Surveillance Drug Resistance Mutations in Recently Diagnosed Antiretroviral Naïve Brazilian People

Ricardo Sobhie Diaz[1]; Rosangela Ferraz Cereda[2]; Vinicius Lima Faustino[2]; Paula de Mendonça Batista[2]; James R. Hunter[1]; Mauro Schechter[1,3]

[1]Universidade Federal de São Paulo, São Paulo, Brazil; [2]MSD Brazil, São Paulo, Brazil; [3]Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

Introduction

- Brazil provides antiretroviral therapy (ART) to all PWH (people with human immunodeficiency virus (HIV)) according to periodically updated guidelines (www.aids.gov.br).
- As of January 2017, the initial recommended ART for adults and adolescents is composed of tenofovir/lamivudine and dolutegravir. All PWH on ART are entitled to free laboratory monitoring through the public health system.
- In Brazil, resistance testing before ART initiation is recommended only for selected situations—pregnancy, children and adolescents, HIV acquired from a treated partner, HIV/TB coinfection, or seroconversion during or after PrEP.
- Transmitted drug resistance (TDR, or Surveillance Drug Resistance Mutations - SDRM) mutations tend to persist due to the clonal transmission of HIV. Therefore, genotype testing is sensitive to detect TDR even long after the transmission event.
- Until 2017, regimens containing Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) were the recommended first-line therapy in Brazil. Accordingly, multiple surveys have shown that transmitted drug resistance (TDR) to NNRTIs is widespread throughout the country.
- The impact of NNRTI TDR on the activity of Doravirine in Brazil, a country where several HIV subtypes co-circulate, is not known. In addition, the effect of natural clade–related polymorphisms on doravirine susceptibility is unknown.
- We hypothesize that the level of TDR to efavirenz and nevirapine will be intermediate, whereas the levels of TDR to the other antiretroviral classes will be low.

Objectives

To determine the prevalence of genotypic TDR to Doravirine among antiretroviral naïve people with recently diagnosed HIV-1 in Brazil.

Methods

- This is a cross-sectional study. One highly populated city from each of the five Brazilian macroregions was selected: Manaus (North Region [N]), Salvador (Northeast Region [NE]), Brasília (Central-West Region [C]), São Paulo (Southeast Region [SE]), and Porto Alegre (South Region [S]). In addition, we included the city of Santos in the SE region, where we previously demonstrated a high prevalence of TDR and the circulation of circulating recombinant forms (CRFs) 28 and 29.[1]
- The HIV Threshold Survey methodology (HIV-THS; World Health Organization [WHO]) was used. Prevalences of transmitted drug resistance of <5%, between 5% and 15%, and >15% are considered low, intermediate, and high, respectively.[2]
- Once ART was prescribed, PWH were invited by the attending physician to sign an informed consent and to collect a pretreatment sample for the study.
- Blood samples were in EDTA tubes and transported to the Retrovirology Laboratory of the Federal University of São Paulo, Brazil.
- Genotyping was performed using HIV proviral DNA, extracted using QIAamp Blood Kit (Qiagen Inc; Chatsworth, CA, USA), and protease, reverse transcriptase and integrase regions of the pol gene amplified and sequenced.[3,4]
- TDR was evaluated according to an algorithm that excludes common polymorphisms.[5] The following were considered high-impact mutations to Doravirine: V106A/M, V108I, Y188L, F227C/L/V, M230I/L, L234I, Y318F. Other lower-impact mutations to Doravirine were A98G, G190E, H221Y, P225H, P236L.
- The subtype assignment was performed by phylogenetic analysis, where sequences were aligned with the reference data set from the Los Alamos database using BioEdit v7.2.3.[6]

Results

- Samples from 391 recently diagnosed treatment-naïve people with HIV-1 were included. The study flow chart is shown in **Figure 1.**
- **Table 1** shows the SDRM prevalence and the demographic, virologic, and immunologic characteristics of participants by geographic region of residence. Overall, the median age of recently diagnosed PWH was 33 years old, in a concentrated epidemic (73.28% of males).
- The prevalence of TDR was intermediate (10.7%), with 1.8% to protease inhibitors (PIs), 2.8% to nucleoside reverse transcriptase inhibitors (NRTIs), 5.1% to NNRTIs, and 1% to integrase strand transfer inhibitors (INSTIs).
- Five PWH harbored mutations related to Doravirine resistance (1.3%; **Table 3**).
- **Figure 2** depicts the prevalence of SDRMs among the distinct antiretroviral classes.
- The regional distribution of viral subtypes is shown in **Figure 3. Table 2** illustrates the clade profile based on genomic regions
- **Table 3** shows all SDRMs identified by city/region and PWH.
- **Figure 4** illustrates the phylogenetic reconstruction of the sequenced samples based on the genomic region. These analyses confirmed clade assignment and excluded sample clustering or polymerase chain reaction (PCR) carryover.

Table 1. SDRM prevalence, demographic, virologic, and immunologic characteristics of participants according to geographic region of residence.

City	Mean/median age, years (range)	Males, %	Mean/median CD4, n (range)	Mean/median CV (range)	TDR, n (%)	PI, n (%)	NRTI, n (%)	NNRTI, n (%)	INSTI, n (%)	More than 1 class	n
Brasília	33.09/32 (20-64)	85.71	539.86/485 (2-1,598)	738,115/89,700 (255-8,840,000)	5 (7.14)	0 (0)	2 (2.86)	3 (4.29)	0 (0)	0 (0.0)	70
Manaus	34.57/31.5 (20-63)	76.39	406.29/377.5 (10-1,412)	525,943.7/127,000 (10.4-10,000,000)	11 (15.28)	2 (2.78)	4 (5.56)	4 (5.56)	1 (1.39)	0 (0.0)	72
Porto Alegre	44.23/43 (23-76)	58.9	280.62/221 (13-1,513)	1,048,161/235,000 (432-10,000,000)	10 (13.7)	1 (1.37)	1 (1.37)	8 (10.96)	0 (0)	0 (0.0)	73
Salvador	33.87/33 (22-60)	84.62	474.17/419 (16-1,745)	513,718.7/87,000 (36-7,010,000)	3 (5.77)	1 (1.92)	0 (0)	2 (3.85)	0 (0)	0 (0.0)	52
São Paulo	37.34/34 (20-61)	89.83	430.07/441 (19-1,491)	524,083.2/57,700 (149-10,000,000)	6 (10.17)	1 (1.69)	4 (6.78)	1 (1.69)	0 (0)	0 (0.0)	59
Santos	36.9/32 (21-70)	49.25	396.4/384 (5-1,515)	577,968.5/99,000 (0-5,800,000)	7 (10.45)	2 (2.99)	0 (0)	2 (2.99)	3 (4.48)	1 (1.49)	67
TOTAL	**36.83/33 (20-76)**	**73.28**	**416.625/384 (2-1,745)**	**667,923.58/97,000 (0-10,000,000)**	**42 (10.69)**	**7 (1.78)**	**11 (2.8)**	**20 (5.09)**	**4 (1.02)**	**1 (0.25)**	**393**

PI, protease inhibitor resistance–associated mutations; NRTI, nucleoside reverse transcriptase inhibitor resistance–associated mutations; NNRTI, nonnucleoside reverse transcriptase inhibitor resistance–associated mutations; INSTI, integrase strand transfer inhibitor resistance–associated mutations.

Table 2. HIV-1 subtype profile according to the HIV-1 genomic region.

Genome Region	HIV-1 Subtypes n (%)							
	A1	B	BC	BF	C	CRF18_cpx	D	F
PR/RT	1 (50)	193 (47.1)	7 (100)	2 (100)	62 (43.7)	1 (100)	1 (25)	26 (50)
INSTI	1 (50)	217 (52.9)	0 (0)	0 (0)	80 (56.3)	0 (0)	3 (75)	26 (50)
TOTAL	2	410	7	2	142	1	4	52

INSTI, integrase strand transfer inhibitor; PR, protease; RT, reverse transcriptase.

Table 3. SDRMs of specific PWH by city/region and HIV subtype

City	ID	Subtype protease/RT	PI	NRTI	NNRTI	Subtype integrase	INSTI	VL	CD4
Brasília	BR10	B	-	M184MI	-	NA	NA	137,000	2
	BR16	B	-	T215L	K101P · K103S	B	-	30,500	763
	BR29	B	-	-	K103S	B	-	2,210	570
	BR47	B	-	-	K101E	B	-	53,200	485
Manaus	MN14	B	F53Y	-·	-	B	-	5,640	860
	MN16	B	-	T215TI	-	B	-	314,000	640
	MN22	B	-	-	-	B	Y143S	6,370	168
	MN23	B	-	-	K101P · K103S	B	-	40,300	647
	MN24	B	L23I	-	-	B	-	42,700	458
	MN34	B	-	-	K103S · G190A	B	-	568,000	430
	MN40	BC	-	M184I	-	C	-	171	334
	MN59	B	-	D67N · T69D	G190A	B	-	187,000	661
	MN64	B	-	M41L	-	B	-	2,010,000	196
	MN66	B	-	-	K101E	B	-	1,220,000	95
Porto Alegre	PA11	C	-	-	K101KE · K103KN	C	-	1,060,000	426
	PA12	C	-	D67N · K70E · K219R	V106M[a]	C	-	1,060,000	66
	PA13	C	-	-	K101E · G190A	C	-	3,000,000	56
	PA19	C	-	-	K103N	C	-	1,240,000	38
	PA25	B	L90M	-	-	C	-	58,900	438
	PA51	C	-	-	K103N	NA	NA	3,740,000	287
	PA59	C	-	-	K103N	C	-	503,000	55
	PA63	C	-	-	K103N	C	-	9,720	298
	PA70	C	-	-	K101E · V106M[a] · Y181C · G190A	C	-	6,470	286
Salvador	SL02	F	-	-	G190E[a]	B	-	74,800	640
	SL03	F	-	-	K103N · Y188L[a]	NA	NA	95,100	36
	SL52	B	N88S	-	-	B	-	40,400	226
São Paulo	SP04	BF	-	M41L · T215S	-	B	-	10,200	389
	SP11	C	-	D67DG	-	C	-	478,000	160
	SP15	B	-	D67N · K219Q	-	B	-	10,000,000	43
	SP21	B	M46I · I50L	-	-	B	-	36,500	496
	SP22	CRF18_cpx	-	D67N · T215I · K219E	-	NA	NA	13,000	280
	SP57	B	-	-	K103N	B	-	1,430	612
Santos	ST10	B	-	-	K103N · Y188L[a]	NA		123,000	276
	ST25	F	-	-	K103N	NA	NA	13,100	580
	ST29	NA	NA	NA	NA	B	Y143S	113,000	398
	ST59	B	-	-	-	B	G140GS	380,000	11
	ST61	B	L76LV	-	-	B	G140S	1,190,000	20
	ST64	B	M46MI	-	-	B	-	13,400	634

[a]Doravirine-specific mutations.

CD4, CD4+ T-cell counts; NA, result unavailable due to lack of PCR amplification; NNRTI, mutations related to nonnucleoside transcriptase reverse inhibitors; NRTI, mutations related to nucleoside transcriptase reverse inhibitors; PI, mutations related to protease inhibitors; VL, HIV RNA viral load.

Figure 1. Study flow chart

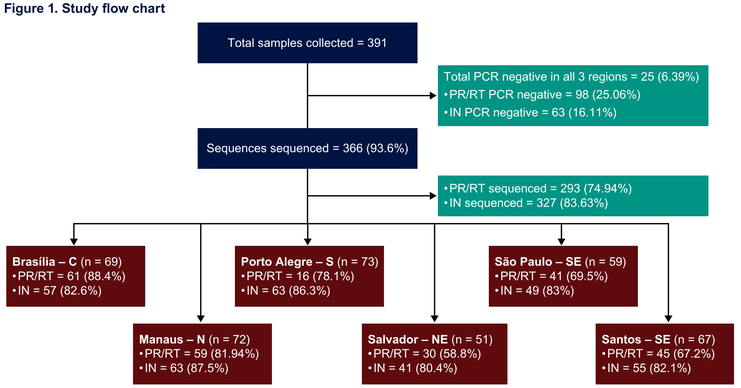
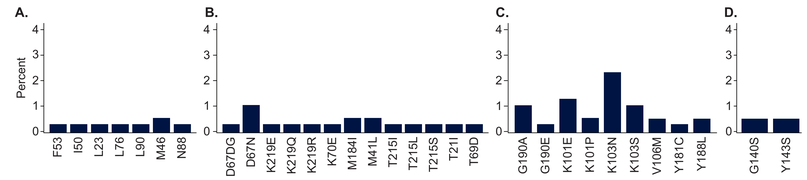
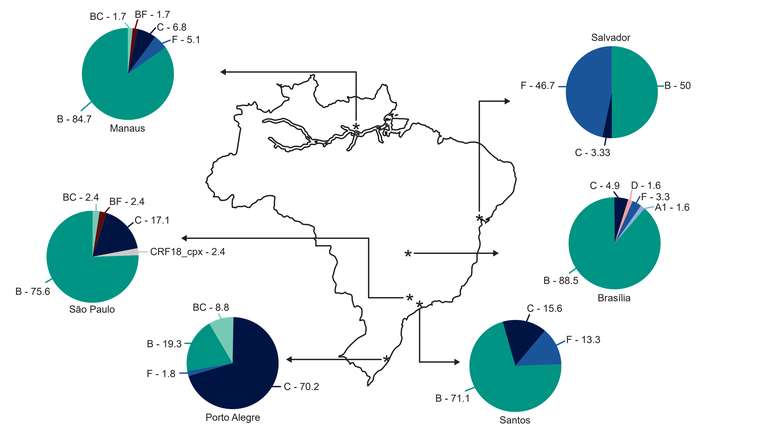


Figure 2. Prevalence of resistance-associated mutations



A, NRTIs. **B**, NNRTIs. **C**, PIs. **D**, INSTIs.

Figure 3. Brazilian map showing the location of the cities and the Brazilian macroregions where samples were collected



HIV-1 subtypes (% prevalence per region)

Region	A1	B	BC	BF	C	CRF18_cpx	D	F	N
Brasília	1.64	88.52	0	0	4.92	0	1.64	3.28	61
Manaus	0	84.75	1.69	1.69	6.78	0	0	5.08	59
Porto Alegre	0	19.3	8.77	0	70.18	0	0	1.75	57
Salvador	0	50	0	0	3.33	0	0	46.67	30
São Paulo	0	75.61	2.44	2.44	17.07	2.44	0	0	41
Santos	0	71.11	0	0	15.56	0	0	13.33	45

The prevalence of the subtype profile is indicated for each city. Regions are N, north; NE, northeast; CW, central west; SE, southeast; and S, south. At the bottom, subtype profiles are presented as percentages, with the first letter describing the recombinant subtype indicating the 5′ region of the *pol* gene. In contrast, the second letter refers to the 3′ region in a concatemer combining the protease + RT (first letter) and integrase (second letter: BC, BF, CB, etc) regions.

Figure 4. Maximum-likelihood phylogenetic trees

A. Dorav_rt_2

https://bit.ly/4apxmDu

B. Dorav_int_2

https://bit.ly/3YwwLZk

C. Dorav_pr_2

https://bit.ly/4aWbLTa

br, Brasília; int, integrase; mn, Manaus; pa, Porto Alegre; pr, protease; rt, reverse transcriptase; sl, Salvador; sp, Sao Paulo; st, Santos.

A, HIV-1 protease (294 bp), **B,** reverse transcriptase (603 bp), and **C,** integrase (594 bp) protein-encoding genetic regions of the pol gene. Colored tips correspond to distinct HIV-1 reference subtypes. Blacktip codes represent sequences from this study.

Conclusions

- The overall prevalence of SDRMs in Brazil was at intermediate levels, as shown previously in another recent survey.[7]
- The prevalence of INSTI and Doravirine SDRMs nationwide was consistent with WHO guidelines to start therapy without prior resistance testing. Phenotypic analysis will further confirm the potential lack of impact on susceptibility to Doravirine among samples with SDRMs or other clade-related polymorphisms.
- Continuous and systematic vigilance is fundamental for formulating effective prevention and treatment strategies for HIV.

References

1. Sá-Filho DJ, et al. *AIDS Res Hum Retroviruses*. 2006;22(1):1-13.
2. Myatt M, et al. *Antivir Ther.* 2008;13(suppl 2):37-48.
3. Sucupira MCA, et al. *AIDS Patient Care STDS*. 2007;21(2):116-128.
4. Mantovani NP, et al. *J Clin Microbiol.* 2012;50(6):2122-2125.
5. Bennett DE, et al. *PLoS One*. 2009;4(3):e4724.
6. Price MN, et al. *PLoS One*. 2010;5(3):e9490.
7. Caldeira DB, et al. *Lancet Reg Health Am*. 2025;52:101283.

Acknowledgments

- The authors thank José Valdez Madruga (São Paulo site principal investigator; role: patients selection/recruitment, sample and data collection), Noaldo Lucena (Manaus site principal investigator; role: patients selection/recruitment, sample and data collection), Denise Arakaki Sanches (Brasília site principal investigator; role: patients selection/recruitment, sample and data collection), Claudia Sfeir (Santos site principal investigator; role: patients selection/recruitment, sample and data collection), Marineide Rocha (Porto Alegre site principal investigator; role: patients selection/recruitment, sample and data collection), Miralba Freire Silva (Salvador site principal investigator; role: patients selection/recruitment, sample and data collection), Alessandra Bassini (Retrovirology Laboratory supervisor; role: data management), Danilo Dias, Juliana Galinskas, and Rafael Schmidt (role: lab data generation and analysis; phylogenetic analysis).

Presented at Conference on Retroviruses and Opportunistic Infections (CROI); February 22-25, 2026; Denver, CO, USA.

Copyright © 2026 Merck & Co., Inc., Rahway, NJ, USA and its affiliates. All rights reserved.