz correlation matrices ................. 58

Appendix Figure 2-4 a,b. Distribution of constructed IPW for the probability of LR, both untruncated and truncated at the 5th and 95th percentiles............................. 62

Chapter 3. Race, Sex, and HIV Risk Disparities in Loss of Clinical Retention after ART Initiation in North America

Figure 3-1 a(i-iii), b(i-iii), c(i-iii). Predicted survival and cumulative incidence of discontinuation from retention........................................................................................................ 99

Figure 3-2. Predicted cumulative incidence of discontinuation from retention, stratified and adjusted by scaled baseline age................................................. 108
Chapter 4. The geography of HIV clinical retention in the United States: regional trends in the NA-ACCORD

Figure 4-1. Geographic distribution of NA-ACCORD clinical cohort sites contributing data to this analysis.......................................................... 149

Figure 4-2. Temporal trends in percentage of individuals successfully clinically retained in the NA-ACCORD by CDC-defined region of the United States, from 2000-2010 ................................................................. 150

Figure 4-3. Risk Ratio estimates and 95% Confidence Intervals for factors associated with retention .............................................................. 152

Figure 4-4 a,b,c,d,e. Predictive margins and 95% Confidence Intervals for factors associated with retention, based on modified Poisson regression model using GEE .......................................................... 153

Figure 4-5. Cluster analysis of ZCTAs with lower than expected proportions of clinically retained patients ................................................... 156

Figure 4-6 a,b,c. (a.) Region-level, (b.) State-level, and (c.) ZCTA-level maps of observed clinical retention status within the study sample .................... 157

Appendix Figure 4-1 a,b,c,d,e,f. Violin plots for the distribution of predicted probabilities of retention over time at the individual-level ..................... 161

Appendix Figure 4-2 a,b,c. Comparison of observed with predicted retention probabilities from ZCTA-level logistic regression model ....................... 166

Appendix Figure 4-3 a,b,c,d,e. Predicted linear fits at the ZCTA-level ............. 168
CHAPTER ONE

Introduction
Overview and specific aims

Retention in clinical HIV care has been widely recognized as a key component in improving HIV disease outcomes in individuals and decreasing HIV transmission in populations. Measures of retention in clinical care have varied depending on the available data and the population under study, and various demographic, clinical, and environmental characteristics have been observed influencing patterns of care over time. Recently, the National HIV/AIDS Strategy (NHAS) for the United States advocated improvement in clinical retention rates and the Institute of Medicine (IOM) outlined measures for assessing both the NHAS and benchmarks in the Affordable Care Act.

This dissertation therefore seeks to quantify clinical, sociodemographic, and geographic patterns and correlates of retention in care among HIV-infected persons in the United States (US) and Canada, with a particular focus on individuals historically deemed to be at greater risk of suboptimal care and HIV outcomes, such as younger, male patients, minorities, and those with a history of injection drug use (IDU). The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) provides a rich data source that has been endorsed by the IOM as an important resource capable of monitoring patterns of care among persons living with HIV/AIDS (PLWHA) in the United States and assessing progress in the NHAS. The results of these analyses will provide evidence to clinic-directors and state and federal policy makers regarding effective strategies to measure and improve clinical retention, in line with recommendations for measures of quality HIV care by the IOM and retention targets in the US National HIV/AIDS Strategy.\(^{(1-3)}\)
Aim 1 addresses the concordance of laboratory measures (used as surrogates for direct measures of clinical encounters) with actual clinical encounters between 2000 and 2010. Because laboratory measures are widely used as indicators of access to clinical care, this analysis is of significant importance and has not been previously addressed in the literature.

Aim 2 addresses the relationship between demographic and clinical characteristics and suboptimal clinical retention after initiation of ART. The analyses appropriately account for differential access to care, potential confounding factors, and the competing risk of death, and focus on disparities in clinical retention among HIV-infected individuals in North America over the first decade of the 2000s. Mediation by immune status will also be modeled over the same time-frame.

Aim 3 addresses geographic factors associated with suboptimal retention in care between 2000 and 2010; regression modeling and spatial statistics are used to compare regions and detect clustering of outcomes over space and time.

The specific aims of this dissertation are:

**Aim 1:** To quantify the agreement between measures of clinical retention defined by clinic encounters (attended appointments) versus laboratory measures (acquisition of CD4 lymphocyte count or HIV-1 viral load, as surrogates for encounters) among individuals with both encounter and laboratory data from 13 NA-ACCORD clinical cohorts between 2000 and 2010.
Hypotheses: There will be significant positive correlation between measures of clinical retention based on encounters and those based on laboratory measures among patients in clinical cohorts in the NA-ACCORD between 2000 and 2010.

Aim 2: To identify disparities in retention by patient characteristics after accounting for access to ART and changes in markers of disease progression (CD4 lymphocyte count) using appropriate mediation analysis and competing risk methods. Inverse probability of selection weighting and cause-specific proportional hazards regression may be used to control for the laboratory measures as mediators of other demographic or geographic factors associated with healthcare access behavior.

Hypotheses: Younger, male, and minority individuals will be at heightened risk of suboptimal retention even after accounting for deteriorating health (lower CD4 count) or improving health (higher CD4) over time. There will also be poorer retention outcomes among individuals with a history of IDU, even after initiation of ART.

Aim 3: To characterize geographic variation and clustering of suboptimal clinical retention among individuals with geographic information (including state, province, or 3-digit postal code of residence) available within the NA-ACCORD between 2000 and 2010; descriptive comparisons and spatial statistics including the Kulldorff spatial scan statistic and spatial cluster detection analysis for longitudinal outcomes will be used.

Hypotheses: Significant differences in retention exist by geographic region and time, with retention outcomes worse in the South vs. other regions of the U.S.
Background

Retention in Clinical Care: A core indicator of quality care for HIV-1 infected individuals

Of the estimated 1.1 million PLWHA in the US, approximately 80% are aware of their infection status\(^4\), and of those, only an estimated 75% are linked to clinical HIV care.\(^5\) The retention of those patients linked to clinical care has been described as a critical component of improving virologic outcomes and driving down HIV transmission, particularly through a “test and treat” strategy.\(^5\)

Since 2009, the US Health Resources and Services Administration (HRSA) HIV/AIDS Bureau (HAB) has defined retention in clinical care for HIV-infected individuals as 2 encounters within 12 months, but greater than 90 days apart, excluding individuals who entered care in the last half of a calendar year. These guidelines were established in reference to a single calendar period for purposes of annual HRSA HAB reporting requirements.\(^6\) In the past several years, others have used multiple measures to assess retention and to assess correlated suppression of HIV-1 viral load after 12 months in clinical populations, and have found high correlation within measures of visit adherence (numbers of missed appointments, proportion of kept appointments, or proportion of time under observation meeting the HRSA HAB standard in serial 12-month periods) and within measures of visit constancy (number of 4- or 6-month intervals with at least one kept appointment), but low correlation across these two categories of clinical retention measures.\(^7-9\) Recently, following healthcare policy...
research under the auspices of government and private industry, the Institute of Medicine of the National Academies endorsed the HRSA HAB measure as one of its core indicators of quality HIV clinical care. The National Institutes of Health (NIH) has noted:

One of the limitations in HIV care continuum research to date is that most current understanding of patients' success and challenges in navigating the care continuum is derived from cross-sectional data. However, initiating treatment and engagement in care is not always a linear process; a substantial portion of patients are intermittently engaged in care. Also, some patients disengage from care for a significant period of time, and are thus defined as "lost to care." … Collectively, this set of issues suggests a need for studies that examine progress through the continuum of care in pathways that are less step-wise.

Population-based data used to summarize HIV continuum outcomes in various catchment areas may also mask important differences between subgroups, and these differences may also vary by context. If the overall goal is to improve patient outcomes and potentially reduce new infections, then it is critical to better understand and intervene with those at highest risk for HIV infection … and those most likely to have difficulties entering and navigating the continuum of HIV care … Therefore, to the extent possible, more fine-grained data, analyses, and study are needed regarding subgroups within the treatment cascade, and to better identify targets for tailored interventions.

The National Institutes of Drug Abuse (NIDA) has also declared domestic research goals of “reducing racial/ethnic disparities in HIV testing, access, and utilization of treatment and services” and “…expanding HIV testing, linkage, and retention in care for hard-to-reach populations” that this research speaks to.
Though laboratory measures have been widely used as surrogates for care (when encounter data is unavailable, as is often the case in larger studies) and shown to be good indicators of initial or overall access to clinical HIV care to date, there have been no longitudinal studies establishing the actual concordance or correlation between direct measures of clinical retention (i.e., those defined by encounters or visits) and those using laboratory measures as surrogates among HIV-infected individuals over time.\(^{(3,9,13-15)}\)

Aim 1 seeks to fill a gap in knowledge and provide quantitative evidence to support the assertions of concordance between CD4 count or HIV-1 viral load measures and clinical encounters, as outlined above.

**Significance of clinical retention for improved HIV disease outcomes and review of published research**

Several studies have established an association between suboptimal clinical retention (defined by absences from care, missed visits, or non-compliance with HRSA HAB guidelines) and increased likelihood of virologic failure while on antiretroviral therapy (ART), increased likelihood of high-risk behavior, and poorer survival.\(^{(15-19)}\) The implication, echoed in the advocacy of improved retention in both US and Canadian national HIV/AIDS strategies, is that retention in clinical care is as important as early diagnosis and linkage to care for blunting the progression of HIV and its clinical sequelae.\(^{(1,5,20-23)}\)

Disparities in the initial access to and subsequent retention in HIV clinical care among PLHWA, according to patient demographic and clinical factors, have been
extensively documented.\cite{13,14,16-19,24-31} At least one study has also tied racial disparities in
HIV virologic outcomes directly to disparities in clinic attendance and retention.\cite{19} Given
the simultaneous priority placed on the reduction of health disparities and inequities, and
the relationship between the narrowing of retention disparities and the narrowing of HIV
disease outcome disparities, there should be a commensurate focus on improving clinical
retention among PLWHA engaged in care.

To date, there have been few longitudinal evaluations of individual disparities in
losses to retention after ART initiation, and in the existent literature, the focus remains on
complete ascertainment of clinical trial outcomes in the developing world.\cite{32-34} Much of
the literature addressing racial or sex disparities in retention either does not specifically
address changes in retention following the initiation of therapy, or adjusts for time on
therapy as a covariate in regression analyses, a technique that may not account for equity
in access to care as well as examining individuals’ retention experience from a common
origin of ART initiation.\cite{27,35,36} Therefore, the disparities noted may be indicative of
more distal relationships between environment and contextual factors or may be related
to more proximal and potentially more immediately addressable clinic-level factors. Aim
2 seeks to capitalize on the longitudinal clinical information available within the NA-
ACCORD in the large variety of clinical settings as they’re currently constituted across
North America to assess ongoing disparities in retention in the US and Canada,
controlling for access to care by examining only those individuals initiating therapy.

Multiple studies have attempted to discern factors associated with suboptimal
retention in a clinical setting. Many of these have found race, sex, age, and historical
injection drug use to be significantly associated with having suboptimal retention (either
through larger numbers of discontinuities in care, or larger proportions of time under follow-up without clinical care), though studies have differed on whether males or females are at greater risk.\(^{8,14,16,19,21,24,25,27,28,31}\) However, these studies addressed suboptimal retention either as an exposure with a clinical outcome (including AIDS-related illnesses, mortality, and CD4 count and HIV-1 viral load) or as an outcome itself, without examining the mediation effects of CD4 count (an indicator of immune health). Aim 2 seeks to remedy this gap through the use of the more sophisticated but well-described epidemiologic method of inverse probability of selection weighting and through direct regression adjustment.\(^{37,38}\) Furthermore, though these studies each identified similar factors, there was not considerable geographic heterogeneity in the patient population of any single study; studies conducted within Birmingham, AL,\(^{19,24}\) Chapel Hill, NC,\(^{27}\) San Francisco, CA\(^{28}\) and New York City, NY\(^{31}\) cannot be assumed to describe larger geographic patterns in clinical care retention among PLWHA across the US on their own, and they may suffer from barriers to external generalizability (e.g., larger distances between residence and clinical site may be related with lower rates of clinical retention for patients outside large urban centers). Aim 3 seeks to clarify these issues by describing and quantifying the geographic heterogeneity of clinical retention among PLWHA.

The consistency of association between the characteristics described above and clinical retention, and the association of these same characteristics with poorer HIV disease outcomes,\(^{25}\) underlines the rationale for continued monitoring of clinical retention within these subpopulations in pursuit of improved HIV outcomes among PLWHA.\(^{18}\)
Study Populations and data sources

The complete evaluation of retention of PLWHA in clinical care would be possible in the case of a nationally linked clinical care network or claims database, through which the clinic encounter records of all people living within the region and accessing clinical HIV care would be available. One ambitious study, the US Centers For Disease Control and Prevention-funded Medical Monitoring Project, was designed to monitor clinical care among a nationally representative sample of HIV-infected individuals, but it is in reality a serial cross-sectional study similar to the National Health and Nutrition Examination Survey (NHANES), and is therefore unsuitable to examine longitudinal trends accounting for within-individual correlation of behavior over time.\(^{(39)}\)

We therefore examined factors associated with retention in clinical HIV care and the geographic patterns of suboptimal retention across the US using data from the largest cohort collaboration including HIV-infected individuals in the US. The NA-ACCORD, the North American member of the NIH-sponsored International epidemiologic Databases to Evaluate AIDS (IeDEA) project, is a collaboration which began collecting data from multi- and single-site interval and clinical cohorts in 2006.\(^{(40)}\) Currently, there are 25 included cohorts comprised of patients from 43 of the 50 US states, Washington, D.C., Puerto Rico, and 9 of the 13 Canadian provinces; more than 120,000 patients were included in the latest data upload. In the NA-ACCORD patient population, 24% are women, 40% are black or African-American, 38% are white, 0.9% are Asian or Pacific Islander, 0.7% are American Indian or Alaskan Native, and 0.7% are Multiracial; 15%
are of Hispanic ethnicity (of any race), and 5% are of unknown or other race/ethnicity. Based on age at study entry, the age distribution among individuals in this population was: age 18-24, 4.2%; age 25-34, 22.5%; age 35-44, 41.1%; age 45-54, 24.8%; age 55-64, 6.2%; age 65+, 1.2%.

Clinical and demographic data (including multiple laboratory values and collection dates, medical diagnoses and dates, antiretroviral medication names and prescription dates, clinic encounter information, basic insurance status, and 3-digit zip code) are transmitted to a centrally-administered Data Management Core semi-annually where all contributed datasets are harmonized. Data undergo quality control for completeness and accuracy, including measures to reduce the probability that an individual was concurrently participating in more than one clinical cohort. Because both historic clinic encounter and laboratory collection data were included in the latest round of data uploads (spanning the period 2000 to 2010), a more complete picture of clinical HIV care in the US and Canada is now available.

According to the IOM, the NA-ACCORD has demonstrated a constituent patient population that is a large proportion of and demographically similar to PLWHA in the US, and has therefore been selected as one of 12 data systems adequate to assess and quantify quality of care measures (including retention in clinical care) that will serve as benchmarks for progress in the NHAS and Affordable Care Act.\(^{(3)}\)

**Conceptual Framework**
Retention in clinical care has been defined in the IOM recommendations on indicators of HIV care as 2 visits within a 12-month period (>90 days apart), either measured by laboratory collection as a proxy or directly by clinical encounters. In addressing the agreement between retention defined by laboratory measures vs. clinic encounters, the time scale over which longitudinal measures are assessed can be defined as elapsed time from patient entry to care, calendar time alone (serial cross-sectional assessments of retention), or a combination of these methods across two time axes. Under the hybrid method or the calendar time method of assessment, a patient may be classified as successfully retained in a calendar period based on clinic encounters, based on laboratory measures such as CD4 count or HIV-1 viral load alone, based on both, or may not qualify as retained in care by either laboratory measure or encounters. An individual may, at the same time, have more laboratory measures than encounters, more encounters than laboratory measures, or the same number of each in a given period.

The relationship between individual demographic characteristics, clinic characteristics, retention in clinical care, markers of individual immune health, receipt of ART, substance abuse behavior, and disease or death is likely quite complex with individual- and clinic-level factors influencing each of the other factors and immune health and substance abuse behavior influencing present and future states of clinical care and disease progression while themselves being affected by prior states of care. The effect of CD4 count and HIV-1 viral load (as markers of immune health) and the effect of substance abuse (indicated by clinical diagnosis) on clinical retention over time could also be encapsulated by a time-varying joint-effects framework (Figure 1-1). The same can be said of patients engaging in substance abuse behavior: depending on the ongoing
nature of their behavior, it may influence their likelihood of returning to care, while their retention in care may bring them into contact with resources capable of helping them alter their substance abuse behavior. And for all that, ongoing substance abuse behavior affects the patient’s health directly, too.\(^{41}\) Therefore, to accurately quantify the association of individual- and clinic-level factors with clinical retention, the mediating effects of immune health and other factors must be properly accounted for.

**Preliminary Studies**

Analysis of data contributed in the NA-ACCORD from 2000 through 2009 have shown a small but substantial decrease, from 11% to 7%, in the percentage of patients experiencing suboptimal retention (at least one gap in clinical retention defined in line with the HRSA HAB measure) in North America over time. A test for trend using GEE (to account for clustering of outcomes by individual) showed the decline to be statistically significant. These trends varied by contributing cohort, and in mixed effects modeling to account for individual clustering within cohorts, there was non- zero variance in the slope term for cohort site (indicating some geographic heterogeneity in the outcome). There has simultaneously been a significant increase in the percent of patients retained over the same time period (Figure 1-2).\(^{42,43}\) Aims 1, 2, and 3 expand on these analyses to include assessments of clinical retention and its relationship with various patient characteristics while accounting for site-specific influences and geographic clustering.
Multiple modeling approaches, including beta-binomial,\textsuperscript{(44)} zero-inflated binomial,\textsuperscript{(45)} logistic mixed effects,\textsuperscript{(46,47)} and Markov transition regression\textsuperscript{(48,49)} revealed considerable clustering of individual patient behavior over time (i.e., with poor retention historically were likely to continue with poor retention throughout the study period), and highlighted male sex, minority racial group, younger age, history of injection drug use, and lack of ART receipt as factors associated with suboptimal retention (Table 1-1). These findings are consistent with prior research and shows that they are fairly consistent across larger geographic areas.

Data collection for clinical population and eligibility criteria

The NA-ACCORD has completed 6 waves of data collection, the latest occurring in 2012 (covering data through December 31, 2010 for most contributing cohorts). The study population for Aims 1, 2, and 3 was comprised of those individuals with encounter data available at least once between January 1, 2000 and December 31, 2010. For Aim 2, the additional inclusion criteria of being ART naïve, initiating ART while in care between 2000 and 2006, and having at least one CD4 count between ART initiation and loss of retention were applied. For Aim 3, the additional inclusion criteria of available 3-digit zip code data and residence within one of four US Census Bureau-defined geographic regions were applied. Exclusion criteria were participation in a non-clinical cohort (e.g., participation in an interval cohort such as the Multicenter AIDS Cohort Study), age <18 years, or lack of encounter data during the study period.
Assessment of mediating factors and interactions between patient characteristics and retention outcomes

As described above, changes in patient health status over time (indicated by CD4 count) were considered potentially mediating for the relationship between other clinical or demographic factors and the outcome of optimal retention. These laboratory measures were available in the standard data already collected by the NA-ACCORD. Changes in substance use diagnoses over time, though potentially a time-varying mediator of the exposure-outcome relationship, were only assessed in the course of normal medical care and through medical diagnostic information currently collected, not based on Diagnostic Statistical Manual criteria,\(^4\) and were therefore excluded as adjustment factors due to potential misclassification which would tend to dilute observed effects. Baseline IDU history was instead accounted for in each model.

Study variables and definitions

For Aims 1, 2, 3, the outcome was based on the binary state of retention in care, anchored in calendar time, and was defined as adherence to the HRSA HAB, IOM, and NHAS measures between entry to the study population (first clinic encounter during the study period) and December 31, 2010. As described above, adherence to the definition was assessed in every calendar year: if there were \(\geq 2\) HIV primary care encounters, \(>90\) days apart, during the calendar year, that year met the criteria for “retention” and was so designated. Death during the study period (either while receiving care or after being lost
to follow-up) was treated as a competing event or “absorbent state”, as it must be since patients are no longer eligible to be “optimally retained” in care after death. Individual-level factors such as age, race, sex, 3-digit zip code of residence, state of residence, region of residence, census-derived measures for the area of residence at each of those levels, laboratory measures, and clinic encounters were analyzed as factors contributing to, mediating, or confounding the relationship between multiple exposures and optimal retention. Antiretroviral therapy (ART) was defined as any regimen consisting of 3 antiretroviral agents, so long as they were not the triple-nucleoside regimens abacavir+tenofovir+lamivudine or didanosine+tenofovir+lamivudine; regimens containing both zidovudine and stavudine were excluded because of their contraindication with one another.

**Overview of this dissertation**

This dissertation is organized as three publishable manuscripts comprising Chapters Two, Three, and Four. Chapter Two quantifies the between-measure agreement for laboratory measure-based and encounter-based retention metrics between 2000 and 2010, appropriately accounting for repeated outcomes within individuals over time and confounding by individual- and site-specific factors. These findings correspond to Specific Aim 1. Preliminary results of these findings have been presented at the 18th International Workshop on HIV Observational Databases in March 2014.
Chapter Three assesses disparities in time from ART initiation until first discontinuation of retention from care by patient demographic and risk factors (i.e., sex, race, and HIV acquisition risk factor), accounting for death while retained in care as a competing risk. It also examines the influence of age on the relative times until discontinuation and the influence of mediating immune health status on discontinuation of retention after therapy initiation.

Chapter Four examines the geographic distribution of retention outcomes in this cohort across the United States and addresses changes in these patterns over time. The effect of residence-related factors on the retention experiences of individuals are also addressed utilizing multiple analytic techniques at the individual-, 3-digit postal code-, state-, and region-levels. Preliminary results of these findings have been presented at the 18th International Workshop on HIV Observational Databases in March 2014.

As policy makers, public health practitioners, and epidemiologists train their focus on improving HIV outcomes across the HIV care continuum, and in particular, on measuring changes in retention among populations of concern in the HIV epidemic, critically evaluating the validity of endorsed metrics, the ongoing disparities in the experience of HIV care, and the differential impact of individual and geographic factors on retention patterns would appear to be rational goals. This dissertation attempts to address these questions on a scale of geography and time that is currently lacking in the scientific literature, and in so doing, to provide epidemiologic evidence for improving both the
practice of epidemiology in measuring HIV care continuum outcomes and the focus of public health actions on populations among whom disparities persist and interventions may be most urgently needed.
Figure 1-1. Conceptual framework for factors influencing, and influenced by, retention in clinical HIV care and HIV disease progression or death over time within the NA-ACCORD (adapted from the Andersen Health Behavior model).
Figure 1-2. “Churn” and clinical retention of patients in the NA-ACCORD, 2000-2010.

- **Entered Care**: initial HIV primary care encounter under clinical observation in NA-ACCORD
- **Retained in Care**: second encounter was within 12 months of, but >90 days after, prior encounter
- **Exited Care** ("Out of Care" Year): failed to meet "Retained in Care" definition

(adapted from Rebeiro, et al. 2013)
Table 1-1. Odds Ratios (OR) and 95% Confidence Intervals (95% CI) for factors associated with suboptimal clinical retention among HIV+ patients in the NA-ACCORD, using various modeling approaches, 2000-2008.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Markov chain transition OR (95% CI)</th>
<th>Beta-binomial OR (95% CI)</th>
<th>Zero-Inflated Binomial OR (95% CI)</th>
<th>Mixed Effects, Intercepts Only OR (95% CI)</th>
<th>Mixed Effects, Intercepts &amp; Slopes OR (95% CI)</th>
<th>Multiple Logistic, Any vs. No “Gaps” OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Sex</td>
<td>0.91 (0.88, 0.94)</td>
<td>0.96 (0.92, 1.01)</td>
<td>0.92 (0.88, 0.95)</td>
<td>0.95 (0.89, 1.02)</td>
<td>0.96 (0.89, 1.02)</td>
<td>0.94 (0.91, 0.97)</td>
</tr>
<tr>
<td>Age (per 10 y)</td>
<td>0.87 (0.86, 0.88)</td>
<td>0.79 (0.77, 0.80)</td>
<td>0.84 (0.83, 0.85)</td>
<td>0.70 (0.69, 0.72)</td>
<td>0.71 (0.69, 0.73)</td>
<td>0.77 (0.76, 0.78)</td>
</tr>
<tr>
<td>Non-Hisp. Black (vs. Non-Hisp. White)</td>
<td>1.03 (1.00, 1.06)</td>
<td>1.26 (1.21, 1.32)</td>
<td>1.16 (1.12, 1.20)</td>
<td>1.38 (1.30, 1.46)</td>
<td>1.38 (1.30, 1.46)</td>
<td>1.26 (1.23, 1.30)</td>
</tr>
<tr>
<td>IDU Risk (vs. non-IDU)</td>
<td>1.20 (1.17, 1.24)</td>
<td>1.58 (1.51, 1.64)</td>
<td>1.33 (1.29, 1.38)</td>
<td>1.95 (1.83, 2.07)</td>
<td>1.93 (1.82, 2.05)</td>
<td>1.59 (1.55, 1.63)</td>
</tr>
<tr>
<td>ART (at baseline)</td>
<td>0.77 (0.75, 0.78)</td>
<td>0.69 (0.66, 0.71)</td>
<td>0.70 (0.68, 0.72)</td>
<td>0.60 (0.57, 0.63)</td>
<td>0.60 (0.57, 0.63)</td>
<td>0.65 (0.64, 0.67)</td>
</tr>
<tr>
<td>Time Since Enrollment (per year)</td>
<td>0.96 (0.95, 0.96)</td>
<td>1.13 (1.12, 1.14)</td>
<td>1.11 (1.11, 1.12)</td>
<td>1.17 (1.17, 1.18)</td>
<td>1.18 (1.17, 1.18)</td>
<td>1.12 (1.12, 1.12)</td>
</tr>
</tbody>
</table>

Markov chain transition among 56,963 individuals after first year in care and conditioned on care status in prior year; all other models among 61,438 individuals contributing ≥1 HIV-lab between 2000 and 2008.

Time since enrollment: years under clinical observation in NA-ACCORD

Mixed Effects model random intercepts are by individual and random slopes are by contributing cohort

All models adjusted for contributing cohort
References

   http://purl.access.gpo.gov/GPO/LPS124282


20. The Federal Initiative to Address HIV/AIDS in Canada: strengthening federal action in the Canadian response to HIV/AIDS. The Federal Initiative to Address HIV/AIDS


CHAPTER TWO

Laboratory measures are imperfect proxies of primary care encounters: implications for quantifying clinical retention among HIV-infected adults in North America
Abstract

**Background:** Retention in clinical care is identified as a priority for the U.S. National HIV/AIDS Strategy. Due to data limitations, retention is often estimated using laboratory measure (e.g., CD4) dates as proxies for clinic encounters. Here we compare calendar trends in encounter- versus laboratory-based definitions of retention in a large North American HIV cohort collaboration.

**Methodology:** The study population included 83,041 HIV+ adults with ≥1 HIV primary care encounters during 2000-2010 from 14 North American HIV cohorts. Encounter-based retention (ER) was defined using the Institute of Medicine’s clinical indicator: >2 encounters in a calendar year, ≥90 days apart. Laboratory-based retention (LR) was defined similarly, but using dates of CD4+ or HIV-1 RNA measurements, not encounters. Kappa statistics (κ) were used to describe agreement between ER and LR and logistic regression with Generalized Estimating Equations (GEE) and stabilized Inverse Probability of Selection Weights (IPW) was used to assess temporal trends and LR’s discriminatory power as predictor of ER. Age, sex, race/ethnicity, and HIV risk were used as additional predictors in the adjusted model.

**Results:** Using ER, 67% (20,591/30,741) and 78% (26,701/34,205) were retained in 2000 and 2010, respectively. Using LR, 65% (20,020/30,741) and 77% (26,357/34,205) were retained in 2000 and 2010, respectively. There were increases with both metrics, though there were higher levels of retention by ER throughout (p<0.01 for trend). There was fair agreement between ER and LR over time (80-86% agreement, κ=0.55-0.62, p<0.01). LR had a strong, but imperfect, ability to discriminate between those retained vs.
not by ER (c-statistic=0.81, p<0.05). The sensitivity and specificity of LR as a proxy for ER were 84% and 77%, respectively, and a discordance of 18%. LR’s discrimination improved in the adjusted model (c-statistic=0.87, p<0.05). Results were similar in shorter periods (2000-2003, 2004-2007, and 2008-2010), though discordance by LR was higher in earlier periods (18% and 19%, respectively) than in the most recent (16%).

**Conclusions:** Clinical retention by both ER and LR improved over time and were strongly correlated. However, LR was an imperfect surrogate for ER. The discordance between encounter retention status and widely used laboratory proxies provides further motivation for integrated health information exchanges and new data sharing techniques to facilitate more accurate measurement of HIV clinical retention.
Background

Retention in clinical HIV care has been widely recognized as a key component in improving HIV disease outcomes in individuals and decreasing HIV transmission in populations. It is a core indicator of quality care for HIV-1 infected individuals and the central feature of the HIV care continuum, following linkage to care and preceding receipt of antiretroviral therapy.\(^{(1-4)}\) Measures of retention in clinical care have varied depending on the available data and the population under study, and various demographic, clinical, and environmental characteristics have been observed influencing patterns of care over time.\(^{(5-7)}\) In 2010, the National HIV/AIDS Strategy (NHAS) for the United States advocated improvement in clinical retention rates and, in 2012, the Institute of Medicine (IOM) outlined measures for assessing both the NHAS and benchmarks in the Affordable Care Act.\(^{(8,9)}\) More recently, the Department of Health and Human Services adopted process indicators for HIV care and the President of the United States issued an Executive Order directing the Office of National AIDS Policy to coordinate a Federal response to improve engagement across the continuum as part of the HIV Care Continuum Initiative.\(^{(10-12)}\)

There is clearly an increased policy emphasis on improving clinical retention, and thus more important than ever to correctly quantify retention at the national, state, and local levels, so that progress toward established benchmarks can be accurately assessed. Laboratory measures have been widely used as surrogates for care when encounter data is unavailable as is often the case in larger studies or with population sampling across counties or states and shown to be good indicators of initial or overall access to clinical
HIV care. However, to date, there have been no longitudinal studies establishing the actual concordance or correlation between measures of clinical retention defined by encounters or primary care visits and those using laboratory measures as surrogates among HIV-infected individuals over time.\textsuperscript{(3,9,13-15)} With the wide use of laboratory measures as indicators of access to clinical care, the need to accurately quantify retention means that agreement across measures which may be based on varying data sources should be clarified, so that policymakers, researchers, and other consumers of epidemiologic information can better understand and interpolate the clinical care experience indicated by alternative measures.

This research therefore seeks to quantify the concordance of laboratory measures (used as surrogates for direct measures of clinical encounters) with actual clinical encounters between 2000 and 2010 in a large, demographically, clinically, and geographically diverse cohort of HIV-infected adults in North America.

Methods

*Population and study design*

The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), the North American region of the NIH-sponsored International epidemiologic Databases to Evaluate AIDS (IeDEA) project, is a collaboration which began collecting data from multi- and single-site interval and clinical cohorts in 2006.\textsuperscript{(16)} According to the IOM, the NA-ACCORD has demonstrated a constituent patient population that is a large proportion of and demographically similar to PLWHA in the
US, and has therefore been selected as one of 12 data systems adequate to assess and quantify quality of care measures (including retention in clinical care) that will serve as benchmarks for progress in the NHAS and Affordable Care Act. Clinical and demographic data from 25 cohorts (including multiple laboratory values and collection dates, medical diagnoses and dates, antiretroviral medication names and prescription dates, clinic encounter information, basic insurance status, and 3-digit zip code) are transmitted to a centrally-administered Data Management Core semi-annually where all contributed datasets are harmonized. Data undergo quality control for completeness and accuracy, including measures to reduce the probability that an individual was concurrently participating in more than one clinical cohort. Both historic clinic encounter and laboratory collection data were included in the latest round of data collection protocols for 2011 (spanning the period 2000 to 2010). The activities of both the NA-ACCORD centrally and each participating cohort have been reviewed and approved by their respective local institutional review boards. Further details on the NA-ACCORD collaboration have been published previously.

Among clinical cohorts, only patients with ≥ 2 clinic visits within 12 months were enrolled into the NA-ACCORD, limiting the NA-ACCORD clinical population to patients established “in care” proximal to cohort entry; this is assessed by sites based on clinic encounter data. For this analysis, we further restricted to adult participants who had ≥ 1 HIV primary care visit between January 2000 and December 2010. Interval cohorts were excluded to allow an exclusive focus on patterns of patient clinical care. The 14 included clinical cohorts were comprised of patients from all 50 U.S. states, Washington, D.C., Puerto Rico, and 9 of the 13 Canadian provinces.
Retention measures, factors associated with retention, and follow-up

The outcome for this study was encounter-based clinical retention (ER), defined as the IOM-based indicator: \( \geq 2 \) encounters within each calendar year, \( \geq 90 \) days apart. Laboratory-based retention (LR) was defined in the same fashion as ER was, but using CD4+ or HIV-1 RNA measure dates, not encounters as markers of care. Data from inpatient visits were excluded.

Participant age (categorized as <40 years, 40-49 years, 50-59 years, and \( \geq 60 \) years of age), sex, race/ethnicity (categorized as white, black, hispanic, or other/unknown), HIV acquisition risk factor (categorized as male sexual contact with men (MSM), injection drug use (IDU), heterosexual contact, or other/unknown), receipt of ART for \( \geq 6 \) months in a year (\( \geq 3 \) antiretroviral agents from \( \geq 2 \) classes, or a triple nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) regimen containing abacavir or tenofovir), CD4+ cell count, HIV-1 RNA and site of clinical care were included in analyses as factors by which the agreement between ER and LR may have differed. ART receipt, CD4+ cell count, and HIV-1 RNA were excluded from regression analyses due to their potential to induce bias as time-dependent confounders of the relationship between LR and ER. All factors were time-varying except for sex, race/ethnicity, and HIV risk factor.

Data from individuals were used to create one observation per year between the year of their entry into the cohort and the year of their final encounter or laboratory measurement prior to the end of 2010. The initial year of care in the cohort was excluded if the patient entered in the final quarter of a calendar year (and were thus ineligible to be “retained” in their year of entry into care). The year of death was excluded for patients
who died before the end of the study (due to individuals not being uniformly at risk for the outcome in the year of death, dependent on the timing of their death during the calendar year). Follow-up time ranged between a minimum of 1 and a maximum of 11 years, and individuals could contribute multiple outcomes over the course of the study.

**Statistical models and methods**

Percent agreement, discordance (percent negative agreement), sensitivity, specificity, and Kappa statistics ($\kappa$) were all used to quantify agreement between ER and LR across and within demographic and clinical characteristics. Differences between ER and LR within strata of baseline characteristics were detected by $\chi^2$ test. Logistic regression using a Generalized Estimating Equation (GEE) was used to assess temporal trends and construct receiver operating characteristic (ROC) curves with their respective c-statistics to assess LR’s discriminatory power as a predictor of ER. A Toeplitz correlation structure based on the means of the unstructured covariance for repeated outcomes within individuals was used in the GEE regression. Stabilized inverse probability of selection weights (IPW) for LR based on cohort site, age, sex, race/ethnicity, and HIV acquisition risk were then applied to reflect estimates in a pseudopopulation reweighted on these characteristics and estimate the marginal relationship between ER and LR while accounting for these factors in the regression model.

Additional details of model diagnostics used in the selection and construction of the Toeplitz correlation structure for the regression with GEE, the construction and implementation of inverse probability of selection weights for the marginal model, and
accompanying tables and plots are available in the Appendix. All analyses were performed using R software, version 3.0.3 (www.r-project.org).

**Results**

Among 83,041 adults included in the study population, the median time contributed was 4 years (Interquartile Range (IQR): 2-6 years). There were significant differences in ER versus LR within every stratum of baseline demographic and clinical factors (Table 2-1). The percent of person-time retained ranged between 60% and 80% for both ER and LR by most characteristics, but was lower among those with an HIV risk factor of IDU and those not receiving ART for ≥6 months per year. There was also good agreement between measures within strata (77-87% agreement, $\kappa=0.39-0.66$, $p<0.01$, Table 2-1).

For ER changes over time, 67% (20,591/30,741) and 78% (26,701/34,205) were retained in 2000 and 2010, respectively. For LR, 65% (20,020/30,741) and 77% (26,357/34,205) were retained in 2000 and 2010, respectively (Figure 2-1). There were increases by both definitions, though there were higher levels of retention by ER throughout ($p<0.01$ for trend, Figure 2-1). There was again fair agreement between ER and LR over time (80-86% agreement, $\kappa=0.55-0.62$, $p<0.01$, Figure 2-1).

Regression models using GEE, with and without stabilized IPW to account for potential variations in practice across clinical sites (ER ranged from 62-85%, and LR from 51-79% across sites) and differences across age, sex, race/ethnicity, and HIV risk categories, were used to construct ROC curves. Using the area under the curves for the
weighted model, LR had a strong, but imperfect, ability to discriminate between those retained vs. not by ER (c-statistic=0.81, p<0.05) (Figure 2-2,a). Using the area under the curve for the robust adjusted model (incorporating IPW and again adjusting for site, age, sex, race/ethnicity, and HIV risk), LR’s discrimination was improved slightly over the unweighted model (c-statistic=0.87, p<0.05) (Figure 2-2,b). Using weighted model estimates, the sensitivity and specificity of LR as a proxy for ER in the pseudopopulation were 84% and 77%, respectively, which resulted in a discordance of 18% (Table 2-2). Results were similar when using predicted probabilities from the weighted regression model and in shorter intervals during the study period (2000-2003, 2004-2007, and 2008-2010), though discordance by LR was slightly higher in earlier periods (18% and 19%, respectively) than in the most recent (16%).

The same approaches applied within subpopulations of special concern, such as younger, minority, male, and IDU patients, revealed similar patterns of improving retention over time, though agreement between ER and LR was lower among those older than 50 years (vs. <50 years old, p<0.05), among males (vs. females, p<0.05), and among IDU patients (vs. non-IDU patients, p<0.05) in weighted regression with age-by-LR and risk-by-LR interactions (Figure 2-3).

Discussion

Retention in care and the movement of patients in and out of care over time (known as “churn”) have implications for the epidemiology and management of HIV in the United States and Canada, as well as the design, implementation, and evaluation of
prevention and treatment strategies.\(^{(8,22)}\) Since improved retention has been recognized as a critical component of quality HIV care, HIV disease management, and consequently, as a means to decreasing HIV transmission through improved virologic control, it is clear that measuring clinical retention accurately and refining targets for improvement are the necessary next steps. Meeting each of these goals, consistent with the recent emphasis on a “test and treat strategy” to rapidly diagnose HIV-infected individuals and engage them in continuous care, has been theorized to “bend the incidence curve” of HIV in the US and Canada downward.\(^{(23,24)}\)

Using multiple methods to address the levels of agreement between encounter and lab-based measures of retention (ER and LR), both across important demographic and clinical groups and over time, it is clear that even in a clinically engaged population successfully linked to care, using laboratory measures as proxies for clinic encounters does not present precisely the same account of clinical care as requested by recently adopted indicators.\(^{(9,10)}\) Though the frequency of laboratory monitoring may be of great concern to a clinician or epidemiologist depending on the condition or needs of the clinic population being served, it is not fully equivalent to the frequency of clinic attendance even at a less granular level (that of an annually-assessed retention indicator), and may not serve the same policy or monitoring purposes despite its utility otherwise. This is denoted in the language of the IOM report, which refers to laboratory measures as “proxies” for encounter based measures. The use of CD4+ cell counts and HIV-1 RNA measures to denote retention in care may also be of particular concern as monitoring frequency guidelines or state/local reporting practices for HIV-related laboratory measures may change over time in different populations.\(^{(14,25)}\) However, it is possible that
incomplete data due to differences in reporting practices could be ameliorated and retention itself improved by the implementation of secure health information exchanges or other emerging data sharing solutions.\(^{(26,27)}\) Whatever the similarities or differences between ER and LR in these different contexts, though, it should at least be clear to whomever conducts analyses or consumes the resultant information (e.g., clinicians, epidemiologists, or policy-makers) that they are not one and the same.

That said, the results of this analysis do not show a gaping chasm between ER and LR. For monitoring purposes, it may be the case that use of one vs. the other may result in different judgments about whether a particular benchmark for clinical retention has been met, but the “misclassification error” comparing one to the other is low enough that the distinction may not be as important above a particularly high benchmark. For example, The NHAS establishes a goal to “Increase the proportion of Ryan White HIV/AIDS Program clients who are in continuous care … from 73 percent to 80 percent…” , but using results from 2010, a population that is considered 77% successfully retained (by LR) may not be meaningfully different for either policy or clinical purposes than a population that is 80% retained (by ER).\(^{(8)}\)

There were limitations in this analysis due to characteristics of the population under study and the statistical traits of some measures of agreement. Because of the high prevalence of retention in this population, the kappa statistic in particular may return artificially low estimates of agreement; this may also occur when the prevalence of the outcome is very low.\(^{(17)}\) However, multiple measures of agreement and predictive discrimination were used to achieve a more complete picture of the relationship between ER and LR over time in this population. Another potential limitation of this analysis is
that results obtained using the NA-ACCORD clinical patient population may not fully represent the continuum of care experienced by patients, particularly if they access clinical care outside of the network of clinical sites inside the NA-ACCORD. Because all data are anonymized before being harmonized at the central Data Management Core, there is no way of tracking the movement of individuals between cohort sites (though the large geographic dispersion of sites makes it likely that individuals are not simultaneously accessing care at disparate locations); there may be misclassification error in the outcome if patients leave care at a member site and access care through a local public health department, private physician’s office, unaffiliated local hospital, or other venue, because they may appear to be experiencing suboptimal retention during that period even though they are not. However, this would be a shortcoming in any setting where there is not a comprehensive, nationally linked medical records or claims database. Despite these potential limitations, the NA-ACCORD has a very large sample size that is demographically representative of persons living with HIV/AIDS in the US, represents individuals living in geographically diverse regions of the US and Canada, and has been formally endorsed as an ideal data source to assess progress in the NHAS, which is an exercise related to just the sorts of issues addressed above.\(^{9,28}\)

Harnessing the resources of North America’s largest collaborative HIV cohort, this analysis showed that clinical retention by both ER and LR improved over time and were strongly correlated. However, LR was an imperfect surrogate for ER. The discordance between encounter retention status and widely used laboratory proxies provides further motivation for novel health information sharing strategies and structures to facilitate the most accurate assessment of HIV clinical retention indicators possible.
Table 2-1. Percent of patients retained in the NA-ACCORD defined by encounters and laboratory measures, and agreement between retention measures, stratified by demographic, clinical, and geographic characteristics, 2000-2010

<table>
<thead>
<tr>
<th>Factor</th>
<th>Number (% Individuals)</th>
<th>Percent of Person-time Retained, Encounter</th>
<th>Percent of Person-time Retained, Laboratory</th>
<th>Kappa</th>
<th>Percent Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>83,041 (100)</td>
<td></td>
<td></td>
<td>0.59</td>
<td>80</td>
</tr>
<tr>
<td>Age (years)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤39</td>
<td>35,713 (43)</td>
<td>62</td>
<td>63</td>
<td>0.64</td>
<td>83</td>
</tr>
<tr>
<td>40-49</td>
<td>29,542 (36)</td>
<td>70</td>
<td>67</td>
<td>0.61</td>
<td>83</td>
</tr>
<tr>
<td>50-59</td>
<td>13,863 (17)</td>
<td>77</td>
<td>68</td>
<td>0.53</td>
<td>81</td>
</tr>
<tr>
<td>≥60</td>
<td>3,923 (5)</td>
<td>84</td>
<td>70</td>
<td>0.39</td>
<td>78</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>67,951 (82)</td>
<td>71</td>
<td>66</td>
<td>0.57</td>
<td>80</td>
</tr>
<tr>
<td>Female</td>
<td>15,090 (18)</td>
<td>69</td>
<td>69</td>
<td>0.57</td>
<td>80</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hisp.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>33,207 (40)</td>
<td>72</td>
<td>69</td>
<td>0.56</td>
<td>82</td>
</tr>
<tr>
<td>Non-Hisp. Black</td>
<td>34,175 (41)</td>
<td>69</td>
<td>62</td>
<td>0.60</td>
<td>82</td>
</tr>
<tr>
<td>Hispanic</td>
<td>9,510 (11)</td>
<td>72</td>
<td>73</td>
<td>0.64</td>
<td>86</td>
</tr>
<tr>
<td>Other/Unk.</td>
<td>6,149 (7)</td>
<td>70</td>
<td>67</td>
<td>0.59</td>
<td>82</td>
</tr>
<tr>
<td>HIV Risk Factor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>30,589 (37)</td>
<td>69</td>
<td>74</td>
<td>0.63</td>
<td>85</td>
</tr>
<tr>
<td>IDU</td>
<td>14,329 (17)</td>
<td>69</td>
<td>58</td>
<td>0.58</td>
<td>80</td>
</tr>
<tr>
<td>Hetero</td>
<td>18,908 (23)</td>
<td>68</td>
<td>71</td>
<td>0.65</td>
<td>85</td>
</tr>
<tr>
<td>Other/Unk.</td>
<td>19,215 (23)</td>
<td>76</td>
<td>59</td>
<td>0.49</td>
<td>77</td>
</tr>
<tr>
<td>CD4+ Cell Count (cells/mm³)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>19,322 (29)</td>
<td>70</td>
<td>69</td>
<td>0.64</td>
<td>85</td>
</tr>
<tr>
<td>200-349</td>
<td>14,718 (22)</td>
<td>73</td>
<td>74</td>
<td>0.63</td>
<td>86</td>
</tr>
<tr>
<td>350-499</td>
<td>12,940 (20)</td>
<td>74</td>
<td>75</td>
<td>0.61</td>
<td>85</td>
</tr>
<tr>
<td>≥500</td>
<td>19,061 (29)</td>
<td>75</td>
<td>76</td>
<td>0.59</td>
<td>85</td>
</tr>
<tr>
<td>HIV-1 RNA (copies/mL)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥200 copies</td>
<td>45,205 (73)</td>
<td>69</td>
<td>68</td>
<td>0.63</td>
<td>84</td>
</tr>
<tr>
<td>&lt;200 copies</td>
<td>16,972 (27)</td>
<td>81</td>
<td>83</td>
<td>0.52</td>
<td>86</td>
</tr>
<tr>
<td>ART Receipt (≥6 months/year)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No ART</td>
<td>46,449 (56)</td>
<td>50</td>
<td>42</td>
<td>0.57</td>
<td>79</td>
</tr>
<tr>
<td>ART</td>
<td>36,592 (44)</td>
<td>83</td>
<td>82</td>
<td>0.46</td>
<td>84</td>
</tr>
<tr>
<td>Country of Care</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U.S.A.</td>
<td>79,236 (95)</td>
<td>70</td>
<td>66</td>
<td>0.58</td>
<td>82</td>
</tr>
<tr>
<td>Canada</td>
<td>3,805 (5)</td>
<td>74</td>
<td>75</td>
<td>0.66</td>
<td>87</td>
</tr>
</tbody>
</table>
Percent perfectly retained during the study by encounter (i.e., no years “out of care” between cohort entry and final encounter) is different from percent perfectly retained by laboratory measure within every stratum ($\chi^2$ test, p<0.01)

MSM: male sexual contact with men; IDU: injection drug use; Hetero: heterosexual contact; ART: antiretroviral therapy ($\geq$3 agents from $\geq$2 classes or a triple-NRTI regimen containing abacavir or tenofovir)

*In the year of cohort entry
Figure 2-1. Temporal trends in encounter- and laboratory-based retention measures, and agreement between measures, in the NA-ACCORD, 2000-2010.
Table 2-2. Agreement between ER and LR, and discrimination of ER by LR, estimated from stabilized IPW constructed using clinic site, age, sex, race/ethnicity, and HIV risk factor.

<table>
<thead>
<tr>
<th>Estimated parameters from weighted data using IPW</th>
<th>Number of Observations</th>
<th>C-statistic</th>
<th>Discordant %</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>κ</th>
</tr>
</thead>
<tbody>
<tr>
<td>468,816</td>
<td>17</td>
<td>86</td>
<td>79</td>
<td>0.63</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Estimated parameters from regression model with IPW</th>
<th>Number of Observations</th>
<th>C-statistic</th>
<th>Discordant %</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>κ</th>
</tr>
</thead>
<tbody>
<tr>
<td>468,816</td>
<td>0.87</td>
<td>18</td>
<td>84</td>
<td>77</td>
<td>0.58</td>
<td></td>
</tr>
</tbody>
</table>
Figure 2-2 a,b. Receiver operating characteristic (ROC) curves quantifying the discrimination of ER by LR, derived from regression models with GEE and IPW. (a.) ROC from robust adjustment for clinic site with IPW (b.) ROC with IPW based on site, age, sex, race/ethnicity, and HIV risk factor.

C-Statistic = 0.868
b. ROC Plot, from GEE w/ IPW by Subsite

C-Statistic = 0.805
Figure 2-3. Odds Ratios and 95% Confidence Intervals for probability of ER conditioned on LR with interactions by subpopulations of concern for suboptimal retention
Appendix

Retention measures

Whether measured by laboratory collection surrogates or by clinical encounters themselves, retention in clinical care has been defined in the IOM recommendations as 2 visits within a 12-month period (>90 days apart).\(^9\) To assess concordance between definitions of retention based on laboratory measures vs. those based on clinic encounters, one can use elapsed time since patient entry to care (and subsequently anchor to calendar time, a hybrid of assessment on two time axes) to define retention. Using the hybrid method, a patient may fulfill criteria for retention in a calendar period based on clinic encounters alone, based on laboratory measures alone, based on both, or may not qualify as retained in care by either laboratory measure or encounters. Further, a patient may have more laboratory measures than encounters, more encounters than laboratory measures, or the same number of each in a given period (Appendix Figure 2-1).
Appendix Figure 2-1. Conceptual framework for continuity and retention in clinical care over time by calendar periods, as defined by laboratory measures or clinical encounters, illustrated for two hypothetical patients “A” and “B”.

<table>
<thead>
<tr>
<th></th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st Qtr.</td>
<td>2nd Qtr.</td>
<td>3rd Qtr.</td>
</tr>
<tr>
<td>Patient A: Clinical Encounters</td>
<td>○</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Patient A: Laboratory Measures</td>
<td>○</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Patient B: Clinical Encounters</td>
<td>○</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Patient B: Laboratory Measures</td>
<td>○</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

IOM: Institute of Medicine
○: Initial encounter in clinical care in NA-ACCORD
✓: Encounter or Lab that contributes to retention by IOM indicator (≥2 encounters/labs within 1 year, >90 days apart)
X: Encounter or Lab that does not contribute to retention by IOM indicator
Calendar year in which patient is “Retained” by IOM indicator
Calendar year in which patient is “Not Retained” by IOM indicator
Selection of Toeplitz correlation structure in the GEE context

The concordance of two longitudinal binary measures can be modeled as odds ratios using estimating equations that properly account for within-individual clustering of outcomes.\(^{(19)}\)

Further, the lorelogram, defined as \(\text{LOR}(t_j, t_k) = \log \text{OR}(Y_{ij}, Y_{ik})\), can be used to quantify the degree of within-individual clustering, and when applied to the recurrence of ER over time, it is clear that an independence correlation structure within the GEE is inappropriate (Appendix Figure 2-2).\(^{(29)}\)

With that understanding, the regression equations for the marginal model and associated covariance/correlation structures are explained further below.

The generalized linear model for the marginal distribution of the outcome \(Y_{it}\) for individual \(i\) at time \(t\) (ER in a calendar year) is specified as:

\[
g(\mu_{it}) = x'_{it}\beta
\]

where \(g\) is the link function (here, the logit, since ER is a binary response), \(x'_{it}\) represents the covariate matrix for individual \(i\) at time \(t\) (including age, sex, race, HIV risk factor, and cohort site), \(\mu_{it} = E(Y_{it} \mid x_{it})\), and \(\beta\) is a scalar for the log odds of the response (intercept and covariate regression coefficients). This can also be written as:

\[
\text{logit}(\mu_{it}) = \beta_0 + \beta_1 x_{it}
\]

The estimating equation for \(\beta\) with a sample of \(i = 1, \ldots, N\) independent clusters with \(\mu_i = (\mu_{i1}, \ldots, \mu_{it})\) is written as:

\[
\sum_{i=1}^{N} \frac{\partial \ell}{\partial \beta_i} V_i^{-1} (Y_i - \mu_i(\beta)) = 0
\]
where the working covariance matrix $V_i$ is specified using the correlation matrix $R_i(\alpha)$ as:

$$V_i = \phi A_i^{1/2} R_i(\alpha) A_i^{1/2}$$

where $\text{Var}(Y_{it}) = \phi a_{it}$, the scale parameter is $\phi$, and $A_i$ is a diagonal matrix with appropriate variance functions $a_{it} = \alpha(\mu_{it})$ as entries. For the binomial, $\alpha(\mu_{it}) = \mu_{it}(1 - \mu_{it})$ where $\mu_{it} \in (0,1)$. The unknown parameter $\alpha$ must be estimated using moment methods or another set of estimating equations.

As shown by Liang and Zeger, the estimating equation produces a consistent estimate of $\beta$, and $N^{1/2}(\hat{\beta} - \beta)$ has an asymptotic multivariate normal distribution with mean 0 and covariance $\Sigma = \lim_{N \to \infty} N \Sigma_0^{-1} \Sigma_0^{-1}$ where $\Sigma_0 = \sum_{i=1}^{N} \frac{\partial \mu_i'}{\partial \beta} V_i^{-1} \frac{\partial \mu_i}{\partial \beta}$ and

$$\Sigma_i = \sum_{i=1}^{N} \frac{\partial \mu_i'}{\partial \beta} V_i^{-1} \text{Cov}(Y_i) V_i^{-1} \frac{\partial \mu_i}{\partial \beta}.$$ 

The sandwich estimator for $\Sigma$, which is consistent regardless of misspecification of the correlation structure, is $\hat{\Sigma} = \sum_{i=1}^{N} \frac{\partial \mu_i'}{\partial \beta} V_i^{-1} (Y_i - \mu_i)(Y_i - \mu_i)' V_i^{-1} \frac{\partial \mu_i}{\partial \beta}$ when $\beta$, $\phi$, and $\alpha$ are replaced by their consistent estimators.

Finally, the correlation matrix $R_i(\alpha)$ for an $n_i \times m$ matrix of the $x_{it}$ covariates, has parameters for the working correlation matrix written as

$$r_i = (r_{i12}, r_{i13}, \ldots, r_{i1n_i}, r_{i23}, \ldots, r_{in_i \cdot n_i})$$. This means the matrix can also be written as

$$r_i = x_{it} \alpha$$. For the independence correlation structure $\text{Corr}(Y_{it}, Y_{lt'}) = 0$, for the exchangeable structure $\text{Corr}(Y_{it}, Y_{lt'}) = \alpha$, for the AR1 (autoregressive) structure $\text{Corr}(Y_{it}, Y_{lt'}) = \alpha^{|t-t'|}$, for the unstructured matrix $\text{Corr}(Y_{it}, Y_{lt'}) = \alpha_{tt'}$ (with each $\alpha$ estimated separately), and for the Toeplitz structure $\text{Corr}(Y_{it}, Y_{lt'}) = \alpha_{t-t'}$; for each of
these, \( t \) and \( t' \) are indicators of adjacent timepoints, and \( t \neq t' \). The Toeplitz structure has equivalent off-diagonal entries \( r_{i,k} = r_{i,k-l} \). The estimates for the lower diagonals from the working correlation matrices using the above structures in a logistic regression of ER on LR with GEE are depicted in Appendix Figure 2-3.

As an example, with 4 timepoints, the exchangeable correlation matrix can be written as:

\[
\begin{bmatrix}
1 & \alpha & \alpha & \alpha \\
\alpha & 1 & \alpha & \alpha \\
\alpha & \alpha & 1 & \alpha \\
\alpha & \alpha & \alpha & 1
\end{bmatrix}
\]

the AR1 correlation matrix can be written as:

\[
\begin{bmatrix}
1 & \alpha & \alpha^2 & \alpha^3 \\
\alpha & 1 & \alpha & \alpha^2 \\
\alpha^2 & \alpha & 1 & \alpha \\
\alpha^3 & \alpha^2 & \alpha & 1
\end{bmatrix}
\]

and the Toeplitz correlation matrix can be written as:

\[
\begin{bmatrix}
1 & \zeta & \xi \\
\zeta & 1 & \zeta \\
\xi & \zeta & 1 \\
\xi & \xi & 1
\end{bmatrix}
\]

In the models used for this analysis, \( \alpha, \zeta, \) and \( \xi \) are the means of the unstructured matrix’s corresponding diagonals.

The quasi-likelihood information criterion (QIC), Copula information criterion (CIC), area under the receiver operating characteristic curve (c-statistic), and variance differences between the model-based and sandwich estimators can be used to assess which of the models incorporating the various correlation structures is closest to the true
model and which produces the most accurate predictions.\textsuperscript{(18,30,31)} These diagnostics, with the exception of the QIC, generally indicated in this analysis that the Toeplitz correlation structure was superior to the independence, exchangeable, AR1, and unstructured structures (Appendix Table 2-1).
Appendix Figure 2-2. Lorelogram of encounter-based retention (ER) for 10,628 individuals with observations present over the entire 11-year study period, showing the within-individual correlation of ER over time.
Appendix Figure 2-3 a,b,c,d. Lower diagonals of the empirical (a.) Exchangeable, (b.) AR1, (c.) Unstructured, and (d.) Toeplitz correlation matrices derived from models of ER predicted by LR. The Toeplitz bands are the means of the Unstructured matrix.

![Exchangeable Correlation Matrix, GEE](image)

![AR1 Correlation Matrix, GEE](image)

![Unstructured Correlation Matrix, GEE](image)

![Toeplitz Correlation Matrix, from Unstructured Means](image)
Appendix Table 2-1. Model diagnostics for different correlation structures used to model ER based on LR. Adjusted models account for age, sex, race, HIV risk factor, and cohort site. QIC is the Quasi-likelihood Information Criterion of Pan. CIC is the Copula Information Criterion. AUC is the area under the receiver operating characteristic curve (the c-statistic).

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Exchangeable Correlation Structure</th>
<th>AR1 Correlation Structure</th>
<th>Unstructured Correlation Structure</th>
<th>Toeplitz Correlation Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference between Sandwich and Model-based Variance (Unadjusted)</td>
<td>0.000096</td>
<td>0.000125</td>
<td>0.0000888</td>
<td>0.0000886</td>
</tr>
<tr>
<td>Difference between Sandwich and Model-based Variance (Adjusted)</td>
<td>0.000189</td>
<td>0.000198</td>
<td>0.000170</td>
<td>0.000170</td>
</tr>
<tr>
<td>QIC (Unadjusted)</td>
<td>406,961</td>
<td>408,526</td>
<td>407,546</td>
<td>407,579</td>
</tr>
<tr>
<td>QIC (Adjusted)</td>
<td>406,812</td>
<td>407,748</td>
<td>407,177</td>
<td>407,206</td>
</tr>
<tr>
<td>CIC (Unadjusted)</td>
<td>3.6</td>
<td>3.55</td>
<td>3.45</td>
<td>3.44</td>
</tr>
<tr>
<td>CIC (Adjusted)</td>
<td>4.43</td>
<td>4.25</td>
<td>4.15</td>
<td>4.15</td>
</tr>
<tr>
<td>AUC for ROC of Unadjusted Models</td>
<td>0.805</td>
<td>0.805</td>
<td>0.805</td>
<td>0.805</td>
</tr>
<tr>
<td>AUC Unadjusted Model, 2000-2003</td>
<td>0.800</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC Unadjusted Model, 2004-2007</td>
<td>0.805</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC Unadjusted Model, 2008-2010</td>
<td>0.808</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Factor</th>
<th>Exchangeable Correlation Structure</th>
<th>AR1 Correlation Structure</th>
<th>Unstructured Correlation Structure</th>
<th>Toeplitz Correlation Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retention by Lab</td>
<td>15.43</td>
<td>13.27</td>
<td>14.38</td>
<td>14.34</td>
</tr>
<tr>
<td>Year of Care</td>
<td>1.04</td>
<td>1.04</td>
<td>1.04</td>
<td>1.04</td>
</tr>
<tr>
<td>Interaction of Lab with Year</td>
<td>1.03</td>
<td>1.02</td>
<td>1.03</td>
<td>1.03</td>
</tr>
</tbody>
</table>
Construction of stabilized inverse probability of selection weights

Inverse probability of selection weights (IPW) are used to address the problem of confounding by re-weighting or balancing populations with respect to the exposure, conditional on potential confounders, thus eliminating the exposure-confounder link when estimating the effect of the exposure on the outcome. In this analysis, the potential confounders of baseline age, sex, race/ethnicity, HIV risk factor, and cohort site were used to construct IPW which were then applied to the marginal model estimating the agreement between encounter-based retention (ER) and lab-based retention (LR). These were time-fixed confounders, so single weights across all timepoints for an individual were used. The weights were also stabilized and truncated at the 5th and 95th percentiles to improve balance (Appendix Figure 2-4). Assuming a model using the untruncated weights is unbiased, truncation reduces variance at the expense of increasing bias in the final estimates of effect, but the modest truncation at the 5th and 95th percentiles is justified here by the reduction of several orders of magnitude in the 1/minimum and maximum weights.\(^{(32)}\)

The weights themselves were constructed using regression to estimate the probability of exposure, conditioning on the appropriate confounding factors. Because the exposure of interest was LR, a logistic regression model was used to create the IPW. The regression model for the stabilized weights was specified as:

\[
\text{IPW}_i = \frac{\Pr(LR_i = 1)}{\Pr(LR_i = 1 | \text{age}_i, \text{sex}_i, \text{race}_i, \text{risk}_i, \text{site}_i)}
\]

The truncated weights based on site alone (as above, but excluding age, sex, race, and risk factor as potential confounders) had a median of 0.92 (interquartile range of
0.69-1.17) and a range of 0.25-2.62 (indicating a lack of extreme values which might lead to unstable effect estimates). The truncated weights based on all potential confounding factors available had a median of 0.92 (interquartile range of 0.65-1.16) and a range of 0.20-2.72. The untruncated and truncated distribution of weights accounting for site alone and for all available confounders are illustrated below (Appendix Figure 2-4).

Using these weights, the regression of ER on LR with GEE was conducted (as outlined above) to adjust for the potential confounding factors and account for clustering of outcomes within individuals while retaining a marginal estimate for the association between ER and LR.
Appendix Figure 2-4 a,b. Distribution of constructed IPW for the probability of LR, both untruncated and truncated at the 5th and 95th percentiles, (a.) based on clinic site alone and (b.) based on clinic site, age, sex, race/ethnicity, and HIV risk factor.
References


CHAPTER THREE

Race, Sex, and HIV Risk Disparities in Loss of Clinical Retention after ART Initiation in North America
Abstract

**Background:** While retention in clinical care has been identified as a key component of the HIV continuum of care, race, sex, and HIV risk disparities in retention and other HIV outcomes have been noted by multiple researchers in the U.S. Retention is a dynamic, non-linear process in the continuum of care through which patients may receive antiretroviral therapy (ART) and be successfully virologically suppressed, without which patients may progress to AIDS and/or death. Here, we examined disparities in discontinuation of care after the initiation of ART by race, sex, and HIV risk factor among patients in a large collaborative cohort in North America.

**Methods:** The study population included 17,171 HIV+ adults with ≥1 HIV primary care encounters during 2000-2010 and initiating ART in one of 13 North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) clinical cohorts. Discontinuation of clinical retention was the event of interest and was defined as failure to comply with the Institute of Medicine’s indicator: ≥2 encounters in a calendar year, ≥90 days apart. Follow-up began at the date of ART initiation and ended at the first of: 1) the last visit in the first calendar year in which retention was interrupted (first discontinuation); 2) date of death; 3) the end of the study period (if the patient neither discontinued care nor died before December 31, 2010). Differences in categorical and continuous variables by race, sex, and HIV risk factor were described by $\chi^2$ and Kruskal-Wallis tests, respectively. Cox proportional hazards regression models were used to assess relative hazards (HR) with 95% Confidence Intervals (95% CI) and compare times from ART initiation until discontinuation of retention by race, sex, and HIV risk.
categories, adjusting for potential confounding factors and treating death before
discontinuation of care as a competing event. Baseline age, baseline CD4+ lymphocyte
count within one year of ART initiation, and cohort site were adjusted for as confounding
factors in the full model.

**Results:** Among 17,171 adults initiating ART while in clinical care in the NA-ACCORD,
the median follow-up time was 3.97 years (Interquartile Range (IQR): 1.85-6.21 years).
During the study period, 49% of participants experienced the event of interest (8,367 / 17,171),
9% died before discontinuing care (1,511 / 17,171), and 43% were right
censored without experiencing any event (7,293 / 17,171). There were significant
differences in the distribution of events by race, sex, and history of injection drug use
(IDU) as HIV risk factor. In adjusted Cox regression models, the cause-specific hazard of
discontinuation from retention was lower for females vs. males (HR: 0.81; 95% CI: 0.77,
0.86) and higher for Black vs. non-Black patients (HR: 1.18; 95% CI: 1.13, 1.24) and for
those with IDU vs. non-IDU risk (HR: 1.35; 95% CI: 1.28, 1.43). The cause-specific
hazard for the competing event (death) was lower for females vs. males (HR: 0.79; 95%
CI: 0.66, 0.93) and higher for Black vs. non-Black patients (HR: 1.16; 95% CI: 1.04,
1.29) and for those with IDU vs. non-IDU risk (HR: 1.16; 95% CI: 1.02, 1.31). Median
times to discontinuation were lower for Black vs. non-Black patients (5.42 vs. 6.37 years)
and for those with IDU vs. non-IDU risk (5.27 vs. 6.46 years); there were no differences
in adjusted median times to discontinuation by sex.

**Conclusions:** Racial and HIV risk disparities in clinical retention persisted after
accounting for the competing risk of death, access and linkage to care, access to therapy,
CD4+ lymphocyte level at the time of ART initiation (accounting for “lateness” of
initiation), immune health changes after initiation of ART, and the age structure of the clinical population. Though there are no sex disparities in retention after adjustment for age and other factors, males progress to death faster than females even after receiving ART and remaining successfully retained in care.
Background

Retention in clinical care has been identified as a key component of the HIV continuum of care, though race, sex, and HIV risk disparities in retention and HIV disease outcomes have been noted by multiple researchers in the U.S. Retention is also part of the dynamic, non-linear continuum of care. Even once patients gain access to antiretroviral therapy (ART) after linkage and engagement in care, they may subsequently progress toward virologic suppression and improved outcomes or toward AIDS and/or death, all while maintaining clinical retention or repeatedly dropping out of and re-entering care.

Race, sex, and HIV acquisition risk factor are obviously not traits that can be modified to alter the trajectory of disease. Hence, the epidemiologic question treated here is not one of causal effect but rather the identification of disparities that can be used for surveillance of HIV care in vulnerable and high-risk populations and for focusing policy or funding toward those groups that may require more intensive interventions or resources. Further, research on retention that has assessed populations with differing access to ART or medical care in general have found these to be important factors associated with retention; in these same studies, poorer immune health has been a powerful predictor of improved retention independent of other characteristics, though at least one recent study in a large private care setting found that lower CD4+ lymphocyte count was associated with increased likelihood of missed visits. In particular, studies examining sex differences in retention or interruption of therapy after balancing populations on access to care have frequently taken place in the context of clinical trials,
in resource-limited settings, or else at single clinical sites not reflective of the real-world patterns of clinical care experienced by patients across North America.\textsuperscript{(16-19)} In addition, a recent systematic review has noted mixed evidence for sex disparities dependent on the HIV outcome being examined, with a disparity present for all-cause mortality but not for progression to AIDS or other clinical outcomes.\textsuperscript{(20)} Where racial and HIV risk disparities in retention and HIV outcomes are concerned, many of the aforementioned studies have also noted significant differences by Black race and IDU risk factor,\textsuperscript{(3,6,7,11,13,15)} though at least one clinical cohort has noted a disappearance of racial disparities in HIV outcomes in its recent history.\textsuperscript{(21)}

Therefore, to minimize potential confounding of the relationship between demographic and risk factors and retention in clinical care by access to ART, and in order to address racial, sex, and risk disparities in HIV outcomes and retention in a broader population of individuals reflective of a more typical clinical care experience in North America, we examined disparities by these factors in discontinuation of care after the initiation of ART while accounting for immune health at and subsequent to initiation of therapy among patients in a large collaborative cohort in North America.\textsuperscript{(5,10,22,23)}

Methods

Population and study design

The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) is a multi-site collaboration of interval and clinic-based cohort studies of HIV-infected individuals receiving care in the US and Canada.\textsuperscript{(24)} NA-ACCORD is one
of the regional cohort studies sponsored by the National Institute of Health’s International epidemiological Databases to Evaluate AIDS (IeDEA) consortium. The Institute of Medicine (IOM) has identified the NA-ACCORD as comprising a large proportion of and demographically similar patient population to persons living with HIV/AIDS (PLWHA) in the US, and has therefore endorsed the NA-ACCORD as one of 12 data systems appropriate to assess quality of care measures (including retention in care) in monitoring progress in the National HIV/AIDS Strategy and Affordable Care Act. Details on the NA-ACCORD collaboration and participating cohort studies have been published previously. Briefly, each contributing cohort has developed standardized cohort-specific methods of data collection. At scheduled intervals, these cohorts submit data regarding enrolled participants’ demographic characteristics, vital status, prescribed antiretrovirals, clinical diagnoses, and dates and results of laboratory tests including HIV-1 RNA viral load and CD4 lymphocyte count (HIV-lab). HIV-lab dates are submitted as dates of specimen collection, not dates of assay performance, and among clinical cohorts, only patients with ≥2 clinical visits within 12 months are enrolled into the NA-ACCORD. Death is determined locally by contributing cohorts using NDI, SSDI, state, and local sources, including death certificates and electronic medical records. These data are transferred securely to the NA-ACCORD’s central Data Management Core, where they undergo extensive quality control for completeness and accuracy per a standardized protocol before they are combined into harmonized data files. Quality control included instituting measures to reduce the probability that an individual was concurrently participating in more than one clinical cohort. The human subjects activities of the NA-ACCORD and each of the participating cohort studies have been reviewed and approved.
by their respective local institutional review boards. Each cohort study has likewise received permission to participate in the NA-ACCORD through the same review and approval process.

**Inclusion criteria and variables of interest.**

Participants in the clinical cohorts of the NA-ACCORD that submitted primary care encounter, race/ethnicity, sex, and HIV acquisition risk data were included in this analysis, allowing us to focus on patterns of care retention as measured by IOM guidelines for HIV clinical care and assess competing risks of discontinuation of care vs. all-cause mortality by racial, sex, and HIV risk group. The interval cohorts in the NA-ACCORD that have independently structured visit schedules by definition, and are therefore not necessarily reflective of clinical practice, were not included in the study. The 13 included cohorts have clinical sites in 50 US states, Washington D.C., Puerto Rico, a Canadian province, and are comprised of patients residing in all 50 US states, Washington D.C., Puerto Rico, and 5 Canadian provinces.

We analyzed data from ART-initiating HIV-infected adults (≥18 years of age) who had ≥1 HIV primary care encounter between January 2000 and December 2010 and ≥1 CD4+ lymphocyte count after ART initiation but prior to death or first discontinuation of retention.

Retention in continuous care was defined concordant with the IOM indicator: ≥2 encounters within 12 months, but >90 days apart, beginning with the year of patient’s ART initiation during the study period. This retention definition was anchored to calendar time to create estimates comparable with other studies and clinic-level reports applying the indicator in regular reporting intervals. Discontinuation of retention was
defined as failure to meet the IOM indicator definition in any calendar year before exiting the study. ART initiation was defined as the first recorded regimen of \( \geq 3 \) antiretroviral agents from \( \geq 2 \) classes, or a triple nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) regimen containing abacavir or tenofovir, received following entry to care and with no recorded HIV-1 RNA measures <200 copies/mL preceding, among treatment naïve individuals.

**Event of interest, competing event, and follow-up**

The outcome or event of interest was first discontinuation of retention in care before the end of the study (December 31, 2010). The competing event was all-cause death, creating a complementary and exhaustive mix of events (e.g., all participants are expected to eventually experience one of the two events). Baseline was ART initiation and the time origin for the analysis was 1 year after ART initiation (denoted as ART initiation +1) because most participants were not truly at risk for a discontinuation in care until exiting this window. In other words, because ART initiation and clinical encounters were likely tethered by definition, and discontinuation required a >12-month lapse from the most recent prior encounter, the year of ART initiation was essentially immortal person-time for this outcome. To create a comparable population for the competing event, participants with deaths within 1 year after ART initiation were excluded. Patients with neither event by study end were administratively censored.

**Exposures of interest and factors associated with death and discontinuity in retention**

Self-reported year of birth, race/ethnicity, HIV transmission risk group, sex, CD4+ lymphocyte count within 1 year prior to ART initiation, CD4+ lymphocyte nadir after ART initiation, and median CD4+ lymphocyte count in each year after ART
initiation were identified as factors potentially associated with death and discontinuation of retention. Sex was categorized as female or male (transgender patients are excluded from participation in NA-ACCORD). Race/ethnicity was categorized as Black or non-Black (including other/unknown). HIV transmission risk group was categorized as injection drug use (IDU) or non-IDU (including men who have sex with men (MSM), heterosexual contact, and other/unknown). Patients with both sexual and IDU transmission risk were categorized as IDU. Patients were classified as using ART if the patient was prescribed ART for \( \geq 1 \) month in a calendar period; measures of adherence to HIV treatment were not available.

**Statistical Methods**

The primary objective of the analysis was to determine whether the risk of first discontinuation of retention after ART initiation in the NA-ACCORD clinical population differed by sex, racial group, or HIV risk group, while recognizing that death was a competing risk for discontinuity.

Bivariate comparisons of patient characteristics and event-types by exposure status (female vs. male, Black vs. non-Black, and IDU vs. non-IDU) were conducted using the \( \chi^2 \) test for categorical variables or the Kruskal-Wallis test for continuous variables.

A competing risks analysis of time from ART initiation to first discontinuation in clinical care or death by sex, racial group, and HIV risk group was conducted in a cause-specific hazard context, censoring one event with respect to the other.\(^{(26)}\) The resultant cause-specific hazard for the event of interest can be interpreted as the factor by which the hazard of discontinuation at any time, \( t \), is different by sex, race, or risk group, among
those who haven’t yet died at time $t$ (or vice versa with respect to cause-specific hazards of the competing event).

All models adjusted for age at ART initiation (scaled by 10 years), baseline CD4+ lymphocyte count (scaled by 100 cells/mm$^3$), sex, and IDU as HIV risk factor (vs. non-IDU), as these variables were either the exposures of interest or else potential confounders for the relationships between the exposures, discontinuation of retention, and all-cause death. Stabilized Inverse Probability of Selection Weights (IPW) were used to produce stratified adjusted survival and cumulative incidence curves in addition to curves and estimates produced through direct adjustment for covariates in Cox models. Nadir CD4+ lymphocyte count after ART initiation and median CD4+ lymphocyte count in each year after ART initiation were used in alternate weighting and regression schema to reveal the direct effect of the demographic and risk factors on retention after accounting for mediation of this relationship by immune health. Details of the construction, truncation, and distribution of weights and checks of the proportionality of hazards assumptions may be found in the Appendix.$^{(27-30)}$ Baseline log$_{10}$ HIV-1 RNA was excluded from analyses as it was unavailable for 2,891 individuals; the effects of baseline HIV-1 RNA at ART initiation on the distribution of times to discontinuity or death could be modeled effectively following a multiple imputation procedure, but was not performed here. All weights were constructed and adjusted models were executed including cohort site as a covariate to account for potential differences in clinical practice across sites.

Analyses were conducted in Stata v. 12.1 (Stata Corporation, College Station, TX), and R v. 3.0.3 (www.r-project.org).
Results

Among 17,171 adults initiating ART while in clinical care in the NA-ACCORD, the median follow-up time was 3.97 years (Interquartile Range (IQR): 1.85-6.21 years). During the study period, 49% of participants experienced the event of interest (8,367 / 17,171), 9% died before discontinuing care (1,511 / 17,171), and 43% were right censored without experiencing the event of interest or the competing event (7,293 / 17,171). There were significant differences in the distribution of events by race, sex, and IDU as HIV risk factor, though the distribution of times until event were shorter for right censoring comparing females to males (median 5.44 vs. 5.87 years, respectively) and longer for death comparing IDU to non-IDU status (median 3.16 vs. 2.66 years, respectively) (Table 3-1, b and c). Females were younger than males (median age 42 vs. 48 years), and patients with IDU risk were older than non-IDU patients (median age 50 vs. 46 years). Baseline CD4+ lymphocyte count at ART initiation was lower among Black compared to non-Black patients, males compared to females, and non-IDU compared to IDU patients (Table 3-1, a, b, and c). Nadir CD4+ lymphocyte count after ART initiation but before first discontinuation, death, or right censoring was lower among Black compared to non-Black patients (144 vs. 176 cells/mm$^3$, respectively). In adjusted Cox regression models accounting for demographic factors, baseline CD4+ lymphocyte count, and nadir CD4+ lymphocyte count after ART initiation, the cause-specific hazard of the event of interest (discontinuation from retention) was lower for females vs. males (HR: 0.81; 95% CI: 0.77, 0.86) and higher for Black vs. non-Black patients (HR: 1.18; 95% CI: 1.13, 1.24) and for those with IDU vs. non-IDU risk (HR:
1.35; 95% CI: 1.28, 1.43) (Table 3-2, a). The cause-specific hazard for the competing event (death) was lower for females vs. males (HR: 0.79; 95% CI: 0.66, 0.93) and higher for Black vs. non-Black patients (HR: 1.16; 95% CI: 1.04, 1.29) and for those with IDU vs. non-IDU risk (HR: 1.16; 95% CI: 1.02, 1.31) (Table 3-2, b). Median times to discontinuation were significantly lower for Black vs. non-Black patients (5.42 vs. 6.37 years) and for those with IDU vs. non-IDU risk (5.27 vs. 6.46 years) (Figure 3-1, b and c); there were no differences in adjusted median times to discontinuation by sex, though the adjusted cumulative incidence curve for females was significantly lower than that for males by the stratified log-rank test (Figure 3-1, a). The overall adjusted cumulative incidence of discontinuation of retention was 0.74 and for death in care was 0.16 at the end of 10 years of follow-up.

A time-dependent Cox regression accounting for median CD4+ lymphocyte count in each year between ART initiation and first discontinuation of retention or death showed similar patterns of association between sex, race, risk and the event of interest (and competing event), except that the weighted regressions appeared to more closely approximate the directly adjusted regressions when incorporating median CD4+ lymphocyte count in the weights and the association of female sex with death was no longer significant in the directly adjusted model (Table 3-3, a,b). The differences in median times until discontinuation appeared to be larger by sex, race, and risk, and there was no association of median CD4+ lymphocyte count comparing the 200-349, 350-500, or ≥500 cells/mm³ categories to the <200 cells/mm³ category in the fully adjusted model (Table 3-3,a). There were significantly lower hazards of progression to death comparing all higher median CD4+ lymphocyte count categories to the <200 cells/mm³ category as a
reference, which is as expected (higher CD4 should be an indicator of increased likelihood of survival) (Table 3-3, b).

Though the stratified adjusted curves presented are set to the mean of the covariates, they are useful to describe the sex, race, and risk differences in median times to discontinuation of retention, accounting for the competing risk of death. Further, they are similar in shape to the weighted curves which are simply stratified by the exposure of interest (Figure 3-1). The stratified predicted cumulative incidence curves for discontinuation of care by sex, adjusted only by scaled baseline age, estimated at the quartiles of the sample age distribution (39.7, 47.1, and 55.0 years) is also provided to demonstrate the confounding influence of age on the association between sex and the event of interest; though the unadjusted stratified curve across all ages (Figure 3-1, a) shows earlier discontinuation for females vs. males, the stratified curve adjusted for age estimated at the quartiles of the age distribution shows earlier discontinuation for males vs. females within each age stratum (Figure 3-2, a). This is the case with IDU vs. non-IDU risk as well (Figures 3-1, b and 3-2, b). The older age distribution of males and IDU patients in this cohort, and the strong effect of age on retention, explain the observed changes in the relative hazards and median times of discontinuation from the unadjusted to the adjusted models for sex and IDU (Table 3-2, a; Figure 3-3).

Discussion

Clinical retention and HIV disparities research have been linked through numerous studies describing the relationship between clinical engagement, access to and
initiation of therapy, continuity of care, and HIV disease progression in various populations and settings, both in resource-rich and resource-limited settings. Few studies, however, have followed a cohort as large as the population observed in these analyses over such a long period of time after ART initiation, indeed, a long enough period to directly observe the median times of first discontinuation of retention in care.\(^{(12,13,15,16,18,31-39)}\)

Here, the analysis of sex, race, and HIV risk factors, by which there have been conflicting mentions of disparities in both retention and other HIV disease outcomes, again implicates Black race and IDU risk as important factors influencing loss of retention. Though there were apparent differences in retention after ART initiation by sex (females leaving care before males) and differences in death in care by Black race (Black patients dying sooner than non-Black patients), both of these relationships were attenuated and became non-significant after adjusting for age and the mediating factors of nadir or median CD4\(^+\) lymphocyte counts after ART initiation. By contrast, the sex disparity in death in care persisted after adjustment (with males dying sooner than females), and there was a marked difference in both retention and death by HIV risk factor (worse outcomes for both events for those with IDU vs. non-IDU risks).

Because the event of interest here was first discontinuation of retention following ART initiation, it is important to note that re-engagement or re-entry into care after individuals leave the risk set in this analysis is very possible. In subsequent analysis, the cumulative incidence curve of time from first discontinuation to re-entry (again treating death after discontinuation as a competing event for re-entry), shows a fairly rapid re-
entry after exit, and the shape of the curve tracks that of the cumulative incidence curve for first discontinuation fairly closely (data not shown).

There were limitations to this analysis. First, we lacked data on socioeconomic, insurance, and other contextual factors which have been shown to be strongly related to both retention and HIV disease outcomes in other studies and which may differ by demographic or risk group factors. Some studies with single-sex populations have noted poverty and housing stability as important influences on retention and ART adherence, and addressing differences in the quality of care experienced by incarcerated populations, while imprisoned and after release, has been found to be strongly associated with retention in HIV care. Though publicly available data on certain health economic factors such as access to Medicaid by state of patient residence or the status of AIDS Drug Assistance Program waiting lists were available for portions of the study period, these were felt to be more distal to the individual care experiences of the patients under study (for example, acting as broad proxies for individual insurance status). Further, the effects of the absence of these data should have been mitigated by the fact that all patients under study were successfully engaged in care (as a prerequisite for entering the NA-ACCORD) and had access to ART since they were at least initially prescribed a regimen. The immune status of individuals at ART start was also taken into account in the adjusted models, helping to account for complications due to “late” initiation of care.

Second, because of the nature of a harmonized, de-identified study population drawing on several independent clinical cohorts, the data available do not represent an exhaustive accounting of all sources of HIV care that participants may have accessed
outside of the cohort. This could lead to misclassification of the event of interest if patients access clinical care apart from the network of clinical sites inside the NA-ACCORD (apparently discontinuing care, but in reality still receiving care). Because data is de-linked and de-identified at the central Data Management Core, there is no way to trace patient movement between cohort sites or from a cohort site to a clinical center outside of the collaborative cohort. A potential mitigating factor for this limitation is that the large geographic dispersion of sites makes it unlikely that individuals access care at disparate locations simultaneously. This sort of data limitation also provides motivation for improved linkage between medical records or state health department surveillance records, perhaps through state health information exchanges. In contrast, ascertainment of death (the competing event) is assumed to be complete due to the cohort use of various national death indices.

Despite these limitations, the NA-ACCORD provided a large study population that is demographically representative of PLWHA in the US, is comprised of patients from varied locations in the US and Canada, and has been endorsed by the IOM as an ideal data source with which to evaluate indicators of HIV care such as clinical retention. We also used survival modeling techniques that help account for the competing risk of death when estimating the hazard of discontinuation from care and obtained information over a decade following the initiation of ART.

Racial and HIV risk disparities in clinical retention persisted after accounting for the competing risk of death, access and linkage to care, access to therapy, CD4+ lymphocyte level at the time of ART initiation (accounting for “lateness” of initiation), immune health changes after initiation of ART, and the age structure of the clinical
population. Though there are no sex disparities in retention after adjustment for age and other factors, males progress to death faster than females even after receiving ART and remaining successfully retained in care. These results highlight the fact that the use of ART, clinical retention, and disease outcomes (including death) are dynamically linked, and successful linkage, engagement, and treatment do not necessarily imply successful retention in care or improved disease progression. Clinical retention must be actively pursued—made a priority by clinicians, communities, and public health officials—particularly focusing resources on the groups repeatedly identified as being at higher risk for discontinuation from care. The fact that disparities in the clinical experience of HIV patients remain, even after accounting for demographic traits, intermediate biological factors, and potential differences in access to care, implies that many factors that differentially influence clinical retention and disease progression may remain. It is precisely those factors that should be the focus of future research and targeted interventions to provide equally high-quality HIV care experiences for all HIV-positive individuals.
Table 3-1 a,b,c. Characteristic differences and endpoint distributions among 17,171 ART initiators in the NA-ACCORD, by (a.) black race, (b.) sex, (c.) HIV risk of history of injection drug use, 2000-2010

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Black</th>
<th>Non-Black</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>7,565</td>
<td>9,606</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Time in Follow-Up (years)</td>
<td>3.82</td>
<td>4.08</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47</td>
<td>47</td>
<td>0.62</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5,815</td>
<td>8,556</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1,750</td>
<td>1,050</td>
<td></td>
</tr>
<tr>
<td>HIV Risk</td>
<td></td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Non-IDU</td>
<td>5,731</td>
<td>8,228</td>
<td></td>
</tr>
<tr>
<td>IDU</td>
<td>1,834</td>
<td>1,378</td>
<td></td>
</tr>
<tr>
<td>CD4+ Lymphocytes† (cells/mm³)</td>
<td>231</td>
<td>270</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Nadir CD4+ Lymphocytes‡ (cells/mm³)</td>
<td>144</td>
<td>176</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HIV-1 RNA§ (log₁₀ copies/mL)</td>
<td>4.521</td>
<td>4.531</td>
<td>0.99</td>
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</table>

Event

<table>
<thead>
<tr>
<th>Event</th>
<th>Number</th>
<th>Years in FU</th>
<th>Number</th>
<th>Years in FU</th>
<th>P-value*</th>
</tr>
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<tbody>
<tr>
<td>Death</td>
<td>738</td>
<td>2.66 (1.51, 4.32)</td>
<td>773</td>
<td>2.88 (1.51, 4.82)</td>
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<tr>
<td>Discontinuity in Care</td>
<td>3,830</td>
<td>2.41 (1.42, 4.19)</td>
<td>4,537</td>
<td>2.46 (1.40, 4.22)</td>
<td>0.75</td>
</tr>
<tr>
<td>Event Free</td>
<td>2,997</td>
<td>5.79 (4.23, 7.88)</td>
<td>4,296</td>
<td>5.85 (4.26, 7.92)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Numbers Presented as "Number (%)" if Categorical, as "Median (IQR)" if Continuous
* $\chi^2$ for Categorical, Kruskal-Wallis for Continuous
† At ART initiation, Available for N=14,356 individuals
‡ After ART initiation, Available for N=17,171 individuals
§ At ART initiation, Available for N=14,261 individuals
## b.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Female</th>
<th>Male</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>2,800</td>
<td>(16)</td>
<td>14,371</td>
</tr>
<tr>
<td><strong>Time in Follow-Up (years)</strong></td>
<td>3.47</td>
<td>(1.7, 5.7)</td>
<td>4.07</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>42</td>
<td>(35, 50)</td>
<td>48</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Non-Black</td>
<td>1,050</td>
<td>(11)</td>
<td>8,556</td>
</tr>
<tr>
<td>Black</td>
<td>1,750</td>
<td>(23)</td>
<td>5,815</td>
</tr>
<tr>
<td><strong>HIV Risk</strong></td>
<td></td>
<td></td>
<td>0.66</td>
</tr>
<tr>
<td>Non-IDU</td>
<td>2,268</td>
<td>(16)</td>
<td>11,691</td>
</tr>
<tr>
<td>IDU</td>
<td>532</td>
<td>(17)</td>
<td>2,680</td>
</tr>
<tr>
<td><strong>CD4+ Lymphocytes† (cells/mm³)</strong></td>
<td>264</td>
<td>(102, 448)</td>
<td>251</td>
</tr>
<tr>
<td><strong>Nadir CD4+ Lymphocytes‡ (cells/mm³)</strong></td>
<td>163</td>
<td>(45, 284)</td>
<td>162</td>
</tr>
<tr>
<td><strong>HIV-1 RNA§ (log₁₀ copies/mL)</strong></td>
<td>4.398</td>
<td>(3.45, 5.05)</td>
<td>4.548</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>Number</th>
<th>Years in FU</th>
<th>Number</th>
<th>Years in FU</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>177</td>
<td>2.65 (1.49, 3.95)</td>
<td>1,334</td>
<td>2.80 (1.51, 4.71)</td>
<td>0.13</td>
</tr>
<tr>
<td>Discontinuity in Care</td>
<td>1,525</td>
<td>2.38 (1.40, 4.00)</td>
<td>6,842</td>
<td>2.45 (1.42, 4.24)</td>
<td>0.10</td>
</tr>
<tr>
<td>Event Free</td>
<td>1,098</td>
<td>5.44 (3.88, 7.63)</td>
<td>6,195</td>
<td>5.87 (4.30, 7.96)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Numbers Presented as "Number (%)" if Categorical, as "Median (IQR)" if Continuous
* χ² for Categorical, Kruskal-Wallis for Continuous
† At ART initiation, Available for N=14,356 individuals
‡ After ART initiation, Available for N=17,171 individuals
§ At ART initiation, Available for N=14,261 individuals
### c.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IDU</th>
<th>Non-IDU</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>3,212</td>
<td>(19)</td>
<td>13,959</td>
</tr>
<tr>
<td>Time in Follow-Up (years)</td>
<td>3.85</td>
<td>(1.8, 6.1)</td>
<td>3.99</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50</td>
<td>(44, 55)</td>
<td>46</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2,680</td>
<td>(19)</td>
<td>11,691</td>
</tr>
<tr>
<td>Female</td>
<td>532</td>
<td>(19)</td>
<td>2,268</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Black</td>
<td>1,378</td>
<td>(14)</td>
<td>8,228</td>
</tr>
<tr>
<td>Black</td>
<td>1,834</td>
<td>(24)</td>
<td>5,731</td>
</tr>
<tr>
<td>CD4+ Lymphocytes†</td>
<td>266</td>
<td>(106, 455)</td>
<td>251</td>
</tr>
<tr>
<td>Nadir CD4+ Lymphocytes‡</td>
<td>160</td>
<td>(48, 281)</td>
<td>163</td>
</tr>
<tr>
<td>HIV-1 RNA§</td>
<td>4.418</td>
<td>(3.28, 5.05)</td>
<td>4.547</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>Number</th>
<th>Years in FU</th>
<th>Number</th>
<th>Years in FU</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>340</td>
<td>3.16 (1.81, 4.86)</td>
<td>1,171</td>
<td>2.66 (1.47, 4.45)</td>
<td>0.001</td>
</tr>
<tr>
<td>Discontinuity in Care</td>
<td>1,623</td>
<td>2.37 (1.40, 4.20)</td>
<td>6,744</td>
<td>2.46 (1.42, 4.21)</td>
<td>0.48</td>
</tr>
<tr>
<td>Event Free</td>
<td>1,249</td>
<td>5.91 (4.24, 7.99)</td>
<td>6,044</td>
<td>5.81 (4.25, 7.88)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Numbers Presented as "Number (%)" if Categorical, as "Median (IQR)" if Continuous  
* \( \chi^2 \) for Categorical, Kruskal-Wallis for Continuous  
† At ART initiation, Available for N=14,356 individuals  
‡ After ART initiation, Available for N=17,171 individuals  
§ At ART initiation, Available for N=14,261 individuals
Table 3-2 a,b. Cause-specific Hazard Ratios (HR) for and median times to (a.) discontinuation of retention and (b.) death before discontinuation, with nadir CD4+ lymphocyte count after ART initiation, from unadjusted, adjusted, and weighted Cox proportional hazards regression models with 95% Confidence Intervals (95% CI)

a.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Discontinuation: Unadjusted HR (95% CI)</th>
<th>Discontinuation: Adjusted* HR (95% CI)</th>
<th>Discontinuation: Weighted† HR (95% CI)</th>
<th>Median Time*† (Years) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 years)</td>
<td>0.55 (0.55, 0.57)</td>
<td>0.59 (0.57, 0.60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Ref.</td>
<td>5.82 (5.69, 5.94)</td>
</tr>
<tr>
<td>Female</td>
<td>1.24 (1.17, 1.31)</td>
<td>0.81 (0.77, 0.86)</td>
<td>1.09 (1.02, 1.16)</td>
<td>6.27 (5.82, 6.68)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Black</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Ref.</td>
<td>6.37 (6.14, 6.68)</td>
</tr>
<tr>
<td>Black</td>
<td>1.12 (1.07, 1.17)</td>
<td>1.18 (1.13, 1.24)</td>
<td>1.14 (1.09, 1.19)</td>
<td>5.42 (5.24, 5.67)</td>
</tr>
<tr>
<td>Risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-IDU</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Ref.</td>
<td>6.46 (6.27, 6.66)</td>
</tr>
<tr>
<td>IDU</td>
<td>1.06 (1.00, 1.12)</td>
<td>1.35 (1.28, 1.43)</td>
<td>1.12 (1.06, 1.19)</td>
<td>5.27 (4.87, 5.63)</td>
</tr>
<tr>
<td>CD4+ Lymphocytes (per 100 cells/mm³)</td>
<td>0.99 (0.98, 0.99)</td>
<td>0.95 (0.94, 0.97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadir CD4+ Lymphocytes‡ (per 100 cells/mm³)</td>
<td>1.04 (1.03, 1.05)</td>
<td>1.06 (1.05, 1.08)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Stratified Log-Rank Test (Score)

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Adjusted</th>
<th>Weighted</th>
<th>P-value*†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Sex</td>
<td>58.0</td>
<td>3741</td>
<td>6.17</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Black Race</td>
<td>26.0</td>
<td>3769</td>
<td>32.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>IDU Risk</td>
<td>4.3</td>
<td>3797</td>
<td>14.8</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
**Bold** results are significant (p<0.05)

Estimates of median time differences are from Cox models stratified on the characteristic of interest, adjusting and weighting by all other variables, including cohort site, and holding covariates at their mean values.

All variables are measured at ART initiation, except for Nadir CD4+ Lymphocyte count.

*Adjusted model includes all factors described in the table and cohort site

†Inverse Probability of Selection Weights for Sex, Race, and Risk constructed using all other covariates with the addition of cohort sub-site (to account for potential differences in clinical practice between sites)

‡After ART initiation, before event or censoring
b.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Death: Unadjusted HR (95% CI)</th>
<th>Death: Adjusted* HR (95% CI)</th>
<th>Death: Weighted† HR (95% CI)</th>
<th>Median Time*† (Years) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 years)</td>
<td>1.10 (1.05, 1.15)</td>
<td>1.07 (1.02, 1.13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Ref.</td>
<td>&gt;10 Years</td>
</tr>
<tr>
<td>Female</td>
<td>0.74 (0.64, 0.87)</td>
<td>0.79 (0.66, 0.93)</td>
<td>0.73 (0.60, 0.87)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Black</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Ref.</td>
<td>&gt;10 Years</td>
</tr>
<tr>
<td>Black</td>
<td>1.27 (1.15, 1.41)</td>
<td>1.16 (1.04, 1.29)</td>
<td>1.19 (1.07, 1.32)</td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-IDU</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Ref.</td>
<td>&gt;10 Years</td>
</tr>
<tr>
<td>IDU</td>
<td>1.28 (1.13, 1.44)</td>
<td>1.16 (1.02, 1.31)</td>
<td>1.29 (1.13, 1.47)</td>
<td></td>
</tr>
<tr>
<td>CD4+ Lymphocytes (per 100 cells/mm³)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDU</td>
<td>0.85 (0.83, 0.88)</td>
<td>0.99 (0.96, 1.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4+ Lymphocytes* (per 100 cells/mm³)</td>
<td>0.70 (0.67, 0.73)</td>
<td>0.71 (0.67, 0.74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stratified Log-Rank Test (Score)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female Sex</td>
<td>13.7</td>
<td>391.9</td>
<td>11.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Black Race</td>
<td>21.8</td>
<td>385.7</td>
<td>10.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>IDU Risk</td>
<td>16.1</td>
<td>394.0</td>
<td>14.6</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
**Bold** results are significant (p<0.05)

Estimates of median time differences are from Cox models stratified on the characteristic of interest, adjusting and weighting by all other variables, including cohort site, and holding covariates at their mean values.

All variables are measured at ART initiation, except for Nadir CD4+ Lymphocyte count.

*Adjusted model includes all factors described in the table and cohort site.

†Inverse Probability of Selection Weights for Sex, Race, and Risk constructed using all other covariates with the addition of cohort sub-site (to account for potential differences in clinical practice between sites).

‡After ART initiation, before event or censoring.
Table 3-3 a,b. Cause-specific Hazard Ratios (HR) for and median times to (a.) discontinuation of retention and (b.) death before discontinuation, with time-varying median CD4+ lymphocyte count after ART initiation, from unadjusted, adjusted, and weighted time-dependent Cox proportional hazards regression models with 95% Confidence Intervals (95% CI)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Discontinuation: Unadjusted HR (95% CI)</th>
<th>Discontinuation: Adjusted* HR (95% CI)</th>
<th>Discontinuation: Weighted† HR (95% CI)</th>
<th>Median Time*‡ (Years) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 years)</td>
<td>0.70 (0.69, 0.72)</td>
<td>0.77 (0.75, 0.79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Ref.</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.24 (1.17, 1.31)</td>
<td>0.86 (0.81, 0.92)</td>
<td>0.88 (0.83, 0.95)</td>
<td>7.53 (7.00, 8.20)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Black</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Ref.</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1.12 (1.07, 1.17)</td>
<td>1.21 (1.15, 1.26)</td>
<td>1.21 (1.17, 1.26)</td>
<td>5.61 (5.30, 5.80)</td>
</tr>
<tr>
<td>Risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-IDU</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Ref.</td>
<td></td>
</tr>
<tr>
<td>IDU</td>
<td>1.06 (1.00, 1.11)</td>
<td>1.26 (1.19, 1.34)</td>
<td>1.36 (1.29, 1.43)</td>
<td>5.45 (5.12, 5.88)</td>
</tr>
<tr>
<td>Median CD4+ Lymphocytes‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200 cells/mm³</td>
<td>Ref.</td>
<td>Ref.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200-349 cells/mm³</td>
<td>1.05 (0.98, 1.03)</td>
<td>1.00 (0.93, 1.08)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>350-499 cells/mm³</td>
<td>1.11 (0.97, 2.36)</td>
<td>1.00 (0.92, 1.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥500 cells/mm³</td>
<td>1.04 (1.13, 1.20)</td>
<td>0.92 (0.84, 1.00)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Difference = -1.28
† Difference = 2.70
‡ Difference = 2.28
<table>
<thead>
<tr>
<th>Stratified Log-Rank Test (Score)</th>
<th>Unadjusted</th>
<th>Adjusted</th>
<th>Weighted</th>
<th>P-value*†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Sex</td>
<td>55.4</td>
<td>3890</td>
<td>13.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Black Race</td>
<td>25.6</td>
<td>3920</td>
<td>102</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>IDU Risk</td>
<td>3.79</td>
<td>3939</td>
<td>112</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**Bold** results are significant (p<0.05)

Estimates of median time differences are from Cox models stratified on the characteristic of interest, adjusting and weighting by all other variables, including cohort site, and holding covariates at their mean values.

All variables are measured at ART initiation, except for Nadir CD4+ Lymphocyte count.

*Adjusted model includes all factors described in the table plus baseline CD4+ lymphocyte count at ART initiation and cohort sub-site

†Inverse Probability of Selection Weights for Sex, Race, and Risk constructed using all other covariates with the addition of baseline CD4+ lymphocyte count at ART initiation and cohort sub-site (to account for potential differences in clinical practice between sites)

‡Time-varying median CD4+ lymphocyte count in each year after ART initiation, before event or censoring
### Table: Risk Factors for Death

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Death: Unadjusted HR (95% CI)</th>
<th>Death: Adjusted* HR (95% CI)</th>
<th>Death: Weighted† HR (95% CI)</th>
<th>Median Time*‡ (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 years)</td>
<td>1.40 (1.34, 1.46)</td>
<td>1.43 (1.36, 1.51)</td>
<td></td>
<td>&gt;10 Years</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Ref.</td>
<td>&gt;10 Years</td>
</tr>
<tr>
<td>Female</td>
<td>0.75 (0.64, 0.87)</td>
<td>0.87 (0.74, 1.04)</td>
<td>0.78 (0.65, 0.93)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Black</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Ref.</td>
<td>&gt;10 Years</td>
</tr>
<tr>
<td>Black</td>
<td>1.27 (1.15, 1.41)</td>
<td>1.23 (1.10, 1.37)</td>
<td>1.13 (1.03, 1.23)</td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-IDU</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Ref.</td>
<td>&gt;10 Years</td>
</tr>
<tr>
<td>IDU</td>
<td>1.27 (1.13, 1.44)</td>
<td>1.18 (1.04, 1.34)</td>
<td>1.35 (1.20, 1.53)</td>
<td></td>
</tr>
<tr>
<td>Median CD4+ Lymphocytes ‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200 cells/mm³</td>
<td>Ref.</td>
<td>Ref.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200-349 cells/mm³</td>
<td>0.38 (0.32, 0.44)</td>
<td>0.38 (0.33, 0.45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>350-499 cells/mm³</td>
<td>0.23 (0.19, 0.28)</td>
<td>0.25 (0.20, 0.30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥500 cells/mm³</td>
<td>0.18 (0.15, 0.22)</td>
<td>0.20 (0.16, 0.25)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stratified Log-Rank Test (Score)</th>
<th>Unadjusted</th>
<th>Adjusted</th>
<th>Weighted</th>
<th>P-value*‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Sex</td>
<td>14.5</td>
<td>912</td>
<td>8.08</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Black Race</td>
<td>21.6</td>
<td>905</td>
<td>6.83</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>IDU Risk</td>
<td>14.8</td>
<td>910</td>
<td>21.9</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
**Bold** results are significant (p<0.05)

Estimates of median time differences are from Cox models stratified on the characteristic of interest, adjusting and weighting by all other variables, including cohort site, and holding covariates at their mean values.

All variables are measured at ART initiation, except for Nadir CD4+ Lymphocyte count.

*Adjusted model includes all factors described in the table plus baseline CD4+ lymphocyte count at ART initiation and cohort sub-site

†Inverse Probability of Selection Weights for Sex, Race, and Risk constructed using all other covariates with the addition of baseline CD4+ lymphocyte count at ART initiation and cohort sub-site (to account for potential differences in clinical practice between sites)

‡Time-varying median CD4+ lymphocyte count in each year after ART initiation, before event or censoring
Figure 3-1 a(i-iii), b(i-iii), c(i-iii). Predicted survival and cumulative incidence of discontinuation from retention, both unadjusted and adjusted and weighted, by (a.) female sex, (b.) Black race, and (c.) IDU risk

a-i. Unadjusted
a-ii. Weighted

Death in Care

Med. Time Diff. = 0.43

Discontinuation

Cumulative Percent

ART Initiation (+1) to Event, Years

Number at Risk: 14042.36 11572.75 9245.91 7682.96 5959.34 4364.26 3069.91 2059.97 1302.34 659.37

of Discont.: 1908.41 1577.18 1264.7 1031.43 781.24 583.75 425.13 286.14 179.02 100.52

0 10 20 30 40 50 60 70 80 90 100

0 10 20 30 40 50 60 70 80 90 100
Death in Care

Cumulative Percent

死亡与配重

Discontinuation

ART Initiation (+1) to Event, Years

Number at Risk: 14038.59  11572.78  9249.59  7696.91  5962.12  4364.51  3089.69  2059.68  1301.91  659.14

Number of Discont.: 1907.31  1576.68  1263.65  1030.65  781.93  585.29  425.82  288.73  179.67  100.64

Med. Time Diff. = 0.45
b-I. Unadjusted

Death in Care

Cumulative Percent

Discontinuation

Median Time Diff. = 0.79

Number at Risk of Discont.: 7454 6169 4884 4039 3086 2249 1588 1061 658 343

ART Initiation (+1) to Event, Years
**b-iii. Adjusted & Weighted**

![Graph showing death and discontinuation rates over time.](image)

- **Death in Care**
  - Median Time Diff. = 0.95

- **Discontinuation**

**Number at Risk**
- Number of Discont.: 6907.63, 5717.34, 4531.41, 3750.63, 2651.72, 2050.01, 1439.42, 949.29, 581.22, 302.95

**ART Initiation (+1) to Event, Years**
Death in Care

Med. Time Diff. = 0.28

Discontinuation

Cumulative Percent

ART Initiation (+1) to Event, Years

Number at Risk

of Discont.: 13758 11430 9224 7696 5979 4399 3113 2096 1308 694

0 2 4 6 8 10
Death in Care

Discontinuation

Cumulative Percent

Number of Risk: 13730.92 11483.33 9335.94 7836.77 6115.28 4522.35 3220.41 2171.54 1354.9 716.57

Number of Discont.: 2525.98 2061.5 1619.42 1335.8 1022.81 757.84 545.17 368.54 241.24 117.14

ART Initiation (+1) to Event, Years

Med. Time Diff. = 1.19
Figure 3-2. Predicted cumulative incidence of discontinuation from retention, stratified and adjusted by scaled baseline age, estimated at quartiles of sample age distribution, by (a.) female sex, (b.) IDU risk

a.

[Graph showing cumulative probability of discontinuation of care over ART initiation (+1) to event, years, with lines for different age groups and quartiles.]
Figure 3-3 a,b,c. Violin plots of sample age distributions at ART initiation (years), by (a.) female sex, (b.) Black race, and (c.) IDU risk.
Appendix

Assessment of proportional hazards assumption

Cox proportional hazards regression in the context of competing events censored for one another assumes a constant cause-specific sub-hazard and, as always the case in Cox regression, proportionality of hazards. This proportionality assumption can be assessed by fit of the scaled Schoenfeld residuals to an estimated ratio coefficient of 1 (or a log difference of 0) for the covariate of interest plotted against the event times. The plots of these residuals should exhibit a flat horizontal fitted line close to a log value of 0 to demonstrate no violations of this assumption. The weighted Schoenfeld residual plots for both discontinuation from retention and death by age, sex, and risk when stratifying estimates by Black race are presented below (Appendix Figure 3-1). They demonstrate no violations of the proportional hazards assumption. Similar procedures were conducted for models stratifying by sex and risk with no violations found.
Appendix Figure 3-1 a,b,c. Plots of weighted Schoenfeld residuals and fitted values for $\hat{\beta}$ over event times by (a.) age, (b.) female sex, (c.) IDU risk, for both the event of interest (discontinuation of retention) and the competing event (death) to assess the proportional hazards assumption, stratified by Black race

a. Age: Discontinuation, Death
b. Female Sex: Discontinuation, Death
c. IDU Risk: Discontinuation, Death
Construction of stabilized inverse probability of selection weights

Inverse Probability of Selection Weights (IPW) were used in this context to eliminate confounding by balancing populations with respect to the exposures of interest (sex, race, and HIV risk) conditional on confounders such as baseline age and CD4+ lymphocyte count, and to assess the direct effect of these exposures on the event of interest by reweighting according to the mediating factor of nadir CD4+ lymphocyte count after ART initiation. In this analysis, the potential confounders of baseline age, sex, race/ethnicity, HIV risk factor, and cohort site were used to construct IPW, excluding sex, race, or HIV risk from the denominator when using that respective factor as the exposure. These weights were applied to the marginal models and, in robust estimation, to the conditional fully adjusted models. Survival curves were created using predictions from both the weighted and adjusted estimates, noting that the stratified adjusted curves used covariate values fixed at their means across strata of the exposure of interest. (27,29) Because these were time-fixed confounders, single weights across all timepoints for an individual were used. The weights were also stabilized and truncated at the 5th and 95th percentiles to improve balance (Appendix Figure 3-2). (28)

The weights were constructed with regression models estimating the probability of exposure received, conditioning on potential confounding or mediating factors. Because the exposures of interest were binary (sex was male vs. female, race was Black vs. non-Black, and risk was IDU vs. non-IDU), a logistic regression model was used to create the IPW. For sex, the regression model for the stabilized weights was specified as:

\[
IPW_i = \frac{\Pr(sex_i = female)}{\Pr(sex_i = female | age_i, race_i, risk_i, Baseline-CD4_i, Nadir-CD4_i, site_i)}
\]
Similar models were used to construct weights by race and risk. The truncated weights for female sex had a mean value of 0.94 (IQR: 0.85-1.04) and a range of 0.42-1.50. The truncated weights for Black race had a mean value of 0.95 (IQR: 0.69-1.06) and a range of 0.58-1.81. The truncated weights for IDU risk had a mean value of 0.96 (IQR: 0.85-1.09) and a range of 0.57-1.34. These distributions indicate a lack of extreme values which could lead to unstable effect estimates. The untruncated and truncated distribution of weights accounting for sex, race, and HIV risk are illustrated below (Appendix Figure 3-2).
Appendix Figure 3-2 a,b,c. Distribution of constructed IPW for the probability of
(a.) female sex, (b.) Black race, and (c.) IDU risk, both untruncated and truncated at the
5th and 95th percentiles, including adjustment for clinic site, baseline age, baseline CD4+
lymphocyte count, nadir CD4+ lymphocyte count after ART initiation, and the other
exposures not under estimation in that model

a. IPW for female sex
b. IPW for Black race

Untruncated Weights

Truncated at 5th & 95th %iles

Log (IPT Weights)

Time

1 2 3 4 5 6 7 8 9 10

-0.5 0.0 0.5 1.0 1.5 2.0 2.5

-0.4 0.0 0.2 0.4 0.6

Log (IPT Weights)

Time

1 2 3 4 5 6 7 8 9 10

c. IPW for IDU risk

Untruncated Weights

Truncated at 5th & 95th %iles

Log (IPT Weights)

Time

1 2 3 4 5 6 7 8 9 10

-1 0 1 2

-0.4 -0.2 0.0 0.2
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CHAPTER FOUR

The geography of HIV clinical retention in the United States: regional trends in the NA-ACCORD
Abstract

**Background:** Clinical retention is central to the HIV care continuum, a key framework for improving individual- and population-level HIV outcomes. Here, we describe trends in retention across time and geographic regions among participants in a large diverse HIV cohort collaboration in the United States.

**Methods:** Data from adults in 12 clinical cohorts of the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) were used to estimate the percentage of individuals successfully retained in care by geographic regions of the United States between 2000 and 2010. Individuals were assigned to regions defined by the U.S. Centers for Disease Control and Prevention (CDC) based on 3-digit ZIP Code Tabulation Area (ZCTA) and state-level residential data (10 cohorts) and clinic location as a proxy for residence (2 cohorts). Successful retention among those with ≥1 HIV primary care encounter during the study period was defined by the National HIV/AIDS Strategy/Institute of Medicine indicator: ≥2 encounters within a calendar year, >90 days apart. Temporal trends and regional differences were analyzed among individuals using modified Poisson regression with a Generalized Estimating Equation (GEE) for clustered outcomes over time, and among ZCTAs of residence using logistic regression with GEE. Individual time in care, age, sex, race/ethnicity, and HIV acquisition risk, and ZCTA-level median age, proportion of female sex, proportion of Black race, proportion of rural residence, and proportion living below the federal poverty line were adjusted for as potential confounders of the geographic relationship with retention.
Results: Among 78,993 adults with 444,212 person-years of follow-up, the median duration of time observed in care was 7 years (Interquartile Range: 4-9 years). Our Midwest study population captured the smallest percentage of regional prevalent HIV cases with 3.5% (3,565/100,967) and the West the most with 7.0% (11,695/167,117), using 2010 CDC data. The percentage of individuals successfully retained increased from 2000 to 2010 in each region: from 73% (5,000/6,875) to 85% (7,189/8,462) in the Northeast, 75% (1,778/2,356) to 87% (1,630/1,880) in the Midwest, 68% (8,451/12,417) to 80% (9,892/12,304) in the South, and 68% (5,147/7,520) to 72% (6,401/8,895) in the West. In adjusted regression models, there was a trend for improved retention over time (p<0.01) across all regions. Additionally, over the study period, the probability of retention was lower in the West and South, and higher in the Midwest, compared to the Northeast (p<0.01).

Conclusions: Differences in HIV outcomes (e.g. disease progression, case fatality) have been noted between regions of the United States. In our clinically engaged population, the percent of patients retained in care improved over time for all regions, with 72-87% retained in care in 2010. However, there were significant differences in retention between regions even after adjusting for population demographic and risk differences. Further analysis incorporating smaller geographic divisions with richer individual- and population-level data (e.g., Medicaid availability for the uninsured) will be required to better understand how geographic factors impact retention in clinical care and HIV outcomes.
Background

The description and analysis of epidemiologic outcomes using geographic or spatial patterns has been central to the practice of epidemiology as a modern science since John Snow produced his iconic map of a deadly cholera outbreak in 19th-century London.\(^{(1)}\) Mapping outcomes and identifying geographic determinants of health disparities have also provided essential evidence in public health policy decision-making, directing funding and interventions to locales of greatest need and most likely positive impact.\(^{(2-7)}\) The field of HIV epidemiology has been no exception, and analyses of geographic variation in determinants of transmission dynamics, intervention effectiveness, and the temporal trends, extent, and severity of the disease have yielded insights into the changing nature and trajectory of the pandemic.\(^{(8-16)}\) In the case of the United States (U.S.), HIV prevalence, incidence, disease progression, mortality, and treatment characteristics have been noted to differ across geographic regions and states of the country.\(^{(17-21)}\)

Retention in care has been shown to be associated with improved access to ART, greater likelihood of virologic suppression, and less rapid HIV disease progression.\(^{(22-26)}\) Similarly, the same demographic, clinical, and socioeconomic factors (e.g., younger age, Black race, higher CD4 count, and unstable housing status) have been repeatedly associated with suboptimal retention in various contexts, though these analyses have focused on geographic heterogeneity in the patient population as a potential source of clinical retention differences in either a limited fashion or not at all.\(^{(27-38)}\) Further, some of the studies in which these patterns of care were discerned may have cohort-specific traits.
that could limit their external generalizability to persons living with HIV/AIDS (PLWHA) in the U.S. Nevertheless, recent major policy initiatives, including the National HIV/AIDS Strategy (NHAS), have identified improving clinical retention as a goal central to improving outcomes across the HIV Care Continuum in the U.S.\(^{39-41}\)

We therefore sought to describe and quantify the geographic heterogeneity of clinical retention between 2000 and 2010 within a large and geographically diverse HIV cohort that is demographically similar to PLWHA in the U.S.\(^{42}\)

**Methods**

*Population and study design*

The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) represents North America as a member of the International epidemiologic Databases to Evaluate AIDS (IeDEA) project. The NA-ACCORD began collecting data from multi- and single-site interval and clinical cohorts in 2006.\(^{43}\) The Institute of Medicine of the National Academies (IOM) has designated the NA-ACCORD as one of 12 data systems appropriate to assess quality of care goals, such as improving clinical retention, in the NHAS and Affordable Care Act due to its size and demographic similarity with PLWHA in the U.S.\(^{24}\) Details of the data collection and submission process for the NA-ACCORD have been published previously.\(^{44}\) Briefly, clinical, demographic, and geographic data from 25 cohorts (including multiple laboratory values and collection dates, medical diagnoses and dates, antiretroviral medication names and prescription dates, clinic encounter information, basic insurance status, state and 3-digit
zip code of residence) are transmitted to a centrally-administered Data Management Core semi-annually where all contributed datasets are harmonized. Data undergo quality control for completeness and accuracy, including measures to reduce the probability that an individual was concurrently participating in more than one clinical cohort. Both historic clinic encounter and laboratory collection data were included in the latest round of data uploads for 2011 (spanning the period 2000 to 2010). The activities of both the NA-ACCORD centrally and each participating cohort have been reviewed and approved by their respective local institutional review boards.

Among clinical cohorts, only patients with \( \geq 2 \) clinic visits within 12 months were enrolled into the NA-ACCORD, limiting the NA-ACCORD clinical population to patients established “in care” proximal to cohort entry; this is assessed by sites based on clinic encounter data.

Adult participants who had \( \geq 1 \) HIV primary care visit between January 2000 and December 2010 were included in this longitudinal, retrospective cohort study. Interval cohorts were excluded to allow an exclusive focus on patterns of patient clinical care. Canadian cohorts were excluded to allow an assessment of the regional differences in clinical retention patterns within the U.S. The 12 included clinical cohorts were comprised of patients from all 50 U.S. states, Washington, D.C., and Puerto Rico, with a median number of 75 (interquartile range: 31-116) of 887 US 3-digit ZIP Code Tabulation Areas (ZCTA)s represented and 167 clinical sites located in areas of dense population across the country (Figure 4-1).

*Retention measures, factors associated with retention, and follow-up*
The outcome was clinical retention, defined using the IOM indicator: ≥ 2 HIV primary care encounters within each calendar year, ≥ 90 days apart. Inpatient visits were excluded.

Participant age (categorized as <40 years, 40-49 years, 50-59 years, and ≥60 years of age), sex, race/ethnicity (categorized as White, Black, Hispanic, or other/unknown), HIV acquisition risk factor (categorized as male sexual contact with men (MSM), injection drug use (IDU), heterosexual contact, or other/unknown), receipt of ART for ≥6 months in a year (≥3 antiretroviral agents from ≥2 classes, or a triple nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) regimen containing abacavir or tenofovir), CD4+ cell count, HIV-1 RNA, and geographic location of residence (US Centers for Disease Control (CDC)-defined region, state, and ZCTA) were included in descriptions and analyses of factors by which clinical retention may have differed.

ART receipt, CD4+ cell count, and HIV-1 RNA were excluded from regression analyses due to their potential to induce bias as time-dependent confounders of the relationship between demographic factors and clinical retention as a repeated outcome. Geographic location of patient residence was collected at cohort entry and did not vary over time.

Individual data were summarized into one observation per year between the year of their entry into the cohort (2000, at the earliest) and the year of their final encounter prior to the end of 2010. The initial year of care in the cohort was excluded if the patient entered in the final quarter of a calendar year (and were thus ineligible to be “retained” in their year of entry into care). Year of death during the study period was excluded from analyses due to individuals not being uniformly “at risk” for successful retention in the
year of their death. Follow-up time ranged between a minimum of 1 and a maximum of 11 years, and individuals contributed multiple outcomes over the course of the study.

**Additional geographic information**

As described above, location of patient residence by ZCTA and state were collected by individual clinical cohorts within NA-ACCORD and transmitted to the Data Management Core. Data consistency checks were performed to ensure that ZCTA of residence corresponded correctly with state of residence (as ZCTAs may be aggregated to the state-level along coterminous boundaries). State of residence was used to assign patients to geographic regions of the U.S. based on CDC and US Census Bureau definitions. US CDC-defined Regions were as follows: Northeast: CT, ME, MA, NH, NJ, NY, PA, RI, VT; Midwest: IL, IN, IA, KS, MI, MN, MO, NE, ND, OH, SD, WI; South: AL, AR, DE, DC, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, WV; and West: AK, AZ, CA, CO, HI, ID, MT, NV, NM, OR, UT, WA, WY.\(^{(45)}\)

Demographic, geographic, and economic characteristics of ZCTAs were derived from 2000 and 2010 US decennial census files and assigned as follows: for years 2000-2003, data from the 2000 census were used; for years 2008-2010, data from the 2010 census were used; for years 2004-2007, the mid-point estimates between census years 2000 and 2010 were used. Census-derived variables included the median age within the ZCTA and the proportions of the ZCTA that were of female sex, of Black race, residing in a rural area, and living below the Federal poverty level. Rural areas were defined by the US Census Bureau as all population, housing, or territory not residing in an urban area (comprised of ≥ 50,000 individuals) or an urban cluster (comprised of ≥ 2,500 but <50,000 individuals). The poverty level defined by the US Census Bureau for an
individual in the 48 contiguous US states in 2000 was $8,350 and in 2010 was $10,830.\(^{(46)}\)

For participants from 2 clinical cohorts whose residential data was unavailable, clinic location was used as a proxy for state of residence, but not for ZCTA of residence; individuals from these cohorts were included in descriptions and analyses of regional and state-level differences in retention but not in analyses using ZCTA-level data. For ZCTA-level analyses, individual characteristics from NA-ACCORD participants were aggregated to the ZCTA level as the median age in the sample within the ZCTA, and the proportion of the sample within the ZCTA that were of female sex, of Black race, and that had IDU as an HIV risk factor.

All proportions at the ZCTA level were mean-centered to ease interpretation in regression modeling.

Statistical models and methods

Regional differences in the percentage of patients clinically retained within strata of demographic and clinical characteristics were detected by \(\chi^2\) test. Modified Poisson regression using a Generalized Estimating Equation (GEE) approach was used to assess temporal trends and determine the relative risks (RR)s and 95% confidence intervals (CI)s of retention based on demographic and geographic factors.\(^{(47)}\) An unstructured working correlation was used for repeated outcomes within individuals in the GEE regression.\(^{(48,49)}\) Time during the study period (i.e., study year) was included in models as a restricted cubic spline with 3 knots (at 2, 6, and 10 years) and as a categorical term for predictive margins.\(^{(50)}\) All individual-level models were also adjusted for total time contributed to the study by an individual (time-fixed).
An alternative mixed effects approach that could be applied would model retention changes among individuals nested within ZCTAs, nested within states, nested within regions. The regression assumptions and interpretation of individual-level effects differs from the population-averaged effects obtained under the GEE regression; as population-averaged effects are generally viewed as more germane to policy decisions, and there is evidence that mixed effects approaches may lead to the induction of bias in this context, the population-averaged model was chosen.\textsuperscript{(51,52)} However, sensitivity analyses using mixed effects models with random effects at the ZCTA-, state-, and region-levels yielded no inferential differences compared to the GEE model (data not shown).

As a complement to these models, ZCTA-level differences were also explored using logistic regression with GEE to model the proportion retained, adjusting for individual and ZCTA-level census characteristics, and applying the predictions derived therefrom in clustering analyses to detect retention below levels expected based on geographic location and time of measurement.\textsuperscript{(53-55)} The Kuldorff scan statistic was used to detect non-random variation in the outcome over space and time based on a Poisson distribution of counts within each ZCTA where observations were available. This was not a global clustering test (e.g., Moran’s I, which tests for any non-random geographic variation in the outcome) but an algorithm that directly identified locations that may be clusters by likelihood ratio testing of overlapping space-time cylinders (volumes which deviate from an assumption of random geographic variation at that specific location over time).\textsuperscript{(55)} Standard Monte Carlo hypothesis testing using 999 random replicates was used
to detect significant deviations from a null hypothesis of no non-random geographic variation in the outcome at a specific location and time.\(^{(56)}\)

Additional details of Poisson and logistic regression models with GEE at the individual and ZCTA levels, respectively, including a comparison of models incorporating alternate terms for study time, descriptive maps, and supplemental tables and plots, are available in the Appendix. Maps were generated using ArcGIS version 10.1 (Environmental Systems Research Institute, Redlands, CA), statistical analyses were performed using Stata version 12.1 (StataCorp, College Station, TX), and cluster detection analyses were performed using SaTScan version 9.3 (www.satscan.org).

**Results**

Among 78,993 adults with 444,212 person-years of follow-up, the median time in care was 7 years (Interquartile Range: 4-9 years). There were significant differences between US geographic regions in the percentage of participants retained within strata of every individual-level characteristic included in our study (Table 4-1). Our Midwest study population captured the smallest percentage of regional prevalent HIV cases with 3.7% (3,583/97,019) and the West the most with 7.5% (12,037/161,308), using CDC data from 2009 (the last year in which all 12 clinical cohorts contributed data).\(^{(45)}\) The percentage of individuals successfully retained increased from 2000 to 2010 in each region: from 73% (5,000/6,875) to 85% (7,189/8,462) in the Northeast, 75% (1,778/2,356) to 87% (1,630/1,880) in the Midwest, 68% (8,451/12,417) to 80% (9,892/12,304) in the South, and 68% (5,147/7,520) to 72% (6,401/8,895) in the West.
In adjusted regression models including the interaction of region by time, there was a trend for improved retention over time (p<0.01) across all regions. Additionally, over the study period, the probability of retention was lower in the West (Risk Ratio (RR): 0.89; 95% Confidence Interval (CI): 0.88-0.91) and South (RR: 0.95; 95% CI: 0.94-0.96), and higher in the Midwest (RR: 1.02; 95% CI: 1.00-1.05), compared to the Northeast (p<0.01). Other factors such as younger age, Black race, and IDU as HIV risk factor were also significantly associated with a decreased likelihood of retention (Figure 4-3). Models testing for a race-by-region interaction showed no significant effect modification for racial differences in retention by region (data not shown). In addition, though state-level patterns generally conformed to the regional patterns observed (Southern and Western states lag in observed and predicted retention probabilities over time), adjusting for state in the full model did not improve the model fit considerably (Appendix Figure 4-1f).

The predictive margins (i.e., the marginal probability of the outcome if every individual in the model were assigned the selected characteristic) interacting with time showed similar patterns of increasing probability of retention over time while differences across age, sex, race/ethnicity, and HIV risk categories persisted (p<0.01 for every category-by-time interaction) (Figure 4-4).(57)

In logistic regression models for the proportion retained at the ZCTA level over the study period, only an increase in the NA-ACCORD sample’s aggregate median age (Odds Ratio (OR): 1.10 per year; 95% CI: 1.09-1.11) and a decrease in the census-based mean-centered proportion of a ZCTA that were of Black race (OR: 0.36 per percentage difference increase from the mean proportion; 95% CI: 0.15-0.87) were significantly
associated with improved retention (Table 4-2). Clustering analyses identified 7 isolated ZCTAs with lower than expected retention (comparing observed to predicted proportions from the fully adjusted ZCTA-level logistic regression model), with 5 of the 7 ZCTAs located in the Northeast region, 1 in the South, and 1 in the West (Figure 4-5).

Discussion

Because geographic, racial, and socioeconomic disparities in the US HIV epidemic have been noted, it is logical to explore whether the demographic, economic, and risk behavior differences in populations residing in different parts of the country fully explains the apparent geographic variation in HIV care and outcomes.\(^{(9,20,21)}\) Retention in clinical care for HIV-positive individuals remains vitally important to advancing the treatment of HIV within individuals and to promoting the prevention of HIV at the population level through improved access to antiretroviral therapy and virologic suppression—downstream stages in the continuum of care.\(^{(25)}\) Yet engagement and retention in care require consistent and ongoing interaction with the healthcare system, a process which may include various obstacles which differ geographically (due to economic, political, cultural, or other factors).\(^{(34,58)}\) In consideration of these issues, our aim in describing the geography of clinical care experiences in a large proportion of US PLWHA over a recent and long time period was to provide evidence for evaluating benchmarks of national HIV policy goals and advancing the understanding of factors pertinent to public health interventions.\(^{(41)}\)
In our clinically engaged population, the percent of patients retained in care improved over time for all regions, with 72-87% retained in care in 2010. The improvement of clinical retention levels over time across all US regions confirms the work of this and other groups, and may provide public health practitioners and clinicians with a note of cautious optimism.\(^{(38,42)}\) Even after adjusting for demographic, geographic, and risk factor differences, and after accounting for differential contributions of time at risk for leaving care, the significant upward trend persists.

However, the same groups that are consistently identified as having increased risks for suboptimal clinical retention, and inferior HIV outcomes in general, emerge again in this analysis as lagging behind in the pursuit of a care continuum without “leaks”: younger individuals, Black patients, and those with IDU as HIV risk factor.\(^{(28,31,59-61)}\) Even though the unadjusted retention rates among these groups approaches the NHAS goal of 80% (among Ryan White clients), there is room for improvement when compared to their HIV-infected peers. Given those deficits, and the fact that risk networks, culture, and socioeconomics may differ radically across regions, states, and more granular geographic levels of the country, the identification of locales that may benefit most from interventions to improve healthcare quality, access, and retention remains as important as ever. The monitoring of geographic trends in HIV clinical care, including all stages of the continuum, is therefore a reasonable and important activity to provide evidence for targeted outreach beyond a simple risk-group basis.

The additional analysis of ZCTA-level data using clustering data illustrates the power of these methods to identify specific jurisdictions of concern for lagging progress
in continuum of care outcomes. Though the clustering analyses exhibited a different pattern of areas with suboptimal retention compared to the differences evident across larger geographic divisions (i.e., ZCTAs located primarily in the Northeast vs. the Southern and Western regions and states), their value lies in the additional layers of evidence they may provide to policy makers, particularly if individual-level data is unavailable. Population-level differences may also be a desirable focus for policy purposes, and when considering aggregate characteristics separately from individual characteristics related to care, these analyses may or may not yield consistent inferences with individual-level analyses. In this case, the differences are unlikely to stem from confounding by measured factors since the clustering analyses were adjusted using individual-level data, though they may be confounded by characteristics of the area of aggregation that were unavailable. These differences may derive from the variable ability of cluster detection to identify outlying populations relative to populations at risk under different levels of aggregation (e.g., comparing ZCTAs to states to regions). The difference in inferences across population levels may also be related to the limits for comparing divisions to one another based on the total population at risk at any single timepoint. For example, it is plausible that, though the South has lower retention rates compared to other regions, because this region itself contains close to 45% of the study population at risk for suboptimal retention, the limit on cluster windows will be reached for most geographic divisions (here, ZCTAs) within the South, and they will therefore not be compared directly with many geographic divisions within other regions. In the case that outcomes are uniformly poor across a large region, then, one may not expect to see as many outlying divisions within that region, relative to other divisions within the
same region. If one were to conduct region-specific cluster detection analyses (limiting the ZCTAs under evaluation to a single region for a given analysis), the patterns that emerge may be quite different, though this would be answering a different epidemiologic question in which the population at risk would not be similar. Despite the inferential limits in this context, with cautious interpretation, these algorithms that evaluate systematic differences between neighbors and between earlier and subsequent timepoints in the same area offer valuable insight into population-level processes that may be occurring in the care continuum at divisions smaller than the state level.

There were limitations in this analysis due to characteristics of the population under study and the unavailability of patient and geographic characteristics relevant to the interaction of HIV-positive individuals with the healthcare system. First, medical insurance status and economic security are important proximal factors influencing access to and retention in clinical care that we did not have access to. We did, however, use census-derived proxies for socioeconomic data such as the proportion of the ZCTA that was rural (which implies longer distances traveled to receive care) and the proportion of the ZCTA living below the Federal poverty line (an indication of the resources available to patients). Second, the group under observation was successfully engaged at cohort enrollment, and therefore they may not represent populations of great concern in the continuum of care (those that are not diagnosed and/or successfully linked to care). The improvement of care quality through the continuum, though, does require monitoring the very type of population included in our analyses, and the NA-ACCORD has been endorsed as one of 12 data systems appropriate to monitor progress in improving patient participation in the continuum of care.\(^{24}\) Third, we did not adjust or stratify our retention
predictions and geographic analyses according to immune health status (CD4+ lymphocyte count or HIV-1 RNA viral load). This was due to the fact that we analyzed individuals longitudinally, and the repeated outcomes (retention status) were both influenced by immune status at prior time-points and influenced future immune status. Analyzing this structure of time-dependent mediation with a recurring outcome that confounds the mediation pathway at future time-points was not possible with the methods we employed here, but we intend to address these questions in the near future. Finally, scrutinizing outcomes at varying levels of geographic resolution is quite useful (and perhaps necessary) for detecting patterns that may otherwise be obscured.\(^{(62)}\) Noting patterns across the ZCTA, state, and region level, our work found fairly consistent trends, though the quality of the inferences may not necessarily reflect the level at which public health actions are likely to be taken and at which effects may be most powerfully felt (Figure 4-6). Further analysis incorporating smaller geographic divisions with richer individual- and population-level data (e.g., Medicaid status at the individual-level, and percentage of population without insurance eligible for Medicaid coverage at the state-level) will be required to better understand how geographic factors impact retention in clinical care and HIV outcomes.

Using the remarkable breadth and depth of data available through North America’s largest collaborative HIV cohort, our analysis demonstrated a persistent upward trend in clinical retention across the U.S., but one that was differential in its extent by region. This corresponds with observations of regional differences in other HIV outcomes and highlights the utility of geographic data and analyses in monitoring progress in the continuum of care on both a national and a local basis. There are policy
prescriptions and public health actions that may help stem the tide of the epidemic, but knowing where and when to apply them is surely a critical piece of information.
Table 4-1. Percent of person-years successfully retained (with % person-years contributed) in the NA-ACCORD, defined by encounters, stratified by demographic, clinical, and geographic characteristics, 2000-2010

<table>
<thead>
<tr>
<th>Factor</th>
<th>Total Person-Years (PY)</th>
<th>Northeast % PY Retained (% PY ctrbtd.)</th>
<th>Midwest % PY Retained (% PY ctrbtd.)</th>
<th>South % PY Retained (% PY ctrbtd.)</th>
<th>West % PY Retained (% PY ctrbtd.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>444,212 (100)</td>
<td>78 (22)</td>
<td>81 (7)</td>
<td>73 (45)</td>
<td>75 (26)</td>
</tr>
<tr>
<td>Age (years)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤39</td>
<td>118,626 (27)</td>
<td>69 (24)</td>
<td>72 (24)</td>
<td>63 (28)</td>
<td>62 (27)</td>
</tr>
<tr>
<td>40-49</td>
<td>166,389 (37)</td>
<td>77 (38)</td>
<td>81 (37)</td>
<td>73 (36)</td>
<td>70 (39)</td>
</tr>
<tr>
<td>50-59</td>
<td>114,784 (26)</td>
<td>83 (28)</td>
<td>84 (27)</td>
<td>80 (26)</td>
<td>76 (24)</td>
</tr>
<tr>
<td>≥60</td>
<td>44,413 (10)</td>
<td>88 (10)</td>
<td>89 (12)</td>
<td>88 (10)</td>
<td>83 (10)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>367,048 (83)</td>
<td>78 (74)</td>
<td>80 (86)</td>
<td>74 (82)</td>
<td>71 (90)</td>
</tr>
<tr>
<td>Female</td>
<td>77,164 (17)</td>
<td>77 (14)</td>
<td>81 (35)</td>
<td>69 (19)</td>
<td>67 (10)</td>
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<td>Race/Ethnicity</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hisp. White</td>
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<td>83 (45)</td>
<td>77 (36)</td>
<td>71 (62)</td>
</tr>
<tr>
<td>Non-Hisp. Black</td>
<td>194,787 (44)</td>
<td>77 (51)</td>
<td>78 (46)</td>
<td>71 (55)</td>
<td>68 (18)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>48,125 (11)</td>
<td>78 (19)</td>
<td>84 (4)</td>
<td>73 (7)</td>
<td>71 (12)</td>
</tr>
<tr>
<td>Other/Unk.</td>
<td>17,720 (4)</td>
<td>70 (2)</td>
<td>81 (5)</td>
<td>72 (2)</td>
<td>67 (8)</td>
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<tr>
<td>HIV Risk Factor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>152,691 (34)</td>
<td>79 (28)</td>
<td>83 (30)</td>
<td>73 (28)</td>
<td>69 (52)</td>
</tr>
<tr>
<td>IDU</td>
<td>86,301 (19)</td>
<td>76 (26)</td>
<td>76 (18)</td>
<td>72 (20)</td>
<td>69 (14)</td>
</tr>
<tr>
<td>Hetero</td>
<td>95,869 (22)</td>
<td>78 (30)</td>
<td>82 (17)</td>
<td>68 (23)</td>
<td>66 (13)</td>
</tr>
<tr>
<td>Other/Unk.</td>
<td>109,351 (25)</td>
<td>78 (16)</td>
<td>81 (35)</td>
<td>79 (29)</td>
<td>77 (21)</td>
</tr>
<tr>
<td>CD4+ Cell Count (cells/mm³)a</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>73,559 (17)</td>
<td>81 (16)</td>
<td>85 (15)</td>
<td>74 (18)</td>
<td>76 (15)</td>
</tr>
<tr>
<td>200-349</td>
<td>75,340 (17)</td>
<td>84 (18)</td>
<td>87 (15)</td>
<td>79 (17)</td>
<td>74 (17)</td>
</tr>
<tr>
<td>350-499</td>
<td>77,588 (17)</td>
<td>85 (17)</td>
<td>89 (16)</td>
<td>81 (17)</td>
<td>74 (19)</td>
</tr>
<tr>
<td>≥500</td>
<td>134,202 (30)</td>
<td>86 (30)</td>
<td>90 (31)</td>
<td>82 (28)</td>
<td>74 (33)</td>
</tr>
<tr>
<td>Missing</td>
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<td>49 (19)</td>
<td>56 (23)</td>
<td>50 (20)</td>
<td>47 (16)</td>
</tr>
<tr>
<td>HIV-1 RNA (copies/mL)b</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥200 copies</td>
<td>178,803 (40)</td>
<td>76 (41)</td>
<td>81 (38)</td>
<td>70 (44)</td>
<td>68 (34)</td>
</tr>
<tr>
<td>&lt;200 copies</td>
<td>198,980 (45)</td>
<td>88 (47)</td>
<td>92 (42)</td>
<td>86 (39)</td>
<td>77 (54)</td>
</tr>
<tr>
<td>Missing</td>
<td>66,429 (15)</td>
<td>46 (12)</td>
<td>56 (20)</td>
<td>56 (17)</td>
<td>46 (13)</td>
</tr>
<tr>
<td>ART Receipt (≥6 months/year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No ART</td>
<td>170,251 (38)</td>
<td>59 (37)</td>
<td>62 (37)</td>
<td>55 (41)</td>
<td>53 (35)</td>
</tr>
<tr>
<td>ART</td>
<td>273,961 (62)</td>
<td>88 (63)</td>
<td>92 (63)</td>
<td>86 (59)</td>
<td>80 (65)</td>
</tr>
</tbody>
</table>
Percent of person-years retained during the study by encounter (i.e., years “in care” between cohort entry and final encounter) is different by region within every stratum ($\chi^2$ test, p<0.01)

a: at the first measurement in each calendar year during follow-up; b: at the last measurement in each calendar year during follow-up

Region information missing for residents of Puerto Rico (N=255), the US Virgin Islands (5), or where state-level residence was missing (N=12)

MSM: male sexual contact with men; IDU: injection drug use; Hetero: heterosexual contact; ART: antiretroviral therapy ($\geq$ 3 agents from $\geq$ 2 classes or a triple-NRTI regimen containing abacavir or tenofovir)
Figure 4-1. Geographic distribution of NA-ACCORD clinical cohort sites contributing data to this analysis; map represents the total US population by 5-digit ZIP code (2010), demonstrating higher population density in locations with clinic sites.
Figure 4-2. Temporal trends in percentage of individuals successfully clinically retained in the NA-ACCORD by CDC-defined region of the United States, from 2000-2010, overlayed on map representing percentage of prevalent HIV cases captured within the NA-ACCORD, based on CDC surveillance estimates, by CDC-defined region of the United States (2009).
Diamonds are National HIV/AIDS Strategy/Institute of Medicine retention indicator percentages (≥2 visits in a calendar year, >90 days apart).

Squares are Department of Health and Human Services retention indicator percentages (≥1 visit in every semester of a 2-year period, >60 days apart).

Circles are Predictive Margins for the Probability of Being Retained by IOM indicator using a Region-by-Time interaction effect (Fully Adjusted Logistic Model with GEE)

U.S. Centers for Disease Control and Prevention (CDC)-defined Regions:
Northeast: CT, ME, MA, NH, NJ, NY, PA, RI, VT;
Midwest: IL, IN, IA, KS, MI, MN, MO, NE, ND, OH, SD, WI;
South: AL, AR, DE, DC, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, WV;
West: AK, AZ, CA, CO, HI, ID, MT, NV, NM, OR, UT, WA, WY
Figure 4-3. Risk Ratio estimates and 95% Confidence Intervals for factors associated with retention, from modified Poisson regression model using GEE and adjusting for total time in care.
Figure 4-4 a,b,c,d,e. Predictive margins and 95% Confidence Intervals for factors associated with retention, based on modified Poisson regression model using GEE. (a.) Marginal probabilities for age-by-time interaction (b.) Marginal probabilities for sex-by-time interaction (c.) Marginal probabilities for race-by-time interaction (d.) Marginal probabilities for risk-by-time interaction (e.) Marginal probabilities for region-by-time interaction.
Table 4-2. Estimated 95% Odds Ratios from ZCTA-level logistic regression models using GEE with an unstructured working correlation structure, including adjusted QIC as a measure of model fit (compared with an independent working correlation structure). QIC is the Quasi-likelihood Information Criterion of Pan.

<table>
<thead>
<tr>
<th></th>
<th>Full Model</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>QIC (Adjusted)</td>
<td>8724.7</td>
<td>8724.7</td>
<td>8722.8</td>
<td>8722.3</td>
</tr>
<tr>
<td>Median Age (Yrs.)</td>
<td>1.09 <strong>1.10</strong></td>
<td>1.09 <strong>1.10</strong></td>
<td>1.09 <strong>1.10</strong></td>
<td>1.09 <strong>1.10</strong></td>
</tr>
<tr>
<td>Mean-centered Sample Proportion Female Sex</td>
<td>0.74 2.39</td>
<td>0.75 2.40</td>
<td>0.75 2.39</td>
<td>0.75 2.39</td>
</tr>
<tr>
<td>Mean-centered Sample Proportion Black Race</td>
<td>0.39 0.65</td>
<td>0.39 0.65</td>
<td>0.39 0.65</td>
<td>0.40 0.65</td>
</tr>
<tr>
<td>Mean-centered Sample Proportion IDU Risk</td>
<td>0.64 1.03</td>
<td>0.64 1.03</td>
<td>0.64 1.03</td>
<td>0.67 1.08</td>
</tr>
<tr>
<td>Mean-centered Census Proportion Female Sex</td>
<td>0.00 10.80</td>
<td>0.00 10.80</td>
<td>0.00 10.80</td>
<td>0.00 10.80</td>
</tr>
<tr>
<td>Mean-centered Census Proportion Black Race</td>
<td>0.15 <strong>0.36</strong></td>
<td>0.16 <strong>0.38</strong></td>
<td>0.17 <strong>0.37</strong></td>
<td>0.17 <strong>0.37</strong></td>
</tr>
<tr>
<td>Mean-centered Census Proportion Rural Area</td>
<td>0.67 1.01</td>
<td>0.66 0.97</td>
<td>0.66 0.97</td>
<td>0.67 0.98</td>
</tr>
<tr>
<td>Mean-centered Census Proportion Living Below Poverty Line</td>
<td>0.14 0.87</td>
<td>0.16 5.38</td>
<td>0.16 5.70</td>
<td>0.16 5.70</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Midwest</td>
<td>0.75 0.96</td>
<td>0.74 0.95</td>
<td>0.74 0.95</td>
<td>0.74 0.95</td>
</tr>
<tr>
<td>South</td>
<td>0.88 1.14</td>
<td>0.87 1.12</td>
<td>0.87 1.12</td>
<td>0.87 1.12</td>
</tr>
<tr>
<td>West</td>
<td>0.68 0.92</td>
<td>0.68 0.89</td>
<td>0.68 0.89</td>
<td>0.68 0.89</td>
</tr>
<tr>
<td>Total Time in Care per 100 Person-Years</td>
<td>1.00 <strong>1.00</strong></td>
<td>1.00 <strong>1.00</strong></td>
<td>1.00 <strong>1.00</strong></td>
<td>1.00 <strong>1.00</strong></td>
</tr>
</tbody>
</table>

Bold point estimates are statistically significant (p<0.05)
Figure 4-5. Cluster analysis of ZCTAs with lower than expected proportions of clinically retained patients, comparing observed to predicted counts from fully adjusted logistic regression models with GEE at the ZCTA-level by Kuldorff’s spatial scan statistic applied over the period 2000 to 2010.
Figure 4-6 a,b,c. (a.) Region-level, (b.) State-level, and (c.) ZCTA-level maps of observed clinical retention status within the study sample in 2009 (N=47,247), the final year in which all 12 clinical cohorts contributed data.
**Appendix**

*Individual-level Analyses*

**Appendix Table 4-1. Comparison of 95% Risk Ratios*95% Confidence Intervals (CIs) from individual-level Poisson regression models using GEE with unstructured working correlation structure and incorporating study time differently. QIC: Quasi-likelihood Information Criterion of Pan.**

<table>
<thead>
<tr>
<th>QIC (Adjusted)</th>
<th>Including a region-by-time interaction</th>
<th>Including a linear term for time</th>
<th>Including a categorical term for time</th>
<th>Including restricted cubic spline with 3 knots for time</th>
</tr>
</thead>
<tbody>
<tr>
<td>852511.1</td>
<td>852029.5</td>
<td>851576.6</td>
<td>852024.1</td>
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</table>

<table>
<thead>
<tr>
<th>Age (years)*</th>
<th>Reference</th>
<th>Reference</th>
<th>Reference</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤39</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>1.09</td>
<td>1.11</td>
<td>1.10</td>
<td>1.12</td>
</tr>
<tr>
<td>50-59</td>
<td>1.16</td>
<td>1.18</td>
<td>1.16</td>
<td>1.20</td>
</tr>
<tr>
<td>≥60</td>
<td>1.22</td>
<td>1.24</td>
<td>1.22</td>
<td>1.27</td>
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<table>
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<th>Sex</th>
<th>Reference</th>
<th>Reference</th>
<th>Reference</th>
<th>Reference</th>
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<tbody>
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<td>Male</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.99</td>
<td>1.01</td>
<td>1.01</td>
<td>1.03</td>
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<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Reference</th>
<th>Reference</th>
<th>Reference</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hisp.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hisp. Hispanic</td>
<td>1.00</td>
<td>1.01</td>
<td>1.01</td>
<td>1.03</td>
</tr>
<tr>
<td>Other/Unk.</td>
<td>0.92</td>
<td>0.94</td>
<td>0.92</td>
<td>0.97</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV Risk Factor</th>
<th>Reference</th>
<th>Reference</th>
<th>Reference</th>
<th>Reference</th>
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</thead>
<tbody>
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<td>MSM</td>
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</tr>
<tr>
<td>IDU</td>
<td>0.95</td>
<td>0.96</td>
<td>0.96</td>
<td>0.98</td>
</tr>
<tr>
<td>Hetero</td>
<td>0.96</td>
<td>0.97</td>
<td>0.96</td>
<td>0.99</td>
</tr>
<tr>
<td>Other/Unk.</td>
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<td>1.01</td>
<td>1.05</td>
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</table>

<table>
<thead>
<tr>
<th>Region</th>
<th>Reference</th>
<th>Reference</th>
<th>Reference</th>
<th>Reference</th>
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</thead>
<tbody>
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<td>Northeast</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midwest</td>
<td>0.97</td>
<td>1.01</td>
<td>1.02</td>
<td>1.05</td>
</tr>
<tr>
<td>South</td>
<td>0.88</td>
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<td>0.94</td>
<td>0.96</td>
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<tr>
<td>West</td>
<td>0.90</td>
<td>0.92</td>
<td>0.89</td>
<td>0.91</td>
</tr>
</tbody>
</table>

| Region-by-Time- | Reference | Reference | Reference | Reference |
| Time-           |           |           |           |           |
| Time-           | 1.01      | 1.02      | 1.01      | 1.02      |
| Time-South      | 1.01      | 1.02      | 1.01      | 1.02      |
| Time-West       | 1.00      | 1.00      | 1.00      | 1.01      |

<table>
<thead>
<tr>
<th>Total Time in Care (per year)</th>
<th>Reference</th>
<th>Reference</th>
<th>Reference</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.01</td>
</tr>
</tbody>
</table>

160
Appendix Figure 4-1 a,b,c,d,e,f. Violin plots for the distribution of predicted probabilities of retention over time at the individual-level by (a.) age category, (b.) sex, (c.) race/ethnicity, (d.) risk, and (e.) ZCTA, (f.) state, and region of residence.

Predicted probabilities are from a fully adjusted modified Poisson regression model with GEE.
**ZCTA-level Analyses**

**Details of the Kulldorff spatial scan statistic and analysis of outcome clustering**

Spatial cluster detection methods were used to analyze non-random geographic variation in the proportion of patients clinically retained in each calendar year of the study at every ZCTA that contained contributed patient data. Specifically, Kulldorff’s spatial scan statistic was used to identify clusters assuming a null distribution of cases according to a discrete Poisson point process:

If \( \{C_i\} \) are the random variables (denoting \( C \) events in area \( i=1,\ldots,I \)) with
\[
E(C_i) = \lambda n_i, \quad \text{where } \lambda \text{ is the baseline rate of the event. That means that the expected number of events in an area is the number at risk in that area multiplied by the baseline rate.}
\]
If the total number of observed cases across all regions is denoted \( c_+ = \sum_{i=1}^{I} c_i \), then the conditional null hypothesis can be stated as
\[
C_1, \ldots, C_i | c_+ \sim \text{multinom}(c_+, \frac{n_1}{n_+}, \ldots, \frac{n_I}{n_+}) \quad \text{where } n_+ = \sum_{i=1}^{I} n_i \text{ is the total number of people at risk for the event across all areas.}
\]
Kulldorff’s spatial scan statistic is then defined by circular zones centered in each area, and increasing in radius successively until 50\% of the at-risk population is covered. The collection of areas within the zone, \( z \), is considered as a potential cluster, and the presence of more (or fewer) cases than expected within the zone (based on the baseline rate and the population at risk) fulfills the alternate hypothesis. The scan statistic is formally a proportionality of likelihood ratio statistics:
\[
L_z = \left( \frac{c_z}{\hat{\lambda} n_z} \right)^{c_z} \left( \frac{c_+ - c_z}{\hat{\lambda} n_z} \right)^{c_+ - c_z} 1[c_z > \hat{\lambda} n_z], \quad \text{where } 1[c_z > \hat{\lambda} n_z] \text{ is an indicator function valued at 1 when the number of events is greater than the number expected under the null hypothesis, and at 0 otherwise.} \]

(55) Statistical inference of the scan statistic
can only be determined through Monte Carlo simulation. This approach was applied using SaTScan version 9.3 software (www.satscan.org).
Appendix Figure 4-2 a,b,c. Comparison of observed with predicted retention probabilities from ZCTA-level logistic regression model fit using GEE and adjusting for total person-time accrued within the ZCTA, sample-aggregated median age, proportion with female sex, proportion of Black race, and proportion with IDU HIV risk factor, and census-derived median age, proportion with female sex, proportion of Black race, proportion that is a rural area, and proportion living below the Federal poverty line. Plots are (a.) Quantile-Quantile, (b.) Normal-Quantile, and (c.) Normal-Probability plots. Structural zeros (ZCTAs with no observed patients contributing data) are excluded.
b.

Pred. Prob. of Retention [Pr(retain = 0)]

c.

Normal F(Pred. - mean)/stdev

Obs. Retention Proportion by ZCTA
Appendix Figure 4-3 a,b,c,d,e. Predicted linear fits at the ZCTA-level are plotted by (a.) sample median age, (b.) census proportion with female sex, (c.) census proportion with Black race, (d.) census proportion of rural areas, and (e.) census proportion living below the Federal poverty line. Predicted probabilities are from logistic regression models with GEE.
d.
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CHAPTER FIVE

Conclusion
Summary of key findings

In this dissertation, we examined the epidemiology of clinical retention among HIV-infected adults in North America, including the magnitude of potential retention outcome misclassification, disparities in times to discontinuity of care after ART initiation, and geographic differences in clinical retention. Using data from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), a large demographically and geographically diverse HIV cohort collaboration in North America with a longitudinally-followed clinical population, we identified non-negligible measurement error when using laboratory proxies for clinical encounters and observed persistent individual- and population-level differences in retention outcomes by age, sex, race, HIV acquisition risk factor, and geographic location, despite observing a general improvement in retention over time.

In Chapter Two, we assessed the potential for measurement error when classifying retention using laboratory measurement dates as proxies for clinical encounter dates, a common practice in large cross-sectional and national surveillance studies related to the HIV continuum of care. The rates of retention judged by both metrics improved over the study period (70% to 80% by encounters and 66% to 77% by laboratory proxies, from 2000 to 2010) and agreed fairly well with each other (percent agreement between 78 and 85%). After accounting for differences in clinical practice across contributing clinical sites, demographic characteristics, and in HIV acquisition risk factors, and using methods appropriate for within-individual correlation of retention (whether defined by laboratory
proxy or directly by encounter), the nearly 20% percent discordance between measures over a decade of observation was modest but significant enough to impact estimates used to measure progress toward policy-related benchmarks.

In Chapter Three, we evaluated demographic and HIV acquisition risk factor disparities in disruptions of clinical retention after initiation of ART. By restricting analyses to the population successfully linked to care, engaged in care, and initiating therapy, we mitigated the influence of potential differences in healthcare access on observed differences in retention by sex, race, and injection drug use as HIV risk factor (IDU). Analyzing those who started ART between 2000 and 2006 to ensure at least 4 years of potential follow-up over the study period (2000 to 2010), the cumulative incidence of loss from retention (at least once) over 10 years of follow-up was high, at nearly 74%. We observed significant differences in loss of retention, with men, Black individuals, and IDU patients discontinuing earlier after initiating ART, though these differences were only made manifest after adjusting for the differing age structures of these populations. We also found that males and IDU patients died earlier than females and non-IDU patients while successfully retained, even after adjusting for the nadir CD4 count after ART initiation as a mediator between demographic or risk factor exposures and retention outcomes.

In Chapter Four, we described the geographic distribution of retention across the U.S. and analyzed individual- and 3-digit ZIP Code Tabulation Area (ZCTA)-level data to assess regional differences and clustering of retention outcomes. Individuals residing in the
South and West were significantly less likely to be retained over the study period (2000 to 2010) compared to those residing in the Northeast or Midwest, even after adjusting for age, sex, race/ethnicity, and HIV acquisition risk differences. Analyses at the ZCTA-level revealed the persistent effects of age and race on retention, with a ZCTA’s predicted odds of retention decreasing with younger mean patient age within the ZCTA and higher proportion of the ZCTA general population being of Black race. Spatial clustering analyses at the ZCTA-level, however, revealed a different pattern, with 5 ZCTAs in the Northeast, 1 in the South, and 1 in the West emerging as clusters of suboptimal retention. States ranked by median predicted probability of retention over the study period revealed patterns similar to those between regions with Southern and Western states faring worse in predicted retention compared to Northeast and Midwestern states.

Public health importance

This dissertation directly addresses goals for improved clinical retention among HIV-infected individuals as outlined in the National HIV/AIDS Strategy (NHAS) and recently highlighted in a Presidential Executive Order establishing the “HIV Care Continuum Initiative.”¹⁻³ Retention in clinical care and patient “churn” (movement through care over time) and their impact on the epidemiology, treatment, and prevention of HIV/AIDS in the United States and Canada have been described previously.⁴⁻⁵ By building on this work and addressing sources of error in large clinical retention surveillance studies and persistent demographic and regional disparities in retention, we may not only alert policy makers, public health officials, and epidemiologists to these issues, but we may also
equip them with the evidence they need to pursue more focused strategies to improve retention and HIV outcomes.\(^6\)

For retention surveillance estimates lacking longitudinal encounter or “visit” data, we may also inform methods such as regression calibration to correct for outcome misclassification in the very studies whose results are critical for policy priority setting and progress assessment in the NHAS. The US Centers for Disease Control and Prevention (CDC), for example, routinely utilizes mandatorily reported laboratory measures to assess clinical retention across jurisdictions and notes this as a limitation in estimating prevalent retention.\(^7,8\) Because our work provides an estimate of the magnitude of the error involved in their estimates, epidemiologists may be better equipped to adjust them or provide upper and lower bounds on their estimates of retention. Providing better evidence to policy makers on whether benchmarks in the NHAS are being met may lead to the marshaling of resources toward those areas that are still in greatest need. In addition, more accurate retention estimates may enable more accurate estimation of program effectiveness for retention-focused interventions when clinic encounter data is unavailable.

With respect to the sex, race, and risk, differences in retention analyzed in this dissertation, the ongoing evaluation of disparities and the tracking of progress in narrowing them is essential to assessing the effect of public policy, public health programs, and changes in clinical practice over time.\(^9,10\) Race and sex are not risk factors that may be intervened on or modified, but noting disparities after accounting for other characteristics provides evidence for shifting policy, funding, and intervention priorities. In addition, observing the “direct effect” of race or sex on retention, accounting for
mediation by disease status (here, nadir CD4 count after ART initiation), is a more powerful method for detecting disparities that may be due to factors outside of clinical care, such as distal contextual factors.\(^{(11-15)}\)

Similarly, noting geographic differences in retention outcomes while accounting for individual- and population-level characteristics that may influence healthcare utilization patterns directs public and political attention toward health disparities that may be experienced across a spectrum of diseases, not just HIV disease or healthcare access.\(^{(16)}\) Our work capitalized on the great geographic diversity of the NA-ACCORD population in clinical care to provide a unique perspective on national HIV care continuum outcomes that federal health policy advisors and research funding agencies may have great interest in. The policies, both social and economic, that differ between the same regions that exhibit retention differences should be examined carefully to determine what, if any, patterns emerge and which policies may be most harmful or most beneficial. The natural starting point for such work is to identify those jurisdictions, whether small or large, which are “good” or “bad” actors. This sort of information can only be derived from rich data sources with longitudinal clinical data available for a large and geographically dispersed population, such as in the NA-ACCORD.\(^{(17)}\) Given the renewed focus at the national and state levels on healthcare utilization outcomes as US healthcare systems undergo massive changes, analyses of retention “stage” outcomes in the HIV care continuum across regions dovetail nicely with national health policy priorities.\(^{(2)}\)

Since improving clinical retention is now widely acknowledged to be a key component of patient progression through the HIV care continuum, with the potential to reduce HIV incidence through improved virologic control and a “Test and Treat”
paradigm, it is also clear that monitoring key populations in which we seek to maximize public health impact and highlighting suboptimal outcomes in groups of special concern are still necessary steps in an iterative process that strengthens our abilities to meet strategic goals. Characteristics associated with negative HIV disease outcomes are also associated with suboptimal clinical retention (e.g., minority race, younger age, male sex, and history of substance abuse),\(^{18-20}\) and poor clinical retention has been shown to be accompanied by more rapid disease progression and lack of HIV virologic suppression.\(^{21,22}\) Hence, addressing inequitable healthcare access and suboptimal retention in such high-risk subpopulations may elucidate the factors that continue to cause HIV outcome disparities.\(^{23}\) Further, evidence regarding these factors may provide local, state, and national policy makers with a framework for eliminating disparities and reduce HIV transmission through increased public engagement and resource allocation.

When the results contained in this dissertation are disseminated to a receptive and knowledgeable audience that is ready to act, the identification of intervention targets (conceptually and spatially) and barriers to accurate surveillance will be powerful tools, perhaps capable of guiding decision-making, resource allocation, surveillance protocols, and improved implementation of already formulated “test and treat” strategies. While the aims of rapid HIV diagnosis and linkage to care remain crucial, engagement and retention in continuous care are essential if these strategies are to accomplish their stated goal of halting the spread of this epidemic.\(^{24,25}\)

**Generalizability of results**
In 2012, the Institute of Medicine of the National Academies (IOM) produced a comprehensive report on recommended indicators and data systems for monitoring outcomes in the HIV care continuum. In the report, the IOM endorsed the NA-ACCORD as an ideal observational study within which longitudinal analyses of their recommended continuum of care indicators could be assessed in a large population of HIV-infected adults that is demographically similar to the population of persons living with HIV/AIDS (PLWHA) in the United States.\(^{(26,27)}\) The recognition of the power of the NA-ACCORD to address questions just such as those posed and answered in this dissertation by an august body such as the IOM is encouraging. Though external validity is not an easily testable epidemiologic construct, the application of internally valid results to target populations at either the present or future times is surely on more solid footing due to fair representation and substantial capture (between 3 and 7% in recent years) of HIV-infected adults in the United States within the study populations of Aims 1 and 3, and of HIV-infected adults initiating ART between 2000 and 2006 in Aim 2.

In Aims 1 and 3, the study populations were comprised of individuals receiving care at clinical cohorts in the NA-ACCORD and with \(\geq 1\) encounter between 2000 and 2010. The only additional restrictions in Aim 3 were relatively generous, by area of residence outside of the four US Census Bureau-defined regions (Northeast, Midwest, South, and West). In both Aims, nearly 80,000 individuals contributed more than 400,000 person-years in follow-up over a decade. The demographic composition in both of these populations closely mirrors the composition of the cohort as a whole, and therefore retains the strength of representativeness, though these are individuals who have been successfully linked to care.
In Aim 2, the target population was more narrowly defined as those successfully linked to HIV care with access to ART, and therefore the study population inclusion criteria were more restrictive. Ensuring the inclusion of only individuals who were ART-naïve at the time they initiated ART during the study, and those who had at least 1 year in care following the year in which they initiated ART meant a drastic narrowing of the cohort population in clinical care. Even so, the participants in Aim 2 analyses of discontinuation of retention after ART initiation numbered more than 17,000 and they resided in all 50 US States and 9 Canadian provinces.

That being said, the clinical population receiving care between 2000 and 2010 and eligible for inclusion in these analyses were almost certainly a more robust group with greater access to healthcare and HIV services than the groups at highest risk for accelerated disease progression and arguably those who may have benefited most from improved access to and successful retention in care. The study population, by dint of their inclusion in the NA-ACCORD, had attended ≥2 clinic visits within some 12-month period before cohort enrollment commenced, and were therefore at least successfully linked to care. The high-risk groups of individuals either not diagnosed, or else diagnosed but not linked to care, may not only benefit personally, but because they may in fact be drivers of transmission early in their disease, they could be high-reward targets of prevention efforts; by engaging them in care and providing them with therapy, a disproportionate number of new infections may be prevented. The results of this work may not be applied as readily in these populations because the environmental, economic, social, cultural, and other contextual factors most relevant to their engagement and retention in healthcare may be very different from what has been measured among the
NA-ACCORD clinical population because these groups are likely underrepresented within the cohort.

Other source populations such as the CDC’s Medical Monitoring Project may employ probabilistic sampling methods to achieve greater demographic representativeness of PLWHA (at least, of the HIV diagnosed population), and therefore may give rise to more representative study populations, but they do not have the longitudinal clinical data nor the geographic diversity that the NA-ACCORD possesses. The fact remains, then, that there may be no sources of longitudinal clinical data in the North American HIV-infected adult population with quite the same magnitude and geographic breadth as the NA-ACCORD. Therefore, studies such as this, conducted in this population, may be the most practically reflective of our desired target population: HIV-infected adults with access to clinical care who are at risk of discontinuing clinical care after engagement.

Other strengths and limitations

There were several limitations in the research presented here. Chapters Two through Four contain detailed discussions of data and methodological strengths and limitations particular to their scope, and they will not be re-presented here. The focus of this section will instead be on general limitations in studying these topics with the available data and the most practical methods.

First, the NA-ACCORD does not currently collect detailed socioeconomic, psychiatrically managed mental health, or structured epidemiologic substance abuse
assessment data elements. The lack of high quality data from validated instruments or proximal sources (i.e., instead of a state Medicaid expansion decision as a proxy for a patient’s access to care, collecting data on a patient’s own health insurance status, whether public payor or private) on these potentially important confounders, mediators, and effect modifiers of the relationship between other patient characteristics and clinical retention status may hinder the construction of internally valid inferences. However, a mitigating factor is that injection drug use history as HIV risk factor was available and used as either a predictor or adjustment factor in every Aim.

Second, if patients leave care and are incarcerated before returning to care, their out-of-care risk experience (for both retention and HIV disease outcomes), and their likelihood of return in subsequent years will by systematically different for obvious reasons.\(^{13,31}\) If however, there are patient characteristics that are strongly predictive of incarceration in the United States (e.g., young age, male sex, and minority race), the models that rely on adjustment by these factors should capture much of this difference. That is, the total effect of, for example male sex, on retention will still be observed, regardless of the unobserved relationship with the mediating factor (imprisonment). On the other hand, analyzing disparities by stratifying analyses on these potential “common causes” may really be revealing differences in incarceration rates. Similarly, if female patients are diagnosed during pregnancy, engage in HIV clinical care during, and then discontinue after delivery, there will be no way to distinguish the “pregnancy” year from the “non-pregnancy” year in such a patient, as the NA-ACCORD does not currently collect pregnancy data. It is therefore possible that measured disparities in sex may really capture some disparities by pregnancy status, if pregnancy is indeed strongly predictive
of retention followed by discontinuation from care (inducing bias, since only one sex may become pregnant). However, adjusting for the age structure of females vs. males may mitigate some of these differences at older ages. In both of these cases, it would still be desirable to assess disparities by these characteristics whether the mediating factors leading to loss of retention are incarceration, pregnancy, or neither. Of course, in these cases, the inferences for public health intervention purposes would be eminently more useful if the mediating factors were identified, too (targeting all women when only the pregnant women need an intervention, or targeting all youth when only juvenile offenders should be assisted with care would be an inefficient use of resources).

Finally, though inverse probability weighting and clustering methods were used for Aims 1 and 2, and Aim 3, respectively, they were not “magical wands” which could eliminate data or design limitations. They are powerful tools, and they worked as well as can be diagnosed within the study data or by simulation (for clustering analysis), but without reliance on external validation or additional data, there were limits to their abilities to overcome potential biases and measurement errors (see discussion of potential data limitations above); and as is always the case with observational data, the potential for unobserved (residual) confounding cannot be completely circumvented with these methods.\(^{32-34}\) Indeed, there are some structures of time-dependent confounding and/or mediation that involve causally complex relationships with the very factors that must be used to construct the weights, entangling their estimation with the outcome at multiple timepoints. For example, use of inverse probability weights to adjust for a confounder-exposure relationship when the outcome at one timepoint confounds or mediates the relationship between the exposure and the outcome at a subsequent timepoint (as is the
case with a retention outcome and multiple types of exposures such as ART use or CD4 count) may be untenable. The interpretation of such weights would be problematic since they depend on both the exposure-outcome relationship and on an exposure-confounding relationship. In the case of the analyses in Aim 1, confounders that were time-fixed and not open to influence by retention status at subsequent timepoints (e.g., sex, race, baseline age) were used with a laboratory-based measure of retention as the “exposure”, and so this limitation did not apply. For Aim 2, a time-to-event analysis was conducted with an outcome of first discontinuation of retention after ART initiation; because outcomes were not repeated, again, this limitation did not apply. Even though it may have been desirable to estimate the influence of certain exposures on changing retention status over time, accounting for time-varying mediation by CD4 count or substance abuse, these analyses would have been impractically complex, and alternative designs were used to circumvent the peculiar causal structures and analytic consequences they might entail. However, the methodologic tail should not wag the epidemiologic dog. The questions posed in the Specific Aims were open to attack using the regression, weighting, and design techniques we applied in our conduct of this research, and the inferences derived are as consequential, and interesting, as those that may have resulted from alternative approaches.

**Future directions**

This dissertation does not present a final answer to the problems of so-called “leaks” in the HIV care continuum, losing patients between HIV infection (in the earliest stage of
the continuum) and successful virologic suppression (at the ultimate stage of the continuum). The NHAS has now been supplemented with the “HIV Care Continuum Initiative”, with concrete benchmarks for improving outcomes along the continuum and a mandate to monitor improvements in these outcomes on a national basis over time.\(^{(2,3)}\)

Because the NA-ACCORD has been endorsed by the IOM as an ideal data source for monitoring these indicators, it is our hope that even more important and impactful epidemiologic evidence in this arena may yet be borne from this already fruitful cohort collaboration.

There are multiple, complex factors likely influencing these losses, and though our work is a worthy contribution to the body of knowledge concerned with outcomes at the antepenultimate stage of the continuum (as formulated by Gardener), it likely has more immediate and tangible downstream impact (in receipt of ART and suppression of HIV-1 RNA) than upstream impact. With that in mind, there may be multiple ways in which we might expand this work in addressing gaps and identifying targets and methods for improved retention in clinical care to greater depth and hopefully to greater breadth across the continuum.

With regard to Aim 1, epidemiologists should engage in an open dialogue with clinicians and policy makers over meaningful definitions of retention, accounting for the influence of changing clinical practice guidelines and massive alterations to the healthcare infrastructure of the United States. As the recommended frequency of CD4 monitoring, for example, is altered among stably treated patients, surveillance for HIV care continuum outcomes based on laboratory measures alone (whether their values or their frequency) may become problematic.\(^{(35,36)}\) Modeling the agreement between
laboratory-based measures and encounter-based measures within different strata of laboratory values may be appropriate to assess different effects in different patient populations. Though there has been research indicating that visit-based retention helps predict virologic suppression or failure independent of immune health, perhaps including a more diverse patient population than that under evaluation in prior work would yield differing results.\(^{(25)}\)

With regard to Aims 2 and 3, expanding the focus of this disparities research to encompass important behavioral, social, economic, cultural, and other contextual factors would provide refinement to the effect estimates and help identify populations most in need of structural or local clinical interventions to improve outcomes across the HIV care continuum. Of course, this would entail measuring and collecting variables such as median household income, maximum education level attained, stability of housing status, ongoing substance abuse, psychiatric care, and others.\(^{(11,12,14,37)}\) For some of these, if individual-level assessment or measurement is impractical, residential information collected at the clinic-level (e.g., census tract of residence) could serve as a powerful proxy measure, though of course care would need to be exercised in interpreting the data at different levels of granularity.\(^{(38,39)}\) Clustering analyses at these more spatially compact levels could also provide more targeted identification of areas that would benefit from public health interventions.

Finally, with regard to all of these analyses and future paths for analyzing clinical retention outcomes to affect policy and monitor progress in stemming the epidemic, we must expand our horizons for tracking patients throughout their interactions with and absences from the healthcare system. As patients move between providers, perhaps
within networks and perhaps without, transition from one healthcare system to another, or from one geographic location to another, linkage of data systems is necessary to improve the longitudinal observation of individuals. To this end, partnering with state or local health department surveillance systems to track whether patients received reportable laboratory testing (indicating at least some interaction with the healthcare system) when absent from the clinical cohort would be incredibly beneficial. This would greatly mitigate the possibility of misclassification of retention status (if measured by laboratory proxy). Such partnerships between clinical cohorts and public health officials already exist in some jurisdictions, and certainly exist fairly commonly for diseases such as tuberculosis to enable improved contact tracing and follow-up for mandatory treatment. Alternatively, random samples of the “out of care” population within clinical cohorts could be selected for intensive tracking and communication efforts to determine a representative sampling of true retention and health status among those absent from care. Similar efforts have been utilized to great effect in the context of determining trial outcomes among participants lost-to-care in resource-limited settings, where even hard outcomes such as death may not be subject to complete ascertainment. Finally, greater utilization of state Health Information Exchanges to track care patterns longitudinally would be the most desirable, though potentially the most distant, future effort. Theoretically, the complete medical history of individuals would be traceable nation-wide, yielding a negligible, essentially null misclassification rate for engagement with or retention within the healthcare system (within the United States, at least).
In conclusion, we identified significant disparities in encounter-based retention by lab-based proxy measures, sex, race, HIV acquisition risk factor, and geographic area of residence using data from participants in the largest North American HIV collaborative cohort. Continuing to monitor progress in meeting national policy benchmarks, including surveillance of HIV care continuum outcomes, will entail an appeal to novel data sources, a continuation and potential expansion of existing cohort resources and data collection efforts, careful application of advanced epidemiologic methods, and attention to the policy implications and real-world impact of public health and clinical interventions deployed in service of improving clinical retention. Because individual advancement through the continuum of care involves the successful navigation of a complex network inside and outside of the healthcare system, overcoming personal, financial, social, and cultural barriers, we must arm those who would enact evidence-based policy to help our fellow man with the compelling, pertinent, and high quality evidence they require. Ultimately, we must all work together to reduce individual- and population-level disparities in the achievement of improved HIV outcomes, both in treatment and prevention. This remains our clarion call as HIV epidemiologists, and though a long journey remains ahead of us, we will extend our progress until the epidemic is ended.
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EDUCATION

PhD, MHS Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Epidemiology (PhD), Biostatistics (MHS), 2014
Thesis Title: The Epidemiology of Clinical Retention Among HIV-infected Persons in North America

ScM Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Epidemiology, 2012
Thesis Title: Retention in Care, Churn, and Methods for their Analysis in the North American HIV Clinical Population, 2000-2008

BA Yale University, New Haven, CT
Biology, Neurobiology focus, 2005
Thesis Title: Clinical Manifestations and Implications of HIV-1 Infection in the Human Central Nervous System

RESEARCH EXPERIENCE

2010-2014 Research Assistant
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Conducted biostatistical analyses and data management, and participated in weekly Epidemiology/Biostatistics Core research and administrative meetings with NA-ACCORD staff

2007-10 Research Coordinator
Vanderbilt/Meharry Center For AIDS Research, Nashville, TN
Conducted literature review and wrote scientific manuscripts; conducted biostatistical analyses; performed data mapping and data quality monitoring; performed medical record abstraction and data validation (as needed), recruited and interviewed prospective Research Analysts, wrote protocol for “Scientific Review Committee” to approve specimen use from VU/CCC Data & Specimen Repository, served on said committee, coordinated IRB submissions, and supervised Research Analysts

209
RESEARCH EXPERIENCE (continued)

2006-07    Research Analyst
2004-05    *Vanderbilt/Meharry Center For AIDS Research, Nashville, TN*

Abstracted and validated clinical, medication, and laboratory data from 
paper and electronic medical records for CFAR database; performed logic 
checks for database management code and syntax checks for biostatistical 
analysis code; trained and supervised Term Technical, Research Analyst I 
employees; wrote and implemented QA and data abstraction procedures; 
compiled and maintained study publication and IRB status information; 
wrote validation, QA, and general cohort descriptions for use in grant 
applications; participated in Epidemiology/Outcomes research, 
administrative, and antiretroviral therapy case conference meetings

2001-03    Research Assistant
2001-03    *Vanderbilt AIDS Clinical Trials Center, Nashville, TN*

Procured and processed informed consents for Vanderbilt 
University/Comprehensive Care Center Data/Specimen Repository for 
genetic research in HIV-1 infected individuals; constructed and 
maintained a “Repository Database” to track patient recruitment; screened 
patients for eligibility in clinical trials based on medical history and 
laboratory results; abstracted and entered pertinent clinical, laboratory, and 
demographic data from patient medical records for ongoing studies

TEACHING EXPERIENCE

Johns Hopkins University, Baltimore, MD

2013–2014    *Zanvyl Krieger School of Arts & Sciences*

Primary Instructor, Gordis Teaching Fellow for “The HIV/AIDS 
Pandemic: An Enquiry Concerning Epidemiologic Understanding”

Designed and taught upper-level seminar course for junior and senior 
deregistered public health studies major at Johns Hopkins 
University. Topics included a review of the natural history and 
pathogenesis of HIV/AIDS, the spread and current geography of the 
disease, contemporaneous prevention strategies, and the impact of 
antiretroviral therapies at the individual and population level. The course 
focused on the methods and mindset of epidemiologic enquiry.

Teaching Assistant, “Fundamentals of Epidemiology”

Led discussion section, proctored exams, conducted office hours, and 
provided annotated exam keys.
TEACHING EXPERIENCE (continued)

Johns Hopkins University, Baltimore, MD

2011-13  
*Bloomberg School of Public Health*

Participant, Preparing Future Faculty Teaching Academy

Content revisor, “Fundamentals of Epi.”, Gateway Sciences Initiative

Lead Teaching Assistant, “Epidemiologic Methods, I”

Teaching Assistant, “Epidemiologic Methods, I”, “Epidemiologic Methods, III”, “Observational Epidemiology”

Invited Panelist, “Problems in the Design of Epidemiologic Studies: Proposal Development and Critique” (Doctoral Grant Writing Class)

Instructed laboratories, proctored exams, graded class materials, and conducted “office hours” for Epidemiologic Methods I and III, and Observational Epidemiology courses; mapped reading assignments, produced instructional slide content for labs; wrote problem set and exam questions as Lead Teaching Assistant for Epidemiologic Methods I

ACTIVITIES & VOLUNTEERISM

2014  
Student Rep. (1 of 2), Johns Hopkins Bloomberg School of Public Health

*Middle States Commission on Higher Education Re-Accreditation of JHU*

2013-14  
Student Faculty Rep., Epidemiology Student Organization (ESO)

2012-13  
Co-President, Epidemiology Student Organization (ESO)

*Johns Hopkins Bloomberg School of Public Health, Baltimore, MD*

2011-12  
Student Coordinator, General Epidemiology/Methods Journal Club

*Johns Hopkins Bloomberg School of Public Health, Baltimore, MD*

2010-11  
Art Contributor, *The STEW: JHSPH Literary & Arts Magazine*

*Johns Hopkins University, Baltimore, MD*

2008-10  
Volunteer Math, Science, Reading and Writing Tutor (K-12th Grade)

*Youth Encouragement Services, Nashville, TN*

2003-03  
Volunteer Diff. and Integral Calculus Tutor (Advanced Placement)

*Hill Regional Career High School, New Haven, CT*

1999-2005  
Member, Yale Student Academic Competitions (Collegiate Quiz Bowl)

*Yale University, New Haven, CT*

1999-2000  
Contributing Arts Reviewer, *Yale Daily News*

*Yale University, New Haven, CT*

EDITORIAL ACTIVITIES

Peer review:  
AIDS Research and Therapy (2013, 2014)  
PloS One (2012)  
HIV Medicine (2012)
HONORS & AWARDS

2014  Gordis Teaching Fellowship
*Johns Hopkins Bloomberg School of Public Health*
Awarded competitively to doctoral students on the basis of experience and quality of overall application, with a focus on course design for undergraduate seminar

2014  Outstanding Clinical Research Poster Presentation
*Johns Hopkins Center For AIDS Research (CFAR) Annual Scientific Meeting*

2013  Student Dissertation Workshop participant
*Society for Epidemiologic Research*
Conference participation and travel scholarship, awarded competitively on the basis of dissertation proposal quality and sophistication of epidemiologic methodology involved

2012  Mary Meyer Scholarship
*Johns Hopkins Bloomberg School of Public Health*
Stipend and full-tuition grant for the first year of the doctoral program and half-funding for the second year, for top matriculating candidates in the department of epidemiology

2012  Departmental Funding, PhD Program
*Johns Hopkins Bloomberg School of Public Health*
100% tuition support for the first year, 85% for the second and third years of the doctoral program, offered to select matriculating candidates in the department of epidemiology

2011  Masters Scholarship
*Johns Hopkins Bloomberg School of Public Health*
75% tuition support for the second year of the Masters program, offered to candidates in the department of epidemiology maintaining a 3.0 grade-point average after the first year

1999  AP Honors Scholarship; National Merit Scholarship

RESEARCH SUPPORT

2013–14  *Principal Investigator*
Ruth L. Kirschstein National Research Service Award for Individual Predoctoral Fellows: Epidemiology of Clinical Retention Among HIV-Infected Persons in North America, F31-DA035713 (NIDA/NIH)

2013–14  *Research Assistant*
WIHS Data Management and Analysis Center (WDMAC), U01-AI042590 (NIAID/NIH)

2010-13  *Research Assistant*
North American AIDS Cohort Collaboration on Research and Design, U01-AI069918 (NIAID/NIH)

2004-10  *Research Assistant/Analyst/Coordinator*
Vanderbilt-Meharry Center for AIDS Research (CFAR), P30-AI54999 (NIAID/NIH)
PEER-REVIEWED PUBLICATIONS


ABSTRACTS


PRESENTATIONS

