Original Articles

Treatment as prevention in resource-limited settings: is it feasible to maintain HIV viral load suppression over time?

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Abstract

Introduction: Recently, there has been increasing interest in the role of "treatment as prevention" (TasP). Some of the questions regarding TasP strategies arise from the perceived difficulties in achieving and maintaining viral load (VL) suppression over time and the risk of emergence of viral resistance that could compromise future treatment options. This study was conducted to assess these questions in a resource-limited setting.

Methodology: We performed a retrospective observational study of HIV-infected patients diagnosed in the pre-HAART era on follow-up at a private center from Buenos Aires, Argentina. Socio-demographic, clinical, and laboratory data were extracted from clinical charts. Analyses were performed to test for potential associations of selected variables with current virologic failure or use of third-line drugs.

Results: Of 619 patients on follow-up, 82 (13.2%) were diagnosed in the pre-HAART era. At the time of our study, 79 (96.3%) patients were on HAART, with a median duration of 14 years (IQR 12–15) of therapy, and exposure to mono or dual nucleoside reverse transcriptase inhibitors regimens in 47.8% of cases. Sixty-nine patients (87.3%) had undetectable VL, 37 (46.8%) never presented virologic failure, and 19 (24.1%) experienced only one failure. Thirteen patients (16.5%) were receiving third-line ART regimens, with an average of 2.7-fold more virologic failures than those on first- or second-line regimens ($p = 0.007$).

Conclusions: Maintaining viral load suppression over time in resource-limited-settings is feasible.

Key words: HIV; antiretroviral therapy; viral suppression; Argentina

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Introduction

The introduction of highly active antiretroviral therapy (HAART) in 1996 was one of the greatest successes in the history of medicine [1,2]. HAART stops HIV replication; consequently, plasma HIV RNA levels decrease to undetectable levels within a matter of weeks. As a result, immune reconstitution takes place, virtually halting the risk of HIV disease progression and death [3]. HAART has dramatically modified the natural history of HIV disease, transforming an otherwise rapidly fatal disease into a chronic manageable condition [4,5,6,7,8].

Studies have repeatedly shown that viral load is the strongest predictor of HIV transmission in any setting [9,10,11]. HAART decreases viral load in blood and simultaneously in other biological fluids, including genital secretions [12,13]. Therefore, the potential role of antiretroviral agents to decrease HIV transmission has been an area of much scientific interest. Strong proof of concept of the effectiveness of the preventive role of HAART has been shown in studies of vertical transmission [9,14], HIV-serodiscordant couples [10,11,15,16], and also at the community level [17,18,19,20]. Evidence continues to grow, increasingly supporting the notion that expansion of HAART coverage represents an invaluable tool to curb the growth of HIV and AIDS [21].

However, some skepticism remains regarding the ability to implement "test and treat" strategies, particularly in resource-limited-settings. Key among these concerns are the perceived difficulties in achieving and maintaining viral load (VL) suppression while taking HAART over time, the risk of emergence of viral resistance that could compromise future treatment options [22], and the emergence of risk compensation that might offset the potential positive impact of HAART on HIV transmission [23,24,25,26].

We assessed the feasibility of current treatment options for achieving and sustaining viral load replication suppression in a resource-limited setting by analyzing the current status of people living with

HIV/AIDS (PLWHA) who were diagnosed before the introduction of HAART in Argentina. Individual charts of patients diagnosed with HIV in the pre-HAART era on active follow-up in our center were reviewed to assess their current immune-virologic status and to identify potential predictors of current virologic failure or use of third-line drugs.

Methodology

Study design and population

This retrospective cohort study was conducted at a private HIV center in Buenos Aires, Argentina. We included PLWHA who were diagnosed before 1 January 1997 (pre-HAART era) and were on active follow-up at our center as of December 2011.

Definitions

The "pre-HAART era" was defined as the period before 1997, which coincides with the first implementation of HAART in Argentina. We considered patients "on active follow-up" who had at least one clinic visit, a laboratory test, or an antiretroviral drug pharmacy visit in the last semester of 2011. According to the Argentinean HIV Program [27], ART-regimens that included at least one of the following drugs were considered as "Third-line ART": etravirine, darunavir, tipranavir, maraviroc, raltegravir or enfurvitide;. "Virologic failure" was defined as confirmed detectable plasma HIV-RNA (> 50 copies/mL) in patients receiving HAART for at least six months. The following standardized categories of VL were used: "undetectable VL" (≤ 50 copies/mL); "suppressed/not suppressed" (cut-off: 200 copies/mL); and "high VL" (> 100,000 copies/mL) [28].

Data collection

Researchers reviewed the medical records of all patients on follow-up in our center to identify eligible patients. A standardized data entry form with socio-demographic, clinical, and laboratory data was completed for each enrolled patient.

Statistical analysis

Quantitative variables were described using means and standard deviations (SD) or medians and interquartile ranges (IQR), depending on their underlying distribution. Student's t-tests and Mann-Whitney tests were used to compare differences in means and medians, respectively. Categorical variables were presented as percentages, and were compared using Fisher's exact tests. Simple linear regression was used to test for potential association of time on ART and number of virologic failures. Fisher's exact test was performed to identify factors associated with current virologic failure or use of third-line drugs. The low occurrence of virologic failure in our cohort did not allow sufficient sample size to test for association in multivariable analysis.

All differences were considered statistically significant at the two-tailed $p < 0.05$ threshold. Analyses were performed using Stata/SE version 11.1 (Stata Corp, College Station, Texas).

To have a proxy measure of access to ART and level of adherence of our population, and to assess the potential of HIV transmission, we calculated in-care VL using the methodology recommended by the Centers for Disease Control and Prevention (CDC) [28]. We reported both arithmetic and geometric means, and the categorical distribution of VL using the standardized categories previously described [28].

Results

Socio-demographic and clinical characteristics

A total of 619 medical charts of HIV-infected patients on active follow-up at our center were reviewed. Out of these, 82 (13.2%) corresponded to individuals who were diagnosed with HIV in the pre-HAART era.

The majority of our pre-HAART cohort consisted of men (n = 69, 84.2%). Sexual contact was the most common risk factor for HIV transmission: 61.7% self-reported to be MSM and 11.7% heterosexual. Other routes of HIV transmission included intravenous drug use in 21.7% of cases, blood transfusion in 3.3%, and vertical transmission in 1.6%. The median age at the time of the study was 47 years (IQR 23–34) and the median time since HIV diagnosis was 18 years (IQR 17–20). Thirty-four percent of patients had a CD4 cell-count nadir ≤ 200 cells/μl and 16.8% had a history of AIDS-defining conditions, according to CDC's 1993 classification [29].

Immune-virologic status as of December 2011

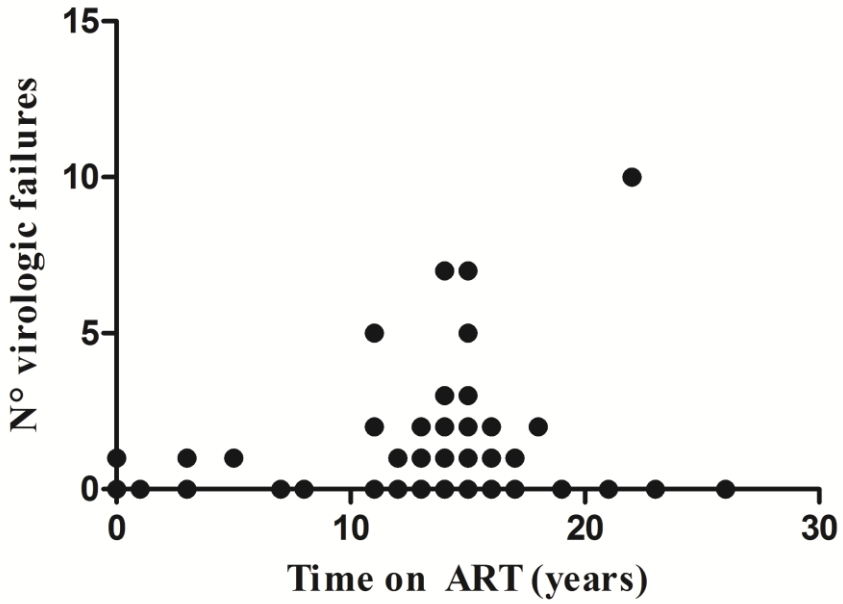
At the time of this analysis, 79 patients (96.3%) were on HAART, with a median duration of ART of 14 years (IQR 12–15). In 41.8% of patients, this treatment duration included exposure to mono or dual nucleoside reverse transcriptase inhibitors (NRTI) regimens. Forty-seven percent never presented virologic failure and 24.1% had only one virologic failure (Table 1). No statistically significant association between the number of virologic failures and time on ART was found ($p = 0.67$, Figure 1). Of the 79 patients who were on HAART, 69 (87.3%) had

Table 1. Characteristics of patients on HAART (n = 79)

	All (n = 79)	Undetectable VL		p
		Yes (n = 69)	No (n = 10)	
Time on ART, median years (IQR)	14 (12–15)	14 (12–15)	14 (11–16)	0.89
History of mono or dual- NRTI regimens, n (%)				0.80
Yes	33 (41.8)	29 (42.0)	4 (40.0)	
No	36 (45.6)	32 (46.4)	4 (40.0)	
ND	10 (12.6)	8 (11.6)	2 (20.0)	
Use of third-line ART, n (%)				0.75
Yes	13 (16.5)	11 (15.9)	2 (20.0)	
No	64 (81.0)	56 (11.9)	8 (80.0)	
ND	2 (2.5)	2 (2.9)	-	
Previous virologic failures, n (%)				
None, n (%)	37 (46.8)	32 (46.4)	5 (50.0)	0.57
1, n (%)	19 (24.1)	18 (26.1)	1 (10.0)	
>1, n (%)	18 (22.8)	15 (21.7)	3 (30.0)	
ND, n (%)	5 (6.3)	4 (5.8)	1 (10.0)	
CD4 nadir <200 cells/µl, n (%)				0.06
Yes	27 (34.2)	24 (34.8)	3 (30.0)	
No	37 (46.8)	35 (50.7)	2 (20.0)	
ND	15 (19.0)	10 (14.5)	5 (50.0)	

VL: Viral load; ART: Antiretroviral therapy; NRTI: Nucleoside Reverse Transcriptase Inhibitors; ND: no data

Figure 1. Relationship between number of virologic failures and cumulative time on antiretroviral therapy



Scatter plot of number of virologic failures and cumulative time on antiretroviral therapy

undetectable VL. We did not find any statistically significant associations between current virologic failure and history of mono or dual NRTI regimens, CD4 cell-count nadir, previous virologic failures, or duration of ART in univariable analysis (Table 2). Thirteen patients (16.5%) were receiving third-line ART regimens. The only factor associated with use of third-line drugs was the presence of at least one previous virologic failure (p = 0.003, Table 3). Patients receiving third-line regimens had an average of 2.7-fold more virologic failures than those who were on first- or second-line regimens (p = 0.007). Only three patients were not receiving HAART at the time of the analysis: two did not meet current national and international recommendations for initiation of antiretroviral therapy [22,30,31,32] and the third underwent structured treatment interruption in 2002 and elected not to re-start therapy to this day.

Overall (including those on and off HAART), more than 90% of the study population had a VL < 200 copies/mL and a median CD4 cell-count of 516 cells/µl (IQR 355–784). Only one patient had a VL higher than 100,000 copies/mL (Figure 2). Arithmetic and geometric means of the in-care VL were 5,822.33 copies/mL (SD: 4054.12) and 39.52 copies/mL, respectively.

Discussion

It is estimated that there are approximately 33 million PLWHA worldwide, and this number continues to increase [33]. Although several preventive strategies exist, their effectiveness remains suboptimal for multiple reasons, as has been demonstrated in many places by the persistence of sexually transmitted infections [20,34,35]. In a recent study completed in Buenos Aires, 11% of PLWHA presented with a new sexually transmitted infection after being diagnosed with HIV [36].

There is growing scientific evidence that supports the use of ART for the prevention of HIV transmission [10,11,15]. Modelling data suggest that expansion of HAART could have a significant impact on morbidity, mortality, and HIV incidence [19,37]. However, concerns about the potential risks associated with earlier initiation of treatment, including potential adverse effects, emergence of drug resistance, difficulties accessing second- or third-line ART, or even exhaustion of treatment options, have also been raised [23,24,25,26].

Therefore, and with the aim of assessing these assumptions in a real-life scenario, we conducted a study to evaluate the rate of viral load suppression among PLWHA diagnosed in the pre-HAART era, considering this group as one of the most heavily

Table 2. Univariable analysis of factors associated with current virologic failure

	Current virologic failure	OR	95% CI	p
Time on ART, n (%)				
<14 years	3/26 (11.5)	Reference		
≥ 14 years	4/41 (9.8)	0.83	0.17–4.04	1
History of mono/dual NRTI regimens, n (%)				
No	4/36 (11.1)	Reference		
Yes	4/33 (12.1)	1.1	0.25–4.81	1
Use of third-line ART, n (%)				
No	8/64 (12.5)	Reference		
Yes	2/13 (15.4)	1.1	0.24–6.82	0.67
Previous virologic failures, n (%)				
No	5/37 (13.5)	Reference		
Yes	4/37 (10.8)	0.78	0.19–3.15	1
CD4 nadir <200 cells/µl, n (%)				
No	2/37 (5.41)	Reference		
Yes	3/27 (11.11)	2.19	0.34–14.1	0.64

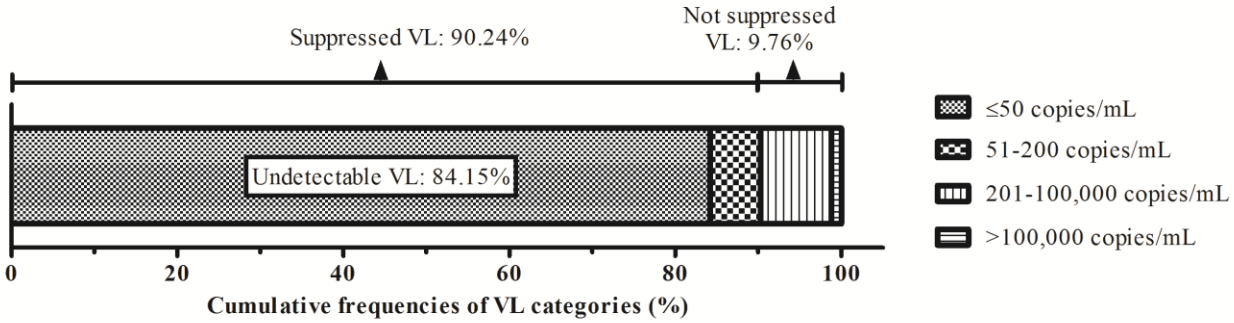
ART: Antiretroviral therapy; NRTI: Nucleoside Reverse Transcriptase Inhibitors

Table 3. Univariable analysis of factors associated with use of third-line drugs

	Use of third-line drugs	p
Time on ART, n (%)		
<14 years	3/26 (11.5)	0.34
≥ 14 years	9/41 (21.9)	
History of mono/dual NRTI regimens, n (%)		
No	4/35 (11.4)	0.21
Yes	8/33 (24.2)	
Previous virologic failures, n (%)		
No	1/37 (2.7)	0.003
Yes	11/37 (29.7)	
CD4 nadir <200 cells/µl, n (%)		
No	4/36 (11.1)	0.3
Yes	6/27 (22.2)	

ART: Antiretroviral therapy; NRTI: Nucleoside Reverse Transcriptase Inhibitors

Figure 2. Categorical distribution of viral load of pre-HAART patients on follow-up (n = 82)



exposed to ART, and most likely to have HIV resistant to antiretroviral drugs as a result of their earlier exposure to regimens that were not fully suppressive, including mono and dual nucleoside regimens.

Our study group had a long history of ART exposure (median time on ART = 14 years), and despite full access to all antiretroviral drugs currently licensed in Argentina, only 16.5% were in need of third-line ART regimens. We found no significant differences between patients who were or were not receiving third-line drugs with regard to duration of treatment or current virologic failure, suggesting that Despite prolonged ART exposure and that almost half of our study group had received either mono or dual NRTI regimens, less than one quarter had more than one virologic failure. In fact, half were on a first-line ART regimen and only 16.5% were on third-line drugs, suggesting that in our pre-HAART cohort both adherence to, and an appropriate choice, of treatment regimens might have prevented the emergence of viral resistance, as has been previously pointed out [38].

Several studies have demonstrated that viral load strongly correlates with the risk of transmission of both wild type and resistant HIV. A recent study found that the per-act risk of sexual transmission of HIV

increases by 2.9-fold for every log (10) increase in plasma viral load [39]. Furthermore, in a meta-analysis that included more than 5,000 heterosexual sero-discordant couples, no transmission events were observed in couples where the HIV-infected individual was on ART and had a viral load level below 400 copies/mL [11]. More than 90% of our population had their viral load suppressed, and among those with virologic failure, only one was receiving third-line ART, suggesting that the risk of HIV transmission is low, and the risk of transmitting resistant viruses is even lower. Also, the high level of viral load suppression as well as the low value of in-care VL suggests a very good level of treatment adherence in our population.

Our study has several limitations. First, we only analyzed patients on follow-up. The Argentinean health-care system is divided into three sub-systems (public, social security and private), with no centralized information; hence we do not have information about patients who were lost to follow-up because they changed their health-care provider, abandoned care, or died. As one of our main objectives was to evaluate current virologic status and its potential impact on HIV transmission, patients who died were not considered for our analysis. Second, this study was performed in a private HIV center in Buenos Aires. Therefore, our pre-HAART cohort may have unique socio-demographics characteristics (i.e., higher socioeconomic status, better access to antiretroviral drugs) that may prevent extrapolating our results to other settings.

Conclusion

Despite a long history of ART exposure, half of our study group was adequately virologically suppressed on a first-line ART regimen, only 16% were in need of third-line drugs, and overall more than 90% of the patients had a viral load below 200 copies/mL. These results suggest that maintaining viral load suppression over time is feasible in resource-limited settings. This hypothesis is relevant to the current desire to implement "Test and Treat" strategies globally. Further studies including other populations with different socio-demographic characteristics are needed to determine if these findings can be extrapolated to other settings.

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