HIV Mutations and Virological Failure in Patients from a Reference Center in Southwestern Bahia, Brazil (2019-2023)

Mutações do HIV e falha virológica em pacientes de um centro de referência no sudoeste da Bahia (2019-2023)

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Abstract

Antiretroviral therapy (ART) is effective in treating people living with HIV/AIDS (PLWHA), but treatment failure may occur due to genetic mutations that confer drug resistance. This study evaluated the viral genotypic and clinical-epidemiological profiles of PLWHA in a municipality in southwestern Bahia, Brazil, between 2019 and 2023, through the analysis of 80 genotyping tests. Most participants were aged 40–49 years (36.2%), with a higher proportion self-identified as "pardo" (mixed race/ethnicity; 40%), and heterosexual contact as the main transmission route (71.2%). Poor adherence to treatment was observed in most patients, with a positive association between adherence and viral-load suppression. The predominant HIV subtypes were B, F, and F1. Among the NRTIs, zidovudine showed the highest susceptibility (84.1%), whereas emtricitabine had the lowest (39.7%), with emphasis on the M184V and K65R mutations. Among the NNRTIs, etravirine and rilpivirine exhibited higher susceptibility (63.5%), while nevirapine and efavirenz showed greater resistance, mainly associated with the K103N and P225H mutations. Protease inhibitors (PIs) demonstrated susceptibility rates above 85%, and integrase inhibitors (INIs) showed full susceptibility, with no resistance-associated mutations (RAMs) detected. This is the first study in the region to assess the genotypic resistance profile of PLWHA, highlighting zidovudine, PIs, and INIs as viable therapeutic options even in cases of virological failure. The findings provide evidence to support clinical management and inform health policy planning aimed at overcoming barriers related to treatment adherence and drug resistance.

Keywords: HIV Infections; Anti-HIV Agents; HIV Reverse Transcriptase; HIV Protease Inhibitors; HIV Integrase Inhibitors.

Resumo

A terapia antirretroviral (TARV) é eficaz no tratamento de pessoas vivendo com HIV/AIDS (PVHA), mas falhas podem ocorrer em razão de mutações genéticas que conferem resistência ao tratamento. Este estudo avaliou o perfil genotípico viral e o perfil clínico-epidemiológico em PVHA, em um município do sudoeste da Bahia, entre 2019 e 2023, através da análise de 80 genotipagens. A maioria dos participantes tinha entre 40 e 49 anos (36,2%), houve maior proporção de indivíduos pardos (40%) e o principal meio de transmissão foi por contato sexual heterossexual (71,2%). Observou-se adesão insatisfatória ao tratamento na maioria dos pacientes, com associação positiva entre adesão e o controle da carga viral. Os subtipos do HIV predominantes foram B, F e F1. Entre os ITRN, a zidovudina apresentou maior sensibilidade (84,1%), enquanto a emtricitabina teve menor sensibilidade (39,7%), com destaque para as mutações M184V e K65R. Nos ITRNN, a etravirina e a rilpivirina mostraram maior sensibilidade (63,5%), enquanto a nevirapina e o efavirenz exibiram maior resistência, associadas às mutações K103N e P225H. Os inibidores de protease (IP) apresentaram sensibilidade superior a 85%, e os inibidores de integrase (INI) mostraram sensibilidade plena, sem mutações de resistência. Este é o primeiro estudo da região a avaliar o perfil genotípico de resistência em PVHA, destacando a zidovudina, os IP e os INI como opções terapêuticas viáveis, inclusive em casos de falha virológica. Os resultados oferecem subsídios para o manejo clínico e o planejamento de políticas de saúde, visando superar barreiras relacionadas à adesão e à resistência ao tratamento.

Palavras-chave: Infecções por HIV; Fármacos Anti-HIV; Transcriptase Reversa do HIV; Inibidores da Protease de HIV; Inibidores de Integrase de HIV.

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INTRODUCTION

Since the 1980s, infections caused by the human immunodeficiency virus (HIV) have had a substantial impact on global public health due to their high transmissibility and associated morbidity and mortality.[1] The progression of HIV infection in the absence of adequate treatment can lead to immunosuppression and the development of neoplasms and opportunistic infections that characterize acquired immunodeficiency syndrome (AIDS).[2] Over the past decades, advances in antiretroviral therapy (ART) have enabled effective viral-load control, reduced viral transmission, preserved immune function, and increased life expectancy among people living with HIV/AIDS (PLWHA).[3-5]

According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), expanded access to ART has reduced the global number of deaths from 1.3 million in 2010 to 630,000 in 2022, preventing an estimated 20.8 million deaths during this period.[6] In Brazil, it is estimated that, by 2023, 96% of PLWHA were aware of their diagnosis, 78% were receiving regular treatment, and 75% of those undergoing treatment had achieved viral suppression.[7,8]

The antiretroviral drug classes currently available for clinical use in Brazil include nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase inhibitors (INIs), protease inhibitors (PIs), and entry inhibitors (CCR5 antagonists and fusion inhibitors).[9] These agents act at different stages of the viral replication cycle by targeting enzymes such as reverse transcriptase (NRTIs and NNRTIs), which synthesizes DNA from viral RNA; integrase (INIs), which incorporates this genetic material into the host-cell genome; and protease (PIs), which mediates viral maturation.[10] Other mechanisms of action include blocking the receptors responsible for viral entry into human cells or inhibiting the fusion of the viral and host-cell membranes.[11]

HIV treatment and prevention in Brazil are provided through the Unified Health System (SUS), and clinical guidance for healthcare professionals is defined by the Clinical Protocols and Therapeutic Guidelines for the Management of HIV Infection (PCDT-HIV), issued by the Brazilian Ministry of Health.[9] The recommended therapeutic regimens generally consist of a combination of three distinct antiretroviral agents, with the preferred first-line regimen comprising two NRTIs and one INI administered once daily, with adjustments made according to treatment response.[9] One rationale for this strategy is that each individual drug can effectively suppress viral replication; thus, even if resistance develops to one agent, the remaining two can still limit viral replication, thereby reducing the likelihood of resistant variant emergence .[12,13]

Even in this context, it is essential that PLWHA undergo regular monitoring of viral load, as treatment failure, also referred to as virological failure, may occur.[9] Virological failure is defined as a viral load > 200 copies/mL after six months of ART or following a period of previously achieved viral suppression.[14] For such patients, it is recommended to investigate viral mutations that confer drug resistance; however, it is also important to assess factors such as poor treatment adherence, potential drug–drug interactions, comorbidities that impair drug absorption, or inappropriate regimen selection.[15]

Viral genotyping is a diagnostic test that identifies viral mutations and is indicated in the following situations: cases of virological failure; individuals infected by a partner on ART; individuals who have used pre-exposure prophylaxis (PrEP); and pregnant women, children, adolescents, and patients with HIV–tuberculosis coinfection.[9] Genotyping enables the determination of a genotypic resistance profile, which consists of the pattern of mutations present in the analyzed virus and its susceptibility to different antiretroviral agents.[16]

Resistance-associated mutations (RAMs) can be classified into two categories: acquired mutations, which arise when factors such as poor adherence to treatment prevent complete viral suppression, allowing the replication of resistant variants; and transmitted mutations, which occur when an individual is infected with a resistant strain, accounting for 9.5% of new infections in Brazil.[17,18] These mutations are identified by their genomic location and specific amino acid substitutions, such as the M184V mutation, which indicates a change at codon 184 where methionine (M) is replaced by valine (V).[16]

In Brazil, HIV genotyping tests coordinated by the Ministry of Health identify mutations in the reverse transcriptase and protease regions of the *POL* gene, with the possibility of analyzing additional genes depending on clinical and epidemiological indications.[9] Therefore, the aim of this study was to describe the clinical-epidemiological profile, identify the prevalence of antiretroviral resistance-associated mutations, and analyze the susceptibility patterns in people living with HIV who underwent viral genotyping between 2019 and 2023 in the municipality of Vitória da Conquista.

MATERIALS AND METHODS

Study Design

This was a cross-sectional, observational, and retrospective study that analyzed HIV genomic mutations associated with virological failure and viral resistance. The study was conducted using clinical and laboratory data from patients treated at the Center for Care and Support for Life (CAAV - Centro de Atenção e Apoio à Vida) in Vitória da Conquista, Bahia, between 2019 and 2023. The CAAV provides clinical and psychosocial care and follow-up for PLWHA and other sexually transmitted infections (STIs). The study protocol was approved by the Research Ethics Committee of the Universidade Federal da Bahia (UFBA) under approval number 7,032,639/2024.

Study Population and Sample

The study sample comprised adult individuals (≥ 18 years) diagnosed with HIV, with or without AIDS-defining conditions, receiving ART, treated by the medical team at the CAAV, and who underwent viral genotyping between 2019 and 2023.

Patients with missing epidemiological or laboratory data were excluded. After participant selection, each individual was assigned a unique random identification code to ensure data confidentiality and anonymity.

Data Collection

Data were collected between September and November 2024. The initial identification of patients who underwent genotyping during the study period was performed using the institutional email service employed to communicate new genotyping requests to the reference laboratory. Patient record codes were retrieved from the Complab Advanced program.

Clinical and laboratory data were obtained from physical medical records and from the following information systems: SICLOM (Logistics Control System of Medicines), SISCEL (Control System of Laboratory Tests), and LAUDO (Laboratory Report System), which provides data on viral load, CD4+/CD8+ T-cell counts, and genotyping results.

The collected variables were grouped into three categories: Sociodemographic: age, marital status, self-reported race/ethnicity, and sex; Clinical: reason for genotyping and treatment adherence (satisfactory or unsatisfactory); Laboratory: viral load and CD4+ T-cell counts at three time points (at diagnosis, at genotyping, and most recent), genotyping results, and antiretroviral drug susceptibility profile.

Treatment adherence was classified according to viral-load control and regularity of medication dispensing at the pharmacy. The primary outcomes were the prevalence of RAMs and the antiretroviral susceptibility profile. All collected data were recorded and organized in KoboToolBox®, and subsequently tabulated in Microsoft Excel Professional Plus, version 2019.

Statistical Analysis

Statistical analyses were performed using Stata®, version 18.5. Categorical variables were expressed as absolute and relative frequencies. Continuous variables were summarized using measures of central tendency (mean and median) and dispersion (standard deviation). For univariate analysis, the chi-square test was applied as part of the descriptive evaluation of the collected variables, with statistical significance set at $p < 0.05$. Microsoft Excel Professional Plus®, version 2019, was used to tabulate the observed mutations and calculate their respective prevalence.

RESULTS

Patient Selection

A total of 104 genotyping records performed between 2019 and 2023 were initially identified. Of these, nine patients younger than 18 years at the time of testing, eight duplicate genotyping records, and seven untraceable medical charts were excluded. After these exclusions, 80 genotyping tests were included in the analysis.

Sociodemographic Data

In the study population, age ranged from 23 to 71 years, with a mean of 46 years (±10.58). The distribution of the population according to sociodemographic characteristics is presented in Table 1.

When stratified, the population showed a relatively homogeneous distribution by sex, marital status, and treatment adherence. Most patients were aged 40–49 years (36.2%), with a higher proportion of married individuals (45%) and those self-identified as mixed-race ethnicity (40%). The main route of HIV exposure was sexual contact, predominantly heterosexual (71.2%).

A significant difference was observed in the reason for genotyping due to requests for pregnant women, which, by definition, included only female patients. Overall, 56.2% of patients exhibited unsatisfactory treatment adherence (Table 1).

Table 1

Sociodemographic distribution stratified by sex in patients who underwent genotyping (2019–2023).

	Female sex n (%)	Male sex n (%)	Total n (%)	x^2 (p)
Total	40 (50%)	40 (50%)	80 (100%)	–
Age Group				
18 - 29 years	3 (3.7%)	0 (0.0%)	3 (3.7%)	7.589 (0.146)
30 - 39 years	11 (13.7%)	9 (11.2%)	20 (25.0%)	
40 - 49 years	16 (20.0%)	13 (16.2%)	29 (36.2%)	
50 - 59 years	6 (7.5%)	13 (16.2%)	19 (23.7%)	
60 - 69 years	3 (3.7%)	5 (6.2%)	8 (10.0%)	
70 - 79 years	1 (1.2%)	0 (0.00%)	1 (1.2%)	
Marital Status				
Not reported	2 (2.5%)	3 (3.7%)	5 (6.2%)	5.377 (0.146)
Married	23 (28.7%)	13 (16.2%)	36 (45.0%)	
Single	14 (17.5%)	21 (26.2%)	35 (43.7%)	
Widowed	1 (1.2%)	3 (3.7%)	4 (5.0%)	
Race/Ethnicity				
Not reported	9 (11.2%)	19 (23.7%)	28 (35.0%)	5.839 (0.120)
White	3 (3.7%)	3 (3.7%)	6 (7.5%)	
Mixed-race	19 (23.7%)	13 (16.2%)	32 (40.0%)	
Black	9 (11.2%)	5 (6.2%)	14 (17.5%)	
Exposure Route				
Not reported	9 (11.2%)	8 (10.0%)	17 (21.2%)	2.88 (0.237)
Sexual (Heterosexual)	30 (37.5%)	27 (33.7%)	57 (71.2%)	
Sexual (Homosexual)	1 (1.2%)	5 (6.2%)	6 (7.5%)	
Vertical	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Blood transfusion	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Injectable drug use	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Occupational accident	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Reason for Genotyping				
Not documented	2 (2.5%)	4 (5.0%)	6 (7.5%)	14.279 (0.001)
Virological failure	26 (32.5%)	36 (45.0%)	62 (77.5%)	
Pregnant	12 (15%)	0 (0.0%)	12 (15%)	
Seroconversion	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Use of PrEP	0 (0.0%)	0 (0.0%)	0 (0.0%)	
TB-HIV coinfection	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Treatment Adherence				
Unsatisfactory	25 (31.2%)	20 (25.0%)	45 (56.2%)	1.269 (0.260)
Satisfactory	15 (18.7%)	20 (25.0%)	35 (43.7%)	

Regarding viral load, there was a decrease in the proportion of patients with viral load ≥ 100,000 copies/mL between the time of diagnosis and the most recent assessment, from 28.6% to 7.5%. In addition, satisfactory adherence was associated with viral load < 100,000 copies/mL at the most recent evaluation (p = 0.02). Conversely, the proportion of patients with CD4+ T-cell counts < 200 increased from 21.2% to 25.0% between diagnosis and the most recent assessment, with no apparent correlation with treatment adherence (Table 2).

Table 2

Viral load and CD4+ T-cell counts at diagnosis, at genotyping, and at the most recent assessment, according to treatment adherence.

	Unsatisfactory Adherence n (%)	Satisfactory Adherence n (%)	Total n (%)	x^2 (p)
Viral Load at Diagnosis*				
< 100.000	24 (38.1%)	21 (33.3%)	45 (71.4%)	0.933 (p=0.334)
≥ 100.000	12 (19.0%)	6 (9.5%)	18 (28.6%)	
Viral Load at Genotyping*				
< 100.000	30 (40.5%)	30 (40.5%)	60 (81.0%)	3.750 (p=0.053)
≥ 100.000	11 (14.9%)	3 (4.0%)	14 (18.9%)	
Most Recent Viral Load				
< 100.000	39 (48.7%)	35 (43.7%)	74 (92.5%)	5.045 (p=0.025)
≥ 100.000	6 (7.5%)	0 (0.0%)	6 (7.5%)	
CD4+ T Lymphocytes at Diagnosis*				
< 200	8 (12.1%)	6 (9.0%)	14 (21.2%)	0.001 (p=0.971)
≥ 200	30 (45.4%)	22 (33.3%)	52 (78.8%)	
Most Recent CD4+ T Lymphocytes				
< 200	12 (15.0%)	8 (10.0%)	20 (25.0%)	0.152 (p=0.696)
≥ 200	33 (41.2%)	27 (33.7%)	60 (75.0%)	

* Information regarding the diagnosis and genotyping periods was not available for all patients.

CD4+ T Lymphocytes: CD4+ T cells.

Analysis of Protease, Reverse Transcriptase, and Integrase

Conventional genotyping was performed for all 80 samples, of which 78.7% had detectable viral load and 21.2% were below the detection limit of the genotyping tests. Integrase analysis of the *POL* gene was conducted in eight samples, all of which had detectable viral load.

Table 3 shows the predominance of subtype B in the study population, found in 74.6% of samples, followed by subtypes F and F1, representing 12.7% and 7.9% of cases, respectively. Subtypes C (3.2%) and CRF29_BF (1.6%) were identified at lower frequencies, highlighting the genetic diversity of HIV within the study population. Among the samples that underwent integrase genotyping (n = 8), the majority (87.5%) also belonged to HIV subtype B.

Table 4 presents the antiretroviral susceptibility panel, which included seven drugs from the class of nucleoside reverse transcriptase inhibitors (NRTIs), four from the class of non-nucleoside reverse transcriptase inhibitors (NNRTIs), eight protease inhibitors (PIs), and three integrase inhibitors (INIs). Among the NRTIs, zidovudine showed full susceptibility in 84.13% of samples, tenofovir in 58.7%, and stavudine in 55.6%. The remaining drugs demonstrated full susceptibility in less than 50% of the genotyped samples. Higher levels of resistance were observed for emtricitabine (23.8%) and lamivudine (22.2%). Within the NNRTI class, etravirine and rilpivirine showed the highest full-susceptibility rates (63.5%), whereas nevirapine and efavirenz exhibited higher resistance levels (30.2%).

Table 3

Distribution of HIV subtypes based on protease and reverse transcriptase analysis.

HIV Subtype	Protease and Reverse Transcriptase n (%*)	Integrase n (%)
B	47 (74,6%)	7 (87,5%)
C	2 (3,2%)	1 (12,5%)
CRF29_BF	1 (1,6%)	0 (0,0%)
F	8 (12,7%)	0 (0,0%)
F1	5 (7,9%)	0 (0,0%)
Total	63 (100%)	8 (100%)

Table 4

Antiretroviral susceptibility panel for NRTI, NNRTI, PI, and INI classes and number of resistance-associated mutations observed.

	Observed Resistance Pattern						Number of Mutations Δ (mean)
	HLR n (%)	LLR n (%)	I n (%)	PLLR n (%)	R n (%)	S n (%)	
NRTIs							
Zidovudine	2 (3,2%)	2 (3,2%)	4 (6,3%)	1 (1,6%)	1 (1,6%)	53 (84,1%)	
Didanosine	8 (12,7%)	7 (11,1%)	5 (7,9%)	9 (14,3%)	13 (20,6%)	21 (33,3%)	
Estavudine	4 (6,35%)	4 (6,3%)	16 (25,4%)	1 (1,6%)	3 (4,76%)	35 (55,6%)	
Lamivudine	14 (22,2%)	0 (0,0%)	1 (1,6%)	2 (3,2%)	21 (33,3%)	25 (39,7%)	0 - 6 (1,682 ±1,624)
Emtricitabine	15 (23,8%)	0 (0,0%)	1 (1,59%)	2 (3,2%)	20 (31,7%)	25 (39,7%)	
Abacavir	6 (9,5%)	12 (19,0%)	10 (15,9%)	1 (1,6%)	12 (19,0%)	22 (34,9%)	
Tenofovir	1 (1,6%)	8 (12,7%)	13 (20,6%)	1 (1,6%)	3 (4,8%)	37 (58,7%)	
NNRTIs							
Nevirapine	19 (30,2%)	0 (0,0%)	2 (3,2%)	1 (1,6%)	18 (28,6%)	23 (36,5%)	
Efavirenz	19 (30,2%)	0 (0,0%)	2 (3,2%)	0 (0,0%)	18 (28,6%)	24 (38,1%)	0 - 4 (1,476 ±1,330)
Etravirine	1 (1,6%)	1 (1,6%)	9 (14,3%)	11 (17,5%)	1 (1,6%)	40 (63,5%)	
Rilpivirine	4 (6,3%)	9 (14,3%)	2 (3,2%)	2 (3,2%)	6 (9,5%)	40 (63,5%)	
PIs							
Indinavir/r	1 (1,6%)	3 (4,8%)	1 (1,6%)	1 (1,6%)	2 (3,2%)	55 (87,3%)	
Saquinavir/r	1 (1,6%)	3 (4,8%)	2 (3,2%)	1 (1,6%)	1 (1,6%)	55 (87,3%)	
Nelfinavir	2 (3,2%)	3 (4,8%)	1 (1,6%)	0 (0,0%)	2 (3,2%)	55 (87,3%)	
Fosamprenavir/r	1 (1,6%)	0 (0,0%)	2 (3,2%)	4 (6,3%)	1 (1,6%)	55 (87,3%)	0 - 9 (0,428 ±1,455)
Lopinavir/r *	0 (0,0%)	1 (1,6%)	3 (4,8%)	1 (1,6%)	1 (1,6%)	56 (90,3%)	
Atazanavir/r *	2 (3,4%)	1 (1,7%)	0 (0,0%)	3 (5,1%)	2 (3,4%)	51 (86,4%)	
Tipranavir/r *	0 (0,0%)	1 (2,8%)	1 (2,8%)	0 (0,0%)	0 (0,0%)	34 (94,4%)	
Darunavir/r *	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	1 (3,2%)	30 (96,8%)	
INIs Δ							
Raltegravir	0 (0,00%)	0 (0,00%)	0 (0,00%)	0 (0,00%)	0 (0,00%)	8 (100%)	
Elvitegravir	0 (0,00%)	0 (0,00%)	0 (0,00%)	0 (0,00%)	0 (0,00%)	8 (100%)	0 (0 ±0)
Dolutegravir	0 (0,00%)	0 (0,00%)	0 (0,00%)	0 (0,00%)	0 (0,00%)	8 (100%)	

* The analysis results were incomplete for some samples, with missing data in one sample for lopinavir/r, three samples for atazanavir/r, 27 samples for tipranavir/r, and 32 samples for darunavir/r.

Δ The results for INIs correspond to the eight samples that underwent integrase genotyping.

HLR: High-Level Resistance; LLR: Low-Level Resistance; I: Intermediate Resistance; PLLR: Probable Low-Level Resistance; R: Resistance; S: Susceptibility; NRTIs: Nucleoside Reverse Transcriptase Inhibitors; NNRTIs: Non-Nucleoside Reverse Transcriptase Inhibitors; PIs: Protease Inhibitors; INIs: Integrase Inhibitors.

Regarding the PI class, all drugs demonstrated full susceptibility in more than 85% of the analyzed samples. It is noteworthy that some results lacked susceptibility data for lopinavir/r, atazanavir/r, tipranavir/r, and darunavir/r. As for the INIs, all samples showed full susceptibility to the three agents evaluated. The number of RAMs ranged from 0 to 6 (mean 1.682 ± 1.624) for the NRTI class, from 0 to 4 (1.476 ± 1.330) for the NNRTI class, and from 0 to 9 (0.428 ± 1.455) for the PI class. No sample presented mutations associated with resistance to INIs (see Table 4).

The most prevalent resistance-associated mutations among NRTIs were M184V (47.6%) and K65R (23.8%). For NNRTIs, the most frequently observed genotypic alterations were K103N (44.4%) and P225H (15.9%). Other RAMs in these classes were found in fewer than 10% of the samples. Regarding PIs, no mutation showed a prevalence greater than 5%, reflecting higher susceptibility to this drug class. Less frequent mutations, present in up to 5% of samples, were broadly distributed among the drugs evaluated (Table 5).

Table 5

Prevalence of resistance-associated mutations observed for NRTIs, NNRTIs, and PIs in patients with virologic failure.

Prevalence	Class of Antiretroviral		
	NRTIs n (%)	NNRTIs n (%)	PIs n (%)
≤ 50%	M184V - 30 (47.6%)	K103N - 28 (44.4%)	—
≤ 25%	K65R - 15 (23.8%)	P225H - 10 (15.9%)	—
≤ 10%	L74I - 6 (9.5%) M184I - 5 (7.9%) M41L - 5 (7.9%) A62V - 4 (6.3%) D67N - 4 (6.3%) K70E - 4 (6.3%) K219E - 4 (6.3%)	V106I - 4 (6.3%) V108I - 4 (6.3%) L100I - 4 (6.3%) V179D - 4 (6.3%)	—
≤ 5%	K70R - 3 (4.8%) T215S - 2 (3.2%) V75M - 2 (3.2%) K219R - 2 (3.2%) K219Q - 2 (3.2%) T215F - 2 (3.2%) Y115F - 1 (1.6%) K218R - 1 (1.6%) T215N - 1 (1.6%) T215Y - 1 (1.6%) T215A - 1 (1.6%) K70G - 1 (1.6%) K70KR - 1 (1.6%) M184MV - 1 (1.6%) K65E - 1 (1.6%) L74V - 1 (1.6%) R44F - 1 (1.6%) L210W - 1 (1.6%) E44D - 1 (1.6%) F77L - 1 (1.6%) T215I - 1 (1.6%) D67G - 1 (1.6%)	V106M - 3 (4.8%) K103S - 3 (4.8%) Y181C - 3 (4.8%) F227L - 2 (3.2%) M184I - 2 (3.2%) H221HY - 2 (3.2%) V179E - 2 (3.2%) G190A - 2 (3.2%) M230L - 2 (3.2%) E138G - 2 (3.2%) Y188L - 2 (3.2%) K103R - 2 (3.2%) E138A - 2 (3.2%) K101P - 1 (1.6%) A98G - 1 (1.6%) K238T - 1 (1.6%) Y181YC - 1 (1.6%) P225PH - 1 (1.6%) Y188C - 1 (1.6%) K238KNT - 1 (1.6%) V106A - 1 (1.6%) E138K - 1 (1.6%) G190 - 1 (1.6%)	M46I - 3 (4.8%) V82A - 2 (3.2%) I50L - 2 (3.2%) G73C - 2 (3.2%) L90M - 2 (3.2%) L33F - 2 (3.2%) G73S - 2 (3.2%) V11I - 1 (1.6%) L24I - 1 (1.6%) V32I - 1 (1.6%) Q58E - 1 (1.6%) I54L - 1 (1.6%) F53L - 1 (1.6%) T74P - 1 (1.6%) I54V - 1 (1.6%)

DISCUSSION

Analysis of the Sociodemographic Profile of the Study Population

The sociodemographic profile of the study population was evaluated according to sex, age group, marital status, and race/ethnicity. Among the analyzed samples, 50% corresponded to male individuals. Other studies investigating people living with HIV/AIDS (PLWHA) with therapeutic failure reported male proportions ranging from 58.0% to 73.5%.[19-21] The lower proportion of men in the present study may be explained by the inclusion of genotyping requests made during pregnancy, which increased the representation of women in the sample.

The study population had a mean age of 46 ± 10.58 years, with 36.2% of patients aged between 40 and 49 years. Previous studies reported lower mean ages: Lima et al.[19] (2016) and Diaz et al.[22] (2023) observed mean ages of 34.0 ± 10.6 years and 36.1 ± 10.77 years, respectively, whereas Cavalcanti et al.[21] (2007) documented a predominant age group between 35 and 49 years, representing 56.8% of the analyzed samples. Differences in age distribution across studies may reflect variations in inclusion criteria or in the demographic characteristics of the regions studied.

Regarding marital status, 45% of patients were married and 43.7% were single, a pattern similar to that reported by Lima et al.[19] (2016) in the Northeast region of Brazil. Conversely, Mmatsoku and Ngcobo[23] (2024), in Mamelodi, South Africa, observed a higher proportion of single individuals compared with married ones, highlighting contextual differences in marital patterns across distinct geographic regions that may be influenced by cultural and socioeconomic factors.

The predominant race/ethnicity in the study population was mixed-race (40.0%); however, 35.0% of medical records lacked information on this variable, underscoring limitations in the recording of sociodemographic data. Additionally, 17.5% (n = 14) of participants were Black and 7.5% (n = 6) were White. Notably, few studies involving PLWHA with virologic failure have examined marital status and race/ethnicity among sociodemographic factors.

In Brazil, a study assessing treatment adherence among men who have sex with men found that 62.4% (n = 1,050) of participants were White, 24.7% (n = 416) were mixed race ("pardo"), and 10.6% (n = 178) were Black.[24] In contrast, a large-scale study evaluating over 132,000 patients undergoing antiretroviral therapy in Brazil reported that 44.5% (n = 57,183) were White, 43.5% (n = 55,772) mixed race, 11.1% (n = 14,181) Black, 0.7% (n = 953) Asian, and 0.2% (n = 271) Indigenous.[25] Differences in racial distribution between the present study and other analyses may be partly attributed to the absence of race data in a significant proportion of medical records, as well as to the specific demographic characteristics of local and regional contexts.

With respect to the route of HIV exposure, sexual transmission among heterosexual individuals predominated (71.2%; n = 57), followed by homosexual transmission (7.5%; n = 6). No other routes of transmission were documented in the study population, although 21.2% (n = 17) of samples corresponded to individuals whose exposure route was not recorded in medical charts. Bahls et al.[26] (2019) reported sexual transmission in 92.3% (n = 36) of patients. Other studies documented heterosexual transmission ranging from 54.8% to 74%, whereas homosexual transmission ranged from 19% to 33.3%.[19,27,28]

Ferreira et al.[20] (2013) evaluated patients with transmitted resistance and found infection routes distributed as follows: 52% (n = 120) via homosexual contact, 40% (n = 87) via heterosexual contact, and 0.4% (n = 2) via injection drug use. Although incomplete medical records limit the precise characterization of the epidemiological profile, the analysis highlights the predominance of sexual transmission, consistent with similar studies conducted in Brazil. However, the relative prevalence of heterosexual versus homosexual transmission varies across populations, underscoring the need to consider regional and population-specific factors in planning HIV prevention and control strategies.

Regarding the reason for genotyping, the main indications observed were virologic failure (77.5%; n = 62) and pregnancy (15%; n = 12), with 7.5% (n = 6) of samples lacking documentation of the indication for testing. Treatment adherence was unsatisfactory in 56.2% (n = 45) of patients. It is important to note that the assessment of adherence refers to the most recent documentation and does not encompass the entire follow-up period of each patient within the service. Furthermore, the criteria for adherence evaluation were uncertain and based on viral load control or consistency of medication pickup at the pharmacy, rather than patient self-report or standardized questionnaires.

A study assessing treatment adherence among 1,719 male patients who have sex with men documented adherence rates ranging from 57.8% to 70.4%, depending on the assessment tool used, and highlighted that stigma against PLWHA was one of the main factors impacting adherence.[24] Another nationwide analysis including 2,424 patients from all regions

of Brazil found that 61.1% of patients presented at least one indicator of poor adherence.[29] Additionally, a study conducted in the state of Roraima suggested that poor adherence may be more strongly associated with therapeutic failure than the presence of resistance-associated mutations,[28] and there is evidence that good adherence is linked to higher chances of therapeutic success.[30] These findings underscore the importance of further investigating treatment adherence in future studies and promoting the use of standardized tools that allow for more accurate assessments. Identifying factors associated with adherence may support targeted interventions, optimizing treatment outcomes and reducing the risk of virologic failure.

Changes in viral load patterns were observed across the periods of diagnosis, genotyping, and most recent follow-up. The proportion of individuals with viral load ≥100,000 copies/mL decreased from 28.6% to 7.5%, suggesting improved virologic control during ART, likely associated with treatment adherence and therapeutic effectiveness. Treatment adherence had a statistically significant impact on the most recent viral load measurement (p = 0.025), indicating that patients who maintained satisfactory adherence achieved better virologic control. Conversely, the proportion of individuals with CD4+ T-cell counts <200 cells/mm^3 increased from 21.2% to 25.0%, suggesting that although virologic control is being achieved, immune recovery may be slower in some patients.

Previous studies corroborate these findings. Diaz et al.[31] (2015), analyzing the Brazilian Ministry of Health database, observed an increase in the proportion of undetectable viral loads between 2001 and 2011 and a reduction in viral loads at diagnosis between 2001 and 2009. Another study conducted in Pernambuco found that 33.3% (n = 46) of patients had viral loads ≥100,000 copies/mL and 34.3% had CD4+ T-cell counts <200 cells/mm^3.[19] Cavalcanti et al. (21) (2007) reported that 30.8% (n = 176) of samples had viral loads >100,000 copies/mL and 42.2% (n = 241) had CD4+ T-cell counts <200 cells/mm^3. A study conducted in São Paulo found that 24.3% (n = 412) of patients presented viral loads >100,000 copies/mL at the time of genotyping.[32]

It is important to note that the timing of sample collection and the documentation of viral load and CD4+ T-cell counts vary among studies, making direct comparisons challenging.[22,26-28] Nonetheless, the present study showed a lower proportion of viral loads >100,000 copies/mL and a comparable distribution of CD4+ T-cell counts relative to other populations. These findings demonstrate improvements in viral load control, likely reflecting better treatment adherence or ART effectiveness. However, the increase in the proportion of patients with CD4+ T-cell counts <200 cells/mm^3 suggests persistent challenges in immune reconstitution, which may be related to individual factors or to clinical follow-up practices.

Genetic Profile of HIV and ART Susceptibility

HIV-1 subtype B was present in 74.6% (n = 47) of the analyzed samples, followed by subtypes F (12.7%; n = 8) and F1 (7.9%; n = 5). Population-based studies conducted in the Northeast Region of Brazil also reported higher prevalence rates of subtype B (82.4%) and subtype F (11.8%).(21) A nationwide study characterizing the distribution of HIV subtypes across Brazil using pre-treatment genotyping (2013–2015) similarly found higher proportions of subtype B (77.0%) and subtype F (10.6%) in the Northeast.[17] The predominance of subtype B observed in the present study is consistent with findings from other population-based studies in Brazil, whereas the presence of non-B subtypes, such as F and F1, together representing approximately 20% of samples, reflects the considerable genetic diversity of HIV-1 circulating in the country.

Regarding the NRTI susceptibility profile, full susceptibility to zidovudine was observed in 84.1% of samples, followed by tenofovir (58.7%). Conversely, didanosine showed the lowest full-susceptibility rate (33.3%; n = 21), followed by abacavir (34.9%; n = 22). The highest proportions of high-level resistance were observed for emtricitabine (23.8%; n = 15) and lamivudine (22.2%; n = 14). These results differ from a study conducted in Minas Gerais, which reported higher resistance levels to lamivudine (77%; n = 187), emtricitabine (72%; n = 175), and zidovudine (63.8%; n = 155), and greater susceptibility to tenofovir (55.1%; n = 134).[33] Regional variations highlight the importance of considering local epidemiological and resistance profiles when managing antiretroviral therapy.

In the present study, the most frequent NRTI resistance-associated mutations (RAMs) were M184V (47.6%; n = 30) and K65R (23.8%; n = 15). Cavalcanti et al.[21] (2007) reported that, among RAMs observed in virologic failure cases, 66% involved codon 184, 61.5% codon 215, and 47.9% codon 41. In our study, the corresponding frequencies were 57.1% (n = 36) at codon 184, 12.7% (n = 8) at codon 215, and 7.9% (n = 5) at codon 41. These results demonstrate comparable frequencies for codon 184 mutations but lower frequencies for other codons, possibly reflecting changes in ART strategies between the period of Cavalcanti's study and the present analysis.

Another study of virologic failure cases identified NRTI RAMs in 91.5% (n = 75) of samples.[27] Investigations in Minas Gerais state and the Northern Region of Brazil reported M184V frequencies of 77.4% and 80.1%, respectively, whereas K65R was present in fewer than 10% of samples in both studies.[34,35] The M184V mutation confers resistance to lamivudine, abacavir, and emtricitabine, but increases susceptibility to zidovudine, stavudine, and tenofovir, which may explain the resistance pattern observed in the present study.[36-39] Conversely, the K65R mutation can confer resistance to nearly the entire NRTI class, sparing only zidovudine.[39,40] Therefore, zidovudine emerges as a potential therapeutic alternative in this population, given its preserved susceptibility in genotypic assays and its favorable interaction profile with the main RAMs identified.

For NNRTIs, 63.5% of samples exhibited resistance to efavirenz and 61.9% to nevirapine, whereas full susceptibility was observed in 63.5% of samples for etravirine and rilpivirine. These results are consistent with those reported by Ferreira et al.[20] (2013), who found efavirenz resistance in 71% (n = 12) of samples, and Chaves et al.[27] (2021), who observed higher resistance rates to efavirenz (82.9%) and nevirapine (66.4%) compared with etravirine (7.7%) and rilpivirine (39.4%).

Among NNRTI RAMs, K103N (44.4%) and P225H (15.9%) were the most frequent in the present study. Previous reports described similar frequencies, with K103N ranging from 40.6% to 71.8% and P225H from 10.6% to 40.6%.[20,27,35] The high prevalence of these mutations reinforces their importance as genotypic markers of NNRTI resistance, particularly to efavirenz and nevirapine.[21] These findings emphasize the need for continued genotypic resistance surveillance and the consideration of alternative regimens including etravirine or rilpivirine in patients experiencing virologic failure.

NNRTIs were formerly part of Brazil's first-line HIV treatment regimens,[9] and even a small number of RAMs can compromise the efficacy of multiple drugs in this class.[20] The high prevalence of resistance observed in the analyzed samples likely reflects the widespread historical use of NNRTIs. These findings underscore the importance of carefully selecting agents with higher susceptibility or, in cases of significant resistance, considering drug-class substitution to optimize therapeutic management in patients with virologic failure.

Full susceptibility was observed in more than 85% of analyzed samples, and the prevalence of RAMs was below 5% for all detected variants. A study conducted in Manaus (AM) reported high levels of PI resistance in 13% of patients with virologic failure.[27] In the HIV-BresNet study, the most frequent PI RAMs in the Northeast Region were M46I/L and V82A/L, each with a prevalence of 1.5% (n = 4).[17]

In the present study, we found a frequency of 4.8% (n = 3) for the M46I mutation and 3.2% (n = 2) for V82A. Despite the presence of mutations such as M46I and V82A, the efficacy of PI/r remains high, given that multiple mutations are required to significantly reduce their activity. This characteristic makes PIs valuable in salvage regimens, even among populations with pre-existing resistance.[41] The HIV genotypic profile observed reinforces the potential of PIs as a viable therapeutic option for managing patients with therapeutic failure. Nevertheless, prolonged exposure to these agents should be carefully monitored due to the risk of emerging specific mutations that may compromise their effectiveness in salvage therapy.

Full susceptibility was observed for raltegravir, elvitegravir, and dolutegravir, with no resistance mutations detected in this class. Studies evaluating pretreatment genotyping in Porto Alegre and São Paulo identified INI resistance-associated mutations in 3 of 234 analyzed samples.[42,43] A Swiss study conducted between 2008 and 2014 reported only 0.1% (1 of 1,316 analyzed samples) of transmitted INI resistance.[44]

These findings support the low prevalence of transmitted resistance to this class, even in regions where INIs are widely used in HIV management.[45] This low prevalence can be attributed to the high genetic barrier of INIs and the relatively recent expansion of their use. This finding reinforces the inclusion of this drug class in the first-line therapeutic regimens recommended by the Brazilian Ministry of Health.[9] However, there remains a paucity of studies evaluating acquired resistance to INIs, as most available analyses focus on pretreatment genotyping.

The main limitations of this study arise from its retrospective design, which may introduce bias, particularly regarding medical record documentation, and from missing sociodemographic and clinical data that limit a more comprehensive characterization of the population. Additionally, the single-center design and small number of genotyping cases constrain the generalizability of the findings to other regions of Brazil, which exhibit distinct resistance and adherence profiles.

Regarding treatment adherence, the definition adopted in this study was restricted to viral load control and was not systematically documented in patient records. This narrow definition may introduce bias both in clinical assessment and in data accuracy, since poor adherence, a key cause of

therapeutic failure, is associated with an increased risk of developing new mutations.[46] Another relevant limitation concerns the timing of genotyping: in many cases, the reason for test requests was not adequately documented, preventing the identification of pretreatment genotyping cases and, consequently, the estimation of transmitted resistance prevalence.

CONCLUSION

This study described the genotypic profile of antiretroviral resistance in PLWHA, identifying subtypes B, F, and F1 as predominant and highlighting zidovudine, protease inhibitors (PIs), and integrase inhibitors (INIs) as effective and viable therapeutic options due to their high susceptibility and low prevalence of resistance mutations. No significant differences were observed in sociodemographic characteristics or CD4+ T-cell counts; however, a positive relationship between adherence and viral load control was identified, emphasizing the importance of interventions that promote adherence, particularly among patients with virologic failure.

The regional resistance profile reported here may inform adaptations to the Clinical Protocols and Therapeutic Guidelines for HIV (PCDT-HIV), aligning them with local needs and contributing to improved clinical outcomes. This study also underscores the importance of training healthcare professionals, standardizing medical record documentation, and adopting systematic tools to assess treatment adherence. As the first study of its kind in the region, this work provides valuable evidence to guide clinical management and public health policy planning aimed at overcoming barriers related to adherence and treatment resistance. Finally, it highlights the need for further research to explore factors influencing adherence among PLWHA and to assess the feasibility of characterizing the regional genomic profile through pretreatment genotyping.

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