Title

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Journal

PLoS ONE, 19(11)

Authors

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Publication Date

2024

DOI

10.1371/journal.pone.0305311

Peer reviewed

PLOS ONE

RESEARCH ARTICLE

Time from treatment initiation to HIV viral suppression in public care facilities in Brazil: A nationwide linked databases cohort

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Citation: Nemes MIB, Sayuri Sato AP, Reis-Santos B, Maroso Alves A, Parra do Nascimento F, Agins B (2024) Time from treatment initiation to HIV viral suppression in public care facilities in Brazil: A nationwide linked databases cohort. PLoS ONE 19(11): e0305311. https://doi.org/10.1371/journal.pone.0305311

Editor: Angelica Espinosa Miranda, Universidade Federal do Espirito Santo, BRAZIL

Received: May 28, 2024

Accepted: July 8, 2024

Published: November 20, 2024

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pone.0305311

Data Availability Statement: All data underlying the findings described in the manuscript are fully available without restriction. All files are available

Abstract

Objectives

To analyze the time between antiretroviral therapy (ART) initiation and the first HIV viral load (VL) test <40 copies—time to suppression (TS)—in a cohort of persons aged ≥15 years, between 2015–2018 in outpatient HIV care facilities of the Brazilian Unified Health System, as well as to analyze whether individual and facility characteristics accelerate or delay TS.

Methods

This was a cohort study with data from a linkage of national HIV databases, following a previously published procedure. Two types of variables were examined: individual-level (sex, age group, race/skin color, education, baseline CD4 cell count and VL, initial ART regimen, adherence, ART regimen change and number of VL tests until suppression) and facility-level (national and metropolitan region, caseload). Multilevel parametric accelerated failure time survival models were used. Fixed and random effects were analyzed through null, sociodemographic, combined sociodemographic and clinical, and facility-related variables, adjusted for the number of VL tests until suppression. Likelihood, interquartile range, and proportion of change in variance were used for comparisons.

Results

Of 132,540 participants, 89.4% (114,696) achieved viral suppression: 20.8% within three months, and 56.4% within six months. Median TS was 161 days, varying from 31 to 1,426 days, depending on the time interval between initiation and VL testing. Among those who had VL testing within 66 days, median TS was 55 days. All individual and facility-related variables were associated with TS, explaining the 16.2% and 13.2% variability, respectively.

from the TimeToSupressin_dataset database on https://figshare.com/ via DOI: 10.6084/m9.figshare.26314996

Funding: CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico | National Council for Scientific and Technological Development) - U$D 9,600.00 (MIBN) https://www.gov.br/cnpq/pt-br OPAS (Organização Pan-Americana da Saúde - Organização Mundial da Saúde - Região das Américas| Pan American Health Organization - World Health Organization - Americas Region)- U$D 31,670.00 (MIBN) https://www.paho.org/en Pró-Reitoria de Pesquisa da Universidade de São Paulo - USP | USP Research and Innovation Deanship University of São Paulo) – U$D 6,360.00 (APSS) https://sites.usp.br/prp/ The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist

Conclusions

This was the first Brazilian nationwide cohort to analyze TS. It is also one of the largest operational cohorts globally to assess healthcare facility characteristics. The findings indicated that both individual and facility-related characteristics contribute to TS. Strengthening VL monitoring should be included as part of a coordinated effort to improve the quality of care provided for people living with HIV/AIDS in Brazil.

Introduction

The clinical and public health benefits of HIV viral load suppression (VS) through combination antiretroviral therapy (ART) are well-established, supported by robust scientific evidence [1–4] which forms the basis for policies and strategies that aim to engage the international community, governments, and civil society in achieving and maintaining VS targets. Cascade-based official reports from HIV national programs [5, 6] compile indicators that are immediately useful for healthcare professionals, HIV care facility managers, and system managers [7, 8]. These indicators are, however, limited by their cross-sectional design, as they assess the VS proportion of the group of persons in care within a fixed time interval (usually six, 12, or 24 months) between ART initiation and VS achievement, without considering temporal evolution [9]. Acknowledging these limitations, researchers have advocated that the parameter used by HIV programs to monitor ART success be time to VS [10–14].

With widespread use of integrase inhibitors [9], an increase has been seen in studies examining time to VS continuously [15–20]. As associated factors, a significant portion of these studies analyze individual characteristics, whereas fewer of them also analyze care facility characteristics [20–23].

Up to the time of writing this paper, we identified only one population-based cross-sectional study in Brazil that assessed the median time between ART initiation and VS, conducted from 2004 to 2018 in one Brazilian state [24]. No study including care facility characteristics in its analysis was, however, found.

This article aimed to analyze the time between ART initiation and first VS in a cohort of persons living with HIV/AIDS (PLWHA) who initiated ART between 2015 and 2018 in outpatient HIV care facilities of the Brazilian Unified Health System (SUS). A further objective was to analyze whether individual characteristics and healthcare facility characteristics accelerate or delay time to VS.

Materials and methods

Study design

This was an observational longitudinal study including PLWHA aged ≥15 years who are participants in the Qualiaids-Brazil Cohort.

Context

In Brazil, the establishment of the national program for STD/AIDS in 1986 [25] prompted the implementation of hospital and outpatient facilities for the treatment of people with AIDS, mostly within pre-existing structures of the public health system [26], which officially became the SUS [27] in 1988. The spread of AIDS in the country and the introduction of ART in 1996, which turned HIV disease into a chronic condition, led to a significant expansion in the

number of outpatient facilities, reaching approximately 1,300 today [28]. These facilities are the exclusive providers of ART medication for approximately 852,000 people. Clinical monitoring of PLWHA can be carried out within the public or private healthcare system. According to the cohort database, it has been estimated that 69% of PLWHA received outpatient monitoring through SUS facilities [28, 29].

Study population

The Qualiaids-Brazil Cohort comprises PLWHA who received treatment at SUS facilities that participated as respondents in a national survey regarding facility characteristics (Qualiaids Survey) [30–34]. PLWHA aged ≥15 years were included if they had their first ART dispensation between 2015 and 2018, a CD4 test conducted between 120 days before and 30 days after the first ART dispensation, and at least two viral load (VL) test results. The exclusion criteria considered inconsistencies in PLWHA data among the data sources used. Further information on the construction of the database and the profile of the Qualiaids-Brazil Cohort can be obtained from a previous publication [29].

For this study, only PLWHA who were in treatment for more than 30 days were included [35]. This was due both to the inability to assess treatment effect for very early suppressions and the possibility of delays in recording the first dispensation date. Those who had their last VL test in the SUS before their first ART dispensation were excluded.

Follow-up

The date of the first medication dispensation was defined as the initiation of ART, and the date of the last VL test was set as the final follow-up date. Deaths and loss to follow-up were classified as censoring events. The mortality data comprised only those deaths attributed to HIV-related causes [29]. Loss to follow-up was attributed to individuals who went more than 100 days without picking up medication or having VL tests until the final follow-up date of the cohort (December 31, 2018) [29]. Administrative censoring referred to individuals who did not achieve VS by the end of the follow-up period.

Study variables

The dependent variable was the time from treatment initiation to VS, defined as the number of days elapsed between the date of the first ART dispensation and the date of the first VL <40 copies/mL after ART initiation. The independent variables included data on individuals and treatment facilities.

The following sociodemographic characteristics of individuals were included: *sex* (female; male), *age group* (15–19; 20–29; 30–39; 40–49; 50–59; ≥60 years), *race/skin color* (white; black; yellow; mixed-race; indigenous), and *education level* (none; 1–3; 4–7; 8–11; ≥12 years). For the variables *race/skin color* and *education level* 7.3% and 18.6% of entries were missing data respectively. Therefore, imputation was performed to reduce potential biases in the analyses by using Stata 15's *mi impute mlogit* library, which employs a multinomial logistic regression model for imputation of nominal variables. The variable *transmission category* was excluded due to the high proportion of missing records (34.2%) in the original database.

Among individual clinical characteristics, *baseline CD4 lymphocyte count* showed considerable variation within the interval between the date of the test and treatment initiation, as has been reported elsewhere in the literature [36, 37]. We thus decided to consider as baseline the CD4 lymphocyte count performed between six months before and 30 days after the treatment initiation date (<200; 200–349; 350–499; ≥500 cells/mm^3). The remaining clinical variables included were: *initial VL count* (≤100,000; >100,000 copies/mL) *and occurrence of active*

tuberculosis episode until the first VS (no; yes). Regarding treatment, the variable *initial therapeutic regimen* comprised ART medications specified in the clinical protocol of the period: preferred regimens–non-nucleoside reverse transcriptase inhibitor + 1 integrase inhibitor (NNRTI+1INI) and nucleoside reverse transcriptase inhibitors + 1 non-nucleoside reverse transcriptase inhibitor (2NRTI+1NNRTI); special regimens authorized by regional technical chambers and unauthorized regimens [38].

Additionally, the following variables were included: *change in therapeutic regimen until VS* (no; yes), *adherence to treatment until the first VS*, measured by the Medication Possession Ratio - MPR (<80%; 80–94%; ≥95%), and the *number of VL tests conducted until VS*.

The variables regarding treatment facility characteristics were: *facility location according to geographical region* (North; Northeast; Central-West; South; Southeast), *metropolitan region* (no; yes), and *total number of PLWHA who initiated ART at the facility between 2015–2018* (≤50; 51–500; >500).

Data analysis

The dependent variable was the distribution of the time from treatment initiation to VS, for which Normal, Log-Normal, Weibull, Exponential, and Gamma distributions were tested [39]. The Log-Normal distribution showed the best fit to the data. We therefore decided to use a parametric multilevel accelerated failure time survival model with a Log-Normal distribution for the analysis of cohort data [40, 41].

Initially, the absolute and relative frequencies of the qualitative variables were examined, and measures of central tendency and dispersion were calculated for the dependent (quantitative) variable. Subsequently, bivariate analyses were conducted between the dependent variable and each individual and facility-related variable. Finally, these variables were analyzed in multiple hierarchical models. The two levels of aggregation in the models (individual and facility-related) and the hierarchy of variables were defined based on the theoretical model presented in Fig 1.

Four models were constructed for the multiple analysis, aiming to measure the fixed and random effects of the variables at each level. Based on the null model, individual variables were included in the following sequence: sociodemographic characteristics, disease severity, and

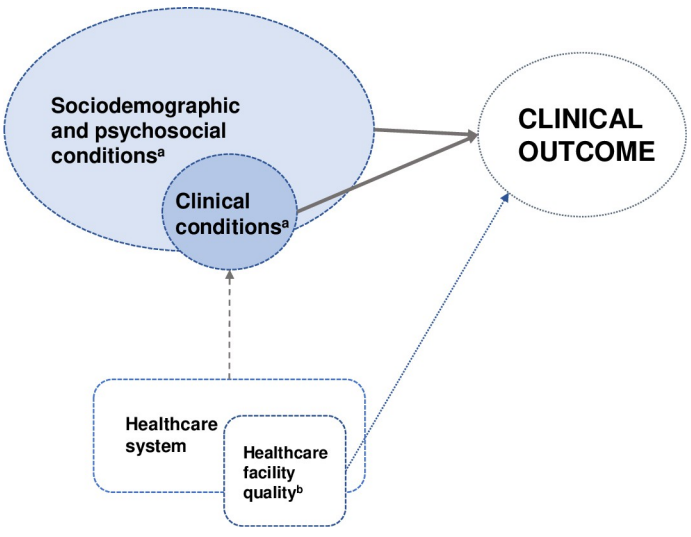


Fig 1. Theoretical model of clinical outcome production in HIV infection treatment.

https://doi.org/10.1371/journal.pone.0305311.g001

treatment. The model relative to treatment facilities included only the block of facility-related variables. Comparisons between the models were conducted using likelihood, interquartile range, and the proportion of change in variance. The results were presented as time ratios (TR) and their respective 95% confidence intervals (95% CI). The significance level used for all analyses was 5%.

For the characterization of random effects, the four analyzed models were compared in terms of random variance (standard error-SE), intraclass correlation coefficient (ICC), log likelihood, and proportional change in variance (PCV) [42–45].

The PCV, at the contextual level, measures the variation of time to VS across healthcare facilities and is defined as [42, 43, 45]:

$$PCV = \frac{\text{Random variance of the null model} - \text{random variance of the final model}}{\text{Random variance of the null model}}$$

Contextual differences in time to VS can be attributed to random effects or differences in individual composition of the facilities in terms of sociodemographic factors, disease severity, or treatment initiation of the patients. Therefore, the PCV was calculated by comparing the null model with the other models that included only individual variables (models 1 and 2) and only facility-related variables (model 3).

The ICC is the proportion of the total variance of time to VS among treatment facilities that is attributed to facility variability; in other words, it measures the heterogeneity of time to VS attributed to differences between facilities, and is calculated for each model using the formula [44]:

$$ICC = \frac{\text{Random variance}}{\text{Random variance} + \text{individual variance}}$$

As detected in observational [24, 46–50] studies, there has been variation in adherence to the VL monitoring protocol, which may affect the estimates [46–51]. To minimize this limitation, all models were adjusted for the number of VL tests received by the individual.

Additionally, a sensitivity analysis was conducted by replicating the models with the inclusion of the variable *transmission category*, using the subset of individuals with complete information for this variable (S2 Table), and without adjustment for the number of VL tests received (S3 Table). All analyses were performed using Stata 15.0's *mestreg* package.

Ethical considerations

The project was approved by the Ethics Committee on Research on Human Beings of the USP School of Medicine on January 23, 2020 (CAAE: 27659220.3.0000.0065; Opinion: 3.807.435), following the recommendations of Resolution No. 466 of 2012 from the Brazilian National Health Council. The data was sent to the research team on May 10, 2020. There were no variables or information that could identify the individuals in the data set received.

Results

The Qualiaids-Brazil Cohort comprises 132,540 PLWHA who initiated ART in Brazil between January 1, 2015, and December 31, 2018. For this study, considering eligibility criteria, 128,360 PLWHA were included who had been in treatment for more than 30 days and received at least one VL test after starting ART. A total of 2,544 (1.9%) individuals who had been in treatment for fewer than 30 days, and 1,636 (1.2%) individuals who did not receive a VL test before the first ART dispensation were excluded. The censoring events were as follows: 1,496 (1.1%) deaths, 3,838 (2.9%) losses to follow-up, and 10,988 (8.3%) administrative censorings [29].

The distribution of time to VS is shown in Fig 2. Of the PLWHA considered in this study, 89.4% (114,696) achieved VS, with 20.8% (23,801) reaching it within 3 months after treatment initiation, 56.4% (64,636) within 6 months, and 87.5% (100,408) within 12 months.

The median time to VS for all included individuals was 161 days, ranging from 31 to 1,426 days, depending on the time interval between treatment initiation and the control VL test. Shorter intervals resulted in smaller medians (S1 Table).

Regarding the distribution of individual characteristics of the participants, higher proportions of PLWHA were identified as male (69.8%), aged 20–39 years (64.3%), with >8 years of schooling (62.8%), and of race/skin color brown or black (54.6%). A total of 26% of participants had an initial CD4 count <200 cells/mm^3, whereas initial VL >100,000 copies/mL was observed in 8.2% of participants. The initial therapeutic regimen was 2NRTI + 1NNRTI for 61.8% of participants; 3.2% changed their therapeutic regimen before the first VS. 42.5% of participants experienced an episode of tuberculosis before the first VS. 42.5% of participants had treatment adherence rates of ≥95%.

Regarding the treatment facilities, Fig 3 shows the distribution of the 941 included facilities and of PLWHA monitored in them, according to geographic region and location in metropolitan areas. The Southeast region accounted for most facilities (59.0%) and PLWHA (41.2%). There was a predominance of facilities located in capital cities or metropolitan regions (66.2%) and facilities assisting 51–500 individuals who started ART during the period (49.0%).

Table 1 shows the observed proportions of individual characteristics and the bivariate analyses between the dependent variable and each of the individual variables (sociodemographic, clinical, and treatment-related).

Table 2 shows the bivariate analysis between the dependent variable and each of the facility-related variables.

The bivariate analysis showed that PLWHA who received care in facilities in the North (TR = 1.13; 95% CI: 1.06; 1.21), Northeast (TR = 1.14; 95% CI: 1.09; 1.19), and Central-West

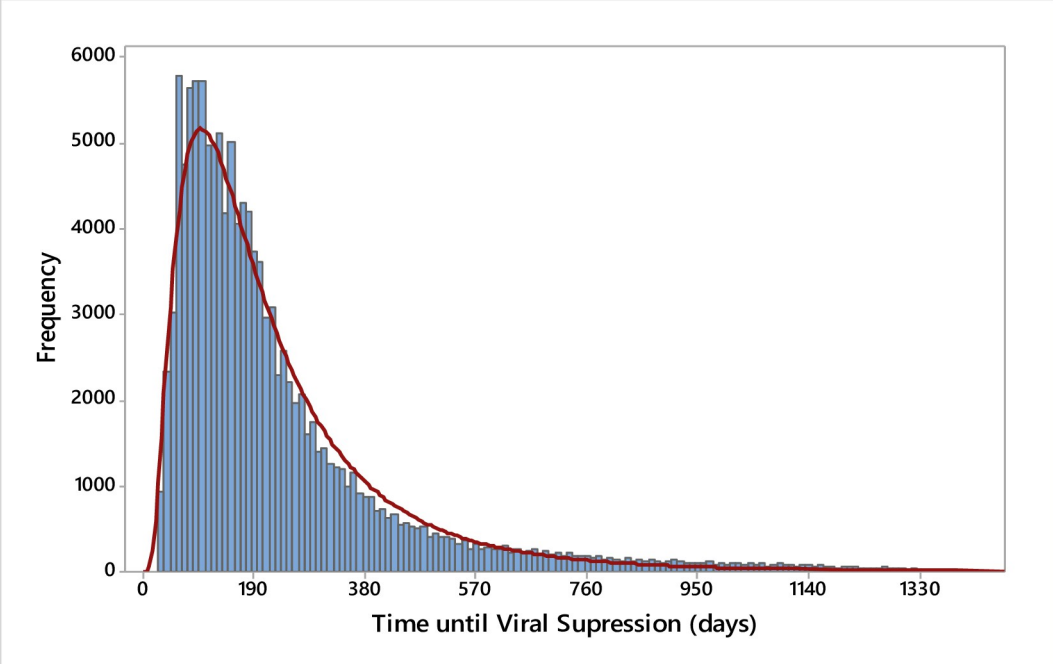
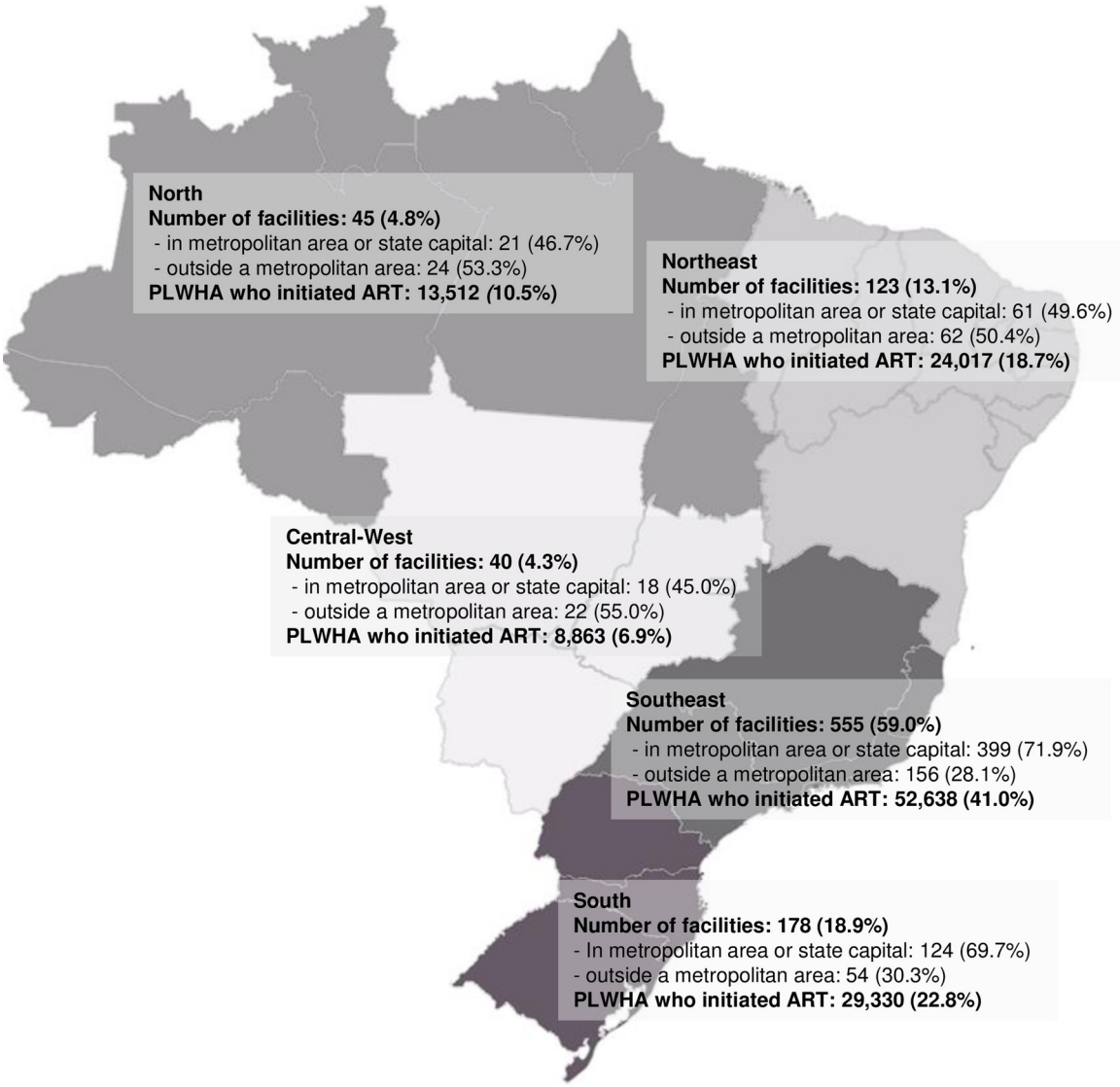


Fig 2. Distribution of time to VS, in days, Qualiaids-Brazil Cohort, 2015–2018 (N = 128,360).

https://doi.org/10.1371/journal.pone.0305311.g002



Number of facilities ranked by size	Central-West		Northeast		North		Southeast		South		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
Up to 50 persons	6	15.0	33	26.8	8	17.8	306	55.1	44	24.7	397	42.2
51 to 500 persons	27	67.5	72	58.5	28	62.2	219	39.5	115	64.6	461	49.0
More than 500 persons	7	17.5	18	14.6	9	20.0	30	5.4	19	10.7	83	8.8
Total	**40**	**100.0**	**123**	**100.0**	**45**	**100.0**	**555**	**100.0**	**178**	**100.0**	**941**	**100.0**

Fig 3. SUS HIV treatment facilities and number of individuals included in the cohort who initiated ART in 2015–2018, categorized by macro-region of the country. Qualiaids-Brazil Cohort, 2022 (N = 941).

https://doi.org/10.1371/journal.pone.0305311.g003

(TR = 1.10; 95% CI: 1.03; 1.18) regions had a longer time to VS compared to those in the Southeast. This finding was also observed for PLWHA treated in facilities located outside the metropolitan region (TR = 1.09; 95% CI: 1.05; 1.12) and in facilities serving <50 PLWHA (TR = 1.15; 95% CI: 1.09; 1.21).

Table 1. Descriptive analysis and bivariate analysis of the time from treatment initiation to VS, according to individual variables. Qualiaids-Brazil Cohort, 2015–2018 (N = 128,360).

Variable	Total	%		Bivariate		
			Suppression*	Time Ratio	LT	HT
Sex						
Male	89,586	69.8	89.5	ref		
Female	38,774	30.2	88.9	0.93	0.93	0.94**
Age group (in years)						
15–19	5,761	4.5	87.1	1.04	1.02	1.07**
20–29	44,823	34.9	89.7	1.01	0.99	1.02
30–39	37,672	29.4	88.8	1.03	1.02	1.05**
40–49	23,214	18.1	89.2	1.03	1.02	1.05**
50–59	12,081	9.4	90.4	ref		
≥60	4,809	3.8	91.3	0.98	0.96	1.01
Race/skin color						
White	57,183	44.5	91.0	ref		
Black	14,181	11.1	87.8	1.04	1.02	1.05**
Yellow	953	0.7	88.9	1.03	0.98	1.09
Brown	55,772	43.5	88.2	1.04	1.03	1.05**
Indigenous	271	0.2	79.3	1.22	1.11	1.34**
Education (in years of schooling)						
None	2,278	1.8	86.7	1.18	1.14	1.22**
1–3	11,132	8.7	85.6	1.21	1.19	1.24**
4–7	34,298	26.7	86.9	1.17	1.16	1.19**
8–11	52,042	40.5	90.1	1.07	1.06	1.08**
≥12	28,610	22.3	92.5	ref		
Initial therapeutic regimen						
Preferred regimen (2017–2018: NNRTI+1INI)	48,410	37.7	89.6	ref		
Preferred regimen (2015–2016: 2NRTI + 1NNRTI)	79,288	61.8	89.3	1.54	1.53	1.55**
Authorized special regimens	118	0.1	83.1	1.39	1.21	1.60**
Unauthorized regimens	544	0.4	85.7	1.48	1.39	1.58**
Initial CD4 lymphocyte count (cells/mm^3)						
<200	33,327	26.0	82.7	1.33	1.31	1.35**
200–349	25,054	19.5	89.1	1.14	1.13	1.15**
350–499	26,329	20.5	91.6	1.07	1.05	1.08**
≥500	43,650	34.0	93.2	ref		
Initial VL count (copies/mL)						
≤100,000	117,864	91.8	91.9	ref		
>100,000	10,496	8.2	82.6	1.39	1.38	1.40**
Active tuberculosis episode until suppression						
No	122,014	95.1	90.2	ref		
Yes	6,346	4.9	72.9	1.45	1.42	1.48**
Therapeutic regimen change before suppression						
No	124,305	96.8	89.0	ref		
Yes	4,055	3.2	100.0	1.45	1.42	1.49**
Adherence						
≥95%	54,618	42.5	92.6	Ref		
80–95%	66,334	51.7	89.4	1.40	1.39	1.41**

(*Continued*)

Table 1. (Continued)

Variable	Total	%		Bivariate		
			Suppression*	Time Ratio	LT	HT
<80%	7,408	5.8	65.4	2.17	2.12	2.21**

* Chi-square p<0.05 for all variables

**P≤0.001

https://doi.org/10.1371/journal.pone.0305311.t001

The variables were then analyzed in the multiple models (Table 3). The time ratios of individual and facility-related variables in the multiple models followed the same direction as in the bivariate models.

Among individual variables, the following were associated with longer time to VS: male sex; age below 50 years; Black and Brown, race/skin color; education ≤11 years of schooling; therapeutic regimen 2NRTI + 1NNRTI; authorized special regimens or unauthorized regimens; initial CD4 count <500 cells/mm^3; initial VL >100,000 copies/mL; active tuberculosis episode; therapeutic regimen change; and treatment adherence <95%. Regarding the characteristics of treatment facilities, PLWHA who received care in facilities in the North, Northeast, and Central-West regions had a longer time to VS. The same was observed for PLWHA assisted by facilities located outside the metropolitan region (TR = 1.06; 95% CI: 1.02; 1.10) and by facilities attending <50 PLWHA (TR = 1.15; 95% CI: 1.05; 1.26).

Table 4 shows the difference in unexplained variability for each model. Model 2 showed the lowest unexplained variability, which is consistent with its higher number of explanatory variables. The model adjusted for facility-related variables (model 3) exhibited the lowest ICC (7.7%), indicating that this adjustment was able to reduce heterogeneity in time to VS. Furthermore, it was observed that 16.2% of the variability in time to VS was explained by individual sociodemographic and clinical variables (model 2); however, 13.2% of this variability can be explained solely by the facility-related variables. The log likelihood indicated that model 2 was the best fit.

The results of the sensitivity analyses were consistent with the findings, showing small variations in effect estimates (S2 and S3 Tables).

Table 2. Bivariate analysis of the time between treatment initiation and VS, according to facility-related variables. Qualiaids-Brazil Cohort, 2015–2018 (N = 128,360).

Variable	TR (95% CI)
Geographic region	
Central-West	1.10[1.03;1.18]
North	1.13[1.06;1.21]
Northeast	1.14[1.09;1.19]
South	0.99[0.96;1.04]
Southeast	Ref
Facility location (municipality)	
Metropolitan region	Ref
Other	1.09[1.05;1.12]
Number of patients served	
≤50	1.15[1.09;1.21]
51–500	1.03[0.98;1.07]
>500	Ref

https://doi.org/10.1371/journal.pone.0305311.t002

Table 3. Results of hierarchically adjusted multilevel models for time to VS, according to individual and facility-related characteristics, Qualiaids-Brazil Cohort, 2015–2018 (N = 128,360).

			Variable	TR (95% CI)
Model 1	Model 2		***Sex***	
			Male	ref
			Female	0.91[0.90;0.92]
			Age group (in years)	
			15–19	1.14[1.11;1.16]
			20–29	1.08[1.07;1.10]
			30–39	1.06[1.04;1.07]
			40–49	1.03[1.02;1.05]
			50–59	Ref
			≥60	0.97[0.95;1.00]
			Race/skin color	
			White	Ref
			Black	1.04[1.02;1.05]
			Yellow	1.01[0.97;1.06]
			Brown	1.03[1.02;1.04]
			Indigenous	1.17[1.07;1.27]
			Education (in years of schooling)	
			None	1.18[1.14;1.21]
			1–3	1.20[1.18;1.22]
			4–7	1.15[1.14;1.16]
			8–11	1.06[1.05;1.07]
			≥12	Ref
			Initial therapeutic regimen	
			Preferred regimen (2017–2018: NNRTI+1INI)	Ref
			Preferred regimen (2015–2016: 2NRTI + 1NNRTI)	1.33[1.32;1.34]
			Authorized special regimens	1.07[0.94;1.21]
			Unauthorized regimens	1.23[1.16;1.31]
			Initial CD4 lymphocyte count (cells/mm^3)	
			≤200	1.09[1.08;1.10]
			200–349	1.09[1.08;1.10]
			350–499	1.04[1.03;1.05]
			≥500	Ref
			Initial VL count (copies/mL)	
			≤100,000	Ref
			>100,000	1.19[1.17;1.20]
			Active tuberculosis episode until suppression	
			No	Ref
			Yes	1.10[1.08;1.12]
			Therapeutic regimen change	
			No	Ref
			Yes	1.15[1.13;1.18]
			Adherence	
			≥95%	Ref
			80–95%	1.19[1.18;1.21]
			<80%	1.83[1.79;1.86]

(*Continued*)

Table 3. (Continued)

			Variable	TR (95% CI)
		Model 3	***Geographic region***	
			Central-West	1.18[1.08;1.28]
			North	1.20[1.11;1.30]
			Northeast	1.20[1.14;1.16]
			South	1.01[0.97;1.06]
			Southeast	Ref
			Facility location (municipality)	
			Metropolitan region	Ref
			Other	1.06[1.02;1.10]
			Number of patients served	
			≤50	1.15[1.05;1.26]
			51–500	0.96[0.89;1.04]
			>500	Ref

Model 1 – sociodemographic characteristics; Model 2 – sociodemographic + clinical characteristics; Model 3 – facility-related characteristics.
All models were adjusted for the number of VL tests performed until VS.

https://doi.org/10.1371/journal.pone.0305311.t003

Discussion

Among PLWHA participating in the Qualiaids-Brazil Cohort who initiated ART in SUS healthcare facilities between 2015 and 2018, nearly 90% achieved VS, half of whom did so within five months of treatment.

Individuals in the following categories had a higher proportion of VS during the cohort's time period: male sex, aged 50–59 years, white race/skin color, with ≥12 years of education, initial treatment regimen NNRTI+1INI, initial CD4 lymphocyte count ≥500 cells/mm^3, initial VL count ≤100,000 copies/mL, without an active tuberculosis episode, without therapeutic regimen change, with ≥95% adherence to treatment, and receiving clinical follow-up in facilities located in the Southeast or South regions, in metropolitan areas, and in facilities serving >500 PLWHA.

Individual variables accounted for most of the variability in time to VS; however, facility-related variables also played a noteworthy role.

Regarding individual characteristics, there was an association with longer time to VS of individuals of brown and black race/skin color, as well as those with lower education levels. In Brazil, these characteristics are proxies for poorer social conditions [52]. This finding is consistent with several international studies on ethnic and social disparities [53–56].

Table 4. Results of the random-effects analysis of models null through 3, Qualiaids-Brazil Cohort, 2015–2018 (N = 128,360).

	Null Model	Model 1	Model 2	Model 3
Random Variance (SE)	0.068 (0.004)	0.066 (0.004)	0.057 (0.003)	0.059 (0.003)
ICC	0.093	0.091	0.083	0.077
PCV	ref	0.029	0.162	0.132
Log Likelihood	-712903.7	-712188.3	-706630.4	-712830.4

SE: standard error; ICC: intraclass correlation coefficient; PCV: proportional change in variance

https://doi.org/10.1371/journal.pone.0305311.t004

Social issues are intertwined with clinical issues. The study demonstrated that late diagnosis, with a low CD4 level (<200) and very high VL (>100,000), delays time to VS, echoing numerous studies that associate these factors with negative outcomes. Since 2015, Brazil has maintained a late diagnosis proportion of around 25% [8]. The trends observed in countries with similar epidemic profiles also confirm the maintenance of late diagnosis proportions. Globally, it is still observed that the proportion of people diagnosed late is changing little as the effectiveness of ART continues to improve [10, 57–59].

In Brazil, especially, the second most important clinical condition associated with negative outcomes is tuberculosis (TB). This situation is similar to that of low-income countries, where TB is the leading cause of death among PLWHA, notably in the first year after diagnosis [60, 61]. Brazil is among the 12 countries with the highest global TB burden. Regarding coinfection HIV and tuberculosis, it has the highest burden of those countries [62]. Coinfection with TB is associated with lower CD4 levels and higher VL levels, underscoring the importance of HIV treatment facilities in diagnosing and treating both latent and active tuberculosis [63, 64].

The negative impact on time to VS resulting from poor adherence to HIV treatment reaffirms numerous studies that, since the HIV treatment became available, have emphasized the crucial role of promotion, monitoring, and support by treatment facilities for those with difficulty in adhering to the prescribed regimen [65, 66].

The longer time to achieving VS among non-white individuals with lower education levels follows the general trend highlighted in studies of mortality, late diagnosis, loss to follow-up, and tuberculosis, reflecting social and ethnic inequality in the country. Despite significant progress in addressing the HIV epidemic through free and universal access to high-effectiveness care and medication across the country, the healthcare system has not successfully mitigated inequalities to achieved desired health outcomes, reflecting disparities in the allocation and organization of treatment facilities. The higher concentration of facilities in the Southeast and South regions and in metropolitan areas corresponds to the greater concentration of PLWHA in these locations. Certainly, there is also a need for smaller facilities, particularly in smaller cities within the regions. On the other hand, the allocation of facilities in both large and small municipalities for a small number of patients (<50) appears to be problematic, suggesting significant diversity of HIV care policies among municipal administrations [28, 67]. While certain geographical conditions may warrant the establishment of small-scale facilities, evidence repeatedly shows a higher likelihood of negative outcomes in facilities with a reduced number of patients [21, 68]. Balancing easy access to treatment with professional training and organization therefore is an important priority to ensure appropriate quality of care. Disparities in the organization of HIV care at regional, district, and even municipal levels have been highlighted in national studies [31–34, 69, 70].

The study revealed a significant flaw in the quality of the care provided by treatment facilities: among PLWHA who achieved VS during the study period, 67.2% did not receive VL testing within the timeframe specified by the protocol (66 days) [38]. The deficiency in monitoring has been pointed out in studies of the records of two populous Brazilian states, Minas Gerais [24] and Rio de Janeiro [47]. The issue appears to be predominantly organizational in nature rather than caused by supply of tests since data indicate high and uniform availability of VL tests across the country's public service network [33, 34]. On the other hand, the request for VL tests and scheduling of follow-up appointments, lacks managerial mechanisms, such as electronic control of appointment scheduling and tests rather than relying on individual physician's request tests. We suggested that this flaw in monitoring, translated into longer-than-recommended intervals between tests, stems from the high demand for medical appointments—a common issue in larger facilities—thus influencing physicians' decisions regarding test and appointment scheduling. Another possibility is that the longer intervals

may be a recommendation from facility managers to alleviate the pressure of demand for appointments. Detailed studies focusing on the organizational processes in treatment facilities are needed to support interventions capable of improving this situation as quickly as possible.

Promptness in having the first VL test after treatment initiation is fully justified by the clinical need for timely detection of viral failures and adherence issues [1, 71]. It may also operate as an incentive to maintain adherence for those who achieve rapid VS [72, 73]. Proper VL monitoring and rapid VS rate are indicators of quality of care [12].

The ability to quickly achieve VS is feasible given the effectiveness of available ART regimen, especially for those who initiate treatment with CD4>200 and low VL and maintain good adherence. ART effectiveness has increased with widespread use of regimens containing integrase inhibitors, especially dolutegravir [74], which is part of the recommended regimen for treatment initiation in Brazil. There is also repeated evidence that rapid treatment initiation accelerates time to VS [75, 76]. However, the time to initiation could not be addressed in this study.

The median time to VS was 55 days for those who had the first VL test after starting treatment within the established timeframe (66 days). The median is similar to that found in observational studies conducted in locations with a comparable epidemic profile to Brazil's (concentrated epidemic) and with free access to treatment, such as Atlanta, 2016 (57 days) [77], and London, 2018 (56 days) [78].

Considering the importance of rapid suppression, Xia [54] and Dombrowski [12] suggested that the treatment time parameter for estimating the "suppressed" bar of the cascade—usually set at 12 months or, as in Brazil, at six months—be reduced to three months. They argue that rapid initiation and the high efficacy of current ART shorten this time, as exemplified by studies that, using a VL threshold of <200 copies/mL in three months, found VS proportions of 37% [54] and 45% [17]. With a lower threshold of <50 copies/mL, the proportion of those who achieved VS, in this study, within the shortest evaluated interval (66 days—27.5%) would likely be higher if the monitoring protocol had been adhered to for most PLWHA. Among all those who achieved VS and were tested within the first three months, VS rate was 36.1%, indicating that it would be possible in Brazil to shorten the threshold to three months, even as an incentive for improving VL monitoring.

This study was the first nationwide cohort, based on a longitudinal database, that analyzed time to VS in PLWHA receiving treatment in the SUS. It was also one of the largest operational cohorts in the international literature. The inclusion of the characteristics of healthcare facilities in the analyses reinforces the study's originality.

As time to VS may be influenced by the number of VL tests conducted during the period, the inclusion of this variable in the analyses is also a strength to be noted.

Nonetheless, there are were limitations to our analysis. First, in the studied database there was no explicit definition of the healthcare system in which PLWHA received care. Thus, a previously published standardized classification strategy, as defined in the methods section, was employed to minimize that limitation. It should also be noted that the use of secondary sources such as developed for operational purposes, involves inconsistencies and missing data, which may lead to misclassification errors and underestimation of the measures of interest. However, the definition of inclusion criteria sensitive to potential inconsistencies and the imputation of data for relevant variables reduces the possibility of interference in the results [29].

This study of a large cohort of PLWA in Brazil was the first to analyze time to viral suppression and the first to include characteristics of healthcare facilities. The results strongly suggest the need for more comprehensive longitudinal studies, including more individual and health facilities characteristics, that can further contribute to healthcare policies for PLWHA in Brazil.

While acknowledging the limitations, the findings seem sufficient to indicate the urgency of improving VL monitoring in the treatment facilities network across the country. This must be carried out as part of a coordinated effort to provide more equitable access and capacity for HIV facilities to optimize quality care and reduce time to viral suppression.

Supporting information

S1 Table. Time between ART initiation and VL testing in the first six months of treatment. Qualiaids-Brazil Cohort, 2015–2018 (N = 101,822).
(DOCX)

S2 Table. Results of hierarchically adjusted multilevel models for time to VS, as well as individual and facility-related characteristics, restricted to those with information on exposure category. Qualiaids-Brazil Cohort, 2015–2018 (N = 84,747).
(DOCX)

S3 Table. Results of hierarchically adjusted multilevel models for time to VS, according to individual and facility-related characteristics WITHOUT adjustment for number of VL tests. Qualiaids-Brazil Cohort, 2015–2018 (N = 84,747).
(DOCX)

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References

1. INSIGHT START Study Group; Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med. 2015 Aug 27; 373(9):795–807. https://doi.org/10.1056/NEJMoa1506816 PMID: 26192873
2. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Antiretroviral Therapy for the Prevention of HIV-1 Transmission. N Engl J Med. 2016 Sep 1; 375(9):830–9. https://doi.org/10.1056/NEJMoa1600693 PMID: 27424812
3. Eisinger RW, Dieffenbach CW, Fauci AS. HIV viral load and transmissibility of HIV infection: undetectable equals untransmittable. Jama. 2019 Feb 5; 321(5):451–2 https://doi.org/10.1001/jama.2018.21167 PMID: 30629090

4. Broyles LN, Luo R, Boeras D, Vojnov L. (2023). The risk of sexual transmission of HIV in individuals with low-level HIV viraemia: a systematic review. Lancet (London, England), 402(10400), 464–471. https://doi.org/10.1016/S0140-6736(23)00877-2 PMID: 37490935

5. Gardner EM, McLees MP, Steiner JF, Del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. Clin Infect Dis. 2011; 52:793–800. https://doi.org/10.1093/cid/ciq243 PMID: 21367734

6. Kay ES, Batey DS, Mugavero MJ. The HIV treatment cascade and care continuum: updates, goals, and recommendations for the future. AIDS Res Ther. 2016 Nov 8; 13:35. https://doi.org/10.1186/s12981-016-0120-0 PMID: 27826353; PMCID: PMC5100316.

7. World Health Organization. Regional Office for the Eastern Mediterranean. (2014). HIV test–treat–retain cascade analysis: guide and tools. World Health Organization. Regional Office for the Eastern Mediterranean. https://iris.who.int/handle/10665/250533

8. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde e Ambiente. Departamento de HIV/Aids, Tuberculose, Hepatites Virais e Infecções Sexualmente Transmissíveis (DATHI). Relatório do Monitoramento Clínico do HIV 2022, Brasília - DF 2023

9. Haber N, Pillay D, Porter K, Bärnighausen T. (2016). Constructing the cascade of HIV care: methods for measurement. Current opinion in HIV and AIDS, 11(1), 102–108. https://doi.org/10.1097/COH.0000000000000212 PMID: 26545266

10. Crepaz N, Ruiguang SO, HALL HI. Estimated time from HIV infection to diagnosis and diagnosis to first viral suppression during 2014–2018. AIDS (London, England). 2021 Nov 11; 35(13):2181. https://doi.org/10.1097/QAD.0000000000003008 PMID: 34172670

11. Vourli G, Katsarolis I, Pantazis N, Touloumi G. HIV continuum of care: expanding scope beyond a cross-sectional view to include time analysis: a systematic review. BMC Public Health 21, 1699 (2021). https://doi.org/10.1186/s12889-021-11747-z PMID: 34535096

12. Dombrowski JC, Baeten JM. It's Time to Make the Time to Viral Suppression After HIV Diagnosis a Metric of HIV Care Success. J Infect Dis. 2019; 219(6):845–847. https://doi.org/10.1093/infdis/jiy539 PMID: 30304499

13. Shoemaker ES, Becker ML, Liddy CE, McClarty LM, Asghari S, Hurd J, et al. Creating clinical cohorts: challenges encountered in two Canadian provinces. Healthc Policy. 2019; 15(1):10–8. https://doi.org/10.12927/hcpol.2019.25942 PMID: 31629452

14. Liu J, Wilton J, Sullivan A, Marchand-Austin A, Rachlis B, Giles M, et al. Ontario HIV Epidemiology and Surveillance Initiative (2019). Cohort profile: Development and profile of a population-based, retrospective cohort of diagnosed people living with HIV in Ontario, Canada (Ontario HIV Laboratory Cohort). BMJ open, 9(5), e027325. https://doi.org/10.1136/bmjopen-2018-027325 PMID: 31133591

15. Bacon O, Chin J, Cohen SE, Hessol NA, Sachdev D, et al. Decreased Time From Human Immunodeficiency Virus Diagnosis to Care, Antiretroviral Therapy Initiation, and Virologic Suppression during the Citywide RAPID Initiative in San Francisco. Clin Infect Dis. 2021 Jul 1; 73(1):e122–e128. https://doi.org/10.1093/cid/ciaa620 PMID: 32449916

16. Nanditha NGA, Dong X, Tafessu HM, Wang L, Lu M, Barrios R, et al. (2022). A province-wide HIV initiative to accelerate initiation of treatment-as-prevention and virologic suppression in British Columbia, Canada: a population-based cohort study. CMAJ open, 10(1), E27–E34. https://doi.org/10.9778/cmajo.20210093 PMID: 35042692

17. Alejos B, Díez C, Galindo MJ, López JC, Moreno-García E, Estrada V, et al. (2022). Progress in the quality of care for newly diagnosed people with HIV in Spain (2004–2019). Antiviral therapy, 27(4), https://doi.org/10.1177/13596535221112729 PMID: 35802475

18. Pyngottu A, Scherrer AU, Kouyos R, Huber M, Hirsch H, Perreau M, et al. Swiss HIV Cohort Study. Predictors of Virological Failure and Time to Viral Suppression of First-Line Integrase Inhibitor-Based Antiretroviral Treatment. Clin Infect Dis. 2021 Oct 5; 73(7):e2134–e2141. https://doi.org/10.1093/cid/ciaa1614 PMID: 33095848

19. Huang SW, Shen MC, Wang WH, Li WY, Wang JH, Tseng CY, et al. High prevalence of HIV-1 transmitted drug resistance and factors associated with time to virological failure and viral suppression in Taiwan. J Antimicrob Chemother. 2021 Dec 24; 77(1):185–195. https://doi.org/10.1093/jac/dkab361 PMID: 34648632

20. Monroe AK, Happ LP, Rayeed N, Ma Y, Jaurretche MJ, Terzian AS, et al. Clinic-Level Factors Associated With Time to Antiretroviral Initiation and Viral Suppression in a Large, Urban Cohort. Clin Infect Dis. 2020 Oct 23; 71(7):e151–e158. https://doi.org/10.1093/cid/ciz1098 PMID: 31701144

21. Wiewel EW, Borrell LN, Jones HE, Maroko AR, Torian LV. (2019). Healthcare facility characteristics associated with achievement and maintenance of HIV viral suppression among persons newly diagnosed with HIV in New York City. AIDS care, 31(12), 1484–1493. https://doi.org/10.1080/09540121.2019.1595517

22. Badejo O, Noestlinger C, Jolayemi T, Adeola J, Okonkwo P, Van Belle S, et al. Multilevel modelling and multiple group analysis of disparities in continuity of care and viral suppression among adolescents and youths living with HIV in Nigeria. BMJ Glob Health. 2020 Nov; 5(11):e003269. https://doi.org/10.1136/bmjgh-2020-003269 PMID: 33154102

23. Sarrazin VMS, Ohl ME, Richardson KK, Asch SM, Gifford AL, Bokhour BG. (2018). Patient and Facility Correlates of Racial Differences in Viral Control for Black and White Veterans with HIV Infection in the Veterans Administration. AIDS patient care and STDs, 32(3), 84–91. https://doi.org/10.1089/apc.2017.0213 PMID: 29620926

24. Mendicino CCP, Silva GJD, Braga LP, Colosimo EA, Guimarães MDC, Pádua CA M. (2020). Monitoring HIV infection in Minas Gerais state: 15-year assessment of adults living with HIV initiating Antiretroviral Therapy. Revista da Sociedade Brasileira de Medicina Tropical, 53, e20200360. https://doi.org/10.1590/0037-8682-0360-2020

25. Greco DB, Simão M. Brazilian policy of universal access to AIDS treatment: sustainability challenges and perspectives. AIDS. (2007) Jul;21 Suppl 4:S37–45. https://doi.org/10.1097/01.aids.0000279705.24428.a3 PMID: 17620751

26. Basso CR. Programa de DST/AIDS no SUS. In: Negri B, Viana ALD, organizadores. O Sistema Único de Saúde em 10 anos de desafio. São Paulo: Sobravime; 2002. p. 43–58

27. Castro MC, Massuda A, Almeida G, Menezes-Filho NA, Andrade MV, de Souza Noronha KVM, et al. Brazil's unified health system: the first 30 years and prospects for the future. The Lancet. 2019 Jul 27; 394(10195):345–356. https://doi.org/10.1016/S0140-6736(19)31243-7 Epub 2019 Jul 11 PMID: 31303318

28. Alves AM, Santos ACD, Kumow A, Sato APS, Helena ETS, Nemes MIB. Beyond access to medication: the role of SUS and the characteristics of HIV care in Brazil. Rev Saude Publica. 2023 Apr 17; 57:26. https://doi.org/10.11606/s1518-8787.2023057004476 PMID: 37075422; PMCID: PMC10118421.

29. Sato APS, Nemes MIB, Alves AM, Souza EL, Santos BDR, Nunes LO, et al. Profile of the cohort of people being treated for HIV infection in the SUS, Brazil, 2015–2018. Rev Saude Publica. 2023 Oct 20; 57:66. https://doi.org/10.11606/s1518-8787.2023057005256 PMID: 37878852; PMCID: PMC10519680.

30. Nemes MIB, Castanheira ERL, Loch AP, Santos MA, Alves AM, Melchior R, et al. Avaliação de serviços de saúde: a experiência do Qualiaids. In: Akerman M, Furtado JP, organizadores. Práticas de avaliação em saúde no Brasil–Diálogos. Porto Alegre, RS: Rede Unida; 2016 [citado 12 nov 2021]. p. 92–145. Available on: http://historico.redeunida.org.br/editora/biblioteca-digital/serie-atencao-basica-e-educacao-na-saude/praticas-de-avaliacao-em-saude-no-brasil-dialogos-pdf

31. Melchior R, Nemes MIB, Basso CR, Castanheira ERL, Alves MTSSB, Buchala CM, et al. Evaluation of the organizational structure of HIV/AIDS outpatient care in Brazil. Rev Saude Publica. 2006; 40(1):143–51. https://doi.org/10.1590/S0034-89102006000100022

32. Nemes MIB, Alves AM, Loch AP. Sistema de avaliação Qualiaids. São Paulo: Faculdade de Medicina da USP, Departamento de Medicina Preventiva; 2016 [cited on May 2024]. Available on: https://equipequaliaids.wixsite.com/qualiaids

33. Nemes MIB, Alencar TMD, Basso CR, Castanheira ERL, Melchior R, Alves MTSSB, et al. Assessment of outpatient services for AIDS patients, Brazil: comparative study 2001/2007. Rev Saude Publica. 2013; 47(1):137–46. https://doi.org/10.1590/s0034-89102013000100018 PMID: 23703140

34. Loch AP, Nemes MIB, Santos MA, Alves AM, Melchior R, Basso CR, et al. Evaluation of outpatient services in the Brazilian Unified National Health System for persons living with HIV: a comparison of 2007 and 2010. Cad Saúde Pública [Internet]. 2018; 34(2):e00047217. Available on: https://doi.org/10.1590/0102-311X00047217

35. Buchbinder SP, Havlir DV. Getting to Zero San Francisco: A Collective Impact Approach. J Acquir Immune Defic Syndr. 2019 Dec;82 Suppl 3(Suppl 3):S176–S182. https://doi.org/10.1097/QAI.0000000000002200 PMID: 31764252

36. The Late Presentation Working Groups in Euro SIDA and COHERE. Estimating the burden of HIV late presentation and its attributable morbidity and mortality across Europe 2010–2016. BMC Infect Dis 20, 728 (2020

37. Hughes RA, Sterne JA, Walsh J, Bansi L, Gilson R, Orkin C, et al. Long-term trends in CD4 cell counts and impact of viral failure in individuals starting antiretroviral therapy: UK Collaborative HIV Cohort (CHIC) study. HIV Med. 2011 Nov; 12(10):583–93. https://doi.org/10.1111/j.1468-1293.2011.00929.x PMID: 21569188

38. Brasil, Ministério da Saúde, Secretaria de Vigilância em Saúde, Departamento de Vigilância, Prevenção e Controle das Infecções Sexualmente Transmissíveis, do HIV/Aids e das Hepatites Virais. Protocolo Clínico e Diretrizes Terapêuticas para Manejo da Infecção pelo HIV em Adultos. Brasília

(DF); 2018 [citado 1 nov 2021]. Available on: http://www.aids.gov.br/pt-br/pub/2013/protocolo-clinico-e-diretrizes-terapeuticas-para-manejo-da-infeccao-pelo-hiv-em-adultos

39. Colosimo EA, Giolo S. Análise de sobrevivência aplicada. São Paulo: Blucher, c2006. 367p

40. Wei LJ. The accelerated failure time model: a useful alternative to the Cox regression model in survival analysis. Stat Med. 1992 Oct-Nov; 11(14–15):1871–9. https://doi.org/10.1002/sim.4780111409 PMID: 1480879

41. Birhan H, Derebe K, Muche S, Melese B. Statistical Analysis on Determinant Factors Associated with Time to Death of HIV/TB Co-Infected Patients Under HAART at Debre Tabor Referral Hospital: An Application of Accelerated Failure Time-Shared Frailty Models. HIV AIDS (Auckl). 2021 Jul 17; 13:775–787. https://doi.org/10.2147/HIV.S319745 PMID: 34305411

42. Merlo J, Chaix B, Yang M, Lynch J, Råstam L. A brief conceptual tutorial of multilevel analysis in social epidemiology: linking the statistical concept of clustering to the idea of contextual phenomenon. J Epidemiol Community Health. 2005 Jun; 59(6):443–9. https://doi.org/10.1136/jech.2004.023473 PMID: 15911637

43. Merlo J, Yang M, Chaix B, Lynch J, Råstam L. A brief conceptual tutorial on multilevel analysis in social epidemiology: investigating contextual phenomena in different groups of people. J Epidemiol Community Health. 2005 Sep; 59(9):729–36. https://doi.org/10.1136/jech.2004.023929 PMID: 16100308

44. Merlo J, Chaix B, Ohlsson H, Beckman A, Johnell K, Hjerpe P, et al. A brief conceptual tutorial of multilevel analysis in social epidemiology: using measures of clustering in multilevel logistic regression to investigate contextual phenomena. J Epidemiol Community Health. 2006 Apr; 60(4):290–7. https://doi.org/10.1136/jech.2004.029454 PMID: 16537344

45. Tesema GA, Mekonnen TH, Teshale AB. (2020) Individual and community-level determinants, and spatial distribution of institutional delivery in Ethiopia, 2016: Spatial and multilevel analysis. PLoS ONE 15 (11): e0242242. https://doi.org/10.1371/journal.pone.0242242 PMID: 33180845

46. Lubega P, Nalugya SJ, Kimuli AN, Twinokusiima M, Khasalamwa M, Kyomugisa R, et al. Adherence to viral load testing guidelines, barriers, and associated factors among persons living with HIV on ART in Southwestern Uganda: a mixed-methods study. BMC Public Health. 2022 Jun 29; 22(1):1268. https://doi.org/10.1186/s12889-022-13674-z PMID: 35768800

47. Bocage AE, Coelho LE, Lake JE, Clark JL, Torres TS, Jalil EM, et al. The Impact of COVID-19 on HIV Care in Rio de Janeiro, Brazil 2019–2021: Disparities by Age and Gender. AIDS Behav (2023). https://doi.org/10.1007/s10461-023-03988-3

48. Costa JM, Torres TS, Coelho LE, Luz PM. Adherence to antiretroviral therapy for HIV/AIDS in Latin America and the Caribbean: Systematic review and meta-analysis. J Int AIDS Soc. 2018 Jan; 21(1): e25066. https://doi.org/10.1002/jia2.25066 PMID: 29356390

49. Harlow AF, Bor J, Brennan AT, Maskew M, MacLeod W, Carmona S, et al. Impact of Viral Load Monitoring on Retention and Viral Suppression: A Regression Discontinuity Analysis of South Africa's National Laboratory Cohort. Am J Epidemiol. 2020 Dec 1; 189(12):1492–1501. https://doi.org/10.1093/aje/kwaa140 PMID: 32648905

50. Hall HI, Tang T, Westfall AO, Mugavero MJ. (2013). HIV care visits and time to viral suppression, 19 U. S. jurisdictions, and implications for treatment, prevention and the national HIV/AIDS strategy. PloS one, 8(12), e84318. https://doi.org/10.1371/journal.pone.0084318 PMID: 24391937

51. Griffin JT, Fraser C, Gras L, de Wolf F, Ghani AC. The effect on treatment comparisons of different measurement frequencies in human immunodeficiency virus observational databases. Am J Epidemiol. 2006 Apr 1; 163(7):676–83. https://doi.org/10.1093/aje/kwj083 Epub 2006 Feb 16. PMID: 16484448.

52. Feller DJ, Agins BD. (2017). Understanding Determinants of Racial and Ethnic Disparities in Viral Load Suppression. Journal of the International Association of Providers of AIDS Care, 16(1), 23–29. https://doi.org/10.1177/2325957416667488 PMID: 27629866

53. Flynn AG, Anguzu G, Mubiru F, Kiragga AN, Kamya M, Meya DB, et al. Socioeconomic position and ten-year survival and virologic outcomes in a Ugandan HIV cohort receiving antiretroviral therapy. PLoS One. 2017 Dec 15; 12(12):e0189055. https://doi.org/10.1371/journal.pone.0189055 PMID: 29244807; PMCID: PMC5731768.

54. Xia Q, Robbins RS, Lazar R, Torian LV, Braunstein SL. Racial and socioeconomic disparities in viral suppression among persons living with HIV in New York City. Ann Epidemiol. 2017 May; 27(5):335–341. https://doi.org/10.1016/j.annepidem.2017.04.005 PMID: 28511865

55. López JD, Qiao Q, Presti RM, Hammer RA, Foraker RE. The impact of neighborhood socioeconomic status on retention in care and viral suppression among people living with HIV. AIDS Care. 2022 Nov; 34(11):1383–1389. https://doi.org/10.1080/09540121.2022.2040724 Epub 2022 Feb 14. PMID: 35164602.

56. Tymejczyk O, Jamison K, Pathela P, Braunstein S, Schillinger JA, Nash D. HIV Care and Viral Load Suppression After Sexual Health Clinic Visits by Out-of-Care HIV-Positive Persons. AIDS Patient Care

STDS. 2018 Oct; 32(10):390–398. https://doi.org/10.1089/apc.2018.0097 PMID: 30277815; PMCID: PMC6198765.

57. Mocroft A, Lundgren J, Antinori A, Monforte AD, Brännström J, Bonnet F, et al. Late presentation for HIV care across Europe: update from the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study, 2010 to 2013. Euro Surveill. 2015; 20(47). https://doi.org/10.2807/1560-7917.ES.2015.20.47.30070 PMID: 26624933

58. UNAIDS, Global AIDS Uptade–Seizing the moment. Tackling entrenched inequalities to end epidemics. Geneve, 2020.

59. Rodrigues A, Struchiner CJ, Coelho LE, Veloso VG, Grinsztejn B, et al. (2021). Late initiation of antiretroviral therapy: inequalities by educational level despite universal access to care and treatment. BMC Public Health, 21 (1), S. 389. http://doi.org/10.1186/s12889-021-10421-8

60. Barr DA, Lewis JM, Feasey N, Schutz C, Kerkhoff AD, Jacob ST, et al. Mycobacterium tuberculosis bloodstream infection prevalence, diagnosis, and mortality risk in seriously ill adults with HIV: a systematic review and meta-analysis of individual patient data. Lancet Infect Dis. 2020; 20(6):742–752. https://doi.org/10.1016/S1473-3099(19)30695-4 PMID: 32178764

61. dos Santos DT, Arroyo LH, Alves YM, Alves LS, Berra TZ, Crispim JA, et al. Survival time among patients who were diagnosed with tuberculosis, the precocious deaths and associated factors in southern Brazil. Trop Med Health. 2021; 49(1):31. Published 2021 Apr 21. https://doi.org/10.1186/s41182-021-00320-4 PMID: 33883022

62. World Health Organization. Global tuberculosis report 2021. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO

63. Magnabosco GT, Lopes LM, Andrade RL de P, Brunello MEF, Monroe AA, Villa TCS. Tuberculosis control in people living with HIV/AIDS. Rev Latino-Am Enfermagem [Internet]. 2016; 24:e2798. Available from: https://doi.org/10.1590/1518-8345.1187.2798 PMID: 27627120

64. Saraceni V, Benzaken AS, Pereira G, Andrade KB, Oliveira PB, Arakaki-Sanchez D, et al. (2018). Tuberculosis burden on AIDS in Brazil: A study using linked databases. PloS one, 13(11), e0207859. https://doi.org/10.1371/journal.pone.0207859 PMID: 30462733

65. Cutrell J, Jodlowski T, Bedimo R. The management of treatment-experienced HIV patients (including virologic failure and switches). Ther Adv Infect Dis. 2020; 7:2049936120901395. Published 2020 Jan 20. https://doi.org/10.1177/2049936120901395 PMID: 32010443

66. McComsey GA, Lingohr-Smith M, Rogers R, Lin J, Donga P. Real-World Adherence to Antiretroviral Therapy Among HIV-1 Patients Across the United States. Adv Ther. 2021 Sep; 38(9):4961–4974. https://doi.org/10.1007/s12325-021-01883-8 Epub 2021 Aug 14. PMID: 34390465

67. Nemes MIB, Alves AM. Relatório Qualiaids 2017. Sistema de avaliação Qualiaids. São Paulo: Faculdade de Medicina da USP, Departamento de Medicina Preventiva; 2016 [cited on May 2023]. Available on: https://equipequaliaids.wixsite.com/qualiaids/publica%C3%A7%C3%B5es

68. O'Neill M, Karelas GD, Feller DJ, Knudsen-Strong E, Lajeunesse D, et al. (2015). The HIV Workforce in New York State: Does patient volume Correlate with quality? Clinical Infectious Diseases, 61 (12),1871–1877. https://doi.org/10.1093/cid/civ719 PMID: 26423383

69. Nemes MIB, Castanheira ERL, Melchior R, Alves MTSSB, Basso CR. (2004). Avaliação da qualidade da assistência no programa de AIDS: questões para a investigação em serviços de saúde no Brasil. Cadernos de Saúde Pública, 20(Suppl. 2), S310–S321. https://doi.org/10.1590/S0102-311X2004000800024

70. Nemes MIB, Melchior R, Basso CR, Castanheira ERL, Alves MTSSB, Conway S. The variability and predictors of quality of AIDS care services in Brazil. BMC Health Serv Res 9, 51 (2009). https://doi.org/10.1186/1472-6963-9-51 PMID: 19298679

71. Mugavero MJ, Napravnik S, Cole SR, Eron JJ, Lau B, Crane HM, et al. Viremia copy-years predicts mortality among treatment-naive HIV-infected patients initiating antiretroviral therapy. Clin Infect Dis. 2011 Nov; 53(9):927–35. https://doi.org/10.1093/cid/cir526 Epub 2011 Sep 2. PMID: 21890751; PMCID: PMC3189165.

72. World Health Organization. The role of HIV viral suppression in improving individual health and reducing transmission: policy brief. ISBN 978-92-4-005517-9 electronic version. © World Health Organization 2023

73. Bouabida K, Chaves BG, Anane E. Challenges and barriers to HIV care engagement and care cascade: viewpoint. Front Reprod Health. 2023 Jul 20; 5:1201087. https://doi.org/10.3389/frph.2023.1201087 PMID: 37547803

74. Meireles MV, Pascom ARP, Duarte EC, McFarland W. Comparative effectiveness of first-line antiretroviral therapy: results from a large real-world cohort after the implementation of dolutegravir. AIDS. 2019 Aug 1; 33(10):1663–1668. https://doi.org/10.1097/QAD.0000000000002254 PMID: 31082860

75. Michienzi SM, Barrios M, Badowski ME. Evidence Regarding Rapid Initiation of Antiretroviral Therapy in Patients Living with HIV. Curr Infect Dis Rep 23, 7 (2021). https://doi.org/10.1007/s11908-021-00750-5 PMID: 33824625

76. Eshleman SH, Wilson EA, Zhang XC, Ou SS, Piwowar-Manning E, Eron JJ, et al. Virologic outcomes in early antiretroviral treatment: HPTN 052. HIV Clin Trials. 2017 May; 18(3):100–109. https://doi.org/10.1080/15284336.2017.1311056 Epub 2017 Apr 7. PMID: 28385131

77. Colasanti J, Sumitani J, Mehta CC, Zhang Y, Nguyen ML, Del Rio C, et al. Implementation of a Rapid Entry Program Decreases Time to Viral Suppression Among Vulnerable Persons Living With HIV in the Southern United States. Open Forum Infect Dis. 2018 Jun 28; 5(6):ofy104. https://doi.org/10.1093/ofid/ofy104 PMID: 29992172; PMCID: PMC6022569.

78. Girometti N, Lander F, McOwan A, Nwokolo N, Boffito M, Whitlock G. and (2020), Rapid ART start in early HIV infection: Time to viral load suppression and retention in care in a London cohort. HIV Med, 21: 613–615. https://doi.org/10.1111/hiv.12900 PMID: 32869951