Rural Residence Is Associated With Delayed Care Entry and Increased Mortality Among Veterans With Human Immunodeficiency Virus Infection

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Context: Rural persons with human immunodeficiency virus (HIV) face many barriers to care, but little is known about rural-urban variation in HIV outcomes.

Objective: To determine the association between rural residence and HIV outcomes.

Design, Setting, and Patients: Retrospective cohort study of mortality among persons initiating HIV care in Veterans Administration (VA) during 1998–2006, with mortality follow-up through 2008. Rural residence was determined using Rural Urban Commuting Area codes. We identified 8489 persons initiating HIV care in VA with no evidence of combination antiretroviral therapy (cART) use at care entry, of whom 705 (8.3%) were rural.

Outcome Measure: All-cause mortality.

Results: At care entry, rural persons were less likely than urban persons to have drug use problems (10.6% vs. 19.5%, $P < 0.001$) or hepatitis C (34.3% vs. 41.2%, $P = 0.001$), but had more advanced HIV infection (median CD4: 186 vs. 246, $P < 0.001$). By 2 years after care entry, 5874 persons had initiated cART (528 rural [74.9%] and 5346 urban [68.7%], $P = 0.001$), and there were 1022 deaths (108 rural [15.3%] and 914 urban [11.7%], $P = 0.004$). The mortality hazard ratio for rural persons compared with urban was 1.34 (95% confidence interval: 1.05–1.69). The hazard ratio decreased to 1.18 (95% confidence interval: 0.93–1.50) after adjustment for HIV severity (CD4 and AIDS-defining illnesses) at care entry, and was 1.17 (95% confidence interval: 0.92–1.50) in a model adjusting for age, HIV severity at care entry, substance use, hepatitis B or C diagnoses, and cART initiation.

Conclusions: Later entry into care drives increased mortality for rural compared with urban veterans with HIV. Future studies should explore the person, care system, and community-level determinants of late care entry for rural persons with HIV.

Key Words: HIV, rural health, veterans

(*Med Care* 2010;48: 1064–1070)

Much attention has focused on racial and socioeconomic disparities in health care in the United States.[1] In contrast, few large studies have examined rural-urban variation in outcomes for persons with chronic illnesses, including human immunodeficiency virus (HIV) infection. Rural persons living with HIV face many barriers to care, such as greater local stigma surrounding HIV infection and fear of disclosing HIV status, limited availability of high volume providers specializing in HIV medicine, and significant travel burdens to obtain care.[2,3] In the early years of the modern combination antiretroviral therapy (cART) era, the HIV Cost and Services Utilization Study found that rural persons living with HIV were less likely than urban persons to receive cART or prophylaxis for *Pneumocystis jiroveci* pneumonia.[4] In a single study of persons obtaining HIV care in 4 clinics affiliated with an academic medical center in New England, rural residence was associated with increased mortality.[5] However, no large, longitudinal studies have reported outcomes for rural persons in care for HIV across a broader range of geographic areas and care sites.

Approximately 7% to 8% of persons with a new AIDS diagnosis in the United States live in rural areas, and the prevalence of HIV/AIDS has steadily increased in these areas over the last 15 years.[6] Over this same period, advances in antiretroviral therapy have improved survival for persons who are aware of their HIV infection and who are engaged in

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Supported by The Department of Veterans Affairs, Veterans Health Administration, Office of Rural Health, Midwest Rural Health Resource Center, and The Veterans Aging Cohort Study, with funding from National Institute on Alcohol Abuse and Alcoholism (U10 AA 13566) and VHA Public Health Strategic Health Care Group, and housed at the West Haven VAMC.

The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

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ISSN: 0025-7079/10/4812-1064

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care.[7] However, late entry into HIV care is common and contributes to mortality.[8,9] Barriers to care facing rural persons with HIV may affect both entry into care and the intensity and quality of therapy once in care. Therefore, it is important to understand rural-urban variation in care entry, care use following entry, and outcomes for persons with HIV in the modern antiretroviral treatment era.

Several factors make Veterans Affairs (VA) health system a useful setting for exploring rural-urban variation in HIV outcomes. First, VA is the largest provider of HIV care in the United States.[10] In 2007, VA provided care for more than 23,000 persons with HIV in more than 130 facilities across the United States ranging in HIV care volume, structure and organization of HIV care, and degree of academic affiliation.[10,11] Second, VA has a national, integrated electronic health record, and maintains rich data on patient demographics, residence, diagnoses, medications, inpatient and outpatient care, and mortality. Third, VA is an equal access healthcare system with limited financial barriers to care in the form of copays for medications and visits. This removes the potentially confounding effects of health insurance status from studies of care variation.

In an effort to understand rural-urban variation in HIV outcomes, we performed a retrospective cohort study of the association between rural residence and mortality among persons initiating HIV care in VA during fiscal years (FY) 1998–2006 (October 1, 1997–September 30, 2006). We hypothesized that mortality would be higher for rural persons than urban.

METHODS

Study Sample

The Veterans Aging Cohort Study includes a virtual cohort that has been described previously.[12] Persons entering VA care for an HIV diagnosis are identified using a previously validated case finding algorithm (1 inpatient or 2 outpatient HIV-related International Classification of Diseases (ICD-9-CM codes 042 or V08, or related diagnostic related groups 488–490). This algorithm identifies veterans with HIV with sensitivity of 0.90 and specificity of 0.999.[12] Veterans with HIV are then matched to HIV-negative controls. The HIV-positive cohort forms the sample for this study.

Patients in the virtual cohort are followed over time using a variety of VA data sources. Available data include the following: (1) demographics, care use, and diagnoses by ICD-9 codes obtained from Patient Treatment Files, (2) medications obtained from Pharmacy Benefits Manager files, (3) mortality from the VA vital status file, and (4) laboratory test results. The Immunology Case Registry (ICR) is the source of laboratory data for 1998–2002, and Decision Support System (DSS) files after 2002.[13] The ICR and DSS contain laboratory data extracted from electronic health record data at the local facility level, and compiled into national data repositories. Mortality obtained from the Vital Status File is accurate and complete when compared with the National Death Registry.[14,15]

Within the virtual cohort, we identified 21,568 persons entering VA care for a diagnosis of HIV in the United States during FY 1998–2006 (Fig. 1). Patients missing either a viral load or CD4 result within 180 days of first HIV-related contact were excluded (n = 9495, 44.0%). Viral load or CD4 results may be missing due to lack of data on laboratory tests performed outside the VA, or to variation in codes used to identify laboratory results leading to inconsistent reporting of results to ICR and DSS.[16] We excluded similar proportions of rural (45.8%) and urban (43.8%) persons because of missing CD4 or viral loads ($P = 0.09$). In general, there were few differences in characteristics of patients with and without viral load or CD4, with similar proportions of patients by rural residence, mortality, age, gender, alcohol or drug abuse problems, depression, and hepatitis B (diagnoses described later). However, persons with missing CD4 or viral load data were more likely than persons with available data to have

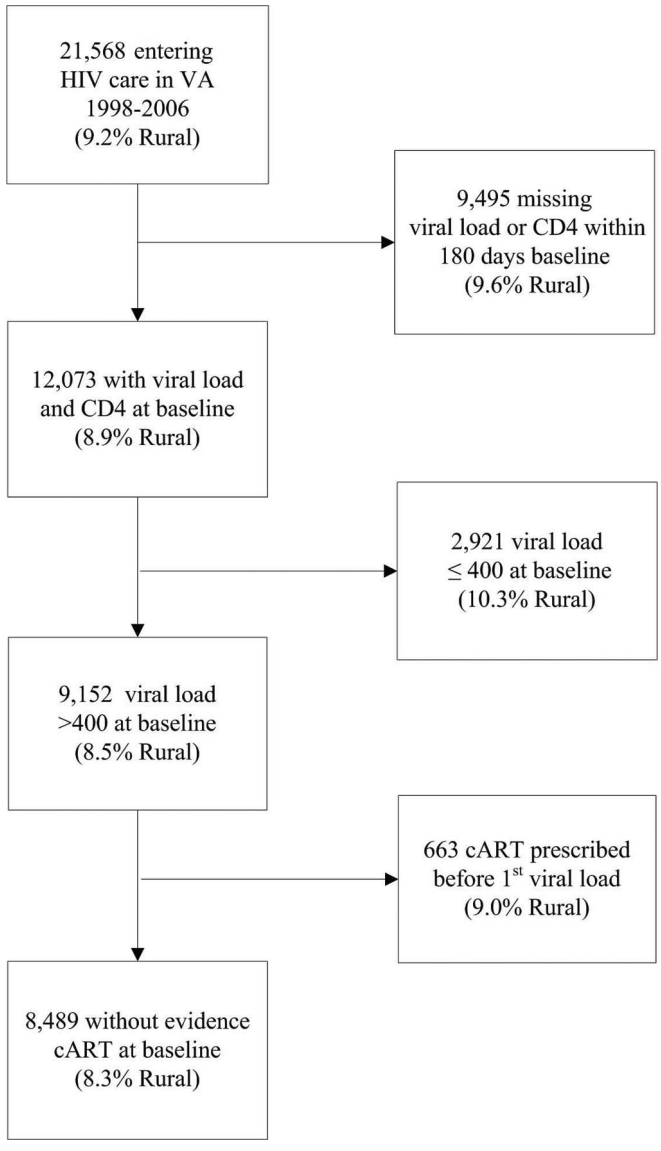

FIGURE 1. Sample derivation.

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race categorized as other/unknown (11.5% vs. 6.6%, $P < 0.001$), less likely to have an AIDS-defining illness diagnosed within 180 days of first HIV-related contact in VA (6.5% vs. 10.5%, $P < 0.001$), less likely to initiate cART within 2 years (42.7% vs. 74.0%), and less likely to have hepatitis C (34.9% vs. 39.4%, $P < 0.001$). This suggest that persons with missing CD4 or viral load data at care entry were less ill and/or less closely engaged in VA care. The patterns and magnitudes of these associations were similar for rural and urban persons.

Persons with evidence of ongoing antiretroviral therapy at time of initiation of HIV care in VA were also excluded (n = 3584; 29.7%). Such patients were presumably transferring care after an unknown period in care outside VA; inclusion of these patients may bias the association between rural residence and outcomes if rural and urban patients use care differently outside the VA. Prior chart review showed that persons with HIV viral loads ≤400 at entry into VA HIV care, or who were prescribed cART before obtaining first HIV monitoring laboratories in VA, were likely to be on cART at time of care entry.[17] We excluded 2921 persons with viral load ≤400 at baseline and 663 with cART prescription before first viral load (Fig. 1). The remaining 8489 (70.3%) persons without evidence of cART use at VA care entry comprised our analytic sample. The 29.7% of persons excluded due to evidence of cART use at care entry is consistent with chart review in Atlanta VA clinic that found 25% of persons were taking cART at care entry in VA.[17] Rural persons were somewhat more likely to have evidence of cART use at care entry than urban (34.4% vs. 29.2%).

Variables

The primary outcome was time to death following initiation of HIV care in VA. We defined time of HIV care entry as the date of first encounter in VA with an HIV-related ICD-9 code. We also examined factors that may influence mortality, including measures of HIV severity and comorbidity at care entry, and engagement in HIV primary care and cART initiation following entry. Measures of HIV severity at care entry were CD4 count and presence of an AIDS-defining illness within 180 days of first HIV-related contact. Comorbid conditions within 180 days of care entry included alcohol or drug use problems, depression, and hepatitis B or C. At least 1 or 2 outpatient ICD-9-CM codes were required to determine the presence of an AIDS-defining illness or comorbid condition, using codes available on the Veterans Aging Cohort Study website (available at: http://VAcohort.org). Requiring 2 outpatient codes improves the accuracy of diagnoses when compared with chart review.[18]

Measures of care following entry included cART initiation, which we defined as a minimum of 3 antiretroviral medications, and engagement in HIV primary care as reflected by outpatient infectious disease and general medicine clinic visits. HIV primary care in VA occurs almost exclusively in infectious disease and general medicine clinics, with some low HIV care volume facilities relying on general medicine clinics alone or in "shared care" arrangements with infectious disease clinics (2009 National Survey of VA HIV care, unpublished data). We calculated the total number of infectious disease and general medicine clinic visits in the first year after HIV care entry.

Rural residence was determined by linking ZIP codes to Rural Urban Commuting Area (RUCA) codes. RUCA codes are measures of rurality used for research and policy that incorporate population density as well as urban commuting patterns.[19,20] The 33 RUCA codes were collapsed into 2 categories, rural and urban, using a standard algorithm.[19]

Analysis

We began by characterizing the 8489 persons entering HIV care without cART use during FY 1998–2006. We estimated associations between rural residence and (1) demographics, comorbid diagnoses, CD4 count, and AIDS-defining illnesses within 180 days of HIV care entry, (2) cART initiation within 2 years of care entry, and (3) number of infectious disease (ID) and general medicine clinic visits within 1 year of care entry. Dichotomous measures were compared using χ^2 and continuous measures using Wilcoxon rank sum statistics.

We determined the time to death following entry in HIV care in VA and generated Kaplan-Meier survival curves for rural and urban persons. The hazards of death for rural persons relative to urban persons were determined using multivariable Cox proportional hazards regression that adjusted for patient age, CD4 count, AIDS-defining illnesses, substance use problems (drug or alcohol diagnosis), and hepatitis B or C diagnoses at care entry, and for cART initiation as a time-dependent covariate. Standard errors were estimated using the robust sandwich estimate to account for clustering of persons within care facilities.[21] Analyses were performed using SAS version 9.2 (Cary, NC).

We initially standardized the mortality observation window to 2 years by censoring persons at this time. This ensured complete and uniform follow-up for all persons. To determine whether uneven entry of rural and urban persons into care during the study years confounded the association between rural residence and mortality, we included the year of care entry in regression models and evaluated for change in the association between rural residence and mortality. We also tested the interaction between rural residence and year of care entry to evaluate whether the association between rural residence and mortality was stable over time. Finally, we repeated analyses with longer follow-up periods, relying on data from persons entering care in earlier study years, and tested for sensitivity of results to follow-up time.

RESULTS

Of the 8489 persons entering HIV care in VA during FY 1998–2006 without evidence of cART use, 7784 (91.7%) resided in urban areas and 705 (8.3%) in rural areas. The median age and gender were similar for rural and urban persons, but rural persons were more likely to be white (44.1% vs. 32.3%, $P < 0.001$, Table 1). Those residing in rural areas were less likely than those in urban areas to have diagnoses of drug use problem (10.6% vs. 19.5%, $P < 0.001$) or hepatitis C (34.3% vs. 41.2%, $P = 0.001$), but had more advanced HIV infection at care entry (median CD4: 186 for rural vs. 246 for urban, $P < 0.001$). Rural persons were more

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TABLE 1. Characteristics of 8489 Persons Entering VA Care for HIV/AIDS During FY 1998–2006

Characteristics	Urban (n = 7784)	Rural (n = 705)	*P*
Age, median yr (IQR)	45.7 (39.6–52.0)	46.7 (39.5–52.9)	0.06
Gender, male, n (%)	7606 (97.7)	682 (96.7)	0.11
Race/ethnicity, n (%)			<0.001
Black	4459 (57.3)	306 (43.4)	
White	2511 (32.3)	311 (44.1)	
Hispanic	377 (4.8)	45 (6.4)	
Other/missing	437 (5.6)	43 (6.1)	
Alcohol problem, n (%)	1423 (18.3)	116 (16.5)	0.23
Drug use problem, n (%)	1519 (19.5)	75 (10.6)	<0.001
Depression, n (%)	1314 (16.9)	119 (16.9)	0.99
Hepatitis C, n (%)	3203 (41.2)	242 (34.3)	<0.001
Hepatitis B, n (%)	297 (3.8)	26 (3.7)	0.87
AIDS-defining illness, n (%)	931 (12.0)	107 (15.2)	0.01
CD4 count			<0.001
Median (IQR)	246 (78–445)	186 (45–317)	
<200, n (%)	3401 (43.7)	375 (53.2)	
200–349, n (%)	1556 (20.0)	134 (19.0)	
≥350, n (%)	2827 (36.3)	196 (27.8)	
cART initiation, n (%)			
Overall	5346 (68.7)	528 (74.9)	0.001
CD4 <200	2730 (80.3)	310 (82.7)	0.27
CD4 200–349	1167 (75.0)	112 (83.6)	0.03
CD4 ≥350	1449 (51.3)	106 (54.1)	0.44
Clinic visits*, median (IQR)			
Total	7 (4–11)	7 (4–10)	0.06
Infectious disease	5 (2–8)	4 (1–6)	0.001
General medicine	1 (0–4)	2 (0–4)	0.01

*Outpatient infectious disease and general medicine clinic visits in first year after care entry.

VA indicates Veterans Affairs; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; FY, fiscal years; IQR, interquartile range; cART, combination antiretroviral therapy.

TABLE 2. Two-Year Survival Analysis Among 8489 Persons Entering VA Care for HIV/AIDS During FY 1998–2006

Variable	Urban (n = 7784)	Rural (n = 705)
Deaths, n (%)	914 (11.7)	108 (15.3)
Deaths per 100 person-yr	6.3	8.5
Mortality hazard ratio		
Univariate	1.0	1.34 (1.05–1.69)
+ HIV severity at care entry*	1.0	1.18 (0.93–1.50)
Multivariate†	1.0	1.17 (0.92–1.50)

*Adjusted for HIV severity at care entry (CD4 and AIDS-defining illness within 180 days).

†Adjusted for CD4, AIDS-defining illness, age, alcohol or drug problem, and hepatitis B or C at baseline, and cART initiation as time dependent covariate.

VA indicates Veterans Affairs; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; FY, fiscal years; cART, combination antiretroviral therapy.

likely to be diagnosed with an AIDS-defining illness within 180 days of HIV care entry (15.2% vs. 12.0%, $P = 0.01$).

Overall, 5874 of the 8489 persons initiated cART in the VA within 2 years of care entry (69.2%). Rural persons were somewhat more likely to initiate cART in total (74.9% vs. 68.7%, $P = 0.001$), and across CD4 strata at care entry (Table 1). Among persons meeting Department of Health and Human Services guideline criteria for starting cART in place at time of care entry, 79.5% of urban and 82.7% of rural persons started cART within 2 years ($P = 0.11$).[22] Levels of cART initiation were also similar for rural and urban persons across CD4 strata at 3, 6, and 12 months following care entry. The median number of combined ID and general medicine clinic visits in first year was 7 for both rural and urban persons, although persons in rural areas had somewhat more frequent general medicine visits (median 2 for rural and 1 for urban persons, $P = 0.01$) and less frequent ID clinic visits (median 4 for rural persons and 5 for urban, $P = 0.001$).

Two years after entering care there were 1022 deaths (108 rural and 914 urban, Table 2). In Kaplan Meier survival analysis (Fig. 2), the mortality at 2 years was 15.3%% (95% CI: 12.9.%–18.2%) for rural persons and 11.7% (95% CI: 11.0%–12.5%) for urban (log rank $P = 0.004$). There were 8.5 deaths/100 person-years in the rural group and 6.3 deaths/100 person-years in the urban group. Hazards of death for rural and urban persons were proportional. The univariate mortality hazard ratio (HR) for rural persons relative to urban was 1.34 (95% CI: 1.05–1.50). Following adjustment for HIV severity at care entry (CD4 count and presence of AIDS-defining illnesses) the (HR) decreased to 1.18 (95% CI: 0.93–1.50). Addition of age, substance use diagnoses, hepatitis B or C at care entry, and cART initiation as a time dependent covariate did not significantly change this result (HR: 1.17, 95% CI: 0.92–1.50).

Hazards of death were lower for persons entering care after 2002 than for those entering care 1998–2002 (HR: 0.85, 95% CI: 0.73–0.98). Inclusion of year of care entry in models did not change the association between rural residence and mortality. The interaction between rural residence and year of care entry was not significant ($P = 0.42$), indicating that the association between rurality and mortality was stable over the study period. The association between rural residence and mortality did not change meaningfully with longer observation periods (HR at 6 years: 1.24, 95% CI: 1.05–1.48).

As would be expected for a population on therapy, the median CD4 count at care entry was higher for the subgroup of 3584 persons with cART use at initiation of HIV care in VA than for the 8489 persons without cART use at entry (375 vs. 241). However, the median CD4 was again lower for rural compared with urban veterans in this subgroup (320 rural vs. 382 urban, $P = 0.001$).

DISCUSSION

We found that rural residence was associated with delayed care entry and increased mortality among persons initiating HIV care in VA. The association between rural residence and mortality decreased after adjustment for HIV severity at care entry and was no longer statistically significant. Moreover, engagement in HIV care following entry was similar for rural and urban persons in VA, as evidenced by

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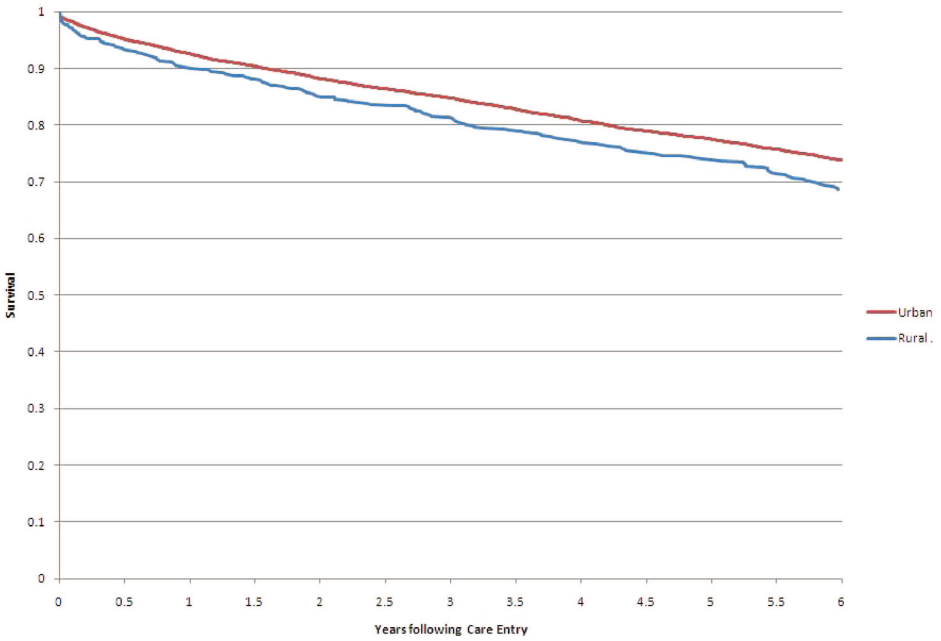

FIGURE 2. Survival following HIV care entry for rural and urban persons.

similar numbers of outpatient visits and levels of cART initiation. Overall, our findings indicate that later care entry mediates increased mortality for rural compared with urban persons with HIV in VA. Interventions to reduce the survival disparity between rural and urban persons with HIV in VA care should promote timely HIV diagnosis and linkage to care for rural persons.

The difference in HIV severity at care entry observed in our study represents a significant delay in care for rural persons. Longitudinal studies in the pre-cART era estimated the average rate of CD4 decline in untreated persons with HIV.[23] Extrapolating from these data, the observed difference in CD4 count at presentation corresponds to an approximately 9- to 12-month relative delay in care entry for rural compared with urban persons.

Later entry into HIV care for rural compared with urban persons could result from later HIV diagnosis or greater delays in linkage to care following diagnosis, but our study cannot distinguish these possibilities. Available evidence indicates that later diagnosis at least partly explains delayed care entry in the rural setting. Recent analysis of HIV surveillance data in South Carolina found that rural residence was associated with more advanced HIV infection at diagnosis.[24]

Greater stigma surrounding HIV infection in rural areas may lead to less disclosure of risk factors and fewer persons seeking HIV testing.[2,25] In addition, rural providers who do not frequently encounter HIV clinical issues in practice may be less likely to recognize HIV risk or early clinical manifestations in the healthcare setting and suggest testing.[26] It is also plausible that geographic isolation and travel burdens further delay linkage to HIV care for rural persons after a positive test. Greater understanding of the relative roles of later diagnosis and delayed linkage to care, and their underlying causes in rural areas, is necessary to inform interventions to improve outcomes for rural persons with HIV. Recent analysis of HIV surveillance data in South Carolina found that rural residence was associated with more advanced HIV infection at diagnosis.[24]

Veterans receive care in a centralized, integrated system that devotes significant resources to promoting evidence-based practice.[27] These characteristics may affect the accessibility and quality of care for rural veterans, and impact generalizability of our findings to non-VA care for rural persons with HIV. Centralization of HIV care in large, mostly urban, VA facilities creates travel burdens for rural veterans seeking care. However, non-VA HIV care is also concentrated in large cities, and persons in HIV care outside VA may not have access to transportation services such as those available to veterans.[3] Geographic barriers to HIV care may actually be greater outside VA. In addition, the VA Center for Quality Management measures and reports HIV care quality at the facility level. These efforts likely contribute to the overall high HIV care quality, and low level of quality variation across facilities, observed in VA.[28] HIV quality measures tracked and reported across VA facilities include frequency of routine laboratory monitoring and use of antiretroviral therapy. This may contribute to the similar levels of primary care engagement and cART initiation observed for rural and urban veterans. Rural-urban variation in HIV care and outcomes may be greater outside VA, where there is less integrated oversight of HIV care in rural areas.

Prior reports have emphasized the relevance of urban to rural migration in assessing outcomes for rural persons with HIV.[29] In the early years of the HIV epidemic in the United States several reports described a "returning home" phenomenon where persons moved to rural areas from urban areas after diagnosis with HIV.[30,31] This may have been a phenomenon of the pre-cART era when treatment options were limited. In the modern era of effective HIV treatment, urban persons may have less incentive to return to rural areas where

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access to specialized HIV care is limited. In the late 1990s HIV Cost and Services Utilization Study data showed that persons with HIV often reported relocating to obtain support, but did not often report relocating to "return home." Urban to rural migration was no more likely than the reverse.[32]

Nonetheless, it is possible that veterans who were receiving HIV care outside of VA in urban areas may enroll in VA care following relocation to rural areas where there are fewer HIV care options. This could bias observational studies of association between rural residence and HIV outcomes in VA if rural persons were more likely than urban persons to have had longstanding HIV diagnoses or have received care before entering VA. Using a previously validated algorithm, we excluded 29.7% of persons with evidence of cART use on care entry. This is consistent with prior chart review in Atlanta VA showing that 75% of persons were cART naive on entering VA care.[17] However, we could not determine whether patients may have received HIV care or cART at other times prior to establishing VA care.

This study has other limitations. We excluded a significant number of persons without an available viral load or CD4 count at care entry, and missing laboratory data may have led to sample bias. The frequencies of rural residence and mortality were similar for persons with available and missing laboratory data, and associations between missing laboratory data and other study variables did not differ by rurality. This suggests that missing laboratory data were unlikely to have introduced significant bias. We used ICD-9 codes to determine diagnoses, and it is possible that accuracy of diagnosis and coding of some conditions, such as drug use problems, may differ in rural and urban areas. There is substantial geographic and socioeconomic variation between rural areas across the United States, and associations between rural residence and HIV outcomes may vary.[20] These effects may be lost in aggregation in a national study such as this. Few women were included in this study, but women constitute an increasing fraction of persons with HIV in the United States. These limitations are inherent to the VA setting and studies using large datasets; however, a large study of rural-urban variation in HIV outcomes would be difficult in other settings.

CONCLUSIONS

We find that later entry into care drives increased mortality for rural compared to urban veterans living with HIV. Future studies should explore person, care system, and community-level determinants of later care entry for rural persons with HIV. Enhanced understanding of these factors is necessary to inform interventions to support timely HIV diagnosis and linkage to HIV care in rural areas.

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