HIV Care Initiation Delay Among Rural Residents in the Southeastern United States, 1996 to 2012

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Background: Delaying HIV care initiation may lead to greater morbidity, mortality, and further HIV transmission. Rural residence may be associated with delayed diagnosis and linkage to care, with negative clinical outcomes.

Objective: To examine the association between rural patient residence and CD4 cell count at HIV care initiation in a large HIV clinical cohort in the Southeastern United States.

Methods: We included HIV-infected patients who initiated care between 1996 and 2012 with a geocodable address and no previous history of HIV clinical care. Patient residence was categorized as urban or rural using United States Department of Agriculture Rural Urban Commuting Area codes. Multivariable linear regression models were fit to estimate the association between patient residence and CD4 cell count at HIV care initiation.

Results: Among 1396 patients who met study inclusion criteria, 988 had a geocodable address. Overall, 35% of patients resided in rural areas and presented to HIV care with a mean CD4 cell count of 351 cells/mm^3 (SD, 290). Care initiation mean CD4 cell counts increased from 329 cells/mm^3 (SD, 283) in 1996–2003 to 391 cells/mm^3 (SD, 292) in 2008–2012 ($P = 0.006$). Rural in comparison with urban patients presented with lower CD4 cell counts with an unadjusted and adjusted mean difference of −48 cells/mm^3 [95% confidence interval, −86 to −10) and −37 cells/mm^3 (95% confidence interval: −73 to −2), respectively, consistently observed across calendar years.

Conclusions: HIV care initiation at low CD4 cell counts was common in this Southeastern US cohort and more common among rural area residents.

Key Words: HIV, AIDS, rural, medical care, cohort study

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INTRODUCTION

HIV infection is a chronic, manageable condition for most individuals who access HIV care and initiate antiretroviral therapy (ART) early and consistently after infection.[1–3] However, delays in HIV care initiation are associated with poor prognosis including less than optimal ART outcomes and greater risk of morbidity and mortality.[4,5] Late care entry is also associated with greater medical care costs and prolonged risk period for HIV transmission.[6–8]

In the United States, an estimated 1 in 8 people infected with HIV are unaware of their infection.[9] Furthermore, a quarter of HIV-infected persons are diagnosed with clinical and/or immunologic AIDS within 3 months, and a third within a year, of HIV diagnosis.[10] The median CD4 cell count at the first presentation for care has increased in recent years, but remains below 350 cells/mm^3 for more than half of U.S. patients.[11,12] A number of patient characteristics may be associated with delays in HIV care initiation, including sex, age, race/ethnicity, and health insurance.[11,13]

Structural and social characteristics may also affect patient care engagement. Rural residence may specifically negatively affect HIV care receipt and clinical outcomes[14–16] as well as retention.[14,17] 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.[18,19]

With increasing emphasis on addressing gaps in the HIV cascade and continuum,[20] 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 United States, 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.

METHODS

Study Design and Population

This study used UNC CFAR HIV Clinical Cohort (UCHCC) data which include HIV-infected patients receiving primary HIV care from 1996 to the present at a large tertiary care facility in the Southeastern United States. UCHCC data include 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.[21] Patients aged at least 18 years 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 provided 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 previous 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 4 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.[22]

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, history of intravenous drug use, $\log_{10}$ HIV RNA level, Hepatitis C coinfection (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.[11,19] 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.[23]

Statistical Analyses

We compared rural and urban patient characteristics using standard statistical approaches including t test, χ^2 test, and the Wilcoxon or Kruskal–Wallis tests. We reported unadjusted and adjusted mean values 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. The change-in-estimate criterion was used to assess confounding after first testing for effect measure modification using an alpha of 0.10. As indicated, we considered alternate parameterization 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 at HIV care entry was compared between urban and rural patients using multivariable log-linear regression. Because 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.[24] 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).

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 (eg, only PO Box provided or address unavailable). These excluded patients were similar to those with geocoded addresses (data not shown). 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 (SD, 11), and 60% were black, 26% white, and 14% of other race or ethnicity, most of whom were Hispanic (60%) (Table 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 3 rural categories. There were 342 patients (35%) who lived in a rural area. Rural in comparison with 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 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*
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				<0.0001
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.
†Sixty percent of other race/ethnicity were Hispanic.
IDU, injection drug use; MSM, men who have sex with men.

TABLE 2. CD4 Cell Count Differences (cells/mm^3) at HIV Care Initiation, UCHCC 1996–2012

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

*All characteristics measured at the HIV care initiation.
†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.
‡Sixty percent of other race/ethnicity were Hispanic.
IQR, interquartile range.

(Table 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 at 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 ($P < 0.0001$). In addition, rural patients were more likely to be coinfected 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, $P = 0.01$). 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 with urban patients of −48 cells/mm^3 [95% confidence interval (CI): −86 to −10] persisted after adjustment for demographic and clinical characteristics (−37 cells/mm^3; 95% CI: −73 to −2) (Table 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 a man who has sex with men, and higher HIV RNA level. Neither distance to care, type of health insurance, nor HCV co-infection was associated with CD4 cell count at HIV care entry. In adjusted analyses, rural patients presented with lower CD4 cell counts

in earlier calendar years (1996–2003) in comparison with later years (2008–2012); however, there seemed to be no difference in later years (2004–2007 versus 2008–2012).

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 to 1.30), and this effect persisted in multivariable analyses (RR = 1.12, 95% CI: 1.02 to 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 to 1.47), although this effect was attenuated after adjusting for other covariates in multivariable analyses (Adjusted RR = 1.13, 95% CI: 0.98 to 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/mm^3 (95% CI: −136 to −38) and −76 cells/mm^3 (95% CI: −124 to −27), respectively. 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 Digital Content Figure 1, http://links.lww.com/QAI/B54). 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 with urban patients was −44 cells/mm^3 (95% CI: −81 to −8), and the adjusted result was −46 cells/mm^3 (95% CI: −85 to −7).

DISCUSSION

In this large HIV clinical cohort in the Southeastern United States, over one-third of patients lived in areas classified as rural, and over one-half traveled 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, the lower CD4 cell count at care entry among rural patients compared with urban patients is consistent with observations from 2 studies of HIV-infected U.S. veterans.[16,25]

Others have observed no difference in the CD4 cell count at the time of HIV diagnosis comparing patients from rural and urban areas,[26–28] suggesting that rural residence may not affect the timing of HIV diagnosis but may rather 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 when 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.[15,19] A few previous studies among U.S. HIV-infected populations have observed that rural residents face increased barriers to care compared with urban residents.[18,19]

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,[15,29,30] and greater travel distance has been associated with delayed care entry and/or poorer care engagement for several health conditions.[31–34] 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 with women, older patients, and racial/ethnic minorities initiated HIV care at lower CD4 cell counts. These findings have been noted by others.[11,13,35] 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.[11] 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, whereas in 2007, whites initiated care with a mean CD4 cell count of 382 versus 328 cells/mm^3 for blacks.[11] Consistent with our findings, the NA-ACCORD also showed older patients entered care with lower median CD4 cell counts than younger patients between 1997 and 2007.[35]

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 with beginning ART at 350 cells/mm^3 or less.[36] 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.[11] The HIV Research Network, a consortium of 18 US 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.[37]

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.[38,39] 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,[40] new diagnostic strategies to detect early HIV infections,[41] and

contemporaneous HIV diagnosis, and ART initiation.[42] In addition, the opioid epidemic is increasingly affecting rural communities, including those geographically close to the source population of this study.[43,44] 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.[44–46]

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 because of 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 underestimation 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. In addition, 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.[14,47] In addition, 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 United States.

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, videoconferencing, basic services provision, transportation assistance, or mobile health units in rural areas warrant further investigation.

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