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Factors Associated With Early Virological Response in HIV-Infected Individuals Starting Antiretroviral Therapy in Brazil (2014–2015): Results From a Large HIV Surveillance Cohort

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Objective: To identify clinical, sociodemographic, and treatment-related factors associated with early virological response in HIV-infected adults starting antiretroviral treatment (ART) in Brazil in 2014–2015.

Methods: Data from 4 information systems from the Brazilian AIDS Program were combined to create a historical cohort. Unconditional logistic regression models were used to assess the likelihood of not achieving viral load suppression (VLS), defined as having either a viral load (VL) count >200 copies per milliliter or an aids-related death recorded within 180 ± 90 days after treatment initiation.

Results: Among 76,950 individuals, 64.8% were men; median age, CD4$^+$, and VL counts were 34 years, 378 cells per micro liter, and 38,131 copies per milliliter, respectively, and 85.2% achieved VLS. In the multivariate analysis, some factors which increased the odds of non-VLS were as follows: lower CD4$^+$ and higher VL counts, younger age, heterosexual or injection drug use groups (relative to men who have sex with men), lower educational level, black/brown race, higher pill burden, and higher dosing frequency. Regimens containing boosted protease inhibitors were similar to those containing nonnucleoside reverse transcriptase inhibitors and superior to those containing unboosted protease inhibitors (all P values <0.001). No difference was observed between patients with CD4$^+$ counts 350–499 and 500+ cells per micro liter.

Conclusions: Our findings support the decision made in Brazil in 2013 to recommend immediate initiation of ART regardless of clinical stage or CD4$^+$. Several factors were found to be associated with poorer virologic outcomes and should be addressed to maximize ART adherence and success rates.

Key Words: HIV, antiretroviral therapy, viral load, adherence, cohort study, Brazil

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INTRODUCTION

By the end of 2016, there were 36.7 million people living with HIV (PLWH) worldwide. In Brazil, this figure was estimated at 830,000, of whom 498,000 (60%) were on antiretroviral treatment (ART).[1] In late 2013, with early reports on the HPTN 052 trial results,[2] Brazil was a pioneer in recommending initiation of ART for all PLWH, regardless of clinical stage or CD4$^+$ cell counts (from this point on referred to as CD4$^+$).[3] At that time, the guidelines also defined lamivudine/tenofovir/efavirenz as the preferred first-line regimen. Ritonavir-boosted protease inhibitors (PIs/r) were recommended as alternative regimens when both efavirenz and nevirapine were contraindicated, with the preferred PI being lopinavir. The preferred regimen for pregnant women was lamivudine/zidovudine/lopinavir-ritonavir.[3] All antiretroviral drugs (ARV) are available free of charge in Brazil since 1996.[4]

Suppression of viral replication is the key goal of ART[5] because it allows immune reconstitution,[6] maintains or improves CD4$^+$ levels,[7] prevents HIV transmission,[2,8] decreases the risk of selecting drug-resistant mutations,[9] and reduces HIV-related morbidity and mortality.[10–13] Early virological response to ART, commonly assessed by HIV viral load (VL) counts 6 months after treatment initiation, is of particular interest because it has proven to be of important prognostic value both in the short and long term for AIDS[14–17] and all-cause mortality.[11,15–17] Virological failure may result from insufficient adherence, presence of pre-treatment HIV drug resistance, issues related to drug absorption or pharmaceutical interactions, or any combination of these factors.[5] Assessment of VL levels early on the course of ART helps clinicians detect potential barriers to adherence and intervene immediately to avoid disease progression.[10] Our objectives were to

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characterize the early virological response in HIV-infected individuals starting ART in Brazil in 2014–2015 and to describe the factors associated with failure to achieve 6-month viral load suppression (VLS) in a large HIV surveillance cohort.

METHODS

This is an HIV cohort study based on historical routine data collected by the AIDS Program at the Brazilian Ministry of Health. Data were obtained from 4 electronic national information systems: (1) the ARV logistics system (SICLOM), which registers all ARV dispensations in the country; (2) the HIV laboratory examination system (SISCEL), which records every $CD4^+$ and VL performed within the public health system, the Brazilian Unified Health System (SUS); (3) the notifiable diseases information system (SINAN), which contains case reports for conditions of legal mandatory reporting, including AIDS since 1986 and HIV infection since 2014; and (4) the Mortality Information System (SIM), which includes data from the declaration of death document for every death happening in the national territory, following WHO-recommended standards. Only AIDS-related causes of death were used for this study, up to December 31, 2015; case reports were available up to June 30, 2016. The databases from these information systems were linked through a probabilistic linkage method, using the patient's name, sex, date of birth, and mother's name, with the software Reclinck III.[18] The detailed method is described elsewhere.[19,20]

The study population comprised antiretroviral-naive adults (aged 15–80 years) initiating ART in Brazil between January 2014 and December 2015 and who were followed up in SUS. Patients who died before 90 days from treatment initiation were not eligible because they did not have enough time to benefit from ART and show the study outcome. Patients with 3 undetectable (<40 copies/mL) VL preceding ART initiation were also excluded because they were considered likely not ART naive.

The study outcome—early virological response—was defined as the 6-month VL, measured within 180 ± 90 days after treatment initiation. The first measurement after 180 days or, when not available, the last within the 90–180-day period after ART initiation was considered for patients who had more than 1 VL during this time window. VLS was defined as a VL ≤ 200 copies per milliliter. Patients with no VL record but with an AIDS-related death recorded within the same time window were included in the nonvirologically suppressed group.

Because ARVs are provided free of charge by SUS′ public pharmacies and there are no sales by private pharmacies, SICLOM captures virtually all ARV dispensations in the country, whereas SISCEL includes only $CD4^+$ and VL performed in SUS. Therefore, HIV individuals followed at private services have their information registered only into SICLOM. Individuals with neither baseline nor follow-up examinations registered into SISCEL were not considered eligible. Patients who had no baseline information on $CD4^+$ or VL but had the 6-month outcome were considered eligible (Fig. 1).

Independent variables included sex, exposure category, age, race/color, years of schooling, region of residence, distance between municipalities of residence and of pharmacy pick-up, baseline $CD4^+$ and VL, drug regimen, number of pills/day, and dosing frequency.

Baseline $CD4^+$ was defined as the count recorded −100/+20 days from treatment initiation and categorized into 7 groups. Baseline VL was defined as the count recorded up to −100 days from treatment initiation and categorized into 8 groups. The assays for $CD4^+$ and VL were, respectively, BD MultiTESTCD3/CD8/CD45/CD4 and Abbott Real Time HIV-1.

All recorded treatments were included, regardless of whether they complied with national or WHO guidelines effective at the time. We used an intention-to-continue-treatment approach, ignoring, therefore, treatment changes or interruptions in the study period. Drug regimens were classified into 5 categories according to the drug classes: 2 nucleoside reverse transcriptase inhibitors (NRTI) + 1 non-nucleoside reverse transcriptase inhibitor (NNRTI), 2 NRTI + 1 ritonavir-boosted protease inhibitor (PI/r), 1 NRTI + 1 PI/r, 2 NRTI + 1 unboosted protease inhibitor (PI), and others. From the pharmaceutical forms dispensed, we computed 2 variables regarding the total number of pills/oral solutions taken per day [from this point on referred to as pills/day, although there were 227 (0.3%) patients on oral solutions]—grouped into 1, 2 to 5, and 6+—and the dosing frequency—once or twice daily.

Presumed HIV exposure category is self-reported, collected only in SINAN and categorized hierarchically into injection drug use (IDU), parenteral (including blood transfusions and occupational accidents), men who have sex with men (MSM), and heterosexual. Parenteral transmission cases (n = 24) were merged with unknown because of the small number of cases. The final exposure categories were merged with sex into 7 groups to better separate individuals according to their vulnerabilities and different barriers to adherence.

Race/color is collected into 5 categories [as recommended by the Brazilian Institute of Geography and Statistics (IBGE)], which were grouped as follows (considering similarities of social indicators): white/yellow, brown/black, indigenous, and unknown. Educational level is collected differently among the information systems and was thus categorized in a manner that enabled all the available information to be used, resulting in 3 groups.

Distance between municipality of residence and municipality of the pharmacy where the patients picked up their ARV was computed using the software TerraView 5.1.4. It was measured as a straight line from the coordinates of the administrative center of each municipality, obtained from IBGE[21] and grouped into 0 km (same municipality), ≤50 km, 50–100 km, 100–200 km, and >200 km.

Associations for the likelihood of not achieving VLS were determined by crude and adjusted odds ratios with respective 95% confidence intervals (95% CI) based on univariate and multivariate unconditional logistic regression. Eligible variables for multivariate analysis were identified in

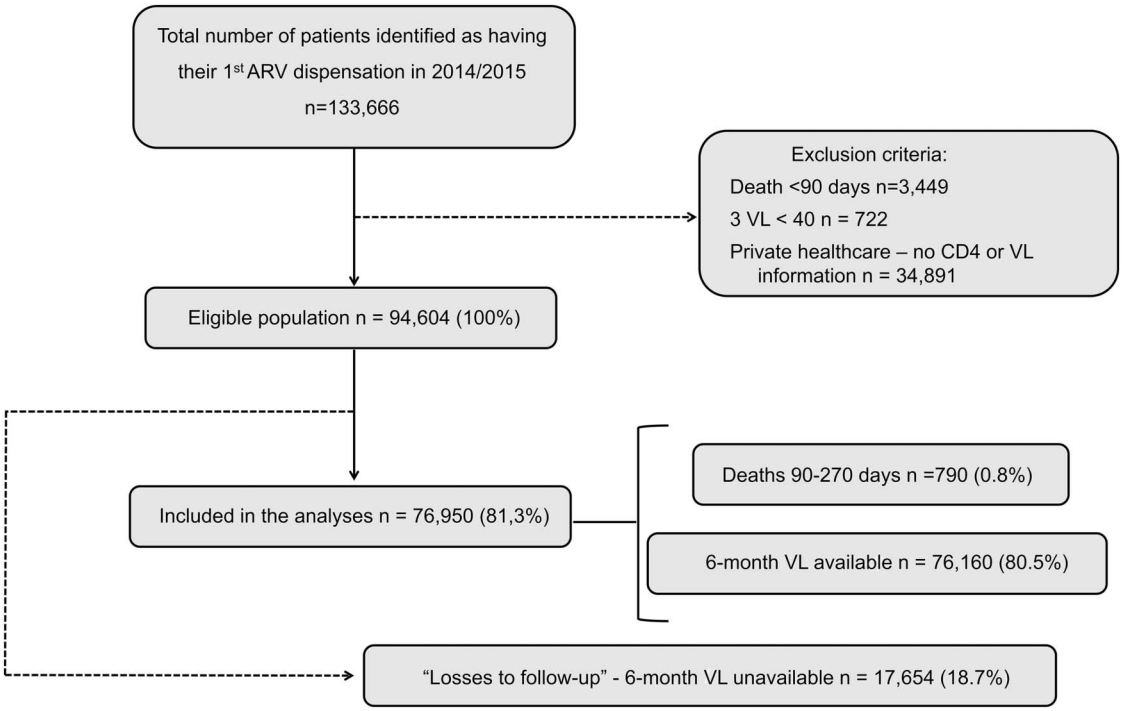

FIGURE 1. Study population flowchart.

the crude analysis by presenting a hypothesis test with a P value <0.20. The final model was selected based on backward selection considering a P value ≤ 0.05 as the cut point for statistical significance. Statistical analyses were performed using SPSS (SPSS Statistics for Windows, version 18.0.0; Chicago, IL). Sensitivity analysis were performed to understand the impact on the study results of (1) using earlier VL (90–180 days) measurements for the outcome and (2) excluding patients with no follow-up information.

This study received ethical approval from the Faculty of Medicine Ethics Review Committee at the University of Brasília (protocol number 096576/2016, approval on October 03, 2016).

RESULTS

A total of 133,666 patients aged 15–80 years were identified as having started treatment in the study period and 94,604 met the inclusion criteria, of whom 17,654 (18.7%) had no 6-month VL or death registration (Fig. 1). We hereafter refer to the latter as patients lost to follow-up (LTFU), although part of them probably migrated to the private sector, as discussed later. Therefore, 76,950 patients were included in the main analyses.

After the linkage process, approximately 7% of duplicate records were excluded. Of the 133,666 patients, 71.8% of patients had at least 1 registration in SISCEL, 66.5% were identified in SINAN, and 3.2% in SIM.

Overall, 65,596 patients (85.2%) achieved a 6-month VL <200 copies per milliliter. There were 55,114 (71.6%) patients with undetectable VL and 68,625 (89.2%) with a VL <1000 copies per milliliter.

Baseline Characteristics

The study population was mainly composed by men (66.2%), aged 20–59 years [median 34, interquartile range (IQR) 27–43], with low educational level (71.2% of those with this information had less than 12 years of schooling) (Table 1). They lived in 3422 municipalities and started treatment in 711 different ARV pharmacies distributed among 531 cities. Most patients (77.5%) lived in the same municipality as the pharmacy, and 9.5% lived more than 50 km away.

At baseline, the median (IQR) $CD4^+$ and VL were 378 (190–558) cells per micro liter and 38,131 (8217–154,370) copies per milliliter, respectively. No information regarding these 2 variables was available for 23.4 and 26.8% of patients, respectively.

The most common drug regimens were lamivudine/tenofovir/efavirenz (75.6%), lamivudine/zidovudine/lopinavir-ritonavir (7.0%), lamivudine/zidovudine/efavirenz (5.3%), and lamivudine/tenofovir/lopinavir-ritonavir (2.7%). Of those on lamivudine/tenofovir/efavirenz, 54.1% (31,479) were on a single-pill fixed-dose combination (FDC). A total of 74,293 (96.5%) patients were either on 2NRTI+1NNRTI or 2NRTI+1PI/r, in compliance with national guidelines. Of the 1777 patients on 1NRTI+1PI/r and 428 on 2NRTI+1PI, 96.0% and 94.2% had atazanavir as the PI in their regimens, respectively (data not shown).

Sociodemographic Factors and Virological Suppression

Lower VLS was observed among heterosexual men [adjusted OR (aOR) = 1.27; 95% CI: 1.18 to 1.37] and

TABLE 1. Characteristics of the 76,950 Treatment-naive Patients Included in the Analysis at the Start of ART, Proportion Lost to Follow-Up Within Each Category (Among the Total 94,604 Eligible Patients), and Proportion of Viral Load Suppression (<200 Copies/mL)

	n	%	% LTFU	VLS (%)	95% CI
Sex + exposure category					
MSM	16,270	21.1	17.9	89.4	88.9 to 89.8
Male Heterosexual	12,286	16.0	18.6	84.0	83.3 to 84.6
Male IDU	860	1.1	23.7	79.0	76.2 to 81.7
Male Unknown	21,507	27.9	20.0	84.7	84.2 to 85.2
Female Heterosexual	14,531	18.9	16.8	84.6	84.1 to 85.2
Female IDU	210	0.3	27.1	72.4	66.3 to 78.4
Female Unknown	11,286	14.7	19.0	83.3	82.6 to 84.0
Age (yr)					
15–19	2798	3.6	24.0	81.9	80.5 to 83.3
20–29	23,946	31.1	20.9	85.6	85.2 to 86.1
30–39	24,218	31.5	18.7	84.7	84.3 to 85.2
40–59	23,210	30.2	15.9	85.6	85.2 to 86.1
60–80	2778	3.6	15.0	86.8	85.5 to 88.0
Race/color					
White/yellow*	33,535	43.6	16.7	86.4	86.1 to 86.8
Black/brown	35,373	46.0	19.6	84.1	83.8 to 84.5
Indigenous	127	0.2	24.0	81.1	74.3 to 87.9
Unknown	7915	10.3	22.3	85.2	84.4 to 86.0
Years of schooling					
0–7	23,229	30.2	19.8	82.0	81.5 to 82.5
8–11	19,717	25.6	17.0	85.6	85.1 to 86.1
12 or more	17,365	22.6	16.6	89.5	89.0 to 89.9
Unknown	16,639	21.6	21.0	84.9	84.4 to 85.5
Region					
Center-west	5185	6.7	20.6	86.3	85.3 to 87.2
South	18,430	24.0	17.2	84.8	84.3 to 85.3
Southeast	32,665	42.4	17.8	86.4	86.0 to 86.8
Northeast	13,431	7.5	20.8	84.0	83.3 to 84.6
North	7239	9.4	20.8	82.8	82.0 to 83.7
Distance†					
Same municipality (0 km)	59,641	77.5	18.6	85.7	85.4 to 86.0
≤50 km	9976	13.0	18.0	84.9	84.2 to 85.6
50–100 km	3556	4.6	18.9	83.0	81.8 to 84.2
100–200 km	2291	3.0	21.2	81.4	79.9 to 83.0
>200 km	1486	1.9	20.7	80.7	78.7 to 82.7
Baseline CD4 (cells/μL)					
<50	4895	6.4	18.0	75.1	73.8 to 76.3
50–99	3944	5.1	19.7	78.4	77.1 to 79.7
100–199	6582	8.6	22.1	82.9	82.0 to 83.8
200–349	11,560	15.0	23.6	87.5	86.9 to 88.1
350–499	13,383	17.4	23.3	89.7	89.2 to 90.2
500+	18,618	24.2	23.6	90.3	89.9 to 90.8
Unknown	17,968	23.4	2.0	80.4	79.8 to 80.9
Baseline VL (copies/mL)					
<40	598	0.8	31.6	95.2	93.4 to 96.9
40–200	1090	1.2	24.5	93.7	92.2 to 95.1
201–1000	2552	3.3	23.5	90.3	89.1 to 91.4
1001–10,000	11,310	14.7	23.5	90.4	89.8 to 90.9
10,001–50,000	15,358	20.0	23.6	90.0	89.5 to 90.5
50,001–100,000	7101	9.2	24.3	88.0	87.2 to 88.7
100,001+	18,299	23.8	22.1	80.3	79.7 to 80.8
Unknown	20,642	26.8	2.7	81.0	80.5 to 81.5
Drug regimen§					
2 NRTI + 1 NNRTI	63,945	83.1	18.8	86.3	86.0 to 86.5
2 NRTI + 1 PI/r	10,348	13.4	18.1	79.8	79.0 to 80.5
1 NRTI + 1 PI/r	1777	2.3	18.3	84.1	82.4 to 85.8
2 NRTI + 1 PI	428	0.6	17.1	77.3	73.4 to 81.3
Others	452	0.6	20.1	77.9	74.0 to 81.7

TABLE 1. (*Continued*) Characteristics of the 76,950 Treatment-naive Patients Included in the Analysis at the Start of ART, Proportion Lost to Follow-Up Within Each Category (Among the Total 94,604 Eligible Patients), and Proportion of Viral Load Suppression (<200 Copies/mL)

	n	%	% LTFU	VLS (%)	95% CI
Pills/d‡					
1	31,525	41.0	19.2	87.6	87.2 to 87.9
2–5	38,309	49.8	18.4	84.7	84.3 to 85.1
6+	7116	9.2	17.7	77.9	76.9 to 78.9
Dosing frequency					
Once	63,274	82.2	18.8		
Twice	13,676	17.8	18.1	79.5	78.8 to 80.2

*Yellow refers to those with Asian descent.

†Distance between the municipality of residence and the municipality of the pharmacy.

‡Includes oral solutions, n = 227 (0.3%), which were counted as pills, that is, one dose of an oral solution = one pill.

§NNRTI = Nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI = unboosted protease inhibitor; PI/r = ritonavir-boosted protease inhibitor.

women (aOR = 1.23; 95% CI: 1.14 to 1.32) and IDU males (aOR = 1.78; 95% CI: 1.49 to 2.13) and females (aOR = 2.41; 95% CI: 1.75 to 3.32) when compared with MSM (Table 2). VLS was lower in black/brown individuals (aOR = 1.12; 95% CI: 1.07 to 1.18) than in white/yellow individuals. Younger patients were less likely to achieve VLS, with a gradient from aOR = 1.90 (95% CI: 1.63 to 2.21) in PLWH aged 15–19 years to an aOR = 1.19 (95% CI: 1.06 to 1.34) in those aged 40–59 years, relative to those aged 60+ years. Educational level was protective, with individuals with less than 8 years of schooling showing an aOR = 1.64 (95% CI: 1.54 to 1.75) relative to those with 12+ years of schooling.

Patients living in the Center-West region of the country had the highest odds of VLS, and those in the South and North (aORs = 1.25; 95% CI: 1.14 to 1.37 and aORs = 1.27; 95% CI: 1.14–1.40) regions had the lowest. Patients who live in municipalities further away from the pharmacy where they pick up their medication showed lower VLS (>200 km aOR = 1.27; 95% CI: 1.11 to 1.46 and 100–200 km aOR = 1.16; 95% CI: 1.04 to 1.30, relative to the same municipality).

Baseline CD4+ and VL and Virological Suppression

VLS was equivalent in patients starting therapy with CD4+ 500+ cells per micro liter and 350–500 cells per micro liter (aOR = 1.01; 95% CI: 0.93 to 1.08) and higher than in those with lower counts, reaching an aOR = 2.23 (95% CI: 2.04 to 2.44) in CD4+ <50 cells per micro liter. Relative to those starting treatment at VL 40–200 copies per milliliter, we observed a gradient from an aOR = 1.62 (95% CI: 1.23 to 2.14) to an aOR = 3.18 (95% CI: 2.44 to 4.08) in those with counts 201–1000 and 100,000+, respectively.

Regimen-related Factors and Virological Suppression

Regimens containing 2NRTI+1NNRTI were superior to all others regarding the association with VLS in the univariate analysis. In the multivariate model, however, they were similar to 2NRTI+1PI/r (aOR = 1.06; 95% CI: 0.96 to 1.17) and 1NRTI+1PI/r (aOR = 1.10; 95% CI: 0.96 to 1.25). Patients on 2NRTI+1PI (aOR = 1.58; 95% CI: 1.25 to 2.00) and those on other regimens (aOR = 1.26; 95% CI: 1.00 to 1.60) showed lower VLS. Pill burden increased the odds of virological nonsuppression (aOR 2–5 pills/day = 1.18; 95% CI: 1.12 to 1.24, and aOR 6+ pills/day = 1.41; 95% CI: 1.24 to 1.59, relative to fixed-dose combination), as did dosing frequency (aOR 2 times/day = 1.29; 95% CI: 1.20 to 1.39, relative to once daily).

Sensitivity Analyses

Median time of the outcome assessment was 188 days. VLS was slightly lower among patients whose VL was assessed before 114 days. Exclusion of these patients from the model did not significantly alter the study results, except for the variable age (aOR were higher with exclusion).

The proportion of patients LTFU within each category is presented in Table 1. At least 1 ARV dispensation in the 180 ± 30 days after treatment initiation was found in 63.2% of patients LTFU, in comparison with 88.9% among the 76,950 included in the main analyses.

Assuming all patients LTFU as having VL >200 copies per milliliter, VLS fell to 69.3%, and, overall, the associations were attenuated but gradients within each variable were preserved. VLS rose to 88.0% when patients LTFU were assumed to have VL <200 copies per milliliter, and very little changes in the aOR were observed.

DISCUSSION

In our large, population-based study, conducted in the 2 years after the implementation of the test-and-treat strategy in Brazil, we have found that a combination of clinical, socio-demographic, and ART-related factors affect the likelihood of achieving early VLS. Among these are lower CD4+ and higher VL counts at baseline, black or brown race/color, lower educational level, type of ART regimen, pill burden, and dosing frequency.

We found gradients of increasing risks of nonsuppression with decreasing CD4+ counts and increasing VL at baseline, which is consistent with previous studies.[22–24] Importantly, there was no difference among individuals with CD4+ counts 350–499 cells per micro liter and 500+ cells per micro liter. This finding mitigates concerns that were raised about PLWH with higher CD4+ counts—and thus generally clinically well—potentially showing lower adherence to ART.[25,26] We found that a quarter of patients still initiate treatment with CD4+ <200 cells per micro liter, which probably reflects barriers to diagnosis.

Less educated and black/brown patients were shown to have less favorable early HIV treatment response in this study. Educational level, which probably reflects the patients'

TABLE 2. Results of the Univariate and Multivariate Logistic Regression Models for Failure to Achieve 6-Month Virological Suppression

	Univariate		Multivariate	
	OR	95% CI	aOR	95% CI
Sex + exposure category				
MSM	1		1	
Male heterosexual	1.61	1.50 to 1.72	1.27	1.18 to 1.37
Male IDU	2.24	1.89 to 2.66	1.78	1.49 to 2.13
Male unknown	1.52	1.43 to 1.62	1.29	1.20 to 1.38
Female heterosexual	1.53	1.43 to 1.63	1.23	1.14 to 1.32
Female IDU	3.21	2.36 to 4.36	2.41	1.75 to 3.32
Female unknown	1.69	1.57 to 1.81	1.33	1.23 to 1.44
Age (yr)				
15–19	1.45	1.26 to 1.68	1.90	1.63 to 2.21
20–29	1.10	0.98 to 1.24	1.52	1.35 to 1.72
30–39	1.19	1.06 to 1.33	1.41	1.26 to 1.59
40–59	1.10	0.98 to 1.24	1.19	1.06 to 1.34
60–80	1		1	
Race/color				
White/yellow*	1		1	
Black/brown	1.20	1.15 to 1.25	1.12	1.07 to 1.18
Indigenous	1.48	0.95 to 2.32	1.36	0.86 to 2.14
Unknown	1.11	1.03 to 1.19	1.05	0.97 to 1.15
Years of schooling				
0–7	1.86	1.75 to 1.97	1.64	1.54 to 1.75
8–11	1.43	1.34 to 1.52	1.33	1.25 to 1.42
12 or more	1		1	
Unknown	1.51	1.41 to 1.61	1.33	1.23 to 1.43
Region				
Center-west	1		1	
South	1.13	1.03 to 1.23	1.25	1.14 to 1.37
Southeast	0.99	0.91 to 1.08	1.11	1.01 to 1.21
Northeast	1.20	1.10 to 1.31	1.12	1.02 to 1.23
North	1.30	1.18 to 1.44	1.27	1.14 to 1.40
Distance†				
Same municipality (0 km)	1		1	
≤50 km	1.07	1.00 to 1.13	1.00	0.94 to 1.06
50–100 km	1.23	1.12 to 1.34	1.07	0.97 to 1.17
100–200 km	1.36	1.23 to 1.52	1.16	1.04 to 1.30
>200 km	1.43	1.26 to 1.63	1.27	1.11 to 1.46
Baseline CD4 (cells/μL)				
<50	3.11	2.87 to 3.37	2.23	2.04 to 2.43
50–99	2.58	2.36 to 2.83	1.88	1.70 to 2.07
100–199	1.93	1.78 to 2.09	1.49	1.37 to 1.63
200–349	1.34	1.24 to 1.44	1.14	1.06 to 1.23
350–499	1.08	1.00 to 1.16	1.01	0.93 to 1.08
500+	1		1	
Unknown	2.29	2.15 to 2.43	1.72	1.56 to 1.90
Baseline VL (copies/mL)‡				
<40	0.75	0.48 to 1.18	0.75	0.49 to 1.14
40–200	1		1	
201–1.000	1.59	1.21 to 2.10	1.60	1.20 to 2.14
1.001–10.000	1.57	1.22 to 2.02	1.68	1.28 to 2.19
10.001–50.000	1.64	1.28 to 2.11	1.78	1.36 to 2.32
50.001–100.000	2.02	1.57 to 2.61	2.10	1.60 to 2.75
100.001+	3.64	2.85 to 4.66	3.14	2.41 to 4.09
Unknown	3.47	2.71 to 4.44	2.51	1.91 to 3.29
Drug regimen‖				
2 NRTI + 1 NNRTI	1		1	
2 NRTI + 1 PI/r	1.59	1.51 to 1.68	1.06	0.96 to 1.17
1 NRTI + 1 PI/r	1.18	1.04 to 1.35	1.10	0.96 to 1.25
2 NRTI + 1 PI	1.84	1.47 to 2.31	1.58	1.25 to 2.00
Others	1.78	1.43 to 2.23	1.26	1.00 to 1.59
Pills/d§				
1	1		1	
2–5	1.27	1.22 to 1.33	1.18	1.12 to 1.24
6+	2.00	1.87 to 2.13	1.41	1.24 to 1.59
Dosing frequency				
Once	1		1	
Twice	1.65	1.57 to 1.73	1.29	1.20 to 1.39

*Yellow refers to those with Asian descent.

†Distance between the municipality of residence and the municipality of the ARV pharmacy.

‡We chose not to set the undetectable VL as the reference group because of uncertainty as to whether they were really ART naive.

§Includes oral solutions, n = 227 (0.3%), which were counted as pills, that is, one dose of an oral solution = one pill. (1) The ORs refer to the likelihood of not achieving VLS; (2) al variables had P values <0.001 in the univariate analyses.

‖NNRTI = Nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI = unboosted protease inhibitor; PI/r = ritonavir-boosted protease inhibitor.

access to information, had already been shown to be a prognostic factor for VLS and treatment adherence in other studies conducted in Brazil.[27,28] In addition, in Brazil, race and educational level are known to correlate to socioeconomic status,[29] which has an impact on adherence as well.[30] There are big inequities in access to health care in Brazil, and race and educational level are among the factors with the highest observed disparities[31,32]; they are also associated with perceived discrimination in health services.[33] Our study shows schooling and race impact on ART outcomes, indicating the need for further investigations to examine disparities in the access to or quality of care related to the specific context of HIV services in Brazil.

We found higher odds of virological nonsuppression among those who lived further away from the pharmacies. Distance to clinics is a frequently reported barrier to treatment adherence,[34] and in Brazil, specialized HIV services and ARV pharmacies are concentrated in large urban centers. Recent guidelines in the country have recommended decentralizing HIV care of asymptomatic patients with high $CD4^+$ counts from specialized HIV services to primary health care units, which are located in around 95% of the 5570 Brazilian municipalities. However, ARV dispensation remains centralized in less than 800 pharmacies in less than 15% of the municipalities, often resulting in patients who live in small cities having to travel long distances to acquire their medication. In light of this, efforts should be made to

improve patients' geographic access to medication and HIV care, notably in remote areas. Patients living in the North, which is the poorer region in the country and also the one with the most disperse population, were the ones to show the worse results.

Consistent with previous studies,[24,35] we also found younger age to be an important risk factor for virological nonsuppression, which is likely associated with lower levels of adherence, especially among adolescents.[36]

In our adjusted analysis, MSM showed the highest levels of VLS, followed by heterosexual individuals and patients with unknown transmission category, both men and women. This finding may point to higher adherence among MSM in the first months of ART. We found no studies comparing early virological response among MSM and other groups in Brazil, but some have reported lower adherence among women when compared with men.[30,37] Brazil has a highly concentrated HIV epidemic,[38,39] and gay men could possibly have more access to social support, either within their social circles or by reaching out to nongovernmental organizations, and also experience less fear of disclosure to friends and partners, both factors being known facilitators for adherence.[40,41]

VLS did not differ among those on 2NRTI+1NNRTI, 2NRTI+1PI/r, and 1NRTI+1PI/r. This finding is intriguing considering that 1NRTI+1PI/r is not a recommended regimen in Brazilian guidelines. Lopinavir-ritonavir/lamivudine has been found to be noninferior to lopinavir-ritonavir plus 2 NRTI[42] and is now considered an alternative choice of first-line therapy by USA guidelines.[43] Startlingly, the most common PI found in 1NRTI+1PI/r regimens in Brazil was atazanavir, for which we found no randomized clinical trials. Therefore, our finding should be viewed with caution because there is no information on longer term efficacy or risk of selecting resistance mutations. Unboosted PIs showed the lowest odds of VLS, which is in consonance with other studies and a recent meta-analysis, which found that both unboosted atazanavir and other unboosted PIs were associated with lesser efficacy.[44] Efforts should be made by the AIDS Program to investigate and potentially discourage these unwarranted treatment choices made by some clinicians, as well as to provide adequate training to prevent this.

Higher pill burden and dosing frequency increased the odds of virological nonsuppression, corroborating previous studies.[34,45,46] Of note is the probable impact of these 2 variables in the observed effectiveness of 2NRTI+1PI/r compared with 2NRTI+1NNRTI. PI-containing regimens are mostly administered twice daily and in 6+ pills, and in our study, 2NRTI+1PI/r showed an unadjusted OR of 1.59 that dropped to 1.06 (with no statistically significant difference) in the adjusted analysis.

Our results must be considered under the light of some limitations. SISCEL and SICLOM systems were developed primarily for logistic purposes and hence lack information on several important factors, for example, clinical stage, pregnancy status, and exposure category. Exposure category was obtained from the case-reporting system, but not all patients were reported to this system, resulting in the unknown categories having more than 40% of patients. Combining sex and exposure category in 1 variable helped us to better classify this unknown group for the purpose of the analysis. Race/color and educational level information were collected in all 4 databases, but still there were 10%–20% with missing data. In addition, other known risk factors for poor adherence, such as alcohol and substance abuse[34] and the presence of depressive symptoms[28] could not be accounted for. Distance of residency and pharmacy pick-ups could not be computed using the exact addresses, which may have underestimated the effect of this variable.

Moreover, we had no individual-level data on primary drug resistance. Pretreatment genotyping is only recommended in Brazil for pregnant women and persons who got infected from partners currently or previously exposed to ART, and the results could not be linked to the databases used in our study. Nonetheless, Brazil has a low prevalence of primary drug resistance.[47]

Furthermore, although SICLOM captures virtually all dispensations in Brazil, SISCEL only captures examinations performed in the public sector, and therefore, the inferences of our study are applied to patients seeking public health services and may not be generalizable to patients followed exclusively in the private health care system. Coverage of private health care plans in Brazil was estimated at 25% by December 2014.[48] These are often paid for by the holder's employer or offered to holders according to their current work contracts, which causes frequent switches between SUS and private health plans.[49] In fact, around 18,000 to 21,000 patients had no baseline information on CD4 and/or VL but had a VL during follow-up (suggesting migration from private to public sector) or a death outcome. Inversely, around 18,000 had baseline examinations but no follow-up information (suggesting treatment discontinuation or migration to a private sector). The first group was included in the statistical models within missing baseline CD4+/VL categories and the latter was considered as LTFU. From information on ARV pick-ups during follow-up—which was somewhat lower in those LTFU—we can assume that a portion of them were indeed disconnected from care, but we could not precisely discern these from cases of migration to private health care services. Nonetheless, sensitivity analyses performed on patients LTFU did not significantly alter our study's results.

Our study consolidates data from 4 HIV national information systems and endorses them as valuable sources of information for the study of ART outcomes, despite limitations inherent to the use of secondary data. Although further studies should be conducted, including longer follow-up times and primary data sources, this study delivered up-to-date information on early virological response to ART after the implementation of test and treat. To our knowledge, this is the first time this outcome is investigated using these large surveillance databases at a national level. Our findings support the decision made in 2013 to recommend immediate initiation of ART regardless of clinical stage or $CD4^+$. Furthermore, it provides policymakers and clinicians with valuable information on vulnerabilities that seem to impact early ART outcomes. These could be used to identify groups of HIV patients on whom attention should be focused to improve adherence and treatment success.

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