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Determinants of Treatment Access in a Population-based Cohort of HIV-positive Men and Women Living in Argentina

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Abstract

Objective: To report emerging data on the use of highly active antiretroviral therapy (HAART) in Argentina by assessing patterns of HAART access and late vs early treatment initiation in a population-based cohort of adults infected with HIV type-1.

Design: The Prospective Study on the Use and Monitoring of Antiretroviral Therapy (PUMA) is a study of 883 HIV-positive individuals enrolled in the Argentinean drug treatment program. Individuals were 16 years of age and older and were recruited from 10 clinics across Argentina.

Methods: Sociodemographic and clinical characteristics were examined using contingency tables (Pearson chi-square test and Fisher exact test) for categoric variables and Wilcoxon rank-sum test for continuous variables. To analyze time to initiation of HAART we used Kaplan-Meier methods and Cox regression.

Results: Patients who initiated HAART were more likely to be older, have an AIDS-defining illness, be an injection drug user (IDU), have a lower median CD4 cell count, have a higher median viral load, and be less likely to be men who have sex with men (MSM). In multivariate analysis, AIDS-defining illness and plasma viral load were significantly associated with time to starting therapy. Patients who received late access were more likely to be diagnosed with AIDS and have higher median plasma viral loads than those receiving early access.

Conclusion: Our results indicate that despite free availability of treatment, monitoring, and care in Argentina, a significant proportion of men and women are accessing HAART late in the course of HIV disease. Further characterization of the HIV-positive population will allow for a more comprehensive evaluation of the impact of HAART within the Argentinean drug treatment program.

Introduction

Highly active antiretroviral therapy (HAART) has been shown to substantially reduce mortality and morbidity for individuals infected with HIV type-1 since the introduction of these regimens in 1996.[1-4] A recently published comparative analysis on the impact of HAART in low- vs high-income countries suggests that HAART is highly effective in both settings;[5] however, little is known regarding access to and impact of HAART in intermediate countries.

Of the nearly 40 million people living with HIV/AIDS worldwide, approximately 1.7 million people are living with HIV in South America.[6] In Argentina, there are currently 130,000 people infected with HIV, and the prevalence among adults is estimated to range from 0.3% to 1.9% of the population.[6] HIV predominantly affects injecting drug users (IDU) and men who have sex with men (MSM);[7-10] however, more recently, heterosexual transmission has become the fastest growing transmission group.[7] The majority of people living with HIV/AIDS reside in Buenos Aires, Cordoba, and Santa Fe.[6]

In Argentina, antiretroviral drugs are provided free of charge to eligible HIV-positive individuals. Since 1990, the National Program has covered the cost of antiretroviral drugs, both generic and nongeneric formulations, as well as patient care, including tests for viral load, CD4 cell counts, and more recently, drug resistance. Currently, it is estimated that 68% of those in need of antiretroviral therapy in South America (315,000 individuals) are provided with medication by established drug treatment programs.[11]

The objectives of this study were to briefly characterize the determinants of access to HAART and to assess late vs early initiation of HAART in a population-based cohort of HIV-positive Argentinean men and women.

Methods

PUMA is an ongoing multicenter cohort study designed to monitor access to and impact of HAART in Argentina using prospectively collected sociodemographic, clinical, and morbidity and mortality data for HIV-positive individuals 16 years and older, who were antiretroviral-naive. Ethical approval was obtained from the institutional review boards of each collaborating center.

Data Collection

Data were collected from 10 public health facilities in Argentina from January 1, 2003, to August 31, 2006, and pooled together at a coordinating center. Participants were recruited from treatment centers located in Rosario, Cordoba, Mar del Plata, and Buenos Aires, which represent the provinces with the highest prevalence of HIV in Argentina. HAART eligibility and the HAART regimens available from the National Program remain consistent with those recommended by the International AIDS Society (IAS)-USA guidelines.[2] The date of therapy initiation was known and participants were required to have at least one documented plasma viral load measurement and one CD4 cell count performed within 6 months prior to the initiation of HAART. Additional data were extracted from enrollment notes, laboratory reports, central microbiological laboratories, pharmacy records, and patient charts. Deaths that occurred during the study period were identified via clinic notes and patient charts. HAART regimens included 2 nucleoside reverse transcriptase inhibitors plus either of the nonnucleoside reverse transcriptase inhibitors efavirenz or nevirapine, or a ritonavir-boosted protease inhibitor (indinavir, saquinavir, lopinavir, atazanavir, or fosamprenavir).

Statistical Analysis

The first analysis evaluated participant characteristics associated with initiation of HAART. Baseline variables were measured within 3 months before starting HAART and included age (years), sex (male and female), transmission group (MSM, IDU, and heterosexual), CD4 cell count (cells/microliter [mcL]), plasma HIV-1 viral load (copies/mL), and AIDS-defining illness. The second analysis was restricted to individuals who started HAART during the follow-up period, rather than at baseline, and examined time to initiation of therapy. The final analysis included all individuals who initiated HAART during the study, and evaluated characteristics associated with late (CD4 ≤ 200 cells/mcL vs early (CD4 > 200 cells/mcL) initiation of HAART. All of the previously mentioned variables were included in the final 2 analyses.

Categoric variables were compared using contingency tables (Pearson chi-square test and Fisher exact test). Comparisons of continuous variables were carried out using Wilcoxon rank sum test. Kaplan-Meier methods and Cox regression were used to analyze time to initiation of HAART. Analyses were performed using SAS software version 8.02 (SAS, Cary, NC). All significance tests were 2-sided and P values < .05 were considered statistically significant.

Results

Between January 1, 2003, and August 31, 2006, a total of 883 patients were enrolled in PUMA, 648 (78%) of whom were eligible for HAART based on the IAS-USA guidelines.[2] A total of 47 (9%) of the treatment-naive individuals at baseline did not return for follow-up visits for greater than 6 months after baseline measurements and were never treated. These individuals were excluded from further analysis.

The baseline sociodemographic and clinical characteristics of all enrolled patients who initiated HAART vs those who did not initiate HAART at baseline are summarized in Table 1 . Compared with individuals who remained HAART-naive at baseline, those who initiated therapy were more likely to be older ($P < .0001$), have an AIDS-defining illness ($P < .0001$), have a lower median CD4 cell count ($P < .0001$), and have a higher median viral load ($P < .0001$). Proportionally more MSM ($P = .04$) and more IDU ($P = .02$) initiated HAART at baseline.

Cox proportional hazard analysis was conducted among those who were not receiving HAART at baseline (n = 303) to assess factors associated with time to starting HAART during the follow-up period. Table 2 provides the results of the univariate and multivariate Cox analyses. In the univariate model, age (risk ratio [RR] = 1.31 per 10 years, 95% confidence interval [CI] 1.091.57), AIDS-defining illness (RR = 6.74, 95% CI 4.2110.80), and plasma viral load (RR = 2.59 per $\log_{10}$ increase, 95% CI 1.873.58) were significantly associated with the incidence of HAART initiation during the follow-up period. In multivariate analysis, AIDS-defining illness (adjusted risk ratio [ARR] = 4.28, 95% CI 2.497.37) and plasma viral load (ARR = 2.17 per $\log_{10}$ increase, 95% CI 1.563.02) were included in the model, both of which remained statistically significant.

Table 1: Baseline Sociodemographic and Clinical Characteristics of HIV-positive Individuals Who Initiated HAART at Baseline vs. Those Who Did Not Initiate HAART at Baseline

	HAART Initiation		
Variable	**No (n = 188)**	**Yes (n = 648)**	***P value***
Sex			
Male	140 (74)	444 (69)	.15
Female	48 (26%)	202 (31%)	
Age† (years)	33 (26.539)	36 (3143)	< .001
MSM (n = 263)*			
No	117 (62%)	456 (70%)	.03
Yes	71 (37)	192 (30)	
IDU (n = 109)*			
No	173 (92%)	554 (85%)	.02
Yes	15 (8%)	94 (15%)	
Heterosexual transmission (n = 426)*			
No	97 (52)	313 (48)	.43
Yes	91 (48)	335 (52)	
Prior AIDS-defining illness*			
No	176 (94)	426 (66)	< .001
Yes	12 (6)	222 (34)	
CD4† (cells/mcL)	468 (316700)	133 (48255)	< .001
HIV RNA† (copies/mL)	17,197 (465155,396)	68,505 (7370236,000)	< .001

*Number (percentage)
†Median (interquartile range)
HAART = highly active antiretroviral therapy; IDU = injection drug use; mcL = microliter; MSM = men who have sex with men

Table 2: Univariate and Multivariate Cox Proportional Hazard Analysis of Factors Associated With Time to Initiation of Therapy Among Persons Starting HAART During the Follow-up Period (n = 303)

Time to Initiation of Therapy	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Sex (male vs female)	0.92 (0.621.37)	--
Age (per 10 years)	1.31 (1.091.57)	--
MSM Risk (yes vs no)	0.77 (0.521.12)	--
IDU Risk (yes vs no)	1.67 (0.932.99)	--
Prior AIDS-defining illness (yes vs no)*	6.74 (4.2110.80)	4.28 (2.497.37)
pVL (per $\log_{10}$ copies/mL increase)	2.59 (1.873.58)	2.17 (1.563.02)
CD4 (per 100 cell/mcL decrease)*	1.00 (0.991.01)	--

*Evaluated from baseline value onward
HAART = highly active antiretroviral therapy; IDU = injection drug use; mcL = microliter; MSM = men who have sex with men; pVL = plasma viral load

Table 3: Sociodemographic and Clinical Characteristics of HIV-positive Individuals by Early or Late Start of Treatment

Variable	Treatment Initiation at Baseline		*P* value
	Early Access (CD4 > 200 cells/mcL)(n = 181)	Late Access (CD4 ≤ 200 cells/mcL) (n = 397)	
	Sex*		
Male	118 (66)	277 (70)	.33
Female	62 (34)	119 (30)	
Age (years)†	35 (3042)	36 (3143)	.20
MSM (n = 178)*	60 (33)	118 (30)	.44
IDU (n = 79)*	18 (10)	61 (15)	.09
Heterosexual transmission (n = 300)*	95 (52)	205 (52)	1.00
	Prior AIDS-defining illness*		
No	155 (86)	233 (59)	< .0001
Yes	26 (14)	164 (41)	
HIV RNA (copies/mL)†	60,559 (16,323181,700)	133,824 (48,541383,000)	< .0001

Note: Documented results of CD4 cell count within 1 year prior to starting treatment were missing for 69 patients, and these patients were eliminated from analysis.
*Number (percentage)
†Median (interquartile range)
IDU = injection drug use; mcL = microliter; MSM = men who have sex with men

Table 3 summarizes the factors contributing to late (CD4 ≤ 200 cells/mcL) vs early (CD4 > 200 cells/mcL) access to HAART. This analysis was restricted to 578 of the 648 patients, because 69 (11%) individuals did not have CD4 measurements within 12 months prior to the initiation of HAART. Compared with those receiving early access to HAART, patients who received late access were more likely to have an AIDS-defining illness ($P < .0001$) and have higher median plasma viral loads ($P < .0001$).

Discussion

This is the first report on selected determinants of treatment access within a prospective multisite cohort in Argentina. We observed that primarily clinical factors were associated with eligibility for HAART, and a significant proportion of patients received late access to therapy. Age, AIDS-defining illness, CD4 count, and plasma viral load were associated with HAART initiation. AIDS-defining illness and viral load were also associated with time to initiation of and late access to HAART.

As expected, those who started HAART in this study had lower median CD4 counts and higher median plasma viral loads. The majority of individuals in PUMA presenting with an AIDS-defining illness were also given HAART. According to the established guidelines, it is recommended that those presenting with symptomatic HIV should be immediately provided treatment.[2] It is therefore of concern that 6% of individuals with an AIDS-defining illness were not provided therapy. There was no indication as to why these individuals were not treated. It should be noted, however, that tuberculosis is a leading AIDS-defining illness in Argentina) and many treating physicians may elect to delay initiation of HAART in HIV/tuberculosis co-infected individuals who have CD4 counts > 200 cells/mcL.[12]

Proportionally more IDU initiated HAART at baseline rather than remaining HAART-naive. A high risk for HIV infection has previously been observed in this group of individuals.[8,13-16] In Buenos Aires, a previous study demonstrated that the prevalence of HIV among IDU was 44.3% in 2001.[8] As IDU was formerly the most common mode of transmission in Argentina, it is expected that individuals belonging to this group would have been infected for a longer period of time compared with other more recently prevalent modes of transmission, such as heterosexual contact. These individuals may therefore have been at greater risk for more advanced disease and thus have required antiretroviral therapy.

MSM have also traditionally been regarded as a high-risk group for HIV infection in Argentina with the prevalence of infection among this group ranging from 7% to 15%.[6,17,18] One interesting observation of the present analysis was the number of MSM present in the population. There were nearly twice as many individuals infected with HIV via heterosexual transmission. It may be that MSM in the Argentinean population were aware of their increased risk and the progression of HIV. Those with more advanced disease may have sought treatment prior to the initiation of the present study, thus making them ineligible for inclusion. This could explain why there are more individuals infected via heterosexual transmission in this cohort. Although a stigma for MSM does exist in Argentina, as in other Latin American countries, it is unlikely that any significant underreporting of this variable would occur in the clinical setting of this cohort.

Individuals receiving late access to therapy were more likely to have an AIDS-defining illness. This observation was anticipated because AIDS-related illnesses are, by definition, associated with decreased immune response and thus lower CD4 counts.[19,20] Similarly, the association between late access to therapy and high plasma viral load indicates that those with the most advanced disease were treated immediately upon entry into the program. Treatment guidelines suggest consideration of increased viral load in decisions about when to initiate HAART.[2]

Several features of our study should be highlighted. First, because access to HAART in Argentina is free of charge, all HIV-infected individuals should have equal access to therapy. It is therefore unlikely that this study had any of the selection biases that may be introduced when therapy is not free of charge. Furthermore, the comprehensive geographic representation of our study reduces any possible bias that may be introduced by focusing on a single site. Individuals at a single site may have unusual characteristics associated with their eligibility for HAART. Including a variety of clinics from different regions of Argentina reduced the possible effect of random variation between sites and any other outlying characteristics. Finally, readers should be cautious about the limitations of the present study. Patients excluded from analysis because of either lack of attendance for follow-up or missing CD4 measurements may bias the analysis of outcome measures. For example, the excluded individuals may have had consistently low CD4 counts and thus may have been too ill to return for follow-up visits. Alternatively, these individuals could have had consistently high CD4 counts and considered their attendance unnecessary. In addition, the small number of active patients in our cohort limits our capacity to generalize our results to all HIV-infected individuals in Argentina. Finally, other variables including income, education, other co-infections or comorbidities, and availability of healthcare services cannot be excluded as other determinants of access to antiretroviral therapy in Argentina. The proportion of patients with AIDS at enrollment suggests that a late HIV diagnosis appears to be common

in Argentina. Seroprevalence studies in middle-income countries indicate that approximately one third of individuals with HIV are unaware of their infection.[21] Considering the wide availability of free HIV testing and treatment in Argentina, a late diagnosis of HIV is more likely associated with underutilization and/or missing opportunities for HIV detection within the healthcare system.

In conclusion, our results indicate that men and women in Argentina are accessing HAART according to established treatment guidelines.[2] However, a considerable number of people initiated therapy late in the course of HIV disease. Further characterization of the population of HIV-positive individuals eligible for HAART in Argentina, in terms of co-infections or socioeconomic status for example, is necessary to better understand the sociodemographic and clinical characteristics of the HIV-infected population as a whole and to perform a more comprehensive evaluation of the HAART treatment program.

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