INITIATION, RETENTION AND SURVIVAL IN HIV CLINICAL CARE: EFFECT OF RESIDENCE

Brettania L.W. Lopes

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Approved by:

Sonia Napravnik

Steven Meshnick

Joseph Eron

William Miller

Michael Mugavero

ABSTRACT

Brettania L.W. Lopes: Initiation, Retention and Survival in HIV Clinical Care: Effect of Residence
(Under the direction of Sonia Napravnik)

Late entry to human immunodeficiency virus (HIV) clinical care and inadequate engagement with care are associated with increased morbidity, mortality and secondary HIV transmission. Among HIV-infected persons in the U.S., approximately a quarter are diagnosed with acquired immune deficiency syndrome (AIDS) within 3 months of HIV diagnosis and a third within a year. After patients initiate HIV care, the majority miss clinic visits, 10-35% do not meet the Institute of Medicine's (IOM) core retention indicator, and 20-50% become lost to follow up (LTFU).

In the U.S., rural residence is associated with factors that may affect HIV care such as socioeconomic status, employment, educational level, and access to health insurance. Rural residence has been associated with delayed entry into care and increased mortality among some HIV-infected populations. However, to date little is known about the association between rural patient residence and HIV care retention and survival in the U.S.

This study relied on the UNC CFAR HIV Clinical Cohort (UCHCC), a clinical cohort enrolling patients receiving primary HIV care at a large tertiary care facility in the Southeastern U.S. Patient residence was categorized as urban or rural using the United States Department of Agriculture Rural Urban Commuting Area codes (RUCAs). The median CD4 cell count at care entry was compared between patients residing in urban versus rural residences using multivariable linear regression. Poisson, log-binomial and Cox proportional hazards regression were used to estimate the association between residence and the incidence rate of missed visits, IOM indicator and time to loss to follow up (LTFU) and death, respectively.

Results revealed the advanced progression of HIV-infection among a sizable group of patients. Rural in comparison to urban residence was associated with a lower likelihood of dropping out of care but was not associated with missed clinic visits or meeting the IOM retention indicator. Rural patients were at greater risk of mortality while in HIV care.

This study provides some of the first evidence of the effects of residing in rural areas on HIV care access. Future studies focusing on geographic factors affecting HIV clinical care access and survival while in care are needed.

Dedicated to:
My dissertation advisor, Sonia Napravnik
My dissertation committee members
My parents
My children, Leonardo and Oliver

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LIST OF ABBREVIATIONS

AIDS   acquired immunodeficiency syndrome

ART   combination antiretroviral therapy

CD4   cluster of differentiation 4

CFAR   Center for AIDS Research

CI   confidence interval

CNICS   Center for AIDS Research Network of Integrated Clinical Systems

DHHS   Department of Health and Human Services

HCV   hepatitis C virus

HHS   Health and Human Services

HIV   human immunodeficiency virus

HR   hazard ratio

HRSA HAB   Health Resources and Services Administration, HIV/AIDS Bureau

IDU   injection drug use

IeDEA   International epidemiologic Databases to Evaluate AIDS

INSIGHT   International Network for Strategic Initiatives in Global HIV Trials

IOM   Institute of Medicine

IQR   interquartile range

IR   incidence rate

IRR   incidence rate ratio

NC   North Carolina

NIH   National Institutes of Health

PO box   post office box

LTFU   loss to follow up

MSM   men who have sex with men

NA-ACCORD North American AIDS Cohort Collaboration on Research and Design

RNA	ribonucleic acid
RR	risk ratio
RUCA	rural urban commuting area codes
SAS	statistical analysis system
SD	standard deviation
UCHCC	University of North Carolina Center for AIDS Research HIV Clinical Cohort
UNC	University of North Carolina
US	United States
USDA	United States Department of Agriculture

CHAPTER I. SPECIFIC AIMS

When HIV-infected patients begin care at a late disease stage and/or when missed clinic visits or LTFU occur, this may lead to greater morbidity, mortality and secondary HIV transmission [1]. In the United States (U.S.), approximately 1 in 8 people infected with human immunodeficiency virus (HIV) is unaware of their infection [2] and a third are diagnosed with acquired immune deficiency syndrome (AIDS) within a year of being first diagnosed with HIV[3]. Late entry into HIV care is associated with worse HIV prognosis including inferior response to ART and greater risk of morbidity and mortality [4, 5]. The longer HIV care is delayed, the worse the patient outcome [5]. Late HIV care entry also leads to increased cost of care and greater community transmission risk due to prolonged time at high-risk of transmitting infection [6-12].

After initiating HIV clinical care, the majority of U.S. patients miss clinic visits, 10-35% are not retained in care according to the IOM core indicator, and 20-50% have at least one LTFU event [13-26]. Treatment non-adherence, treatment interruption and missed clinic visits are associated with increases in morbidity and mortality [13, 27]. On the other hand, consistent retention in HIV care has been shown to increase receipt of ART, HIV RNA suppression [28, 29], and reduce morbidity and mortality [30]. In addition, better retention in care leads to fewer secondary HIV infections [31, 32]. Factors associated with late entry into HIV care, missed visits and loss to follow-up (LTFU) may be used to identify patient groups at high-risk of receiving suboptimal HIV care and support the design of interventions promoting HIV care engagement before care is compromised.

In summary, regular HIV clinical care and ART can improve the health of HIV-infected patients but, in order to achieve maximum results, patients must initiate care soon after HIV

infection and remain consistently engaged in care [5, 13]. However, there is substantial

occurrence of late HIV diagnoses and late entry into care in NC [33] [34].

In general, in the southern U.S., persons living with HIV are often rural and poor and

reside in communities where HIV prevalence has increased faster than other areas of the U.S.

[35]. The place where patients live may be of particular importance to HIV care initiation and

retention. Rural residence is known to be associated with delayed entry into care and increased

mortality among some HIV-infected populations [36]. To the best of our knowledge, no study

has previously quantitatively examined patient rural residence and its association with: a) CD4

cell count at entry into HIV care; b) the incidence of missed HIV clinic visits; c) the risk of not

being retained in care according to the IOM indicator; d) time to first LTFU event; and e) time to

death among HIV-infected patients in care in the southern U.S. Therefore, to better understand

the effect of rural residence on HIV care initiation, engagement, and mortality, this study was

designed to address the following five specific aims:

Aim 1: Examine the association between rural residence and CD4 cell count at HIV care

initiation.

Hypothesis 1.1: After controlling for confounders, patients living in rural areas will have

lower CD4 cell counts at HIV care initiation, compared to patients living in urban areas.

Aim 2: Examine the association between rural residence and missed HIV clinic visits.

Hypothesis 2.1: After controlling for confounders, patients living in rural areas will be

more likely to miss HIV clinic visits, compared to patients living in urban areas.

Aim 3: Examine the association between rural residence and retention in care.

Hypothesis 3.1: After controlling for confounders, patients living in rural areas will be

less likely to be retained according to the IOM indicator, compared to patients living in urban

areas.

Aim 4: Examine the association between rural residence and HIV care attrition due to

LTFU.

Hypothesis 4.1: After controlling for confounders, patients living in rural areas will be at higher risk of being lost to follow-up and have a shorter time to the first LTFU event, compared to patients living in urban areas.

Aim 5: Examine the association between rural residence and HIV care attrition due to death.

Hypothesis 5.1: After controlling for confounders, patients living in rural areas will be at higher risk of mortality while in HIV care and under observation and have a shorter time to death, compared to patients living in urban areas.

For our analyses, we used data from the University of North Carolina (UNC) Center for AIDS Research HIV Clinical Cohort (UCHCC). The UCHCC includes data from January 1996 to present for > 5,000 HIV-infected patients who have received (or are still receiving) HIV care at UNC. Data come from electronic institutional resources, medical chart review and external data sources and includes demographic and mortality data, clinic visit data, antiretroviral therapy (ART) history, comorbidities, and laboratory data such as CD4 cell counts and HIV RNA levels. For this project, patient residence was assessed using the residence reported in the medical record. Census tract of residence was classified as a dichotomous urban / rural variable using a common algorithm [37] based on Rural-Urban Commuting Area Codes (RUCAs), a robust 2000 census-tract classification based on urbanized area/cluster definitions of core population size and work commuting data.

CHAPTER II. BACKGROUND AND SIGNIFICANCE

A. HIV Infection and Clinical Care in the United States

An estimated 1.2 million people are HIV-infected and approximately 44,000 new infections are diagnosed each year in the United States (U.S.) [2]. In the U.S., HIV disproportionately affects men who have sex with men (MSM), especially young Black MSM [38]. Racial and ethnic minorities in general are also disproportionately affected by HIV and HIV and AIDS diagnosis rates are highest in the U.S. South [2].

In the U.S., HIV infection has changed from an almost inevitably fatal disease to a chronic, manageable condition for patients who know their infection status and access effective care in a timely and consistent manner [39, 40]. Modern ART has substantially increased in efficacy, tolerability and convenience, with most individuals who initiate ART achieving and maintaining HIV RNA suppression and increasing their CD4 cell counts [40, 41]. ART can reduce HIV RNA levels to undetectable levels in most treated patients [42], and greatly reduces HIV RNA levels in the female genital tract and in semen [43, 44]. ART has become less toxic and now has more simple dosing [45].   HIV-infected patients treated with combination ART have increased life expectancy [45]. As ART has become more effective, AIDS-related deaths have decreased and HIV-infected patients are increasingly dying of other causes [46].

Therefore, it is critically important that HIV-infected persons learn their HIV status quickly, start care early and consistently stay in care since treatment non-adherence and missed clinic visits are associated with worse HIV health outcomes [13, 27], while early HIV diagnosis and treatment is associated with reduced morbidity and mortality [47], and reduced secondary HIV transmission [1]. Furthermore, the U.S. South is the region of the country where HIV-infected

persons are least likely to know they are infected and are least likely to enter care in a timely manner [48], making this region a high priority.

B. Evaluating Clinical Care Initiation and Retention in the United States

There are several ways to approximate the timing between HIV infection and clinical care initiation and to measure how a patient is retained in care. To approximate the timing between HIV infection and clinical care initiation, researchers and clinicians may use the time between HIV diagnosis and care initiation and/or may rely on clinical proxies of disease progression such as CD4 cell count or an AIDS diagnosis at the time of care initiation.

Retention in HIV care refers to whether patients remain consistently in care after beginning care. Knowing how often clinic visits are generally recommended and having a record of all scheduled visits allows for the development of indicators to assess how patients are retained in care. The main ways to assess retention are by looking at attended visits, missed visits, and/or gaps in care, however, there is no one gold standard for assessing retention [49].

Until recently in the U.S., a clinic visit was recommended approximately every 3 months for HIV patients [50]. More frequent clinic visits may be indicated when initially starting ART, switching to a new ART regimen, or as indicated clinically (e.g. when the CD4 cell count is < 200/mm^3) [50]. In more recent years, it has become more common for clinicians to recommend less frequent clinic visits. Laboratory monitoring of CD4 counts is recommended at entry into care and then every 3-6 months, when clinically indicated, whenever ART is modified or initiated, or when there is treatment failure [41]. The exception is for clinically stable adherent patients who have suppressed viral loads for more than 2-3 years, these patients may have their CD4 cell counts monitored every 6-12 months [41]. Viral load should be monitored at entry into care, 2-8 weeks post-ART initiation or modification, then every 3-6 months, when clinically indicated, whenever ART is modified or initiated, or when there is treatment failure [41].

Missed visits has widely been used as a research variable, often defined as a count of scheduled clinic visits the patient did not attend over an observation period [49]. Visits canceled

or rescheduled by the patient or healthcare provider are generally not counted as missed visits. Studies have looked at missed visits as a dichotomous variable and as a count variable [13, 51, 52]. The missed visits variable has been suggested for preliminary research or research with short-term observation periods [49]. An advantage to using a count of missed visits is the optimal number of appointments per patient per year and appointment frequency do not need to be estimated.

In 2012, the Institute of Medicine core clinical indicators were approved by the Department of Health and Human Services (HHS). These measures are based on attended visits and cover the HIV treatment cascade. The current IOM retention indicator is 2 attended visits with at least 90 days between them in a 12 month observation period [53].

There is no gold standard for calculating a summary LTFU measure and no consensus on what time period since the last attended visit should define LTFU [54-57]. Therefore, defining LTFU depends on the research purpose, available data, and clinic scheduling practices [49]. Some researchers have looked at total length of time of the gap the patient was out of care while others have compared the gap time to a pre-determined threshold time that ranges between 4 to 12 months [58-60]. Measuring LTFU according to time elapsed since the last attended clinic visit is likely to be a useful measure across programs [56].

Other retention in care measures have been proposed [49, 57, 61] but were not used in this study. Examples of other types or variations of retention measures include different definitions of LTFU or ways to define LTFU (e.g. different time periods or definitions based on the number of missed visits) [62], appointment adherence, visit constancy, attended visits divided by all scheduled visits, DHHS core indicators, and hybrid measures such as the Human Resources and Services Administration HIV/AIDS Bureau (HRSA HAB) medical visit performance indicator [49, 57, 61].

C. HIV Diagnosis, Clinical Care Initiation and Retention in the United States

While U.S. HIV diagnoses, and likely new HIV infections, have declined significantly in the past 10 years, the HIV care continuum still shows serious barriers to effective HIV treatment in the U.S. Approximately 1 in 8 people infected with HIV in the U.S. is unaware of their infection [2]. Most patients in the U.S. present for care with a CD4 cell count < 350 cells/mm^3 and more than 50% of HIV patients have late entry into HIV care with an initial CD4 cell count < 200 cells/mm^3 [5, 12, 13, 63, 64]. Approximately a third of HIV-infected people in the U.S. are diagnosed with AIDS within a year of being first diagnosed with HIV [3]. Approximately half of HIV-infected persons are not engaged in consistent clinical care due to missed visits and/or LTFU [13, 16], 75% have not achieved viral suppression [16], and only approximately a third know their HIV status, are in regular clinical care, take ART and have undetectable HIV RNA levels [65]. The current state of HIV diagnosis, care initiation and retention indicates a great need to better understand the causes of delayed care initiation and poor retention and to identify patients at greatest risk.

D. HIV in the Rural South of the United States

The U.S. South faces the greatest burden of HIV infection, morbidity and mortality when compared with the rest of the country and the region includes 8 of the 10 states with the highest HIV diagnosis rates [48]. The South is the area where groups disproportionately affected by HIV live with 90% of rural African Americans and 60% of black MSM with HIV, respectively [48]. When compared to the rest of the country, parts of the U.S. South, and rural areas in particular, are disproportionally characterized by poverty, healthcare shortages, less access to HIV experts, stigma, privacy concerns, unemployment, lack of health insurance, low education and increased time and cost to travel to health care [48, 66-70], factors which can affect HIV care initiation and retention and mortality.

Although the majority of U.S. HIV diagnoses are from urban areas, including in the South, suburban and rural HIV diagnosis rates are higher in the South than any other region of

the U.S. [48]. In addition, the incidence of new HIV diagnoses in rural areas is 3-4 times higher in the South than other regions of the U.S. [71] while the proportion of total HIV diagnoses and total AIDS diagnoses among rural residents versus residents from other areas are highest in the South compared with other U.S. regions [71].

However, we know little about how rural residence affects patients' HIV care and survival, overall and in the U.S. South in particular, despite the fact that so many HIV patients are located in the rural South. While associations between place of residence and HIV stigma have been researched [72-74], few U.S. studies have specifically investigated rural-urban differences in HIV care initiation and retention [75, 76] even though rural patient residence may be a barrier to entry into care and retention in care. Our own work has shown rural residence is associated with delayed entry into HIV care [77] and, although few studies have been done on rural residence and mortality among HIV-infected persons, rural residence has been associated with increased mortality among some HIV-infected populations (e.g. Veterans, patients in New England) [36, 78].

E. Summary

Notwithstanding substantial evidence of the importance of early and consistent HIV clinical care engagement to individual and public health and the elevated burden of HIV in rural areas of the Southern U.S., little work has directly focused on geographic differences in accessing HIV care and staying in HIV care. Therefore, this study fills an important gap in the scientific literature focusing specifically on rural residence and aspects of the HIV treatment cascade.

CHAPTER III. RESEARCH DESIGN AND METHODS

A. Description of Data Source

For this study we relied on the University of North Carolina (UNC) CFAR HIV Clinical Cohort (UCHCC) which includes data from HIV-infected patients receiving primary HIV care from 1996 to the present at a large tertiary care facility in the Southeastern U.S. The UCHCC patients are representative of HIV-infected patients in clinical care in NC overall. Data include information from electronic institutional resources, periodic medical reviews, and integrated data from external sources such as mortality data. Specifically, information is available on demographics, health insurance, clinic appointments, laboratory tests, HIV clinical encounters, HIV risk factors, diagnoses of other illnesses, hospitalizations, medications and patient reported outcomes. The cohort and its procedures have been previously described in more detail [27].

Data are collected at point-of-health care during UNC clinic visits as part of clinical care, reducing volunteer and non-response bias. The type and timing of collected data depend on the patient's needs. Cohort data are checked for completeness, plausibility and consistency. Medical chart abstraction is standardized. Precise data on patient medications and treatments are available. The longitudinal cohort allows for direct estimation of incidence rates and assessment of multiple exposures and outcomes. Patients provide written informed consent to participate in the UCHCC, and the UCHCC as well as this specific study were approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

B. Study Population

UCHCC participants aged 18+ years who attended ≥1 HIV clinical care visit at UNC between 1996 and 2012 were eligible for analyses in this study. Patients were excluded if they did not have a geo-codable address of residence. For study aim 1 only, focused on HIV care

initiation, we excluded patients who initiated HIV care at a different institution to ensure complete data were available on HIV care parameters at care initiation. For study aims 2-5, focused on HIV care retention and mortality, in order to allow for at least 1 year of follow-up we excluded patients who did not have their first UNC clinical care visit at least 1 year before the date of administrative censoring (December 31, 2012). For aims 2-5, additional analyses were conducted in which: 1) patients with prior clinical care before entering UNC clinical care were excluded; and 2) patients who attended only one visit at the UNC clinic were excluded. For aims 2-5, we defined baseline as the latter of January 1, 1996 or the first UNC HIV clinical care visit.

Our study population is likely representative of HIV-infected persons in the U.S. South and of HIV-infected patients in clinical care in NC. North Carolina has a large percentage of rural residents, a diverse population density with which to study urban-rural differences, and NC patients experience a large range of driving distances to reach care as the UNC HIV clinic in Chapel Hill is located at a geographic point that may be quite close to some patients while being as far as 150-200 miles from other patients' residences in NC. In 2015, 20% and 28% of newly diagnosed HIV cases in NC among men and women, respectively, also were AIDS cases indicating substantial occurrence of late diagnoses and late entry into care in NC [79]. Furthermore, in 2013, only approximately 50% of NC HIV-infected persons were retained in care and virally suppressed [80].

C. Exposure Measurement

Rural residence was defined according to the U.S. Department of Agriculture (USDA)'s Rural-Urban Commuting Area Codes (RUCAs), a robust 2000 census-tract classification based on urbanized area/cluster definitions of core population size and work commuting data. We used Arc-GIS to geocode the patient's first reported home address and assign RUCA codes. Although we first assigned residence based on four RUCA codes (urban, large rural, small rural, and isolated small rural); given the limited sample sizes in small and isolated small rural areas we ultimately decided on a common algorithm (USDA's Categorization C, version 2) that

dichotomizes residence as rural or urban [37]. For all study aims, we conducted sensitivity analyses using multiple imputation methods to assign residence to patients missing an address of residence.

D. Outcome Measures

Aim 1

Our primary outcome of interest for aim 1 was the patient's CD4 cell count at first presentation to HIV clinical care. The CD4 cell count is the major laboratory indicator of immune function of HIV-infected patients [41]. We considered both a continuous measure of CD4 cell count as well as a variety of cutpoints representing varying degrees of immunosuppression.

Aims 2-5

For study aims 2-5, baseline was defined as the latter of January 1, 1996 or the first UNC HIV clinical care visit.

Aim 2

Our primary outcome for aim 2 was the incidence rate of missed visits, chosen in order to account for person-time at risk of a missed visit. A variable based on missed visits allows for an immediate intervention and captures whether the patient has consistent access to care. Use of an incidence of missed visits focuses on care adherence rather than constancy and does not require an estimate of the optimal number of appointments per year. In addition, an incidence measure is beneficial because it accounts for the time that each patient was at risk of missing visit(s) across their entire time in care. The incidence rate of missed clinic visits was defined as the sum of all non-attended clinic visits divided by total person-time in care. Person-time was calculated as the time from baseline until the first of LTFU (365+ days out of care after last attended visit), death or administrative censoring at the end of the study (December 31, 2012). Walk-in, urgent care and emergency department visits were not considered clinic visits, and visits that were canceled or rescheduled prior to the appointment were not considered to be

missed. Patients who initiated care less than 365 days before the end of the study were excluded from aim 2 analyses.

<u>Aim 3</u>

Our outcome of interest for aim 3 was the IOM retention indicator developed by the Institute of Medicine. The IOM retention indicator for each 12-month care period was defined as attending ≥2 clinic visits, ≥90 days apart. A patient's first potential 12-month care period began at baseline. A patient who died or became LTFU was ineligible for the IOM analyses in the 12-month care period when the death or LTFU event occurred as well as all subsequent periods. Walk-in, urgent care and emergency department visits were not considered clinic visits. Patients who initiated care less than 365 days before the end of the study or did not contribute person-time for a full 12-month period each year following baseline (e.g. due to death or LTFU) were excluded from the IOM retention indicator analysis for each corresponding 12-month period and all subsequent 12-month periods.

<u>Aim 4</u>

Our outcome of interest for aim 4 was time to the first LTFU event, calculated as the date of the last attended HIV clinical care visit plus 365 days. We chose 365 days because of current trends in HIV clinical care that generally allow patients to have longer time periods between visits without compromising care. Walk-in, urgent care and emergency department visits were not considered clinic visits. Patients who initiated care less than 365 days before the end of the study were excluded from the aim 4 analysis. In sensitivity analyses, we also examined a different cut-point for LTFU (18 months).

<u>Aim 5</u>

For aim 5 we studied the outcome of time to all-cause mortality. Survival time was calculated from baseline until the time of death or administrative censoring, whichever came first. A patient's date of death was based on data from a variety of sources, including state

records from North Carolina and U.S. federal database searches including the National Death Index.

E. Other Measures

We considered a number of patient demographic and clinical characteristics at UNC care entry or baseline as possible effect measure modifiers or confounders of the relationship between residence and HIV care initiation, retention or survival, including driving distance to the clinic, age, sex, insurance, men who have sex with men (MSM), intravenous drug use (IDU), calendar year of care entry, HCV status, CD4 cell count, HIV RNA level, and diagnosis of an AIDS clinical condition (**Table 3.3**).

<u>Statistical Analysis</u>

For all covariates, we first examined descriptive statistics and distributions in order to make initial decisions about variable categorization.   We first assigned residence based on 4 RUCA codes (urban, large rural, small rural, and isolated small rural); however, the limited sample sizes in small and isolated small rural areas led us to instead use a common algorithm (USDA's Categorization C, version 2) dichotomizing residence as rural or urban [37]. For all analyses, we conducted descriptive analyses and compared rural to urban patient characteristics using standard statistical approaches such as t test, Chi-square and the Wilcoxon or Kruskal-Wallis tests.

For all study aims and models, we followed the same basic approach. We first assessed for effect measure modification and confounding in stratified analyses. This preliminary work then informed how we fit a full model, which included factors *a priori* identified as relevant to the association between rural residence and our outcome of interest. Factors included in models were also chosen based on a directed acyclic graph we created. Effect measure modification was considered present if the p-value for interaction was >0.10. The multivariable analyses were fit to adjust for, depending on the study aim, confounding by factors reported at UNC entry to care including sex, age, race/ethnicity, MSM, IDU, CD4 cell count, HIV RNA $\log_{10}$ level, HCV

status, health insurance, calendar year of UNC care initiation, diagnosis of an AIDS-defining clinical condition and one-way driving distance to the UNC clinic. We then removed variables in a step-wise manner that were not deemed to be confounders based on a change-in-estimate criterion (10% change in estimate). We assessed for confounding using the change-in-estimate criterion after first testing for effect measure modification. In all analyses, we examined the effect on model fit and estimation of using continuous variables in continuous form, categorical form and using flexible spline parameterizations. Data for all analyses were analyzed using SAS version 9.3 (SAS Institute, Cary, NC, USA). Hypothesis testing was 2-sided with an alpha level of 0.05.

F. Statistical Analysis- Aim 1

Our primary outcome for aim 1 was the patient's first known CD4 cell count. We used the first available CD4 cell count within 60 days of the patient's first UNC HIV clinical care visit. We excluded patients with prior HIV clinical care from this analysis. The association between area of patient residence and mean CD4 cell count was examined using multiple linear regression and by comparing the median CD4 cell count difference between rural and urban patients. Adjusted and unadjusted mean CD4 cell count differences and their 95% CIs were estimated.

In a secondary analysis, the proportion of patients with a CD4 cell count < 200 cells/mm^3, and in addition a CD4 cell count of <350 cells/mm^3, at entry to care was compared between urban and rural patients relying on log-linear regression. We also conducted a secondary analysis using quantile regression instead of linear regression. We also conducted an analysis restricting our primary analyses to patients who initiated HIV care in more recent calendar years, specifically 2001 to 2012, due to changing HIV testing guidelines over time.

G. Statistical Analysis- Aim 2

Our primary outcome of interest for aim 2 was the incidence rate of missed clinic visits. The association between area of patient residence and the incidence of missed visits was examined using Poisson regression. The incidence rate of missed visits was estimated for urban versus rural patient residence. Unadjusted and adjusted incidence rate ratios (IRRs) and their 95% CIs were estimated. Sensitivity analyses were done to assess the effects of coding continuous variables in different ways, including flexible spline coding. A sensitivity analysis examined the effect of excluding patients who were only seen once at the UNC clinic. A sensitivity analysis also examined the robustness of results when restricted to patients without prior HIV care before UNC HIV care. We conducted another analysis restricting our analysis to patients who initiated HIV care in more recent calendar years, specifically 2001 to 2012.

H. Statistical Analysis- Aim 3

Our primary outcome of interest for aim 3 was whether or not patients were retained according to the IOM core retention indicator. The IOM retention measure for each 12 month care period was defined as attending ≥2 clinic visits, ≥90 days apart [53]. Baseline was defined as the latter of January 1, 1996 or the first UNC HIV clinical care visit. We defined a patient's first 12-month care period as starting at baseline. If a patient died or was LTFU then we did not include that patient in calculations of the IOM measure in the 12-month period when the death or LTFU event occurred, or any subsequent periods. Log-binomial regression was used to estimate unadjusted and adjusted risk ratios for the association between rural residence and the risk of not being retained in care according to the IOM indicator. We estimated unadjusted and adjusted risk ratios for the IOM measure by individual years of care as well as conducting a repeated measures analysis fit via generalized estimating equations to combine all eligible years of care. Sensitivity analyses were done to assess the effects of coding continuous variables in different ways, including flexible spline coding.

A sensitivity analysis examined the effect of excluding any patients who were only seen once at the UNC clinic. A sensitivity analysis also examined the robustness of results when restricted to patients without prior HIV care before UNC HIV care. We conducted another analysis restricting our analysis to patients who initiated HIV care between 2001 to 2012.

I. Statistical Analysis- Aim 4

Our primary outcome of interest for aim 4 was the time to the first loss-to-follow-up event for each patient. Person-time at risk of a first LTFU event for each patient was based on time from baseline until a first LTFU event (last attended HIV clinical care visit plus 365 days), administrative censoring (December 31, 2012), or death, whichever occurred first. Only the first LTFU event was analyzed. We fit Kaplan-Meier plots and the time to the first LTFU event was assessed using Cox proportional hazards models to examine the association between patient residence and attrition. Deviations from the proportional hazard assumption were assessed. Unadjusted and adjusted hazard ratios (HRs) and 95% CIs were estimated.

We repeated the same sensitivity analyses as for aims 2-3: separate sensitivity analyses examined the effect of excluding patients who were only seen once at the UNC clinic, restricting the population to patients without prior HIV care before UNC HIV care and restricting our analysis to patients who initiated HIV care in more recent calendar years, specifically 2001 to 2012.

J. Statistical Analysis- Aim 5

Our primary outcome of interest for aim 5 was the time to death. Survival time under observation was calculated for each patient based on time from baseline until death or administrative censoring (December 31, 2012), whichever occurred first. We fit Kaplan-Meier plots and Cox proportional hazards models were used to examine the association between patient residence and time to death. We assessed whether the proportional hazard assumption was met and we estimated unadjusted and adjusted hazard ratios (HRs) and 95% CIs.

Again, we repeated the same sensitivity analyses: separate sensitivity analyses examined the effect of excluding patients who were only seen once at the UNC clinic, restricting the population to patients without prior HIV care before UNC HIV care and restricting our analysis to patients who initiated HIV care in more recent calendar years, specifically 2001 to 2012.

K. Statistical Analyses- Multiple Imputation

We repeated all of our primary analyses using multiple imputation to include patients who did not have a geocodable address of residence. We used a multivariate normal model for multiple imputation to impute missing rural residence 50 times and we used Rubin's rule to combine imputations [81]. The same variables included in each primary analysis were used for the corresponding multiple imputation model.

Table 3.1 Study Variable Descriptions

Variable	Description	Type
	Outcomes	
CD4 cell count	CD4 cell count at baseline	Continuous or categorical
Incidence rate of missed visits	The number of scheduled HIV clinic visits that the patient did not attend / person-time in care since baseline.	Continuous
IOM indicator	IOM retained or not retained in each 12-month care period.	Binary
Time to first LTFU event	Time from baseline to 1st LTFU event (last attended visit plus 365 days). LTFU = no visit in ≥ 365 days.	Time-to-First-Event
Time to death	Time from baseline to death.	Time-to-Event
	Primary Exposure	
Rurality of patient residence (urban / rural)	Based on categorized 2000 RUCA codes and geo-coded census tract of patient residence at time of entry into UNC care.	Binary
	Covariates (at UNC care entry)	
CD4 cell count	CD4 cell count	Continuous
HIV RNA level	HIV RNA level	Continuous
AIDS-defining condition	Any AIDS-defining clinical condition(s) within 180 days after UNC care entry, from the medical record.	Binary
Age	Patient's age (years).	Continuous or categorical
Sex	Patient's sex. Male or female.	Binary
Race/ethnicity	White, Black, Other (including Hispanic).	Categorical
Sexual orientation	Men who have sex with men (MSM) or heterosexual.	Binary
Health insurance	Private, public or none	Categorical
Injection drug use (IDU)	Reported history of injection drug use, from medical record.	Binary
Hepatitis C	Hepatitis C virus infection, from medical record.	Binary
Calendar Year	Calendar year of UNC care initiation	Continuous or categorical
Driving distance	One-way driving distance to the UNC clinic, based on geo-coded reported patient residential address, from medical record.	Continuous or categorical
	Other variable	
Death	If patient died, date of death. From the medical record or death registry. Categorized as whether or not death occurred during the time the patient was under study.	Date and Binary

CHAPTER IV. RESULTS: HIV CARE INITIATION DELAY AMONG RURAL RESIDENTS IN THE SOUTHEASTERN UNITED STATES, 1996 TO 2012

A. Introduction

HIV infection is a chronic, manageable condition for most individuals who access HIV care and initiate antiretroviral therapy (ART) early and consistently following infection [45, 82, 83]. However, delays in HIV care initiation are associated with poor prognosis including less than optimal ART outcomes and greater risk of morbidity and mortality [5, 84]. Late care entry is also associated with greater medical care costs and prolonged risk period for HIV transmission [85-87].

In the U.S., an estimated 1 in 8 people infected with HIV are unaware of their infection [88]. Furthermore, a quarter of HIV-infected persons are diagnosed with clinical and/or immunologic acquired immune deficiency syndrome (AIDS) within 3 months, and a third within a year, of HIV diagnosis [89]. The median CD4 cell count at first presentation for care has increased in recent years, but remains below 350 cells/mm^3 for more than half of U.S. patients [12, 90]. A number of patient characteristics may be associated with delays in HIV care initiation, including sex, age, race/ethnicity, and health insurance [12, 91].

Structural and social characteristics may also affect patient care engagement. Rural residence specifically may negatively affect HIV care receipt and clinical outcomes [36, 67, 75] as well as retention [75, 92]. HIV-infected persons living outside urban centers may have less access to HIV experts and facilities, incur greater costs and time traveling for care, face greater stigma, have more concerns about privacy and anonymity, and have fewer or no ancillary care services [68, 93].

With increasing emphasis on addressing gaps in the HIV cascade and continuum,[94] we undertook this study to specifically assess the effect of rural residence on HIV care entry. Relying on a large HIV clinical cohort study in the Southeastern U.S., we evaluated differences in patient characteristics at care entry by rural residence and examined whether living in a rural area affected timing of HIV care initiation.

B. Methods

Study Design and Population

This study used UNC CFAR HIV Clinical Cohort (UCHCC) data which includes HIV-infected patients receiving primary HIV care from 1996 to the present at a large tertiary care facility in the Southeastern U.S. UCHCC data includes information from electronic health and administrative institutional records, periodic medical chart reviews, and links to external sources including mortality data. The UCHCC and its procedures have been previously described [27]. Patients at least 18 years of age who initiated HIV care between 1996 and 2012 were eligible for this study. We excluded patients who initiated HIV care at a different institution. Patients provide written informed consent to participate in the UCHCC, and the UCHCC as well as this study were approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

Measures

Our primary outcome of interest was the patient's CD4 cell count at first presentation to HIV clinical care, defined as first available CD4 cell count available within 60 days of the first HIV clinical care visit among patients with no prior HIV care. We considered a continuous CD4 measure as well as categories representing varying degrees of immunosuppression. Our primary exposure of interest was rural residence, which was defined according to the U.S. Department of Agriculture (USDA)'s Rural-Urban Commuting Area Codes (RUCAs), a robust 2000 census-tract classification based on urbanized area/cluster definitions of core population size and work commuting data. We used Arc-GIS to geocode the patient's first reported home

address and assign RUCA codes. We first assigned residence based on four RUCA codes (urban, large rural, small rural, and isolated small rural); however, given the limited sample sizes in small and isolated small rural areas we chose to use a common algorithm (USDA's Categorization C, version 2) that dichotomizes residence as rural or urban [37].

We considered a number of patient demographic and clinical characteristics as possible effect measure modifiers and confounders of the relationship between residence and CD4 cell count at HIV care initiation, including sex, age, race/ethnicity, being a man who has sex with men (MSM), history of intravenous drug use (IDU), $\log_{10}$ HIV RNA level, Hepatitis C co-infection (HCV), health insurance, driving distance to the clinic and calendar year. These factors were chosen based on a directed acyclic graph we created for this project, and based on evidence that these factors may be different between rural and urban residents, and may affect timing of HIV care initiation [12, 68]. Patients of reported Hispanic ethnicity were included as "other" race/ethnicity and not as White or Black. Patients were classified as having an AIDS-defining clinical condition if diagnosed with a CDC category C condition within 180 days of first clinical care entry [95].

Statistical Analyses

We compared rural and urban patient characteristics using standard statistical approaches including t-test, Chi-square and the Wilcoxon or Kruskal-Wallis tests. We reported unadjusted and adjusted means for CD4 cell count. The association between patient residence (urban or rural) and continuous CD4 cell count was examined using multiple linear regression. Multivariable analyses were fit to adjust for confounding by demographic and clinical factors measured at first presentation to HIV care. Change-in-estimate criterion was used to assess for confounding after first testing for effect measure modification using an alpha of 0.10. As indicated, we considered alternate parametization of continuous characteristics including fitting flexible splines to improve model fit and estimation.

In sensitivity analyses, having a CD4 cell count <200 cells/mm^3 or <350 cells/mm^3 at HIV care entry was compared between urban and rural patients using multivariable log-linear regression. Since HIV testing guidelines have changed over the course of this study we also performed our primary analyses among patients who initiated HIV care in more recent calendar years, specifically 2001 to 2012. Furthermore, we performed our primary analyses using multiple imputation including patients who we were not able to geocode. For the multiple imputation, we used a multivariate normal model to impute missing rural residence 50 times and used Rubin's rule to combine imputations [81]. Variables included in the imputation model were the same as variables used in the primary analysis. Hypothesis testing was 2-sided with an alpha level of 0.05. Data were analyzed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

C. Results

Between 1996 and 2012, 1396 UCHCC patients initiated HIV care and met our inclusion criteria. In the primary analysis we excluded 408 patients (29%) without a geocodable address (e.g., only PO Box provided or address unavailable). These excluded patients were similar to those with geocoded addresses (**Table A.1**). The final study population of patients with geocodable addresses of residence included 988 patients of whom 69% were men. The mean age at care entry was 37 years (Standard Deviation [SD], 11), and 60% were Black, 26% White, and 14% of other race or ethnicity, most of whom were Hispanic (60%) (**Table 4.1**). At HIV care initiation, the mean CD4 cell count was 351 cells/mm^3 (SD, 290), with 18%, 19%, 18%, 18% and 27% having CD4 cell counts <50, 50-199, 200-349, 350-499 and ≥500 cells/mm^3 respectively. The mean log$_{10}$ HIV RNA level was 4.5 (SD, 0.98), and 20% were diagnosed with an AIDS-defining clinical condition. The mean year of HIV care initiation was 2003 (SD, 4.8). We noted a modest increase in mean CD4 cell count at care initiation over calendar time, with a CD4 cell count of 329 cells/mm^3 (SD, 283) for 1996-2003 versus 391 cells/mm^3 (SD, 292) for 2008-2012 (P=0.006).

Patients resided in urban (65%), large rural (25%), small rural (8%) and isolated small rural areas (1%), and for this study we combined the three rural categories. There were 342 patients (35%) who lived in a rural area. Rural in comparison to urban patients were older (mean 38 versus 36 years) and started care in earlier calendar years (mean 2002 versus 2003), (P=0.0001 and P=0.0005, respectively) (**Table 4.1**). Rural patients were less likely to have private health insurance but more likely to have public insurance than urban patients (P=0.002). Rural patients were more likely to reside longer distances from the clinic with a mean one-way driving distance of 74 miles (SD, 36) versus 46 miles (SD, 36) for urban patients (P<.0001). Additionally, rural patients were more likely to be co-infected with HCV than urban patients (20 versus 13%, P=0.006).

Rural patients had lower CD4 cell counts at HIV care initiation compared with urban patients (mean 320 cells/mm^3; SD 279; versus 368 cells/mm^3; SD 295, respectively, P=0.0XX). Overall, 42% of rural versus 34% of urban patients initiated care with a CD4 cell count <200 cells/mm^3 (P=0.008); and 60% of rural versus 53% of urban patients initiated care with a CD4 cell count <350 cells/mm^3 (P=0.009).

The unadjusted mean CD4 cell count difference comparing rural to urban patients of -48 cells/mm^3 (95% Confidence Interval [CI], -86, -10) persisted after adjustment for demographic and clinical characteristics (-37 cells/mm^3; 95% CI, -73, -2) (**Table 4.2**). Additional factors associated with entering HIV care at more advanced immunosuppression in multivariable analyses included male sex, older age, non-white race (with both Black and primarily Hispanic other race/ethnicity patients presenting with lower CD4 cell counts than whites), not being MSM and higher HIV RNA level. Neither distance to care, type of health insurance or HCV co-infection were associated with CD4 cell count at HIV care entry. In adjusted analyses rural patients presented with lower CD4 cell counts in earlier calendar years (1996 to 2003) in comparison to later years (2008 to 2012), however there appeared to be no difference in later years (2004 to 2007 versus 2008 to 2012).

Rural patients were more likely to initiate care with a CD4 cell count <350 cells/mm^3 when compared with urban patients (Relative Risk [RR]=1.17, 95% CI, 1.04, 1.30) and this effect persisted in multivariable analyses (RR=1.12, 95% CI, 1.02, 1.23). In unadjusted analyses rural patients were also more likely to initiate HIV care with a CD4 cell count <200 cells/mm^3 compared with urban patients (RR=1.25, 95% CI, 1.06, 1.47), although this effect was attenuated after adjusting for other covariates in multivariable analyses (Adjusted RR=1.13, 95% CI, 0.98, 1.30).

Our main study findings were also comparable when restricting the study cohort to HIV care initiation between 2001 and 2012, in these analyses the unadjusted and adjusted rural-urban mean CD4 cell count difference was -87 cells/mm3 (95%CI -136, -38) and -76 cells/mm3 (95%CI -124, -27), respectively (**Table A.6**). A secondary analysis using quantile regression gave comparable unadjusted and adjusted estimates to linear regression, indicating differences across the CD4 distribution, although with less precision (**Supplemental Figure 4.1**). Furthermore, our main study findings were also robust in sensitivity analyses where we included patients we could not geocode, using multiple imputation methods. In these analyses the unadjusted mean CD4 cell count difference comparing rural to urban patients was -44 cells/mm^3 (95% CI, -81, -8), and the adjusted result was -46 cells/mm^3 (95% CI, -85, -7).

D. Discussion

In this large HIV clinical cohort in the Southeastern U.S., over one-third of patients lived in areas classified as rural, and over one-half travelled over 50 miles one way to receive HIV care. Consistently we observed that rural residence was associated with initiating HIV care at lower CD4 cell counts, even after accounting for other demographic and clinical characteristics. Although few studies have examined the association between rural residence and CD4 cell count at care entry, lower CD4 cell count at care entry among rural patients compared with urban patients is consistent with observations from two studies of HIV-infected U.S. veterans [36, 96].

Others have observed no difference in CD4 cell count at time of HIV diagnosis comparing patients from rural and urban areas [97-99], suggesting rural residence may not affect the timing of HIV diagnosis but rather may affect the time from HIV diagnosis to care initiation. Reasons for late care initiation among rural residents may be multifaceted. HIV-infected persons living outside urban centers may have less access to HIV experts and facilities, greater costs and time incurred traveling for care, face greater stigma, have more concerns about privacy and anonymity, perceive they are at lower risk of HIV infection, and have fewer or no ancillary care services [67-69]. A few prior studies among U.S. HIV-infected populations have observed that rural residents face increased barriers to care compared with urban residents [68, 100].

In general, our patients had substantial travel distances to care and rural patients in our study had longer travel distances than urban patients. Transportation and/or distance barriers to care have been reported by HIV-infected populations [67, 101, 102], and greater travel distance has been associated with delayed care entry and/or poorer care engagement for several health conditions [103-106].   In this study, we did not observe a strong effect of distance to the clinic on CD4 cell count at HIV care initiation but our study was not designed to specifically examine distance to care.

We observed that men in comparison to women, older patients, and racial/ethnic minorities initiated HIV care at lower CD4 cell counts. These findings have been noted by others [12, 64, 91]. For example, in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) men versus women initiated HIV care at a mean CD4 cell count of 300 versus 349 cells/mm^3 in 1997 and 353 versus 395 cells/mm^3 in 2007 [12].   In the NA-ACCORD, participants of white race initiated HIV care with a mean CD4 cell count of 328 cells/mm^3 versus 305, 293, or 281 cells/mm^3 for participants of Black, Latino or other race/ethnicity, respectively, in 1997 while in 2007 whites initiated care with a mean CD4 cell count of 382 versus 328 cells/mm^3 for Blacks [12]. Consistent with our findings, the NA-

ACCORD also showed older patients entered care with lower median CD4 cell counts than younger patients between 1997-2007 [64].

In our cohort, less than a quarter of patients presented to HIV care with a CD4 cell count > 500 cells/mm^3. This finding is concerning as the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) START study group recently reported a benefit to beginning ART at a CD4 cell count over 500 cells/mm^3 compared to beginning ART at 350 cells/mm^3 or less [107]. Reassuringly in more recent calendar years, we observed an increase in CD4 cell counts at care entry, and mitigation of the rural-urban difference. These results are in line with other North American studies. For example, in a large cohort collaboration of the International epidemiologic Databases to Evaluate AIDS (IeDEA), the NA-ACCORD observed an increase in median CD4 cell count in more recent years, increasing from 256 to 317 cells/mm^3 between 1997 and 2007 [12]. The HIV Research Network, a consortium of 18 U.S. clinics, also observed an increase in median CD4 cell count at HIV care initiation, rising from 285 to 317 cells/mm^3 over the years 2003-2007 and 2008-2011 [108].

Notwithstanding increases in CD4 cell count at HIV care initiation among both rural and urban residents in more recent calendar years, substantial delays in HIV testing and/or initial HIV care linkage remained in our cohort even in most recent years, consistent with national estimates [109, 110]. Therefore ongoing design, evaluation and implementation of innovative approaches to HIV testing and care linkage is needed, such as promising projects detecting HIV-infected individuals based on geotargeted community based interventions reaching marginalized populations [111], new diagnostic strategies to detect early HIV infections [112], and contemporaneous HIV diagnosis and ART initiation [113]. Additionally the opioid epidemic is increasingly affecting rural communities, including those geographically close to the source population of this study [114, 115]. Treatment programs and public health responses to the opioid epidemic should incorporate HIV testing and linkage to care. Moreover as many rural communities may be especially vulnerable to new HIV and HCV infections in areas with high

rates of prescription opioid abuse and unsterile injection drug use, bundled interventions and services are needed to respond to the growing HIV, HCV and opioid epidemics [115-117].

Our study was limited by relying on medical record data for the patient's residence which was not geocodable for 29% of the study population, however, our findings were robust in analyses using multiple imputation for missing residence data. As in all observational studies we may have had residual confounding due to unmeasured variables that may have biased our results in either direction. Future studies could be improved by including data on structural, community, and socioeconomic factors that may be associated with rural residence and affect HIV care initiation. Referral bias may have affected our study results as we included only patients in care at a large tertiary care center, and it is possible that patients diagnosed with HIV infection in rural areas were preferentially referred to our center if they had more advanced HIV disease progression. We cannot exclude the possibility that this may have occurred although we did exclude patients who had received any HIV clinical care at another facility. Finally, patients with multiple risk factors for poor health and/or delaying care may be the most likely to not enter HIV clinical care at all, which could lead to an underestimate of rural residence on HIV care initiation in our study.

Strengths of our study include the use of a rigorous method for classifying patient residence. Additionally, we relied on a large well-characterized HIV clinical cohort for this study. Although this patient population includes patients accessing HIV care at a large tertiary care facility, we believe these patients represent the experience of HIV-infected individuals residing in rural areas in the Southeastern US. As has been observed by others, given the paucity of available health care in rural areas, especially specialty care, the vast majority of HIV-infected patients in rural areas receive care at major medical centers [75, 118]. Additionally, to the best of our knowledge this is one of the first studies to examine the effect of rural residence on differences in CD4 cell count at care initiation in the Southeastern U.S.

E. Conclusion

In our population, patients entered care with advanced HIV disease and rural residence was associated with later care initiation. CD4 cell counts in the study population increased over calendar time, and we observed an attenuation of the rural-urban difference in more recent calendar periods, deserving ongoing monitoring. Given the substantial effects on individual and public health of delays in HIV care and ART initiation, additional research, especially among rural HIV-infected populations, is indicated to identify factors of rurality that affect patient care access. Interventions that may increase earlier care entry such as counseling, video-conferencing, basic services provision, transportation assistance or mobile health units in rural areas warrant further investigation.

Table 4.1 Patient Characteristics at HIV Care Initiation, Stratified by Rural/Urban Residence, UCHCC 1996 to 2012

Characteristic*	All Patients (N=988)	Rural (N=342)	Urban (N=646)	P Value
Male sex, no. (%)	686 (69)	234 (68)	452 (70)	0.6
Age, yr				0.0001
Mean (SD)	37 (11.0)	38 (11.3)	36 (10.7)	
Race, no. (%)				0.009
White	256 (26)	84 (25)	172 (27)	
Black	593 (60)	194 (57)	399 (62)	
Other	139 (14)	64 (19)	75 (12)	
MSM, no. (%)	397 (40)	118 (35)	279 (43)	0.008
IDU, no. (%)	103 (10)	42 (12)	61 (9)	0.2
CD4 cell count, cells/ mm^3				0.01
Mean (SD)	351 (290)	320 (279)	368 (295)	
HIV RNA level, log10 copies/µL				0.8
Mean (SD)	4.54 (0.98)	4.55 (0.98)	4.54 (0.99)	
AIDS clinical condition, no. (%)	194 (20)	77 (23)	117 (18)	0.1
HCV, no. (%)	151 (15)	67 (20)	84 (13)	0.006
Insurance, no. (%)				0.002
None	487 (49)	162 (47)	325 (50)	
Private	248 (25)	71 (21)	177 (28)	
Public	253 (26)	109 (32)	144 (22)	
Distance to clinic one way, miles				<.0001
Mean (SD)	56 (38.4)	74 (35.7)	46 (36.0)	
Calendar year				0.0005
Mean (SD)	2003 (4.8)	2002 (4.7)	2003 (4.8)	

*All characteristics measured at UNC HIV care entry.
** 60% of Other race/ethnicity were Hispanic.
SD, Standard Deviation; MSM, men who have sex with men; IDU, injection drug use; HCV, Hepatitis C Virus co-infection.

Table 4.2 CD4 Cell Count Differences (cells/mm3) at HIV Care Initiation, UCHCC 1996 – 2012

	Mean CD4 Cell Count Difference (95%CI)	
Characteristic*	**Unadjusted**	**Adjusted***
Residence		
Rural	-48 (-86, -10)	-37 (-73, -2)
Urban	0	0
Sex		
Male	-90 (-129, -51)	-74 (-118, -31)
Female	0	0
Age, yrs		
≥40	-84 (-121, -47)	-56 (-91, -21)
18-39	0	0
Race**		
Black	-9 (-52, 34)	-46 (-85, -7)
Other	-50 (-108, 7)	-64 (-119, -9)
White	0	0
MSM		
No	-17 (-54, 20)	-50 (-93, -8)
Yes	0	0
IDU		
No	13 (-47, 72)	-47 (-112, 18)
Yes	0	0
HIV RNA level (log10 copies/µL)		
≥ 4.5	-251 (-284, -218)	-240 (-273, -207)
< 4.5	0	0
HCV		
Yes	-37 (-88, 13)	-3 (-58, 53)
No	0	0
Insurance		
Public	10 (-36, 55)	15 (-28, 58)
Private	-51 (-94, 8)	-29 (-70, 12)
None	0	0
Distance to clinic one way, miles		
<40	-18 (-56, 21)	-27 (-64, 10)
40-59	-37 (-93, 18)	-17 (-64, 30)
60+	0	0
Calendar year		
1996-2003	-62 (-106, -18)	-67 (-108, -22)
2004-2007	-25 (-81, 31)	-7 (-56, 42)
2008-2012	0	0

*All characteristics measured at HIV care initiation.
**60% of Other race/ethnicity were Hispanic.
***Adjusted analyses using multiple linear regression including all characteristics in the table. Variable parameterization for continuous variables was based on stratified analyses and model fit.
IQR, Interquartile Range; MSM, men who have sex with men; IDU, injection drug use; HCV, Hepatitis C Virus co-infection.
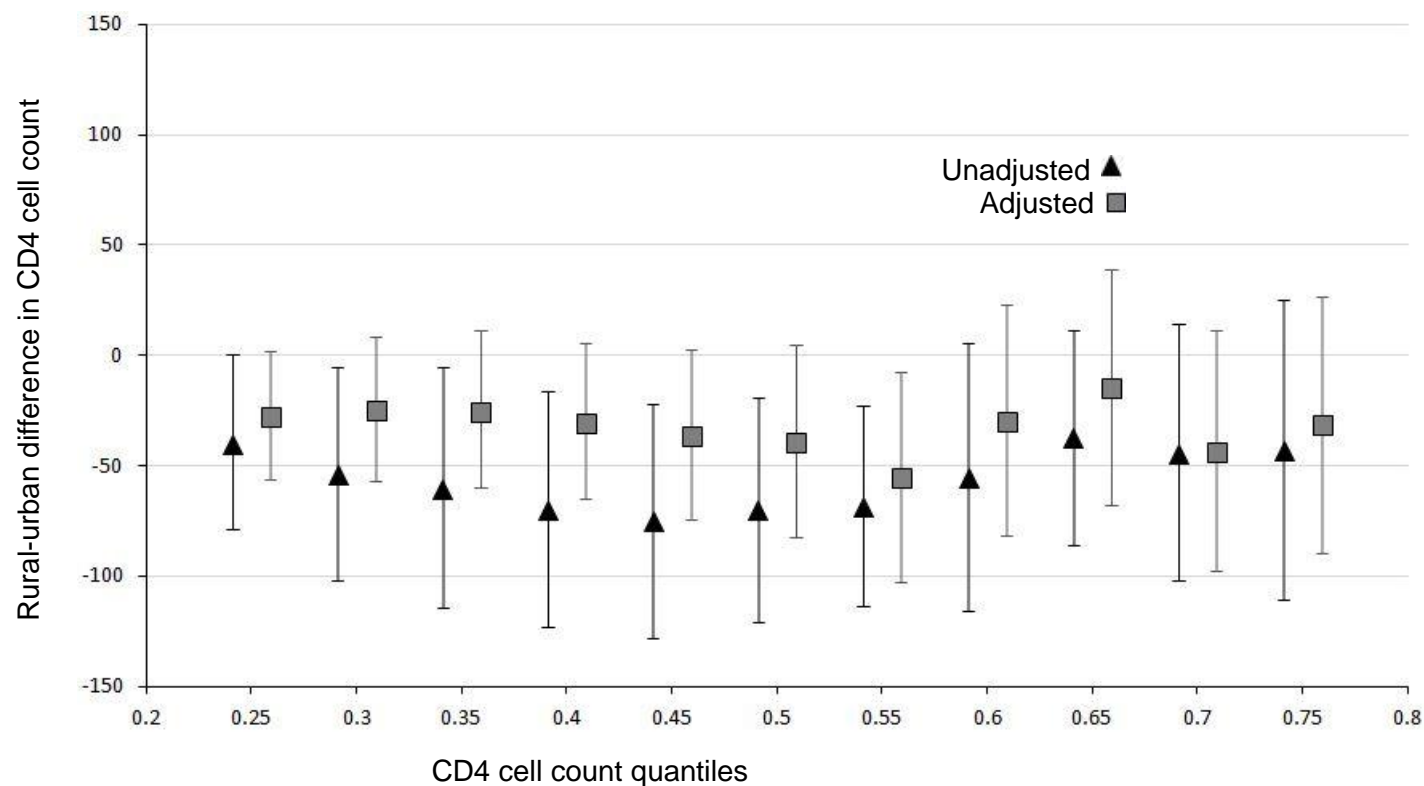
Figure 4.1 (Supplemental) Unadjusted and adjusted rural-urban differences in CD4 cell count at HIV care initiation across the CD4 distribution, UCHCC 1996-2012
Estimates are based on quantile regression, differences between the 25th and 75th percentile are presented at 5 percentile increments, and bars represent 95% confidence intervals. Multivariable quantile regression models were adjusted for sex, age, race, MSM, IDU, HIV RNA level, HCV co-infection, insurance, distance to clinic and calendar year of starting HIV care.

CHAPTER V. RESULTS: HIV CARE RETENTION AND SURVIVAL AMONG RURAL AND URBAN PATIENTS IN THE SOUTHEASTERN UNITED STATES, 1996 TO 2012

A. Introduction

Receiving adequate and uninterrupted HIV clinical care including antiretroviral therapy (ART) is associated with HIV RNA suppression, reductions in HIV associated morbidity and mortality, and decreased secondary HIV transmission [29, 32, 45, 82-84, 86, 119]. However, many patients miss HIV clinic visits [13-16], and 10-35% do not meet the Institute of Medicine's (IOM) core retention criteria [16-22]. Longitudinal studies indicate many patients experience long gaps during which no appointments are attended, and some may remain lost to clinical follow-up (LTFU) for years [23-26].

A number of patient characteristics may be associated with inadequate HIV care retention including male sex, younger age, non-White race/ethnicity, lack of private health insurance, socioeconomic status, sexual orientation, injection drug use (IDU), and CD4 cell count [14, 18, 120, 121]. Additionally, patients residing in rural areas may face greater barriers to HIV care receipt in part due to factors such as lower employment, income and education compared with patients from urban areas, and lack of health insurance [69, 122, 123]. Rural residents may also disproportionately experience limited or no access to local specialized HIV care, face increased time and financial resources needed to travel to clinic appointments and face greater stigma, privacy and anonymity concerns [67, 69, 123, 124].

Prior results conducted in the United States on the effect of living in a rural area on HIV care retention have been mixed. Two prior national studies observed lower levels of HIV care engagement among rural versus urban residents, using clinic attendance records and laboratory measures [75, 92]. A report relying on surveillance data observed limited differences in clinic

appointments by rural versus urban residence, with rural patients more likely to drop out of care [30]. A prior study by our group found comparable clinic visit attendance by residence, and greater long-term retention in HIV care among rural versus urban patients [24].

Given the central role of HIV care provision on patient clinical outcomes, and public health, and the limited information on the effects of geographic location on patients' engagement in HIV care and clinical outcomes, we undertook this present study to specifically address differences in HIV clinical care and mortality by rural versus urban residence. For this project, we relied on a large HIV clinical cohort located in the Southeastern US, the University of North Carolina (UNC) CFAR HIV Clinical Cohort (UCHCC). We assessed rural-urban differences in mortality and in HIV clinical care engagement using four distinct measures, including the incidence rate of missed clinic visits, the IOM indicator, LTFU, and death.

B. Methods

Study Design and Population

We included all UCHCC HIV-infected patients, ≥18 years old, who attended ≥1 HIV clinical care visit between 1996 and 2012, and had a first UNC HIV care visit before 2012 to allow for at least 1 year of follow-up. Baseline was defined as the latter of January 1, 1996 or the first UNC HIV clinical care visit. The UCHCC includes electronic institutional resources, medical record review and mortality data and has been previously described [27]. The UCHCC and our study were approved by the University of North Carolina at Chapel Hill's Institutional Review Board and patients provided informed consent to participate in the UCHCC.

Measures

We evaluated four outcomes: missed clinic visits, the IOM retention indicator, LTFU, and mortality. Walk-in, urgent care and emergency department visits were not considered HIV clinic visits, and visits that were canceled or rescheduled were not considered missed. The IOM retention measure for each 12 month care period was defined as attending ≥2 clinic visits, ≥90 days apart [53]. A patient's first 12-month care period began at baseline. A patient who died or

was LTFU was not included in calculating the IOM measure in the 12-month period when the death or LTFU event occurred, or any subsequent periods. LTFU was defined as not attending a visit in >365 days. Mortality analyses included deaths from any cause from baseline until administrative censoring (December 31, 2012).

We used the U.S. Department of Agriculture (USDA)'s Rural-Urban Commuting Area Codes (RUCAs), a vigorous 2000 census-tract classification using urbanized area/cluster definitions of core population size and work commuting data, to classify rural residence according to the patient's geocoded (using Arc-GIS) first reported home address. We started out by assigning residence based on four RUCA codes (urban, large rural, small rural, and isolated small rural); however, limited sample sizes in small and isolated small rural areas led us to use a different common algorithm for our analyses, (USDA's Categorization C, version 2) that dichotomizes residence as rural or urban [37]. We examined patient demographic and clinical characteristics that may affect HIV care retention and/or mortality including sex, age, race, being a man who has sex with men (MSM), CD4 cell count, AIDS-defining CDC category C clinical condition [95] diagnosed no later than 180 days after the first UNC HIV care visit, Hepatitis C coinfection (HCV), insurance, driving distance to the clinic, and calendar year of UNC care entry.

Statistical Analyses

The incidence rate of missed clinic visits was defined as the sum of all missed clinic visits divided by total person-time in care. Person-time was calculated as the time from baseline until the first of LTFU (last clinic visit plus 365 days), death or administrative censoring (December 31, 2012). The association between patient residence and the incidence rate (IR) of missed visits was estimated using Poisson regression. Log-binomial regression was used to estimate risk ratios (RR) for the association between rural residence and the risk of not being retained in care according to the IOM indicator. The IOM measure RRs were calculated for each 12-month period in care sequentially and combined across care years relying on repeat

measures analyses fit via generalized estimating equations. Time to death and LTFU were calculated separately as time from baseline until first of administrative censoring, death or event of interest (LTFU and death). Kaplan-Meier plots were fit separately for time to LTFU and survival time and separate multivariable Cox proportional hazards regression models were fit to estimate hazard ratios (HR) for LTFU and death.

For all analyses, multivariable adjusted models were fit to adjust for confounding by factors measured at baseline. For continuous variables we examined alternate parametization including flexible splines. We performed sensitivity analyses excluding patients who only attended a single visit and using a longer 18-month window without a clinical visit as a definition for LTFU. We conducted analyses excluding patients who received HIV clinical care prior to entering UNC care. We also conducted analyses restricted to more recent calendar years, focused on patients entering care between 2001-2012, to account for changes in HIV testing guidelines. Our primary analyses excluded patients without geo-codable addresses, and therefore we repeated primary analyses using multiple imputation to include patients lacking residence data. A multivariate normal model was used for multiple imputation to impute missing residence 50 times and we used Rubin's rule to combine imputations [81]. SAS version 9.3 (SAS Institute, Cary, NC, USA) was used for analyses with 2-sided hypothesis testing with an alpha level of 0.05.

C. Results

Overall 2,503 patients met our study inclusion criteria, and of these we excluded 698 (28%) from the primary analyses because of missing residence data. Patients with and without geocodable addresses were comparable on demographic and clinical characteristics, except clinical AIDS which was more common among those excluded (25% vs 22%, P<0.01) (**Appendix B**). In the final study population of 1805 patients, 70% were male with a median age of 38 years (interquartile range [IQR], 30-45) at start of follow-up (**Table 4.1**). Over one-half of patients were Black (61%), 28% were White and 11% were of other race (primarily Hispanic,

57%). At baseline the overall median CD4 cell count was 297 cells/mm^3 (IQR, 91-500), median log$_{10}$ HIV RNA level was 4.5 (IQR, 3.6-5.2), and 22% were diagnosed with clinical AIDS.

Approximately one-third of patients resided in a rural area (n=611, 34%). In general, rural in comparison to urban patients were older, less likely to be white or MSM, and less likely to have private but more likely to have public health insurance (all P<0.05) (**Table 4.1**). Rural patients faced greater travel distances to clinic than urban patients (median one-way distance of 68 versus 40 miles), and had lower CD4 cell counts at beginning of follow-up (median 249 versus 319 cells/mm^3), (both P<0.05).

A total of 10,387 person-years of follow-up were observed; 3,816 and 6,571 person-years among rural and urban patients, respectively. Rural patients were followed for a median of 5 years (IQR, 2, 10) versus 4 years (IQR, 2, 8) for urban patients. Overall 20,530 and 11,722 clinic visits were observed, with a median of 13 visits (IQR, 6-28) and 12 visits (IQR, 4-25), among rural versus urban residents, respectively. The incidence rate of attended visits was 3.07 (95%CI 3.02, 3.13) and 3.12 (95%CI 3.08, 3.17) per 1 person-year, for rural versus urban patients, respectively (P=0.21).

Across follow-up, 36%, 20%, 12%, 18%, 11% and 3% of patients missed 0, 1, 2, 3-5, 6-10 and >10 visits, respectively. The incidence rate of missed clinic visits overall was 0.42 missed visits per 1 person-year (95%CI 0.41, 0.44), and comparable among rural versus urban residents [0.43 (95% CI, 0.41, 0.45); 0.42 (95% CI, 0.40, 0.43)]; respectively, P=0.20]. The unadjusted incidence rate ratio (IRR) of missed visits comparing rural to urban patients was 1.03 (95%CI 0.97, 1.10). After adjusting for demographic and clinical factors, the IRR of missed visits increased to 1.06 (95%CI 0.99, 1.14) (**Table 4.2**). In multivariable analyses a number of factors were associated with an increase in missed clinical visits, including shorter driving distance to the clinic, younger age, male sex, non-white race, not being MSM, not having private health insurance, no prior clinical AIDS diagnosis and having started care in later calendar years.

Overall, averaged across follow-up and care years, 18% did not meet IOM criteria in a given year, comparable by rural and urban residence (18% and 20%, respectively). At 1, 2, 5 and 10 years of follow-up, 19%, 22%, 25% and 20% of rural, and 21%, 26%, 23% and 20% urban patients did not meet IOM criteria. The risk ratios (RRs) for not being retained by the IOM indicator, comparing rural and urban patients were 0.93 (95%CI, 0.83, 1.05) unadjusted, and 0.90 (95%CI, 0.78, 1.02) adjusted (**Table 4.2**). In adjusted analyses, factors associated with not meeting IOM criteria included younger age, being male, not being MSM, not having health insurance, not having a clinical AIDS diagnosis and earlier calendar years of care entry.

During follow-up, 806 (45%) patients were LTFU (>365 days without a clinic visit), 350 (19%) died, and 649 (36%) were administratively censored. Rural in comparison to urban patients were less likely to be LTFU (log rank P<0.001) (**Figure 4.1 Panel A**). The HR for LTFU comparing rural to urban patients was 0.78 (95%CI 0.67, 0.90) unadjusted, and 0.59 (95%CI 0.50, 0.71) adjusted (**Table 4.3**). Patient characteristics including living closer to clinic, older age, female sex, having private insurance, being MSM and initiating HIV care in more recent calendar years were associated with longer time to LTFU in adjusted analyses.

The crude mortality rate was 33.7 deaths per 1000 person-years overall, 40.1 and 30.1 deaths per 1000 person-years, among rural and urban residents, respectively. Rural in comparison to urban patients had shorter survival times in Kaplan-Meier analyses (log rank P=0.0002) (**Figure 4.1**), and unadjusted Cox proportional hazards estimates (HR=1.48, 95%CI 1.20, 1.83). No difference in mortality by rural-urban residence was observed in fully adjusted analyses, (HR=1.11, 95%CI 0.87, 1.40) (**Table 4.3**). A number of factors were associated with mortality in the adjusted model including longer distance to care, older age, male sex, Black race, public insurance, and a CD4 cell count <200 cells/mm^3.

Given the notable association between distance to clinic and rural-urban residence we further assessed the effect of distance to care. Living further from care increased LTFU and mortality in unadjusted and adjusted analyses (**Table 4.3**). Removing distance to HIV care from

the otherwise fully adjusted model estimating the effect of rural-urban residence on mortality, the HR increased from 1.11 (95%CI, 0.87, 1.40) to 1.29 (95%CI, 1.04, 1.60). In comparison, the rural-urban difference in LTFU was smaller after removing distance to HIV care from the otherwise fully adjusted model, with the HR decreasing from 0.59 (95%CI, 0.50, 0.71) to 0.74 (95%CI, 0.63, 0.87). When not adjusted for distance to HIV care, small differences were also observed in multivariable models for missed visits where there was a change from IRR=1.06 (95%CI 0.99, 1.14) to IRR=1.02 (95%CI 0.96, 1.09) and for not meeting IOM retention, where there was a change from RR=0.90 (95%CI, 0.78, 1.02) to RR=0.94 (95%CI, 0.83, 1.06).

Separate sensitivity analyses, excluding 76 patients with only one HIV clinic appointment and using 18 months as a definition of LTFU, did not affect our primary findings (**Appendix B**). Our findings were also reasonably consistent in subgroup analyses including only 957 patients who were observed to newly initiate HIV care during follow-up; missed visits (IRR adjusted=1.20, 95%CI 1.09, 1.31); IOM retention indicator (RR adjusted=0.96, 95%CI 0.80, 1.15); LTFU (HR adjusted=0.66, 95%CI 0.52, 0.85) and mortality (HR adjusted=1.40, 95%CI 1.00, 1.96) (**Appendix B**). Similarly, our sensitivity analysis results when restricting the population to patients who began care in 2001 or later, showed results in line with our primary analyses: missed visits (IRR adjusted 1.12, 95%CI 1.02, 1.22); IOM retention indicator (RR adjusted 0.85, 95%CI 0.70, 1.02); LTFU (HR adjusted=0.64, 95%CI 0.51, 0.81) and mortality (HR adjusted=0.96, 95%CI 0.65, 1.41) (**Appendix B**). However, the sensitivity analysis results for the risk of missed visits do indicate that there may be a rural-urban effect depending on prior clinical care and calendar year.

Our primary results were also consistent in analyses including patients with missing residence information using multiple imputation; missed visits (IRR adjusted= 1.06, 95%CI 0.99, 1.14); IOM retention indicator (RR adjusted=0.93, 95%CI 0.82, 1.06); LTFU (HR adjusted= 0.59, 95%CI 0.50, 0.71) and mortality (HR adjusted= 1.12, 95%CI 0.89, 1.42) (**Appendix B**).

D. Discussion

A large proportion of our population of HIV-infected patients in the Southeastern U.S. lived in rural areas, which affected HIV care retention and mortality, although with differing results. Our primary findings suggest living in a rural area does not increase risk of missing clinical appointments or retention in care measured by the IOM indicator. On the other hand, rural patients were less likely to be LTFU than those residing in urban areas. The effect of residence on missed visits may depend on prior clinical care and calendar year of care. The effect of rural residence on mortality was confounded by travel distance to clinic. In analyses adjusted for demographic and clinical factors but not adjusted for distance to care, rural patients were at greater risk of death than urban patients, however, after adjusting for distance to care this association was attenuated.

A large body of research is emerging on the HIV care cascade in the United States, and elsewhere [125]. An important finding is the possibility of obtaining differing results based on which retention measure is examined and/or finding different effects when examining core and clinical retention measures in combination [16]. In our study missed visits were reasonably common and consistent with prior work from national cohort collaborations [16], intervention studies [15], and results from Alabama [13], and California [14]. Our observed retention rates based on the IOM indicator and our LTFU findings were also comparable to recent results from national cohort collaborations [16-18, 23, 24].

To date little work has focused specifically on the effect of residing in rural communities on HIV clinical care access and engagement. Our prior work shows patients from rural areas initiate HIV care at lower CD4 cell counts than patients from urban areas [77]. In this study our primary analyses showed rural residence affected LTFU, but not missed visits or retention in care based on IOM criteria. However, we did find that rural residence affected missed visits in a analyses of patients without prior clinical care and among patients initiating care in more recent calendar years. To our knowledge, no other studies have examined the effect of residence on

missed visits and LTFU. Our IOM measure results are consistent with some [126], but not all [127], prior results, possibly due to differences in rural-urban classification and length of follow-up.

As observed by others, younger patients were more likely to miss clinic appointments, not meet the IOM retention measure and be LTFU [29]. Not having health insurance was also associated with all three HIV care retention measures we considered, as in prior work [29]. Prior research suggests patients with higher CD4 cell counts and without a clinical AIDS condition may be less likely to be retained in HIV care [24-26, 127]. In our study, having an AIDS defining clinical condition at start of follow-up was associated with a greater likelihood of not missing clinical appointments and meeting the IOM retention indicator; however lower CD4 cell counts were not consistently associated with HIV care retention. Notably, meeting the IOM retention measure and remaining in longitudinal HIV care improved among patients initiating HIV care in more recent calendar years, although the risk of missing clinical visits increased.

Our estimated crude mortality rate of 33.7 deaths per 1000 person-years is higher than reported by other studies [82, 128] , likely because we included all patients in care from 1996 through 2012, including patients who may have initiated HIV care many years before 1996. In line with previous studies, we noted higher mortality among older patients [28, 129-131], males [129, 130], Blacks [82, 129], non-MSM [82, 129, 131], patients on public insurance, with HCV infection [28], and with the lowest CD4 cell counts [28, 82, 130].

Higher mortality rates among rural in comparison to urban patients has been observed in other studies of HIV-infected patients, and patients with other clinical conditions, with at least one study suggesting that mortality increases with increasing levels of rurality [36, 78, 132, 133]. Others have also observed the substantial effect on rural-urban mortality differences by distance to clinical care.[99]

Our study has limitations. Our generalizability may be limited by including only patients from one institution in the Southeastern U.S. Additionally, patients at greatest risk of poor HIV

clinical outcomes may not enter HIV outpatient clinical care at all, and we did not include these patients. We were also unable to ascertain whether patients who were LTFU transferred HIV care to another facility. We only considered a number of factors measured at baseline, including CD4 cell counts and clinical conditions, and further work using time-updated measures is indicated. Additional work specifically assessing changes in HIV care retention and mortality across calendar years is warranted.

Our study strengths include use of a large HIV clinical cohort, situated in the Southeastern U.S., capturing a large number of patients in clinical care over many years. We used a rigorous method to evaluate patient residence and fit models with multiple imputation to account for patients missing residence data. To the best of our knowledge, our study is the first to examine differences in retention by rural residence using a variety of retention measures, which is important since different retention measures may not be in agreement regarding whether a patient is "retained", may reflect different barriers to care, and may be associated with different patient characteristics and/or outcomes [16, 61].

E. Conclusion

In summary, using data from a large clinical cohort in the Southeastern U.S., with existing rural-urban health disparities [134], our results suggest patients residing in rural areas may be less likely to drop out of HIV care and equally likely to miss clinical appointments and to be retained in HIV clinical care when compared with patients from urban areas. Patients from rural areas may be at greater risk of mortality than patients from urban areas, but this may depend on how far patients reside from HIV clinical care. Our findings lend further support for the use of a variety of retention measures as these may measure different phenomena. Further work identifying unique aspects of rurality that affect patient retention and survival are needed, including those focusing on factors such as poverty, employment, disparities, stigma, confidentiality, substance abuse, addiction, mental health services, family obligations, childcare, transportation, and distance to care.
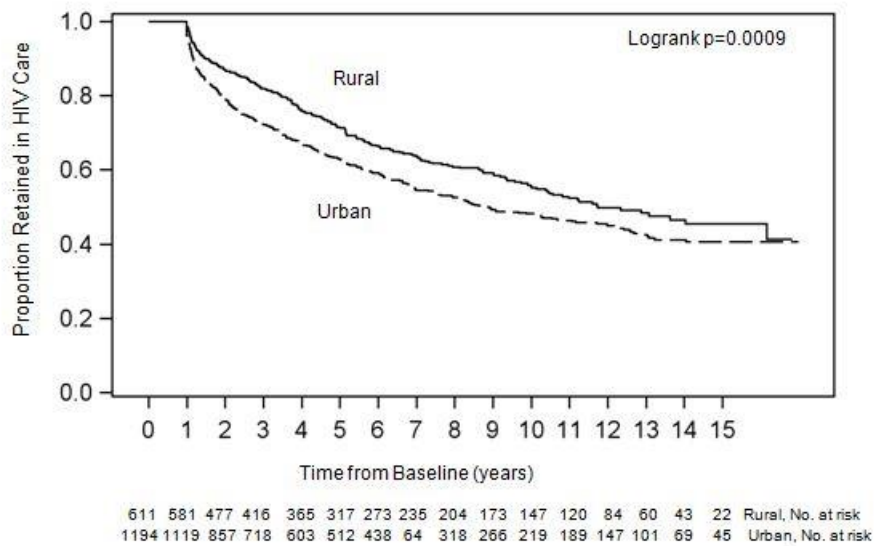
Panel A
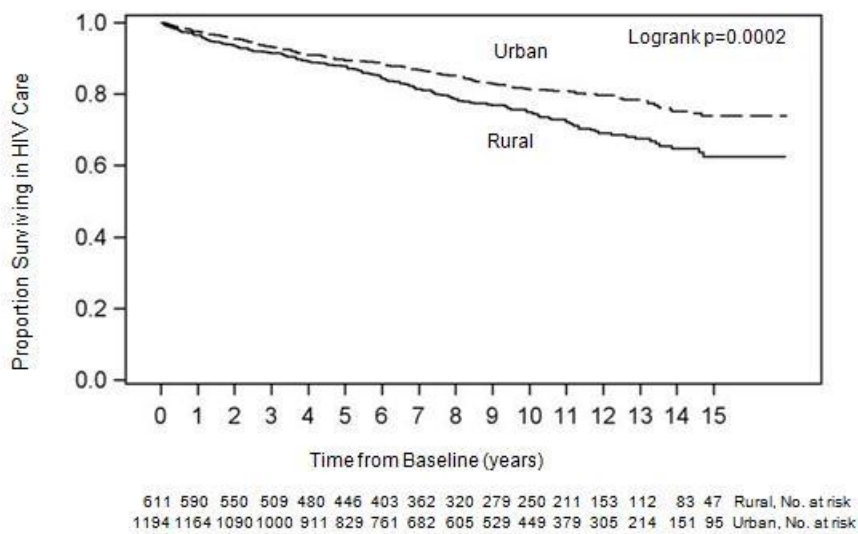
Panel B

Figure 5.1 Primary End Points
Shown are unadjusted Kaplan-Meier estimates of time to loss to follow-up (Panel A), and survival time (Panel B), by rural-urban residence.

Table 5.1 Patient Characteristics Stratified by Rural-Urban Residence, UCHCC 1996 to 2012

Characteristic*	All Patients (N=1805)	Rural (N=611)	Urban (N=1194)	P Value
Male sex, no. (%)	1268 (70)	412 (67)	856 (72)	0.06
Age, yr				
Median (IQR)	38 (30-45)	38 (31-47)	37 (29-44)	0.03
Race,** no. (%)				<0.01
White	504 (28)	156 (26)	348 (29)	
Black	1097 (61)	366 (60)	731 (61)	
Other	204 (11)	89 (15)	115 (10)	
MSM,*** no. (%)	711 (56)	198 (48)	513 (60)	<0.01
CD4 cell count,**** cells/ mm^3				
Median (IQR)	297 (91-500)	249 (80-458)	319 (101-515)	<0.01
AIDS clinical condition, no. (%)	397 (22)	158 (26)	239 (20)	<0.01
HCV, no. (%)	234 (13)	83 (14)	151 (13)	0.63
Insurance, no. (%)				<0.01
None	839 (46)	283 (46)	556 (47)	
Private	444 (25)	115 (19)	329 (28)	
Public	522 (29)	213 (35)	309 (26)	
Distance to UNC clinic one way, miles				
Median (IQR)	50 (30-78)	68 (53-89)	40 (25-66)	<0.01
Calendar year, UNC care entry				
Median (IQR)	2002 (99-07)	2002 (99-06)	2003 (00-07)	<0.01

*All characteristics measured at baseline.
**57% of Other race/ethnicity were Hispanic.
***MSM among men only.
**** 11 urban patients and 3 rural patients missing data on CD4 cell count.
IQR, Interquartile Range; MSM, men who have sex with men; HCV, Hepatitis C Virus co-infection.

Table 5.2 Unadjusted and Adjusted Incidence Rate Ratios for Missed Clinic Visits and Risk Ratios for Not-Retained in Care by the IOM Indicator, UCHCC 1996-2012

Characteristic*	Missed Visits IRR (95% CI)**		Not Retained in Care- IOM Measure RR (95% CI)***	
	Unadjusted	Adjusted**	Unadjusted	Adjusted**
Residence				
Rural	1.03 (0.97, 1.10)	1.06 (0.99, 1.14)	0.93 (0.83, 1.05)	0.90 (0.78, 1.02)
Urban (ref)	1	1	1	1
Driving distance to clinic one way, miles				
<40 miles	0.96 (0.90, 1.03)	1.09 (1.01, 1.18)	1.02 (0.88, 1.18)	0.87 (0.76, 1.00)
40-60 miles	1.01 (0.93, 1.10)	1.11 (1.03, 1.21)	0.89 (0.76, 1.04)	0.98 (0.84, 1.15)
>60 miles (ref)	1	1	1	1
Age, yr				
18-39	1.28 (1.20, 1.36)	1.33 (1.24, 1.42)	1.35 (1.20, 1.52)	1.33 (1.17, 1.50)
40+ (ref)	1	1	1	1
Sex				
Male	0.92 (0.86, 0.98)	1.09 (1.01, 1.18)	1.00 (0.89, 1.13)	1.22 (1.05, 1.41)
Female (ref)	1	1	1	1
Race				
White (ref)	1	1	1	1
Black	1.56 (1.45, 1.68)	1.43 (1.32, 1.54)	1.22 (1.07, 1.39)	1.12 (0.98, 1.28)
Other	1.40 (1.25, 1.56)	1.24 (1.10, 1.39)	1.01 (0.82, 1.25)	0.98 (0.80, 1.22)
Insurance				
None	1.44 (1.33, 1.55)	1.27 (1.17, 1.37)	1.15 (1.00, 1.32)	1.18 (1.02, 1.37)
Public	1.46 (1.35, 1.58)	1.30 (1.20, 1.42)	1.15 (0.99, 1.33)	1.07 (0.92, 1.25)
Private (ref)	1	1	1	1
MSM				
Yes (ref)	1	1	1	1
No	1.23 (1.15, 1.31)	1.20 (1.11, 1.30)	1.17 (1.04, 1.31)	1.26 (1.09, 1.47)
HCV				
Yes	1.15 (1.06, 1.25)	1.15 (1.05, 1.25)	1.08 (0.92, 1.26)	1.05 (0.89, 1.24)
No (ref)	1	1	1	1
CD4 count (cells/mm^3)				
<200 (ref)	1	1	1	1
200-349	1.12 (1.03, 1.21)	1.09 (1.00, 1.19)	1.05 (0.92, 1.20)	1.14 (0.98, 1.34)
350-500	1.04 (0.96, 1.14)	0.99 (0.90, 1.09)	1.21 (1.06, 1.39)	1.26 (1.07, 1.49)
>500	1.14 (1.05, 1.22)	1.05 (0.97, 1.14)	1.13 (0.99, 1.28)	1.17 (1.00, 1.37)
AIDS clinical condition				
Yes (ref)	1	1	1	1
No	1.21 (1.12, 1.31)	1.12 (1.03, 1.23)	1.48 (1.25, 1.76)	1.28 (1.07, 1.53)
Yr of care entry				
1996-2003	0.73 (0.65, 0.83)	0.75 (0.67, 0.85)	1.51 (1.26, 1.81)	1.58 (1.31, 1.91)
2004-2007	0.70 (0.63, 0.77)	0.68 (0.61, 0.75)	1.38 (1.12, 1.69)	1.43 (1.17, 1.75)
2008-2012 (ref)	1	1	1	1

*All characteristics measured at baseline.

MSM, men who have sex with men; HCV, Hepatitis C Virus co-infection.

**Incidence rate ratios (IRR) for the association between patient residence and missed visits were estimated using Poisson regression.

***Risk ratios (RR) for the association between rural residence and the risk of not being retained in care according to the IOM indicator, with repeat measures, was fit with log-binomial regression and generalized estimating equations. The fully adjusted results for each outcome did not differ appreciably from a partially adjusted model.

Table 5.3 Unadjusted and Adjusted Hazard Ratios from Cox Regression Models for Loss to Follow-up and Mortality, UCHCC 1996-2012**

Characteristic*	Loss to Follow-up HR (95% CI)		Mortality HR (95% CI)	
	Unadjusted	Adjusted**	Unadjusted	Adjusted
Residence				
Rural	0.78 (0.67,0.90)	0.59 (0.50,0.71)	1.48 (1.20, 1.83)	1.11 (0.87, 1.40)
Urban (ref)	1	1	1	1
Driving distance to clinic one way, miles				
<40 miles	0.73 (0.63, 0.85)	0.61 (0.51, 0.72)	0.58 (0.45, 0.74)	0.68 (0.52, 0.89)
40-60 miles	0.65 (0.54, 0.79)	0.53 (0.43, 0.65)	0.76 (0.58, 1.00)	0.75 (0.56, 1.01)
>60 miles (ref)	1	1	1	1
Age, yr				
18-39	1.29 (1.11, 1.50)	1.29 (1.09, 1.52)	0.52 (0.42, 0.64)	0.63 (0.50, 0.79)
40+ (ref)	1	1	1	1
Sex				
Male	1.06 (0.90, 1.23)	1.29 (1.07, 1.56)	1.29 (1.02, 1.64)	1.52 (1.17, 1.98)
Female (ref)	1	1	1	1
Race				
White (ref)	1	1	1	1
Black	1.12 (0.96, 1.32)	0.96 (0.81, 1.15)	1.49 (1.15, 1.92)	1.31 (1.00, 1.71)
Other	1.04 (0.81, 1.34)	1.15 (0.88, 1.50)	0.64 (0.39, 1.06)	0.66 (0.40, 1.10)
Insurance				
None	1.36 (1.13, 1.62)	1.49 (1.23, 1.80)	1.12 (0.84, 1.50)	1.19 (0.88, 1.61)
Public	1.35 (1.12, 1.63)	1.34 (1.09, 1.65)	1.87 (1.42, 2.46)	1.61 (1.21, 2.15)
Private (ref)	1	1	1	1
MSM				
Yes (ref)	1	1	1	1
No	1.18 (1.02, 1.36)	1.32 (1.09, 1.59)	1.46 (1.16, 1.85)	1.26 (0.96, 1.65)
HCV				
Yes	1.18 (0.97, 1.43)	1.16 (0.94, 1.44)	1.72 (1.33, 2.22)	1.19 (0.90, 1.56)
No (ref)	1	1	1	1
CD4 count (cells/mm^3)				
<200 (ref)	1	1	1	1
200-349	1.10 (0.89, 1.35)	0.97 (0.77, 1.20)	0.54 (0.40, 0.73)	0.59 (0.43, 0.80)
350-500	1.27 (1.04, 1.56)	1.16 (0.93, 1.44)	0.38 (0.27, 0.54)	0.46 (0.32, 0.67)
>500	1.30 (1.08, 1.56)	1.19 (0.97, 1.45)	0.35 (0.26, 0.48)	0.42 (0.30, 0.58)
AIDS clinical condition				
Yes (ref)	1	1	1	1
No	1.15 (0.96, 1.37)	0.85 (0.68, 1.07)	0.53 (0.42, 0.67)	0.81 (0.62, 1.05)
Yr of care entry				
1996-2003	1.43 (1.03, 1.99)	1.79 (1.25, 2.59)	1.38 (0.70, 2.74)	1.27 (0.64, 2.53)
2004-2007	1.58 (1.17, 2.12)	2.06 (1.47, 2.90)	2.16 (1.17, 3.99)	1.74 (0.93, 3.26)
2008-2012 (ref)	1	1	1	1

*All characteristics measured at baseline.
MSM, men who have sex with men; HCV, Hepatitis C Virus co-infection.
**LTFU was defined as not attending a visit in >365 days.
Multivariable Cox proportional hazards regression models were separately fit to estimate hazard ratios (HR) for LTFU and death.
The fully adjusted results for each outcome did not differ appreciably from a partially adjusted model.

CHAPTER VI. DISCUSSION

A. Summary of Findings

This first, to our knowledge, comprehensive clinical cohort study of the effect of rural residence on HIV clinical care initiation and retention in the Southern U.S., has led to a number of notable findings. Our clinical cohort study population included more than one-third of patients coming from rural areas and more than half of patients traveling 50 miles or more one-way to reach the HIV clinic. Of concern, in our study less than a quarter of patients presented to HIV care with a CD4 cell count >500 cells/mm^3 and we noted only a moderate increase in CD4 cell count at care initiation over calendar time. Also of concern, our patients had substantial difficulties in maintaining clinical care retention with 64% of patients missing at least one clinic visit, 18% of our patients not meeting the IOM criteria in a given year, and 45% of patients dropping out of care at least once.

Among close to 1,000 patients newly initiating HIV clinical care at UNC, we observed a rural-urban difference in CD4 cell count at HIV clinical care initiation with patients residing in rural areas more likely to enter care at lower CD4 cell counts. When we included patients with prior HIV clinical care for study aims 2-5, among our 1,805 patients contributing more than 10,000 person-years of observation, we noted comparable rural-urban results for missed visits and the IOM retention indicator while noting patients from rural areas were less likely to drop out of care when compared with patients from urban areas. It is possible that, once rural residents make the large commitment to begin HIV clinical care despite the typically long travel distance to the clinic, that they are more committed to not dropping out of care than their urban counterparts even though they are still affected by circumstances that lead to individual missed visits to a similar extent as patients from urban areas. It is also possible that patients whom we

are classifying as dropping out of HIV clinical care could include patients actually moving to a new area and continuing HIV clinical care at a different clinic. The likelihood of moving long distances or even out-of-state could differ by initial rural-urban residence and could be associated with the LTFU results we have noted.

We noted a high overall crude mortality rate among our patients of 33.7 deaths per 1000 person-years of study observation between 1996-2012. This crude mortality rate differed for patients from rural versus urban areas (40.1 versus 30.1 deaths per 1000 person-years, respectively). Although survival time was comparable between patients from rural and urban areas in our fully adjusted Cox proportional hazards model, we noted an increased risk of mortality for patients from rural areas when driving distance to the clinic was not adjusted for. This mortality finding that was mitigated by driving distance makes sense as rural residence and longer driving distances to care are strongly associated.

We noted associations with calendar time in our study. There was a greater rural-urban difference in CD4 cell count at care initiation in earlier calendar years (1996-2003) compared with more recent years (2008-2012). Interestingly, we noted that missed visits were less likely in earlier calendar years compared with more recent calendar years while the risk of not being retained in care according to the IOM indicator, LTFU, and mortality all decreased in more recent calendar years (2008-2012).

Overall, these results support the need for future studies to identify which unique factors of rurality are affecting HIV care initiation, retention, and survival. These results also show the importance of examining a variety of HIV care retention measures.

B. Impact and Significance

This study addressed a gap in our knowledge about HIV care barriers by classifying patients by rurality of their area of residence and examining the effects of area of residence on steps in the HIV care cascade. Our findings suggest that one or more aspects of rural residence negatively affect patients' ability to navigate HIV clinical care resources. Additionally, our results

identified that patients from rural residences initiate HIV clinical care at lower CD4 cell counts than patients from urban residences. In addition, we identified a higher mortality risk, depending on driving distance, among HIV-infected patients residing in rural areas even after successfully linking to HIV care. We were unable to assess specific aspects of rural residence that may reduce or inhibit patient initiation and engagement in HIV clinical care; however, our findings clearly indicate that this area of research would offer additional insights into disparities observed in both clinical and public health outcomes.

In addition to providing evidence to support further work evaluating specific aspects of rural residence associated with HIV clinical care initiation, engagement and mortality, this study also further contributes to a discussion about geographic variability in HIV outcomes. If geographic variability, including rurality, is observed to impact HIV outcomes then interventions can be directly focused to address identified vulnerabilities. For example, interventions may include targeted provision of basic services, remote telephone or Internet-based care, use of peer mentors, case management systems, and use of mobile health units deployed to rural areas.   Interventions for HIV-infected patients in rural areas may also be linked to HCV prevention and treatment interventions in rural areas.

C. Strengths

Our study had several strengths. First, we relied on a large well-characterized HIV clinical cohort in the U.S. South that is likely generalizable overall to patients receiving HIV clinical care in the U.S. South and likely generalizable to all HIV patients in care in NC. Cohort data were checked for completeness, plausibility and consistency, and medical chart abstractions were standardized. Data came from the patients' medical records so all patients who obtained HIV clinical care were included. In North Carolina, it is extremely unlikely for HIV patients to have access to local HIV clinical care in rural areas, which means our study likely accurately captured the experience of rural HIV patients. We also used a rigorous method for classifying patient residence and used multiple imputation to account for patients with missing

residence data.   Our study covered many years of observation and more than 10,000 person-years of person-time. Our analytic approach was also rigorous as we relied on multiple approaches and variables to assess delays in HIV care initiation and ongoing clinical care retention.

D. Limitations

Our study also has limitations. First, we relied on data from an observational cohort, and there may be bias from unmeasured confounding. We were unable to assess other factors that may differ in rural versus urban areas and affect HIV clinical care access, such as socioeconomic status, education, type of employment, marital status, presence of minor children in the family and behavioral factors. A substantial limitation was our inability to identify what specific factors about living in a rural environment are meaningful to how patients initiate and access HIV clinical care and mortality. A number of studies have suggested factors such as stigma, stress and coping, religious values, and family ties may be differentially present in rural versus urban areas and possibly affect medical care [74, 124, 135].

Our study results may not be generalizable to HIV-infected persons in all areas of the U.S. or other urban/rural areas of the country. Notably only patients who accessed care at UNC were included, and individuals who do not access HIV care at all were not represented.

There are limitations to using census-based data such as RUCA codes. Most census data are only updated every 10 years so there is the potential for misclassification if neighborhood characteristics change greatly during this time frame. We are assuming that the rurality of the census tract that the RUCA codes are based on did not change between 1996 (the first year our study included) and 2012. Even if a patient does not move, the rurality of the patient's census tract may have changed over the course of the years of the study. In addition, the same year (2000 decennial census) of RUCA data was used for all patients regardless of when patients were in care.

The validity of using census tract-based data depends on the extent to which census tracts make up meaningful geographical units and to what extent all people within the geographical unit experience the same or similar conditions. Census tracts are frequently used as a proxy for whether or not residents are likely to face similar social, economic and structural circumstances, however, a census tract may be larger or smaller than a typical neighborhood and circumstances may vary by neighborhood. The boundaries of census tracts are often not well suited to health research as census tracts were developed for political purposes. Census units often have boundaries based on roads, streams, etc. rather than based on land use. Cultural limits that reflect how people actually perceive social interaction boundaries are not accounted for in census boundaries. In rural areas, census tracts are usually small and development in rural areas is clustered and discontinuous [136]. As a result, highly irregular units of census geography are often produced due to large areas of undeveloped land [137] and census geographic units tend to underestimate residential density in more rural areas due to this inclusion of undeveloped land areas [136]. Finally, a lack of variation in health outcomes based on place of residence may not reflect a lack of an actual effect, instead it may reflect lack of sufficient variation in area-level exposures within the population studied [138]. Census units are known to underestimate residential density in rural areas [136] and the strength of and the mechanism of an observed epidemiological association may vary by level of aggregation (e.g. census tract, census block, counties) [138].

Even though we used multiple imputation to include patients with missing residence data, there are limitations related to geocoding an address and measuring residential address at a single time point. A patient may be in HIV care for decades and it is possible for a patient to move repeatedly during their HIV care. We classified patients based only on their address at time of entry into UNC clinical care, and not necessarily the address where they lived most of their life or the address they were at immediately before initiating HIV care. This implies a focus on a short lag time between the rurality exposure and our study outcomes, despite the fact that

the actual lag time may be considerably longer. Life events, including HIV health problems or risk factors, could cause people to move. People who move to other neighborhoods may do so because the new neighborhood is more supportive and more in line with their cultural values [139]. For example, it has been noted that some urban residents returned home to rural areas after an HIV diagnosis probably due to support provided by family members [140, 141], such patients would be classified as rural in our study despite having recently come from an urban residence. Moves among HIV-infected persons may not be more likely to occur in one direction than another, as other research noted that urban to rural migration is similar to rural to urban migration among a national sample of HIV-infected adults in the U.S. [142]. In addition, where someone works or spends their free time may influence the contextual influences they are exposed to but we did not have data on work or other addresses.

Another potential limitation in our study is lack of active follow-up for patients who drop out of care, which may lead to misclassification. According to our study definition, a patient may be considered LTFU even if the patient remains in (non-UNC) HIV care, for example if a patient moves away from NC or temporarily is not in NC due to travel and decides to attend a different clinic.

In addition, although our method for calculating the incidence of missed visits has many advantages, patients who do not schedule adequate or any follow-up visits may have a misleadingly low number of missed visits [49]. Also no data were available on why a patient missed or cancelled an appointment.

E. Future Directions

Further research may contribute to our understanding of the association between residence and HIV care initiation, retention and survival. In future prospective studies, data could be collected on previous and current places of patient residence, length of time at each residence, and work address, if applicable. Accurate and up-to-date residence data are especially important given that a person's HIV status, decision to initiate care, and ongoing

health may affect moving. Approximately 10-12% of the U.S. population moves each year [143, 144]. Moving is likely not equal for all HIV patients. A census survey [143] noted that a greater proportion of people of minority race/ethnicity versus non-Hispanic Whites and a greater proportion of renters versus homeowners move. Furthermore, a study of urban African Americans noted that recent HIV testing was associated with a change in residence [145]. Longer distance moves are also important to collect data on as it has been reported that patients with foreign family connections, who may be higher risk minority patients, are more likely to travel away from their area of primary care [146].

Additionally, in order to better understand barriers faced by patients who have late entry to care and/or poor retention in care, it would be useful to collect data on the specific reasons for delays in care entry, missed visits, cancelled visits and LTFU events. In addition, active follow-up of patients lost to care would provide information on whether these patients are truly out of care versus transferred to a different HIV clinic.

Further insights could be gained by including data on structural, community, and socioeconomic factors such as variables that reflect education, income, type of employment, other health conditions, concerns about stigma and privacy, marital status, and family obligations such as minor children to care for. Data could also be collected on how patients specifically travel to the HIV clinic including type of travel (e.g. on their own or dependent on others), average travel time, cost and other reported travel barriers.

Future studies may provide additional insights into rural-urban differences in HIV care access, retention and outcomes by including the effects of time-varying covariates when studying care retention such as longitudinal CD4 cell counts, HIV RNA levels, AIDS diagnoses, and age. Other measures of HIV care receipt may be studied that we were unable to include in this work, including specifically assessing long-term gaps in HIV care access. We did not directly assess whether rural residence affects HIV diagnosis timing which may further shed light on effects of rural residence on HIV care initiation. As our sensitivity analyses showed an

effect of rural residence on missed visits among patients without prior clinical care and among patients who initiated HIV clinical care in 2001 or later, further research studying the risk of missed visits in these populations and others is warranted. Given our findings of attenuation of the rural-urban mortality difference by distance to clinical care, it may be especially fruitful to further study how rural-urban residence and travel time to clinic interact to affect HIV care provision. Since our study included patients who had initiated HIV care at a large tertiary care facility in the Southeastern U.S., expanding to other populations may be indicated, including to patients who have unstable housing and move frequently, and those living in other areas of the U.S.

Finally, the experience of living in a rural area is multifaceted and depends on many factors that are likely to vary for a given person in a given rural area. A critical area of future work will be to identify and tease apart specific unique factors of rurality that affect HIV-infected persons. We know that not all rural areas are the same in the U.S., even rural areas within the same geographic region such as the Deep South may differ from one another. It is likely that there are pockets of certain areas, either encompassing an entire rural area or just a part of a rural area, where a combination of factors makes it more difficult for patients to initiate HIV care and/or stay in HIV care. In reality, the effect of geographic residence is certainly not a binary rural versus urban effect but rather a much more complex effect. The possible factors associated with rural residence are numerous: income, education, employment, access to primary care and specialized care, health disparities, cultural factors, family and community support, social isolation, mental health issues, alcohol use and addiction, drug use and addiction, transportation issues, stigma and privacy concerns, the difficulty of being a single parent, childcare options, and many more. Future studies will need to develop ways to classify an area of residence based on what it is actually like for a person to live in that area. Only when researchers have a better understanding of which unique factors related to rural residence are

having the greatest impact will we have a better chance of developing tailored interventions to help rural patients enter and stay in HIV clinical care and to help them stay healthy.

F. Conclusions

This study demonstrated that one or more aspects of rural residence are associated with HIV clinical care initiation, retention, and survival. These results support future work identifying factors of rural residence that negatively affect the health of HIV-infected patients. Additionally, these findings suggest efforts to reach HIV-infected individuals in rural areas are needed to both support earlier access to HIV care and ongoing clinical follow-up.

APPENDIX A: SENSITIVITY AND SECONDARY ANALYSES FOR CHAPTER V

To go along with chapter V, sensitivity analyses were done among patients who did not have prior clinical care before entering UNC clinical care and limited to patients who attended more than one UNC clinic visit. We also compared patients with residence data to patients lacking residence data.

The only notable difference between the patients included in primary analyses (with residence data available) and patients excluded due to lack of residence data was calendar year of care entry (P=0.02) (**Table A.1**). Our primary findings did not differ from multiple imputation findings that included patients missing residence data.

A break down by categorical CD4 cell count at UNC care initiation is presented (**Table A.2**). The association between residence and binary CD4 cell cut-points of < 200 cells/mm^3 (**Table A.3**) and < 350 cells/mm^3 are presented (**Table A.4**). The association between patient residence and binary CD4 cell count cut-points did not substantially differ from the primary results.

Median CD4 cell count rural-urban differences are presented in **Table A.5**.

A sensitivity analysis restricted to patients who initiated HIV clinical care in 2001 or later did not differ from our primary findings (**Table A.6**).

Table A.1 Patient Characteristics at HIV Care Initiation, Stratified by Residence and by Availability of a Residential Address

Characteristic	Included Patients (N=988)	Rural Patients (N=342)	Urban Patients (N=646)	Excluded Patients (N=408)	p-value comparing included and excluded patients
Male sex, no. (%)	686 (69)	234 (68)	452 (70)	286 (70)	0.8
Age, yr					
Median	36	38	35	36	0.5
Interquartile Range	28-45	30-47	27-44	29-45	
Race, no. (%)					0.6
White	256 (26)	84 (25)	172 (27)	98 (24)	
Black	593 (60)	194 (57)	399 (62)	257 (63)	
Other	139 (14)	64 (19)	75 (12)	52 (13)	
Men who have sex with men, no. (%)	397 (40)	118 (35)	279 (43)	150 (37)	0.2
Injection drug use, no. (%)	103 (10)	42 (12)	61 (9)	40 (10)	0.7
CD4 cell count, cells/mm^3					
Median	311	269	335	295	0.3
Interquartile Range	99-517	81-489	121-532	93-490	
HIV RNA level, log10 copies/µL*					
Median	4.7	4.7	4.7	4.6	0.6
Interquartile Range	3.9-5.3	4.0-5.3	3.9-5.2	4.1-5.3	
AIDS clinical condition, no. (%)	194 (20)	77 (23)	117 (18)	78 (19)	0.8
Hepatitis C infection, no. (%)	151 (15)	67 (20)	84 (13)	48 (13)	0.2
Health insurance, no. (%)					0.6
None	487 (49)	162 (47)	325 (50)	198 (49)	
Private	248 (25)	71 (21)	177 (28)	96 (24)	
Public	253 (26)	109 (32)	144 (22)	114 (28)	
Calendar year of HIV care initiation					
Median	2003	2001	2003	2001	0.02
Interquartile Range	1999-2007	1999-2006	1999-2008	1998-2006	

*Of the excluded patients, 5 (1%) were missing data on HIV RNA level. Of the included patients, 4 (0.4%) were missing data on HIV RNA level.

Table A.2 Categorical CD4 cell count at UNC Care Initiation, by Residence

CD4 cell count (cells/mm^3)	Rural n (%)	Urban n (%)
<50	69 (20)	107 (17)
50-99	31 (9)	42 (7)
100-199	45 (13)	71 (11)
200-349	63 (18)	117 (18)
350-499	52 (15)	127 (20)
500+	82 (24)	182 (28)

Table A.3 Predictors of Presenting to HIV Care with a CD4 cell count < 200 cells/mm^3

| | Bivariate Analyses
Unadjusted RR
(95% CI) | Multivariate Analyses | |
		Model 1 Fully Adjusted RR* (95% CI)	Model 2 Partially Adjusted RR* (95% CI)
Residence			
Rural	1.25 (1.06, 1.47)	1.06 (0.92, 1.23)	1.13 (0.98, 1.30)
Urban	Referent	Referent	Referent
Sex			
Male	1.25 (1.03, 1.51)	1.18 (0.98, 1.41)	
Female	Referent	Referent	
Age, yrs			
40+	1.56 (1.33, 1.83)	1.18 (1.01, 1.38)	1.17 (1.01, 1.36)
18-39	Referent	Referent	Referent
Race			
Black	1.17 (0.95, 1.44)	1.14 (0.93, 1.40)	
Other	1.35 (1.04, 1.75)	1.27 (0.99, 1.63)	
White	Referent	Referent	
MSM			
No	1.32 (1.10, 1.57)	1.30 (1.08, 1.57)	1.33 (1.13, 1.58)
Yes	Referent	Referent	Referent
IDU			
Yes	1.34 (1.07, 1.67)	1.05 (0.81, 1.35)	
No	Referent	Referent	
HCV			
Yes	0.71 (0.59, 0.85)	1.10 (0.88, 1.37)	
No	Referent	Referent	
HIV RNA level (log10 copies/µL)			
≥4.5	3.43 (2.73, 4.32)	3.21 (2.54, 4.06)	3.31 (2.62, 4.17)
<4.5	Referent	Referent	Referent
Insurance			
Public	1.07 (0.88, 1.31)	1.02 (0.85, 1.23)	
Private	1.13 (0.93, 1.37)	1.01 (0.85, 1.19)	
None	Referent	Referent	
Distance to clinic one way, miles			
<40	1.08 (0.90, 1.31)	1.13 (0.96, 1.34)	1.13 (0.96, 1.34)
40-59	1.50 (1.22, 1.84)	1.28 (1.07, 1.52)	1.30 (1.10, 1.54)
60+	Referent	Referent	Referent
Calendar year			
1996-2003	1.11 (0.84, 1.45)	1.05 (0.82, 1.34)	
2004-2007	1.29 (1.04, 1.61)	1.24 (1.00, 1.53)	
2008-2012	Referent	Referent	

*Model 1 based on a log-linear binomial regression model including residence, race/ethnicity, age, sex, driving distance, MSM, IDU, HCV, log$_{10}$ HIV RNA viral load, and year of care entry. Results of model 1 did not change when using categorical versus continuous coding of driving distance and/or age.

**Model 2 based on a log-linear binomial regression model including residence, driving distance, log$_{10}$ HIV RNA viral load. Results of model 2 did not change when using categorical versus continuous coding of driving distance. IQR, Interquartile Range; MSM, men who have sex with men; IDU, injection drug use; HCV, Hepatitis C Virus co-infection.

Table A.4 Predictors of Presenting to HIV Care with a CD4 cell count < 350 cells/mm^3

	Bivariate Analyses	Model 1	Model 2
	Unadjusted RR (95% CI)	Fully Adjusted RR* (95% CI)	Partially Adjusted RR* (95% CI)
Residence			
Rural	1.17 (1.04, 1.30)	1.04 (0.97, 1.11)	1.12 (1.02, 1.23)
Urban	Referent	Referent	Referent
Sex			
Male	1.24 (1.08, 1.42)	1.07 (0.98, 1.16)	
Female	Referent	Referent	
Age, yrs			
40+	1.36 (1.22, 1.51)	1.09 (1.02, 1.16)	1.20 (1.09, 1.32)
18-39	Referent	Referent	
Race			
Black	1.02 (0.89, 1.17)	1.04 (0.96, 1.12)	
Other	1.24 (1.05, 1.47)	1.11 (1.00, 1.23)	
White	Referent	Referent	
MSM			
No	1.12 (1.00, 1.26)	1.06 (0.98, 1.14)	
Yes	Referent	Referent	
IDU			
Yes	0.86 (0.73, 1.01)	1.02 (0.90, 1.16)	
No	Referent	Referent	
HCV			
Yes	1.22 (1.06, 1.39)	1.02 (0.92, 1.13)	
No	Referent	Referent	
HIV RNA level (log10 copies/µL)			
≥4.5	2.04 (1.78, 2.34)	1.28 (1.19, 1.37)	1.96 (1.70, 2.25)
<4.5	Referent	Referent	Referent
Insurance			
Public	1.03 (0.89, 1.18)	1.01 (0.92, 1.10)	
Private	1.13 (0.99, 1.29)	1.03 (0.95, 1.11)	
None	Referent	Referent	
Driving distance, miles, one-way			
<40	1.09 (0.96, 1.23)	1.04 (0.97, 1.12)	
40-59	1.12 (0.95, 1.31)	1.01 (0.93, 1.09)	
60+	Referent	Referent	
Calendar year			
1996-2003	1.19 (0.99, 1.43)	1.04 (0.95, 1.14)	
2004-2007	1.27 (1.09, 1.48)	1.09 (1.00, 1.19)	
2008-2012	Referent	Referent	

*Model 1 based on a log-linear binomial regression model including residence, race/ethnicity, age, continuous driving distance, sex, MSM, IDU, HCV, log_{10} HIV RNA viral load, year of care entry. Results of model 1 did not change when using categorical versus continuous coding of driving distance and/or age.

**Model 2 based on a log-linear binomial regression model including residence, age, log_{10} HIV RNA viral load.

IQR, Interquartile Range; MSM, men who have sex with men; IDU, injection drug use; HCV, Hepatitis C Virus co-infection.

Table A.5 Median CD4 Cell Counts and Median CD4 Cell Count Differences at HIV Care Initiation by Rural/Urban Residence, UCHCC 1996 – 2012 (n=988)

Characteristic*	Median CD4 Cell Count (IQR) cells/mm^3			Median CD4 Cell Count Rural Urban Difference	P Value
	All Patients	Rural	Urban		
All patients	311 (99-517)	269 (81-489)	335 (121-532)	-66	0.009
Sex					
Male	296 (85-477)	230 (66-443)	313 (103-495)	-83	0.005
Female	368 (152-606)	343 (100-585)	381 (159-612)	-38	0.5
Age, yrs					
18 - 39	361 (145-560)	339 (141-547)	368 (150-565)	-29	0.6
≥ 40	229 (58-444)	175 (41-384)	263 (78-479)	-88	0.009
Race**					
White	331 (133-510)	256 (82-510)	345 (173-509)	-89	0.1
Black	324 (93-529)	286 (84-501)	339 (103-558)	-53	0.09
Other	245 (72-473)	210 (73-441)	282 (72-530)	-73	0.4
MSM					
Yes	338 (137-510)	333 (93-510)	345 (159-504)	-12	0.4
No	287 (82-528)	244 (73-469)	333 (94-564)	-89	0.02
IDU					
Yes	233 (59-486)	205 (48-398)	233 (70-576)	-28	0.4
No	321 (103-519)	276 (87-506)	338 (130-531)	-62	0.02
HIV RNA level (log10 copies/µL)					
<4.5	445 (288-669)	430 (234-626)	459 (321-671)	-29	0.06
≥4.5	172 (46-382)	148 (40-329)	187 (49-400)	-39	0.09
HCV					
Yes	210 (54-480)	180 (54-462)	232 (62-510)	-52	0.5
No	328 (102-519)	287 (88-501)	343 (131-533)	-56	0.02
Insurance					
None	333 (108-533)	286 (73-468)	359 (133-571)	-73	0.01
Private	290 (91-450)	210 (72-405)	313 (97-489)	-103	0.02
Public	323 (104-565)	302 (102-566)	324 (113-563)	-22	0.9
Distance to clinic one way, miles					
<40	311 (118-491)	287 (152-443)	332 (104-500)	-40	0.6
40-59	285 (54-519)	130 (20-447)	304 (72-558)	-174	0.02
60+	332 (127-536)	277 (82-510)	369 (202-576)	-89	0.003
Calendar year					
1996-2003	288 (89-491)	254 (83-491)	300 (94-492)	-46	0.5
2004-2007	313 (105-528)	230 (88-407)	363 (145-570)	-133	0.01
2008-2012	376 (133-565)	333 (56-520)	382 (149-606)	-49	0.1

*All characteristics measured at HIV care initiation.

** 60% of Other race/ethnicity were Hispanic.

IQR, Interquartile Range; MSM, men who have sex with men; IDU, injection drug use; HCV, Hepatitis C Virus co-infection.

Table A.6 CD4 Cell Count Differences (cells/mm3) at HIV Care Initiation, UCHCC 2001 – 2012. Restricted to patients who began UNC HIV clinical care in 2001 or later (n=623)

Characteristic*	Mean CD4 Cell Count Difference (95%CI)	
	Unadjusted	Adjusted***
Residence		
Rural	-87 (-136, -38)	-76 (-124, -27)
Urban	0	0
Sex		
Male	-79 (-130, -29)	-40 (-99, 20)
Female	0	0
Age, yrs		
≥40	-107 (-153, -61)	-85 (-131, -40)
18-39	0	0
Race**		
Black	-11 (-64, 42)	-72 (-121, -22)
Other	-74 (-143, -4)	-99 (-165, -33)
White	0	0
MSM		
No	-3 (-49, 43)	-12 (-68, 43)
Yes	0	0
IDU		
No	-39 (-131, 53)	-62 (-157, 34)
Yes	0	0
HIV RNA level (log10 copies/µL)		
≥ 4.5	-229 (-271, -186)	-215 (-258, -172)
< 4.5	0	0
HCV		
Yes	-4 (-80, 72)	13 (-66, 92)
No	0	0
Insurance		
Public	36 (-26, 98)	27 (-34, 87)
Private	-52 (-108, 4)	-35 (-88, 17)
None	0	0
Distance to clinic one way, miles		
<40	-6 (-58, 46)	-24 (-75, 28)
40-59	-9 (-70, 54)	-20 (-78, 39)
60+	0	0
Calendar year		
1996-2003	-54 (-110, 2)	-60 (-114, -7)
2004-2007	-25 (-80, 30)	-9 (-59, 41)
2008-2012	0	0

*All characteristics measured at HIV care initiation.
**60% of Other race/ethnicity were Hispanic.
***Adjusted analyses using multiple linear regression including all characteristics in the table. Variable parameterization for continuous variables was based on stratified analyses and model fit.
IQR, Interquartile Range; MSM, men who have sex with men; IDU, injection drug use; HCV, Hepatitis C Virus co-infection.

APPENDIX B: SENSITIVITY AND SECONDARY ANALYSES FOR CHAPTER IV

To go along with chapter IV, sensitivity analyses were done among patients who did not have prior clinical care before entering UNC clinical care and limited to patients who attended more than one clinic visit. We also compared patients with residence data to patients lacking residence data.

The only notable difference between the patients included in primary analyses (with residence data available) and patients excluded due to lack of residence data was diagnosis with an AIDS-defining clinical condition (P=0.005) (**Table B.1**). Our primary findings did not differ from multiple imputation findings that included patients missing residence data.

There were differences between the patient population with prior care versus without prior care. The population of patients who began their first care at UNC was slightly younger(P=0.003), consisted of a slightly different racial breakdown (P=0.0007) and insurance breakdown (P=0.007), lived closer to the clinic (P=0.01), was more likely to report a history of IDU (P=0.0002), less likely to have Hepatitis C infection (P=0.003), and had a higher HIV RNA level at entry to UNC care (P <.0001) (**Table B.2**). Primary results did not differ from the sensitivity analyses for patients without prior clinical care for the IOM indicator, LTFU, and mortality; however, an increased incidence of missed clinic visits was seen among patients without prior care in contrast to our primary findings (**Tables B.3 and B.4**). When including only patients without prior care, there was no longer a rural-urban difference in LTFU based on Kaplan-Meier estimates (log-rank P=0.2) (**Figure B.3**).

For all outcomes, primary results did not differ from the sensitivity analyses for patients who attended only a single HIV care visit at UNC (**Tables B.5 and B.6**).

We repeated our LTFU analyses using a longer 18-month definition of LTFU and these results did not differ from our primary results based on a 12-month definition of LTFU (**Table B.7 and Figure B.4**).

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The incidence rate of missed visits by patient characteristics is shown in **Figure B.1** while IOM retention and the mean number of missed visits, per 12-month intervals, is presented in **Figure B.2**.

Table B.1 Patient Characteristics at UNC HIV Care Initiation, Stratified by Availability of a Residential Address, UCHCC 1996 to 2012

Characteristic	Main study patients (N=1805)	Missing residence (N=698)	P-value
Male sex, no. (%)	1268 (70)	525 (75)	0.06
Age, yr			
Median	38	37	0.3
Interquartile Range	30-45	30-45	
Race, no. (%)			
White	504 (28)	196 (28)	0.6
Black	1097 (61)	464 (66)	
Other	204 (11)	89 (13)	
Men who have sex with men, no. (%)	711 (56)	270 (51)	0.08
Injection drug use, no. (%)	240 (13)	82 (12)	0.1
CD4 cell count*, cells/ mm^3			
Median	297	268	0.1
Interquartile Range	91-500	77-490	
HIV RNA level**, log10 copies/µL			
Median	4.5	4.5	0.8
Interquartile Range	3.6-5.2	3.6-5.3	
AIDS clinical condition, no. (%)	397 (22)	184 (26)	0.005
Hepatitis C infection, no. (%)	234 (13)	118 (17)	0.06
Insurance			
None	839 (46)	330 (47)	0.08
Private	444 (25)	169 (24)	
Public	522 (29)	250 (36)	
Calendar year of HIV care initiation			
Median	2002	2002	0.06
Interquartile Range	1999-2007	1999-2006	

* Main dataset: 10 urban patients and 3 rural patients missing data on CD4 cell count. Excluded dataset: 4 patients missing data on CD4 cell count.
** Main dataset: 11 urban patients and 4 rural patients missing any data on HIV RNA level. Excluded dataset: 7 patients missing data on HIV RNA level.
MSM among men only.

Table B.2 Patient Characteristics at UNC HIV Care Initiation, Stratified by Prior Care Before Entering UNC Clinical Care, UCHCC 1996 to 2012

Characteristic	Main study patients (N=1805)	No prior care before UNC (N=957)	P-value
Male sex, no. (%)	1268 (70)	659 (69)	0.2
Age at first care entry, yr			
Median	38	37	0.003
Interquartile Range	30-45	28-45	
Race, no. (%)			
White	504 (28)	247 (26)	0.0007
Black	1097 (61)	578 (60)	
Other	204 (11)	132 (14)	
Men who have sex with men, no. (%)	711 (56)	373 (57)	0.7
Injection drug use, no. (%)	240 (13)	244 (26)	0.0002
CD4 cell count*, cells/ mm^3			
Median	297	309	0.05
Interquartile Range	91-500	97-512	
HIV RNA level**, log10 copies/μL			
Median	4.5	4.7	<.0001
Interquartile Range	3.6-5.2	3.9-5.3	
AIDS clinical condition, no. (%)	337 (19)	192 (20)	0.1
Hepatitis C infection, no. (%)	234 (13)	103 (11)	0.003
Insurance			
None	839 (46)	469 (49)	0.007
Private	444 (25)	241 (25)	
Public	522 (29)	247 (26)	
Distance to UNC clinic one way, miles			
Median	50	48	0.01
Interquartile Range	30-78	26-75	
Calendar year of HIV care initiation			
Median	2002	2002	0.4
Interquartile Range	99-07	99-07	

*All characteristics measured at baseline.
MSM, men who have sex with men; HCV, Hepatitis C Virus co-infection.

Table B.3 Unadjusted and Adjusted Incidence Rate Ratios for Missed Clinic Visits and Risk Ratios for Not-Retained in Care by the IOM Indicator, UCHCC 1996-2012, among patients with no prior HIV clinical care before entering UCHCC (n=957)

| Characteristic* | Missed Visits IRR (95% CI)** | | Not Retained in Care- IOM Measure RR (95% CI)*** | |
	Unadjusted	Adjusted**	Unadjusted	Adjusted**
Residence				
Rural	1.10 (1.01, 1.19)	1.20 (1.09, 1.31)	0.96 (0.81, 1.12)	0.96 (0.80, 1.15)
Urban (ref)	1	1	1	1
Driving distance to clinic one way, miles				
<40 miles	1.07 (0.97, 1.17)	1.18 (1.07, 1.31)	0.91 (0.77, 1.09)	0.96 (0.80, 1.16)
40-60 miles	1.20 (1.08, 1.33)	1.33 (1.19, 1.49)	0.99 (0.81, 1.21)	1.05 (0.85, 1.30)
>60 miles (ref)	1	1	1	1
Age, yr				
18-39	1.22 (1.12, 1.33)	1.26 (1.15, 1.38)	1.37 (1.16, 1.61)	1.32 (1.11, 1.56)
40+ (ref)	1	1	1	1
Sex				
Male	0.93 (0.85, 1.01)	1.08 (0.97, 1.19)	0.95 (0.81, 1.11)	1.17 (0.96, 1.43)
Female (ref)	1	1	1	1
Race				
White (ref)	1	1	1	1
Black	1.64 (1.47, 1.82)	1.56 (1.39, 1.74)	1.21 (1.01, 1.45)	1.10 (0.91, 1.31)
Other	1.65 (1.43, 1.90)	1.41 (1.22, 1.64)	1.00 (0.77, 1.31)	0.90 (0.69, 1.19)
Insurance				
None	1.40 (1.26, 1.55)	1.20 (1.08, 1.34)	1.14 (0.95, 1.37)	1.20 (0.99, 1.46)
Public	1.52 (1.36, 1.69)	1.42 (1.27, 1.60)	1.15 (0.94, 1.40)	1.04 (0.85, 1.28)
Private (ref)	1	1	1	1
MSM				
Yes (ref)	1	1	1	1
No	1.17 (1.07, 1.27)	1.14 (1.03, 1.27)	1.23 (1.05, 1.45)	1.33 (1.09, 1.62)
HCV				
Yes	1.16 (1.03, 1.31)	1.21 (1.07, 1.37)	1.01 (0.79, 1.30)	0.99 (0.77, 1.28)
No (ref)	1	1	1	1
CD4 count (cells/mm^3)				
<200 (ref)	1	1	1	1
200-349	1.19 (1.07, 1.33)	1.28 (1.14, 1.44)	1.28 (1.04, 1.58)	1.26 (1.02, 1.55)
350-500	1.04 (0.93, 1.17)	1.06 (0.93, 1.20)	1.37 (1.11, 1.69)	1.27 (1.02, 1.59)
>500	1.09 (0.98, 1.21)	1.04 (0.93, 1.17)	1.35 (1.10, 1.66)	1.27 (1.02, 1.57)
AIDS clinical condition				
Yes (ref)	1	1	1	1
No	0.92 (0.83, 1.01)	1.00 (0.89, 1.12)	1.47 (1.17, 1.84)	1.24 (0.97, 1.58)
Yr of care entry				
1996-2003	0.74 (0.65, 0.86)	0.76 (0.65, 0.87)	1.62 (1.26, 2.09)	1.66 (1.28, 2.16)
2004-2007	0.67 (0.60, 0.76)	0.62 (0.55, 0.71)	1.38 (1.03, 1.85)	1.44 (1.08, 1.92)
2008-2012 (ref)	1	1	1	1

*All characteristics measured at baseline.
MSM, men who have sex with men; HCV, Hepatitis C Virus co-infection.
**Incidence rate ratios (IRR) for the association between patient residence and missed visits were estimated using Poisson regression.
***Risk ratios (RR) for the association between rural residence and the risk of not being retained in care according to the IOM indicator, with repeat measures, was fit with log-binomial regression and generalized estimating equations. The fully adjusted results for each outcome did not differ appreciably from a partially adjusted model.

Table B.4 Unadjusted and Adjusted Hazard Ratios from Cox Regression Models for Loss to Follow-up** and Mortality, UCHCC 1996-2012, among patients with no prior HIV clinical care before entering UCHCC (n=957)

	Loss to Follow-up HR (95% CI)		Mortality HR (95% CI)	
Characteristic*	Unadjusted	Adjusted**	Unadjusted	Adjusted
Residence				
Rural	0.88 (0.71,1.09)	0.66 (0.52,0.85)	1.66 (1.23, 2.24)	1.40 (1.00, 1.96)
Urban (ref)	1	1	1	1
Driving distance to clinic one way, miles				
<40 miles	0.64 (0.51, 0.81)	0.55 (0.43, 0.71)	0.62 (0.44, 0.89)	0.80 (0.54, 1.19)
40-60 miles	0.52 (0.39, 0.71)	0.46 (0.33, 0.63)	0.92 (0.63, 1.34)	1.00 (0.66, 1.51)
>60 miles (ref)	1	1	1	1
Age, yr				
18-39	1.41 (1.12, 1.76)	1.28 (1.01, 1.62)	0.49 (0.36, 0.66)	0.63 (0.45, 0.86)
40+ (ref)	1	1	1	1
Sex				
Male	1.11 (0.88, 1.38)	1.30 (0.99, 1.71)	1.30 (0.94, 1.81)	1.47 (1.01, 2.14)
Female (ref)	1	1	1	1
Race				
White (ref)	1	1	1	1
Black	1.00 (0.79, 1.28)	0.91 (0.70, 1.17)	1.65 (1.13, 2.42)	1.65 (1.11, 2.46)
Other	1.02 (0.71, 1.44)	1.09 (0.76, 1.58)	0.68 (0.35, 1.35)	0.72 (0.36, 1.45)
Insurance				
None	1.40 (1.08, 1.83)	1.51 (1.15, 1.99)	1.05 (0.71, 1.57)	1.18 (0.78, 1.78)
Public	1.25 (0.94, 1.67)	1.15 (0.84, 1.56)	1.70 (1.15, 2.50)	1.62 (1.08, 2.43)
Private (ref)	1	1	1	1
MSM				
Yes (ref)	1	1	1	1
No	1.04 (0.84, 1.30)	1.23 (0.94, 1.60)	1.28 (0.92, 1.77)	0.95 (0.65, 1.39)
HCV				
Yes	1.09 (0.80, 1.50)	1.12 (0.80, 1.57)	1.86 (1.28, 2.69)	1.28 (0.87, 1.90)
No (ref)	1	1	1	1
CD4 count (cells/mm^3)				
<200 (ref)	1	1	1	1
200-349	1.11 (0.82, 1.52)	0.93 (0.67, 1.29)	0.50 (0.33, 0.76)	0.61 (0.39, 0.96)
350-500	1.26 (0.93, 1.70)	1.07 (0.77, 1.48)	0.33 (0.20, 0.56)	0.44 (0.26, 0.76)
>500	1.52 (1.17, 1.97)	1.32 (0.99, 1.76)	0.38 (0.25, 0.57)	0.47 (0.30, 0.74)
AIDS clinical condition				
Yes (ref)	1	1	1	1
No	0.62 (0.46, 0.84)	0.75 (0.53, 1.05)	0.53 (0.42, 0.67)	0.71 (0.49, 1.02)
Yr of care entry				
1996-2003	1.38 (0.90, 2.12)	1.51 (0.98, 2.33)	2.11 (0.79, 5.61)	1.96 (0.73, 5.24)
2004-2007	1.47 (1.00, 2.16)	1.65 (1.10, 2.48)	3.09 (1.24, 7.69)	2.34 (0.92, 5.96)
2008-2012 (ref)	1	1	1	1

*All characteristics measured at baseline.
MSM, men who have sex with men; HCV, Hepatitis C Virus co-infection.
**LTFU was defined as not attending a visit in >365 days.
Multivariable Cox proportional hazards regression models were separately fit to estimate hazard ratios (HR) for LTFU and death.
The fully adjusted results for each outcome did not differ appreciably from a partially adjusted model.

Table B.5 Unadjusted and Adjusted Incidence Rate Ratios for Missed Clinic Visits and Risk Ratios for Not-Retained in Care by the IOM Indicator, UCHCC 1996-2012, among patients who attended >1 HIV clinic appointment (n=1713)

Characteristic*	Missed Visits IRR (95% CI)**		Not Retained in Care- IOM Measure RR (95% CI)***	
	Unadjusted	Adjusted**	Unadjusted	Adjusted**
Residence				
Rural	1.04 (0.98, 1.10)	1.07 (1.00, 1.15)	0.93 (0.83, 1.05)	0.90 (0.79, 1.03)
Urban (ref)	1	1	1	1
Driving distance to clinic one way, miles				
<40 miles	1.02 (0.95, 1.09)	1.10 (1.02, 1.19)	1.02 (0.88, 1.18)	0.86 (0.75, 0.99)
40-60 miles	1.09 (1.00, 1.17)	1.12 (1.03, 1.21)	0.89 (0.76, 1.04)	0.99 (0.85, 1.15)
>60 miles (ref)	1	1	1	1
Age, yr				
18-39	1.27 (1.20, 1.36)	1.32 (1.24, 1.42)	1.35 (1.20, 1.52)	1.33 (1.17, 1.51)
40+ (ref)	1	1	1	1
Sex				
Male	0.91 (0.86, 0.97)	1.09 (1.01, 1.17)	1.00 (0.89, 1.13)	1.20 (1.04, 1.40)
Female (ref)	1	1	1	1
Race				
White (ref)	1	1	1	1
Black	1.56 (1.45, 1.68)	1.43 (1.32, 1.54)	1.22 (1.07, 1.39)	1.11 (0.97, 1.27)
Other	1.40 (1.25, 1.56)	1.23 (1.10, 1.38)	1.01 (0.82, 1.25)	0.98 (0.79, 1.21)
Insurance				
None	1.43 (1.33, 1.55)	1.26 (1.16, 1.37)	1.15 (1.00, 1.32)	1.18 (1.02, 1.36)
Public	1.45 (1.33, 1.57)	1.28 (1.18, 1.40)	1.15 (0.99, 1.33)	1.06 (0.91, 1.24)
Private (ref)	1	1	1	1
MSM				
Yes (ref)	1	1	1	1
No	1.24 (1.16, 1.32)	1.21 (1.12, 1.31)	1.17 (1.04, 1.31)	1.25 (1.07, 1.46)
HCV				
Yes	1.15 (1.06, 1.25)	1.15 (1.05, 1.25)	1.08 (0.92, 1.26)	1.06 (0.89, 1.25)
No (ref)	1	1	1	1
CD4 count (cells/mm^3)				
<200 (ref)	1	1	1	1
200-349	1.12 (1.03, 1.21)	1.09 (1.00, 1.19)	1.05 (0.92, 1.20)	1.15 (0.98, 1.34)
350-500	1.06 (0.97, 1.15)	1.00 (0.91, 1.10)	1.21 (1.06, 1.39)	1.25 (1.06, 1.48)
>500	1.14 (1.06, 1.23)	1.06 (0.97, 1.15)	1.13 (0.99, 1.28)	1.17 (1.00, 1.37)
AIDS clinical condition				
Yes (ref)	1	1	1	1
No	0.83 (0.76, 0.90)	1.12 (1.02, 1.22)	1.48 (1.25, 1.76)	1.28 (1.07, 1.53)
Yr of care entry				
1996-2003	0.73 (0.65, 0.82)	0.75 (0.66, 0.84)	1.51 (1.26, 1.81)	1.56 (1.29, 1.88)
2004-2007	0.69 (0.63, 0.76)	0.67 (0.61, 0.75)	1.38 (1.12, 1.69)	1.42 (1.16, 1.74)
2008-2012 (ref)	1	1	1	1

*All characteristics measured at baseline.
MSM, men who have sex with men; HCV, Hepatitis C Virus co-infection.
**Incidence rate ratios (IRR) for the association between patient residence and missed visits were estimated using Poisson regression.
***Risk ratios (RR) for the association between rural residence and the risk of not being retained in care according to the IOM indicator, with repeat measures, was fit with log-binomial regression and generalized estimating equations. The fully adjusted results for each outcome did not differ appreciably from a partially adjusted model.

Table B.6 Unadjusted and Adjusted Hazard Ratios from Cox Regression Models for Loss to Follow-up** and Mortality, UCHCC 1996-2012, among patients who attended >1 HIV clinic appointment. (n=1713)

Characteristic*	Loss to Follow-up HR (95% CI)		Mortality HR (95% CI)	
	Unadjusted	Adjusted**	Unadjusted	Adjusted
Residence				
Rural	0.82 (0.70, 0.96)	0.63 (0.53, 0.75)	1.42 (1.14, 1.77)	1.05 (0.82, 1.34)
Urban (ref)	1	1	1	1
Driving distance to clinic one way, miles				
<40 miles	0.72 (0.60, 0.85)	0.60 (0.50, 0.72)	0.57 (0.44, 0.74)	0.68 (0.51, 0.90)
40-60 miles	0.61 (0.49, 0.75)	0.52 (0.41, 0.65)	0.77 (0.58, 1.03)	0.78 (0.57, 1.05)
>60 miles (ref)	1	1	1	1
Age, yr				
18-39	1.32 (1.12, 1.56)	1.30 (1.09, 1.55)	0.53 (0.43, 0.66)	0.64 (0.51, 0.81)
40+ (ref)	1	1	1	1
Sex				
Male	1.07 (0.90, 1.26)	1.28 (1.04, 1.56)	1.31 (1.02, 1.68)	1.60 (1.21, 2.12)
Female (ref)	1	1	1	1
Race				
White (ref)	1	1	1	1
Black	1.03 (0.87, 1.22)	0.91 (0.76, 1.10)	1.44 (1.11, 1.87)	1.24 (0.95, 1.64)
Other	1.06 (0.82, 1.39)	1.17 (0.89, 1.54)	0.63 (0.38, 1.06)	0.65 (0.39, 1.11)
Insurance				
None	1.32 (1.08, 1.60)	1.42 (1.16, 1.74)	1.16 (0.86, 1.58)	1.25 (0.91, 1.71)
Public	1.37 (1.12, 1.68)	1.35 (1.08, 1.68)	1.96 (1.47, 2.61)	1.71 (1.27, 2.31)
Private (ref)	1	1	1	1
MSM				
Yes (ref)	1	1	1	1
No	1.12 (0.96, 1.31)	1.27 (1.04, 1.54)	1.54 (1.20, 1.96)	1.35 (1.01, 1.80)
HCV				
Yes	1.22 (0.99, 1.51)	1.22 (0.98, 1.54)	1.73 (1.33, 2.26)	1.17 (0.88, 1.56)
No (ref)	1	1	1	1
CD4 count (cells/mm^3)				
<200 (ref)	1	1	1	1
200-349	1.02 (0.82, 1.28)	0.90 (0.71, 1.14)	0.61 (0.46, 0.83)	0.66 (0.48, 0.91)
350-500	1.24 (1.00, 1.54)	1.14 (0.90, 1.44)	0.42 (0.29, 0.60)	0.51 (0.35, 0.74)
>500	1.32 (1.09, 1.60)	1.21 (0.98, 1.49)	0.37 (0.27, 0.52)	0.45 (0.32, 0.63)
AIDS clinical condition				
Yes (ref)	1	1	1	1
No	0.75 (0.61, 0.93)	0.86 (0.68, 1.10)	0.55 (0.43, 0.70)	0.79 (0.60, 1.04)
Yr of care entry				
1996-2003	1.39 (0.96, 2.01)	1.48 (1.02, 2.15)	1.65 (0.75, 3.61)	1.51 (0.69, 3.32)
2004-2007	1.62 (1.16, 2.26)	1.73 (1.22, 2.44)	2.73 (1.34, 5.59)	2.18 (1.05, 4.53)
2008-2012 (ref)	1	1	1	1

*All characteristics measured at baseline.
MSM, men who have sex with men; HCV, Hepatitis C Virus co-infection.
**LTFU was defined as not attending a visit in >365 days.
Multivariable Cox proportional hazards regression models were separately fit to estimate hazard ratios (HR) for LTFU and death.
The fully adjusted results for each outcome did not differ appreciably from a partially adjusted model.

Table B.7 Unadjusted and Adjusted Incidence Rate Ratios for Missed Clinic Visits and Risk Ratios for Not-Retained in Care by the IOM Indicator, UCHCC 2001-2012. Restricted to patients who began UNC HIV clinical care in 2001 or late (n=1155)

Characteristic*	Missed Visits IRR (95% CI)**		Not Retained in Care- IOM Measure RR (95% CI)***	
	Unadjusted	Adjusted**	Unadjusted	Adjusted**
Residence				
Rural	1.10 (1.01, 1.19)	1.12 (1.02, 1.22)	0.89 (0.75, 1.06)	0.85 (0.70, 1.02)
Urban (ref)	1	1	1	1
Driving distance to clinic one way, miles				
<40 miles	0.93 (0.85, 1.02)	1.02 (0.93, 1.13)	0.85 (0.72, 1.02)	0.94 (0.62, 1.41)
40-60 miles	1.05 (0.95, 1.17)	1.14 (1.02, 1.27)	0.95 (0.78, 1.16)	1.09 (0.70, 1.70)
>60 miles (ref)	1	1	1	1
Age, yr				
18-39	1.42 (1.31, 1.55)	1.48 (1.35, 1.62)	1.39 (1.18, 1.65)	1.88 (1.18, 3.01)
40+ (ref)	1	1	1	1
Sex				
Male	0.88 (0.81, 0.96)	1.09 (0.99, 1.21)	0.96 (0.81, 1.14)	0.96 (0.60, 1.52)
Female (ref)	1	1	1	1
Race				
White (ref)	1	1	1	1
Black	1.71(1.55, 1.89)	1.53 (1.38, 1.70)	1.27 (1.06, 1.51)	1.27 (0.84, 1.93)
Other	1.42 (1.24, 1.64)	1.26 (1.09, 1.46)	1.15 (0.89, 1.50)	0.90 (0.51, 1.80)
Insurance				
None	1.24 (1.12, 1.37)	1.12 (1.01, 1.24)	1.03 (0.86, 1.24)	0.88 (0.52, 1.49)
Public	1.42 (1.27, 1.59)	1.15 (1.02, 1.30)	1.15 (0.92, 1.44)	0.96 (0.51, 1.80)
Private (ref)	1	1	1	1
MSM				
Yes (ref)	1	1	1	1
No	1.28 (1.18, 1.38)	1.23 (1.10, 1.35)	1.15 (0.98, 1.34)	1.26 (0.81, 1.97)
HCV				
Yes	1.33 (1.19, 1.49)	1.32 (1.17, 1.48)	1.22 (0.98, 1.53)	0.60 (0.22, 1.59)
No (ref)	1	1	1	1
CD4 count (cells/mm^3)				
<200 (ref)	1	1	1	1
200-349	1.15 (1.04, 1.28)	1.11 (0.99, 1.24)	1.12 (0.90, 1.40)	1.14 (0.60, 2.18)
350-500	1.05 (0.93, 1.17)	0.98 (0.87, 1.11)	1.34 (1.08, 1.66)	1.83 (1.07, 3.14)
>500	1.22 (1.10, 1.35)	1.09 (0.98, 1.22)	1.36 (1.12, 1.66)	1.94 (1.16, 3.24)
AIDS clinical condition				
Yes (ref)	1	1	1	1
No	0.76 (0.69, 0.85)	1.18 (1.05, 1.34)	1.54 (1.22, 1.94)	1.32 (0.67, 2.61)

*All characteristics measured at baseline.
MSM, men who have sex with men; HCV, Hepatitis C Virus co-infection.
**Incidence rate ratios (IRR) for the association between patient residence and missed visits were estimated using Poisson regression.
***Risk ratios (RR) for the association between rural residence and the risk of not being retained in care according to the IOM indicator, with repeat measures, was fit with log-binomial regression and generalized estimating equations.
The fully adjusted results for each outcome did not differ appreciably from a partially adjusted model.

Table B.8 Unadjusted and Adjusted Hazard Ratios from Cox Regression Models for Loss to Follow-up** and Mortality, UCHCC 2001-2012. Restricted to patients who began UNC HIV clinical care in 2001 or later (n=1155)

Characteristic*	Loss to Follow-up HR (95% CI)**		Mortality HR (95% CI)***	
	Unadjusted	Adjusted**	Unadjusted	Adjusted**
Residence				
Rural	0.79 (0.64, 0.97)	0.64 (0.51, 0.81)	1.40 (0.99, 1.98)	0.96 (0.65, 1.41)
Urban (ref)	1	1	1	1
Driving distance to clinic one way, miles				
<40 miles	0.77 (0.63, 0.96)	0.66 (0.53, 0.84)	0.61 (0.41, 0.89)	0.72 (0.47, 1.10)
40-60 miles	0.65 (0.49, 0.85)	0.56 (0.42, 0.74)	0.64 (0.40, 1.02)	0.69 (0.42, 1.12)
>60 miles (ref)	1	1	1	1
Age, yr				
18-39	1.44 (1.17, 1.77)	1.50 (1.20, 1.87)	0.48 (0.34, 0.68)	0.56 (0.39, 0.82)
40+ (ref)	1	1	1	1
Sex				
Male	0.97 (0.79, 1.19)	1.17 (0.91, 1.51)	1.33 (0.90, 1.97)	1.76 (1.14, 2.73)
Female (ref)	1	1	1	1
Race				
White (ref)	1	1	1	1
Black	1.10 (0.88, 1.37)	0.93 (0.73, 1.17)	1.60 (1.05, 2.44)	1.48 (0.95, 2.30)
Other	1.09 (0.79, 1.50)	1.08 (0.77, 1.51)	0.85 (0.42, 1.70)	0.95 (0.46, 1.96)
Insurance				
None	1.29 (1.00, 1.66)	1.24 (0.96, 1.60)	0.95 (0.59, 1.52)	0.97 (0.60, 1.56)
Public	1.43 (1.07, 1.90)	1.31 (0.96, 1.78)	2.17 (1.35, 3.48)	2.15 (1.30, 3.54)
Private (ref)	1	1	1	1
MSM				
Yes (ref)	1	1	1	1
No	1.19 (0.98, 1.45)	1.33 (1.04, 1.71)	1.47 (1.02, 2.12)	1.27 (0.83, 1.95)
HCV				
Yes	1.33 (1.02, 1.75)	1.43 (1.06, 1.92)	1.45 (0.92, 2.30)	0.92 (0.56, 1.51)
No (ref)	1	1	1	1
CD4 count (cells/mm^3)				
<200 (ref)	1	1	1	1
200-349	0.99 (0.75, 1.30)	0.90 (0.67, 1.21)	0.50 (0.31, 0.80)	0.55 (0.34, 0.91)
350-500	1.24 (0.95, 1.62)	1.13 (0.84, 1.52)	0.37 (0.21, 0.63)	0.47 (0.26, 0.84)
>500	1.27 (1.00, 1.62)	1.12 (0.85, 1.47)	0.28 (0.16, 0.48)	0.34 (0.19, 0.60)
AIDS clinical condition				
Yes (ref)	1	1	1	1
No	0.79 (0.61, 1.02)	0.93 (0.69, 1.25)	0.46 (0.32, 0.66)	0.77 (0.51, 1.16)

*All characteristics measured at baseline.
MSM, men who have sex with men; HCV, Hepatitis C Virus co-infection.
**Incidence rate ratios (IRR) for the association between patient residence and missed visits were estimated using Poisson regression.
***Risk ratios (RR) for the association between rural residence and the risk of not being retained in care according to the IOM indicator, with repeat measures, was fit with log-binomial regression and generalized estimating equations. The fully adjusted results for each outcome did not differ appreciably from a partially adjusted model.

Table B.9 Unadjusted and Adjusted Hazard Ratios from Cox Regression Models for Loss to Follow-up**, UCHCC 1996-2012, using an 18-month definition of LTFU

	Loss to Follow-up, 18-month definition	
	HR (95% CI)	
Characteristic*	Unadjusted	Adjusted**
Residence		
Rural	0.77 (0.66, 0.90)	0.59 (0.50,0.70)
Urban (ref)	1	1
Driving distance to clinic one way, miles		
<40 miles	0.73 (0.62, 0.85)	0.60 (0.51, 0.72)
40-60 miles	0.62 (0.51, 0.76)	0.52 (0.42, 0.65)
>60 miles (ref)	1	1
Age, yr		
18-39	1.30 (1.12, 1.52)	1.29 (1.09, 1.51)
40+ (ref)	1	1
Sex		
Male	1.06 (0.91, 1.24)	1.29 (1.07, 1.56)
Female (ref)	1	1
Race		
White (ref)	1	1
Black	1.09 (0.92, 1.29)	0.96 (0.81, 1.15)
Other	1.05 (0.81, 1.36)	1.14 (0.88, 1.49)
Insurance		
None	1.37 (1.13, 1.67)	1.50 (1.24, 1.82)
Public	1.41 (1.17, 1.69)	1.34 (1.09, 1.65)
Private (ref)	1	1
MSM		
Yes (ref)	1	1
No	1.15 (0.99, 1.34)	1.32 (1.09, 1.59)
HCV		
Yes	1.18 (0.97, 1.44)	1.17 (0.94, 1.45)
No (ref)	1	1
CD4 count (cells/mm^3)		
<200 (ref)	1	1
200-349	1.10 (0.89, 1.35)	0.96 (0.77, 1.20)
350-500	1.28 (1.04, 1.56)	1.15 (0.92, 1.43)
>500	1.30 (1.08, 1.56)	1.18 (0.96, 1.44)
AIDS clinical condition		
Yes (ref)	1	1
No	0.73 (0.60, 0.90)	0.85 (0.68, 1.07)
Yr of care entry		
1996-2003	1.45 (1.01, 2.09)	1.55 (1.08, 2.24)
2004-2007	1.59 (1.14, 2.22)	1.71 (1.21, 2.40)
2008-2012 (ref)	1	1

*All characteristics measured at baseline.

MSM, men who have sex with men; HCV, Hepatitis C Virus co-infection.

**LTFU was defined as not attending a visit in >548 days.

Multivariable Cox proportional hazards regression models were fit to estimate hazard ratios (HR) for LTFU.
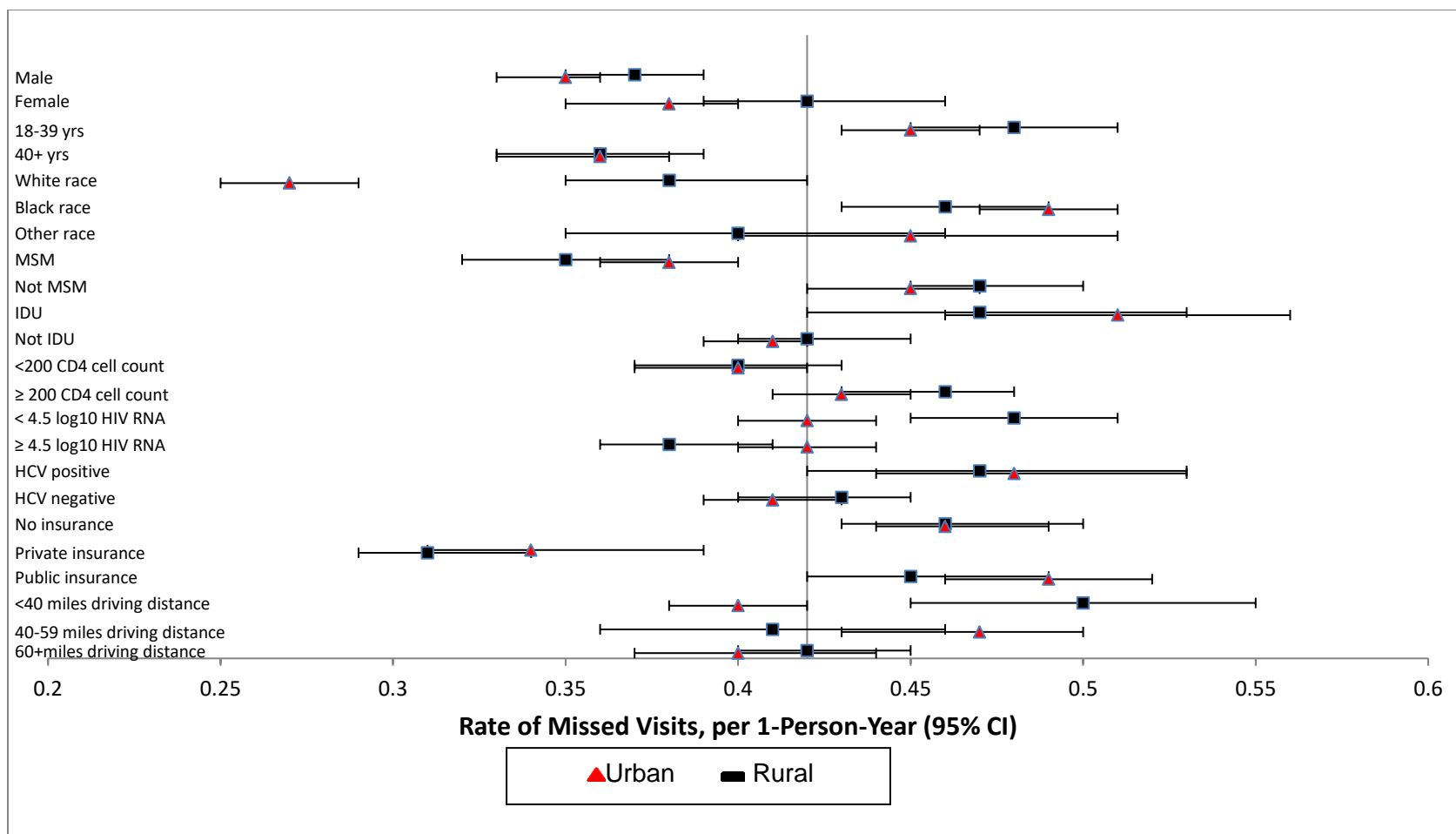
Figure B.1 Incidence Rate of Missed Visits per 1 Person-Year, UCHCC 1996-2012, by patient characteristics
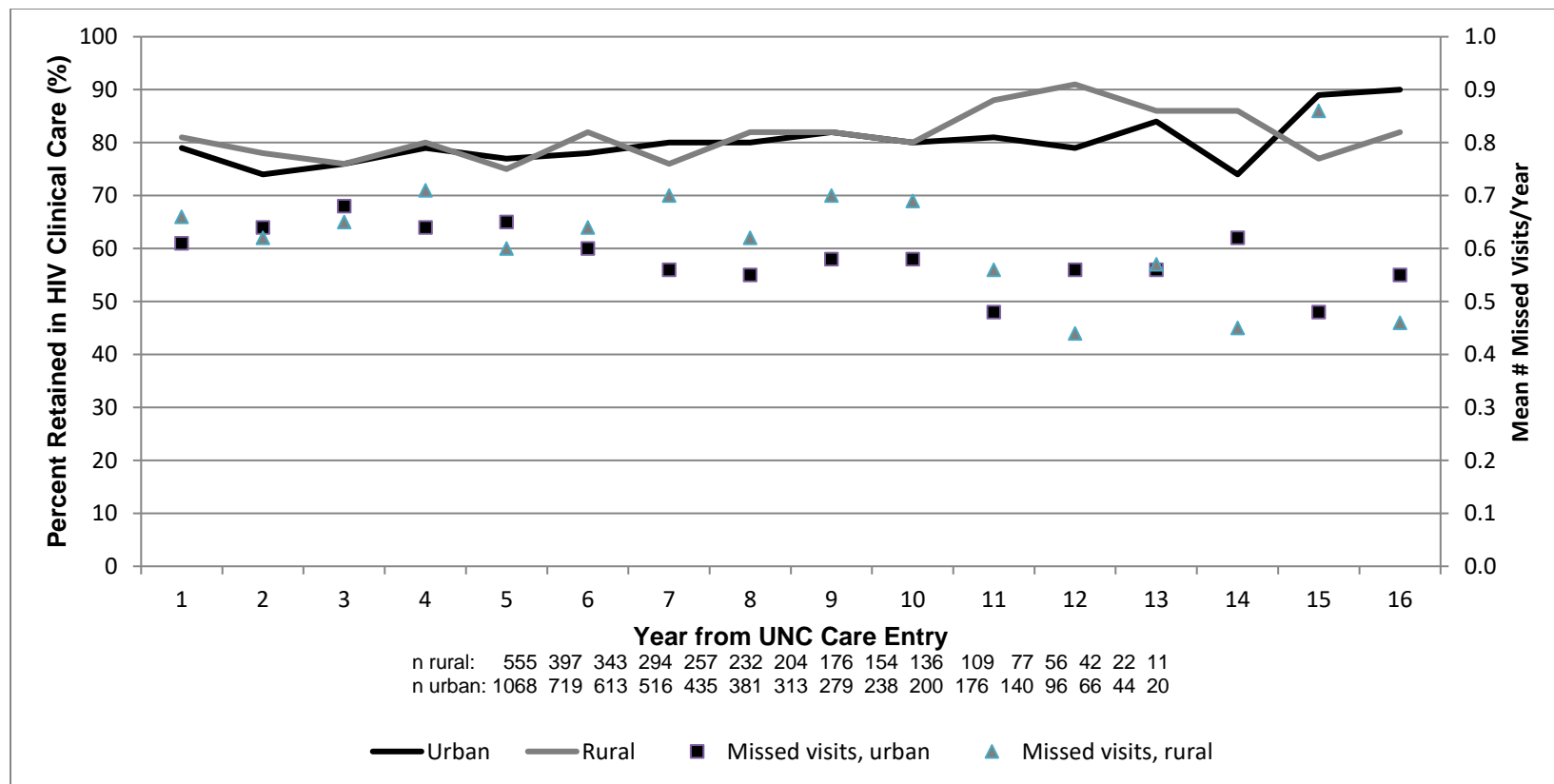
Figure B.2 Retention in HIV Clinical Care
Left axis- Percent retained in HIV clinical care (IOM retention measure: attending ≥2 clinic visits, ≥90 days apart, within 12 months).
Right axis- Mean number of missed visits in 12 months. Patients were included if they were in care during the entire year.
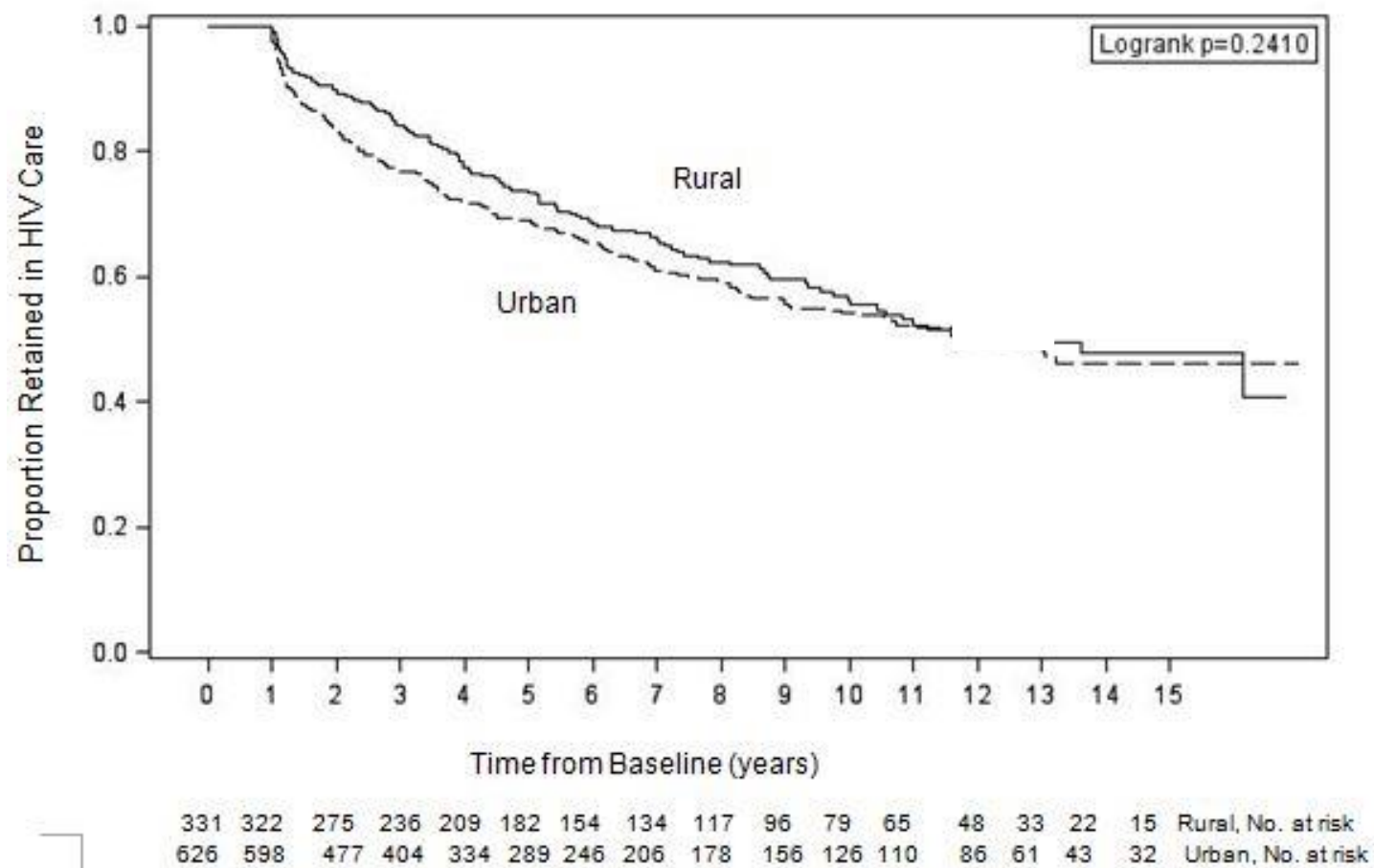
Figure B.3 Unadjusted Kaplan-Meier estimates of time to loss to follow-up among patients with no prior HIV care before UCHCC, by rural-urban residence (n=957)
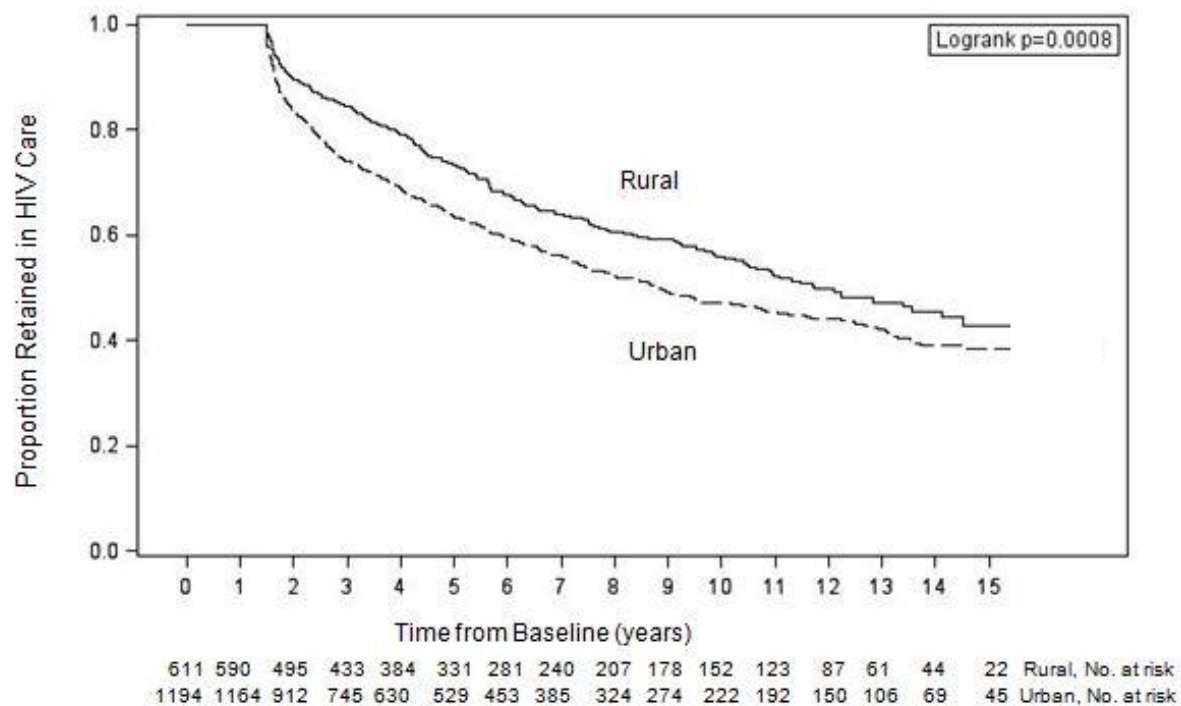
Figure B.4 Unadjusted Kaplan-Meier estimates of time to loss to follow-up using an 18-month definition of loss to follow up, by rural-urban residence (n=1805)

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