DEPARTMENT OF VETERANS AFFAIRS

Antiretroviral Adherence Among Rural Compared to Urban Veterans with HIV Infection in the United States

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Introduction

Combination antiretroviral therapy (cART) has brought great improvements to the survival rate and quality of life of persons living with HIV infection.[1,2,3] To experience the maximum benefits of cART therapy, however, persons living with HIV must maintain high levels of adherence to often complex antiretroviral regimens.

Rural-dwelling persons in the US with newly diagnosed HIV infection (constituting approximately 8–9% of the total number of those living with HIV) experience higher mortality than do their urban counterparts. Though the reasons for this difference remain unclear,[5,6] it has been demonstrated that rural persons with HIV face barriers to care that are related to the rural environment, including travel burdens, limited availability of HIV care providers, limited peer support, and significant HIV-related social stigma that brings with it greater concern for discretion regarding treatment.[7,8,9]

These factors may contribute to the poor adherence to antiretroviral therapy among rural populations with HIV[10], which may in turn play a role in the higher mortality among this group. Rural Veterans with HIV share many of the same obstacles to care as do rural non-Veteran experiencing HIV. They also share a similar higher mortality rate, with rural Veterans entering care at more advanced stages of HIV infection.[6]

Thus, this study used the Veterans Administration (VA) integrated electronic health record to examine

Key Findings

In a comparison of adherence to antiretroviral HIV medications between 1,781 Veterans living in rural areas and 18,519 Veterans classified as urban, this study revealed greater medication adherence among the rural group. Predictors of high adherence were

- Residence in a rural-small town/remote setting
- Increasing age, white race
- Absence of alcohol or substance abuse
- Absence of hepatitis C infection

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antiretroviral adherence among rural and urban-dwelling Veterans in the U.S., testing the hypothesis that rural-dwelling Veterans would have lower antiretroviral adherence than urban-dwelling Veterans.

Methods

This retrospective cohort study examined the association between rural and urban residence and antiretroviral adherence among veterans initiating cART in the U.S. during fiscal years (FY) 1998–2007, with follow-up complete through FY 2008.

Data sources and study sample

Persons entering VA care for HIV infection were identified in terms of one or two inpatient HIV-related ICD-9-CM codes, 042 or V08, or related diagnostic related groups 488–490. Patients were followed using 1) Patient Treatment and Outpatient care files, 2) prescription records obtained from Pharmacy Benefits Manager files, 3) mortality from the VA status file, and 4) laboratory test results from the Decision Support System (DSS) files. cART was defined as a minimum of three antiretroviral medications and the start date of cART treatment. Excluding 815 persons who died in the year following cART initiation, the remaining study sample included 20,301 Veterans.

Variables

The primary independent variable was rural vs. urban residence at the time of cART initiation. Residence was determined by linking ZIP codes to Rural Urban Commuting Area (RUCA) codes. The 33 RUCA codes were collapsed into a three-level residence variable: 1) urban, 2)rural, micropolitan (urban clusters of 10,000–49,000), and 3) rural, small town/remote. This divided the sample into 1,781 Veterans classified as rural, 18,519 as urban.

Dependent variables were two separate pharmacy-based refill measures of antiretroviral adherence during the year following cART initiation. These were the MEDOUT index (which determines the proportion of days in which the patient was without medication)[10], and the proportion of days covered (PDC) by cART. The time interval analyzed was the period between the first and last antiretroviral fills in the year following cART initiation. Here, (1–MEDOUT) was used to reflect the proportion of days with available medication, representing the upper bound of antiretroviral adherence, assuming no medication fills were obtained outside the VA.

Refill data was used to calculate the PDC by cART during the year after starting therapy (the number of days on which cART criteria were met, divided by 365). The time denominator for (1–MEDOUT) was the number of days between the first and last refills in the year, which may be less than 365 for persons who stop refilling medications well before the year's end. Dichotomous measures of high adherence were defined as either (1–MEDOUT) of greater than 0.90 or PDC greater than 0.90, both having a theoretical maximum of 1.0.

Covariates included variables that may confound associations between residence and antiretroviral adherence. These included age, sex, race/ethnicity, CD4 count (an indicator of HIV severity), and comorbid diagnoses, the latter involving alcohol and illicit substance use disorders, depression, AIDS defining illnesses, and hepatitis C infection. Race/ethnicity was categorized as 1)black, 2)white, non-Hispanic, 3) Hispanic, or 4)other.

Analysis

Multivariable regression analysis was used to determine associations between residence categories and the dichotomous measures of high adherence after adjusting for cofounding effects of covariates. CD4 data was available for 15,340 of the total cohort, and was fitted to the entire cohort to test for potential bias due to missing CD4 data. Analyses were repeated using a two-year time frame to ensure uniform follow-up time for all persons. Analyses were also repeated using a slightly lower adherence threshold of 0.85.

Findings

Compared to urban-dwelling Veterans, rural Veterans were older and more likely to be white, while being less likely to have an alcohol or substance use disorder or hepatitis C infection. However, rural Veterans had more advanced immune compromise at care entry as revealed by lower CD4 counts (Table 1).

Distributions for both (1–MEDOUT) and PDC were skewed towards generally lower adherence, antiretroviral adherence increasing as the residential environment became progressively more rural (Table 2). This relationship between residence area and adherence did not change substantially with the introduction of the four dichotomous measures of high adherence (Table 3).

Table 1. Characteristics of 20,301 veterans initiating antiretroviral therapy during 1998–2007, by residence

Characteristic	Overall N = 20,301	Urban N = 18,519 (91.2 %)	Rural		χ^2 (DF)[b]	p
			Micropolitan N = 1,028 (5.1 %)	Small town/remote N = 754 (3.7 %)		
Age, median (IQR), years	45 (39–52)	45 (39–52)	46 (39–53)	46 (40–53)	9.7 (2)	0.008
Sex, male, N (%)	19,851 (97.8)	18,117 (97.8)	997 (97.0)	737 (97.8)	3.2 (2)	0.20
Race/ethnicity, N (%)						
Black	10,162 (50.1)	9,525 (51.4)	381 (37.1)	256 (34.0)	209 (6)	<0.0001
White	7,699 (37.9)	6,755 (36.5)	516 (50.2)	428 (56.8)		
Hispanic	1,071 (5.3)	990 (5.4)	56 (5.4)	25 (3.3)		
Other/missing	1,369 (6.7)	1,249 (6.7)	75 (7.3)	45 (5.9)		
Substance use disorder, N (%)	3,208 (15.8)	3,058 (16.5)	87 (8.5)	63 (8.4)	80.1 (2)	<0.0001
Alcohol Use Disorder, N (%)	2,783 (13.7)	2.600 (14.0)	115 (11.2)	68 (9.0)	21.3 (2)	<0.0001
Depression, N (%)	3,078 (15.2)	2,812 (15.2)	163 (15.9)	103 (13.7)	1.7 (2)	0.42
AIDS defining illness, N (%)	1,470 (7.2)	1,323 (7.1)	80 (7.8)	67 (8.9)	3.7 (2)	0.15
Hepatitis C, N (%)	8,193 (40.4)	7,564 (40.8)	396 (38.5)	233 (30.9)	31.3 (2)	<0.0001
CD4[a], median (IQR), cells/mm^3	295 (126–476)	300 (128–478)	269 (106–462)	247 (92–440)	18.1 (2)	0.0001

[a]CD4 results were available for 15,340 patients
[b]Chi-square value and degrees of freedom for Chi-square or Kruskal–Wallis tests

During the first year after starting cART, 90 % of antiretroviral prescription fills were for 30 days and the median number of fills was 8. Distributions for both (1 − MEDOUT) and PDC were skewed towards lower adherence. Antiretroviral adherence increased as the residential environment became progressively more rural (Table 2). This finding was independent of adherence definition. The median PDC by cART in the first year on therapy was 0.72 for urban veterans, 0.75 for rural-micropolitan veterans, and 0.79 for rural veterans residing in small towns or remote areas (Kruskal–Wallis $\chi^2 = 35.8$, DF = 2, $p < 0.0001$). The percentage of veterans with PDC greater than 0.90 in the first year covered by at least three medications ranged from 26.8 % among urban veterans to 35.3 % among rural veterans in small town and remote settings ($\chi^2 = 30.2$, DF = 2, $p < 0.0001$).

Multivariate analysis involving the entire cohort showed an association between high adherence and increasing age, white race, presence of an AIDS defining illness, absence of an alcohol or substance use disorder, and absence of hepatitis C infection. Adjustment for these variables showed a decrease in the relationship of high adherence and rural residence. Addition of CD4 count to the multivariate model did not significantly change the adjusted odds ratios for high adherence.

Table 2. Antiretroviral adherence, by residence

Adherence measure	Overall N = 20,301	Urban N = 18,519 (91.2 %)	Rural		χ^2 (DF)[d]	p
			Micropolitan N = 1,028 (5.0 %)	Small town/remote N = 754 (3.8 %)		
1 − MEDOUT, median (IQR)	0.86 (0.67–0.96)	0.85 (0.66–0.96)	0.87 (0.69–00.96)	0.89 (0.71–0.98)	26.2 (2)	<0.0001
High adherence MEDOUT[a], N (%)	8,217 (40.5)	7,426 (40.1)	428 (41.6)	363 (48.1)	20.1 (2)	<0.0001
PDC[b], median (IQR)	0.73 (0.47–0.91)	0.72 (0.43–0.90)	0.75 (0.49–0.92)	0.79 (0.53–0.94)	35.8 (2)	<0.0001
High adherence PDC[c], N (%)	5,544 (27.3)	4,969 (26.8)	309 (30.1)	268 (35.3)	30.2 (2)	<0.0001

[a]1 − MEDOUT greater than 0.90
[b]Proportion of days covered
[c]Proportion of days covered greater than 0.90
[d]Chi-square value and degrees of freedom for Chi-square or Kruskal–Wallis test
The relative relationships between rural versus urban residence and high adherence did not vary substantively depending on which of four dichotomous measure of high adherence we examined [use of 0.85 or 0.90 cutoff for (1 − MEDOUT) or PDC measures, respectively]. For simplicity, we present unadjusted and multivariable adjusted results for relative associations (odds ratios) between predictor variables and high adherence defined as PDC greater than 0.90 (Table 3).

Conclusion

Contrary to the study's hypothesis, rural-dwelling Veterans showed greater adherence to antiretroviral therapy than did urban Veterans. Apart from the rural demographic which included factors shown to enhance retroviral adherence (such as white race and relatively older age, and less alcohol and substance abuse), it is important to note that since this study was confined to Veterans it may not be generalizable to the HIV population as whole in that Veterans are provided resources which may not be accessible to the larger non-Veteran population of persons living with HIV. These advantages include travel reimbursement and more discreet ways of delivering cART medications, such as through VA's centralized mail order pharmacy program. *However*, the study's results demonstrate that cART adherence—which was found to be suboptimal in both rural and urban Veterans--could be strengthened by removing certain barriers specific to geographic context.

Impact

- Measures taken by the VA system to overcome barriers to HIV medication adherence in rural settings can constitute a successful response to the disparity between rural and urban treatment contexts. These measures include travel reimbursement to Veterans living with HIV and more discreet ways of delivering medications.
- This finding can inform clinics outside the VA system in their efforts to enhance antiretroviral adherence, providing resources similar to those accessible to rural Veterans.

Table 3. Predictors of high antiretroviral adherence

Predictor	Unadjusted odds ratio (95 % CI)	Multivariable model odds ratio (95 % CI)
Residence		
Urban	Ref	Ref
Rural, micropolitan	1.17 (1.02–1.34)	1.04 (0.90–1.20)
Rural, small town/remote	1.49 (1.28–1.73)	1.24 (1.09–1.56)
Age		
<50	Ref	Ref
50–64	1.60 (1.49–1.71)	1.48 (1.39–1.59)
≥65	1.95 (1.68–2.26)	1.60 (1.38–1.86)
Race/ethnicity		
White	Ref	Ref
Black	0.58 (0.45–0.51)	0.55 (0.51–0.59)
Hispanic	0.69 (0.60–0.80)	0.79 (0.68–0.91)
Other/missing	0.85 (0.75–0.96)	0.82 (0.72–0.92)
AIDS defining illness		
Yes	1.17 (1.04–1.31)	1.18 (1.05–1.33)
No	Ref	Ref
Alcohol/drug use disorder		
Yes	0.54 (0.49–0.59)	0.71 (0.65–0.78)
No	Ref	Ref
Hepatitis C		
Yes	0.58 (0.54–0.62)	0.70 (0.65–0.75)
No	Ref	Ref

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