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Mutations associated with viral resistance to integrase in individuals initiating dolutegravir-containing antiretroviral therapy: retrospective cohort, Brazil 2017–2019

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ABSTRACT

Retrospective cohort aimed to analyze viral resistance mutations to integrase in people living with HIV/Aids (PLWHA) in Brazil. Patients receiving first-line therapy with a three-drug antiretroviral (ART) regimen containing dolutegravir (DTG), with HIV-1 genotypic resistance test available after starting treatment, were included. Data from three national databases related to antiretroviral dispensing, LT CD4+ cell count and HIV viral load (VL), and genotyping resistance testing were linked. Ideal adherence was defined as the proportion of days covered (PDC) $\geq$ 80%. Thirty (7.0%) of the 430 participants had resistance to DTG; five had high and 11 had moderate resistance levels. The N155H ($n = 9$) and E138K ($n = 7$) mutations were the most prevalent. DTG mutations were significantly more prevalent among males, whites, and those with HIV-VL count > 100,000 copies/mL, switching to alternative regimens or with resistance mutations to other classes of antiretroviral drugs ($p < 0.05$). Ideal ART adherence was observed in 52.8% of the participants and it was associated with DTG mutations ($p < 0.001$). This study described the resistance mutations to DTG in individuals starting treatment with this drug and the characteristics of such individuals. Understanding such a profile is crucial to regions where a DTG-containing regimen is the recommended first-line therapy.

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SUSTAINABLE DEVELOPMENT GOALS
Good Health and Well Being; Reduced Inequalities

Introduction

Dolutegravir (DTG) is an integrase strand transfer inhibitor (INSTI) with high potency, a high genetic barrier to developing viral resistance to the drug, and low toxicity in clinical trials (Molina et al., 2015; Patel et al., 2014). Real-world studies show that DTG-containing regimens have a more favorable safety profile than regimens based on protease inhibitors (Asare et al., 2024) and a better viral resistance profile than first-generation INSTIs, such as raltegravir (RAL) (Kouamou et al., 2020; Underwood et al., 2022).

DTG is recommended as part of the preferred first-line regimen for people living with HIV/AIDS (PLWHA) in World Health Organization (WHO) guidelines (WHO, 2019). Furthermore, WHO has highlighted the need to accelerate the transition to DTG-containing regimens due to high rates of pre-treatment viral resistance in the non-nucleoside reverse transcriptase inhibitor (NNRTI) class (WHO, 2021). In January 2017, the Brazilian Ministry of Health (MS) incorporated DTG- 50 mg into the first-line regimen combined with tenofovir plus lamivudine (3TC/TDF+DTG) for adults and adolescents living with HIV and, recently, for women of childbearing age, pregnant women, children, and HIV/TB coinfection (Ministério da Saúde, 2019, 2022a, 2023a, 2023b). In 2022, 731,000 PLWHA were receiving ART in the country, of which 94% were using the 3TC+TDF/DTG regimen (Ministério da Saúde, 2022b). This widespread DTG use can increase the prevalence of resistance to this drug, with potential cross-resistance with other INSTIs (Gil et al., 2022).

Globally, differences have been observed in the prevalence of HIV-1 resistance to DTG. In Spain, the level of DTG resistance among INSTI-experienced patients was 2.6% (Gil et al., 2022), but higher

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levels of 6.0% were observed in a multicohort global study where most participants had prior exposure to first-generation INSTIs (Loosli et al., 2023). In clinical trial studies of patients failing first-line ART, levels of DTG resistance ranged from 2.0% (Underwood et al., 2022) in South Africa to 4.0% in Kenya, Uganda, and Zimbabwe (Paton et al., 2022). The most recent WHO Report on HIV Drug Resistance reported an increased trend in the proportion of DTG resistance, ranging from 3.9% to 8.6% and reaching up to 19.6% in highly treatment-experienced individuals with high HIV viral load switching to a DTG-containing regimen (WHO, 2024). The most prevalent viral resistance mutations to DTG were R263K, followed by S230R (Gil et al., 2022). In Brazil, 6.2% of individuals had resistance mutations to DTG after initial treatment failure and R263K, G188R, E138A, and G140S were the most common (Diaz et al., 2023).

Notably, the continuous need for monitoring and preventing resistance to antiretroviral drugs aligns with WHO recommendations and strengthens adherence in the initial months of ART (WHO, 2024). Moreover, we observe a lack of longitudinal studies that evaluated viral resistance in ART-naïve individuals who specifically used 3TC+TDF/DTG in Brazil. This study aimed to analyze the frequency of viral resistance mutations to IN in PLWHA starting ART with a regimen containing DTG and who underwent genotyping after starting treatment.

Methods

Design and inclusion criteria

This Brazilian retrospective cohort study included treatment-naïve PLWHA starting ART with the preferred regimen (TDF/3TC/DTG) between January 2017 and December 2019, who had a genotypic resistance testing (GRT) performed at least 12 weeks after starting ART. GRT is performed in Brazil on PLWHA with confirmed virological failure, defined as two consecutive tests with detectable HIV-VL, with the last result a viral load greater than or equal to 500 copies/mL. The study is nested in the ECOART project (Effectiveness of antiretroviral therapy in people living with HIV, HIV/tuberculosis, HIV/leprosy or HIV/visceral leishmaniasis in Belo Horizonte and Brazil), approved by the Research Ethics Committee of the Federal University of Minas Gerais under the Ethical Appreciation Presentation Certificate (CAAE) N° 31192914.3.0000.5149. The Brazilian Ministry of Health granted the databases to the Research Group for Advanced Studies in Pharmacoepidemiology of Infectious Diseases (GEADIC).

Procedures

Data were retrieved from three databases of national information systems, namely, the Medication Logistics Control System (SICLOM), the Laboratory Control System for CD4+/CD8+ Lymphocyte Count and HIV Viral Load Testing (SISCEL), and the Genotype Testing Control System (SISGENO). SICLOM contains sociodemographic information and information on ARVs dispensed to all PLWHA enrolled in Brazilian public health services. SISCEL includes data on laboratory parameters, i.e., CD4+ T lymphocyte counts (LT-CD4+) and CV-HIV performed in public laboratories. More than 97% of people undergoing treatment receive ARVs through the SUS (Dos Santos et al., 2020). SISGENO contains results of CV-HIV-1 tests, LT-CD4+/CD8+ counts, HIV-1 genotyping, and HLA-B*5701 allele typing.

We identified individuals who started ART from January 1, 2017, to December 2019 in SICLOM, with no age restriction. In SICLOM, we verified whether the identified individuals had not previously received ART from 2011 to 2017. Individuals were followed up until the date of the genotyping test, which was considered the final follow-up date. The minimum follow-up time was 90 days. Those with no record of this test until December 2019 and those with a genotyping record before 90 days after starting ART were excluded from the study.

Database preparation

We initially performed deterministic and probabilistic data matching in SICLOM to identify records that refer to the same person but have one or more identification fields with different values. We considered records of the same person, those with the same name, mother's name, Individual Taxpayer Registry (CPF), and date of birth. We employed Dedupe, a Python library that uses an artificial intelligence model to perform deduplication on structured data (Gregg & Eder, 2015). This same process was applied to the SISCEL and SISGENO databases. Duplicate registrations and typing errors in all three databases were identified and eliminated. After the deduplication process, a unique identifier number was created in each database to allow linkage between the three databases. Then, data were anonymized for analysis. After this process was completed, we paired the SICLOM and SISCEL databases. Computer science

researchers from the Institute of Exact Sciences (ICEx) of the Federal University of Minas Gerais (UFMG) and members of GEADIC performed all of these processes.

Finally, we paired this database with SISGENO to identify eligible individuals with genotyping records. To identify individuals with viral resistance mutation to DTG, all fields of clinical interpretation in the SISGENO database were checked, and the presence of words related to integrase inhibitors was evaluated: "dolutegravir", "DTG", "integrase", "IIN", and "INI".

Variables

The dependent variable was a viral resistance mutation to DTG identified in GRT results available at the SISGENO database.

We adopted the Genotypic Resistance Interpretation Algorithm (HIVdb Program, Stanford – https://hivdb.stanford.edu/hivdb/by-patterns/) to classify mutations as primary or accessory. The level of viral resistance to DTG was estimated by adding the penalty score[open-strick]s[close-strick] associated with each of the resistance mutations: high-level resistance (score $\geq$ 60), intermediate resistance (total score 30–59), low-level resistance (total score 15–29), potentially low-level resistance (total score 10–14), and susceptible (total score 0–9).

The independent variables selected were sociodemographic characteristics: biological sex, age group, age at the start of ART, region of residence, schooling, race/skin color, marital status; treatment-related characteristics: adverse reaction to first-line ARVs, use of RAL after the need for change (TDF/3TC/DTG), a record of the need for a change of ART regimen, number of additional regimens used, record of resistance to Nucleoside/Nucleotide Analogue Reverse Transcriptase Inhibitor (NRTI) and NNRTI, adherence to ART, viral resistance mutation to DTG and level of viral resistance to DTG; and immunovirological characteristics: RNA-HIV-1 and LT-CD4+ cell counts on the date of the first ART dispensing and the date of the genotyping test record. A period between 180 days before and 15 days after the first ART dispensing was defined to identify the results of the HIV-1 and LT-CD4+ cell counts, choosing the date closest to the dispensing. SISCEL was used to verify the information on all LT-CD4+ and HIV-1 counts up to the date of the genotyping test record.

Data on ART, such as ART regimen change and the number of additional regimens used during the follow-up period, were obtained via SICLOM. Adherence was measured using the proportion of days covered (PDC). PDC is an indirect method of measuring adherence through dispensing records per the Continuous Multiple Interval Measure of Medication Acquisition (CMA). The CMA5 measure was used to calculate the total number of days in which the medication dispensed by SICLOM was theoretically used (observation window), divided by the total number of days between the first and last dispensing until the date of genotyping registration (Dima & Dediu, 2017; Vollmer et al., 2012). The number of additional tablets is included in the previous dispensing, and this value is limited to 100%. The cutoff point was defined as $\geq$ 80% for ideal adherence and <80% for non-ideal adherence, aligned with the recommendations of the Brazilian Ministry of Health (MS) clinical guidelines (Ministério da Saúde, 2023a).

The clinical description in the SISGENO database identified individuals with viral resistance to the NRTI and NNRTI classes. Viral resistance to the NRTI class was estimated as the mean mutation penalty score of abacavir, zidovudine, lamivudine, and tenofovir individual scores. Viral resistance to the NNRTI class was estimated as the mean mutation penalty socre of efavirenz, etravirine, and nevirapine individual scores (Loosli et al., 2023).

Statistical analysis

For descriptive statistics, we performed frequency distribution for categorical variables and measures of central tendency (mean or median) and variability (SD = standard deviation) for continuous variables. We compared groups for qualitative variables using Pearson's chi-square test and, when appropriate, Fisher's exact test. The Student's t-test and the nonparametric Mann–Whitney test were performed when appropriate for quantitative variables. All analyses considered a 95% confidence level (95% CI) with 5% statistical significance.

The deduplication, anonymization, and database treatment processes were performed using Python version 3.9.12 (2022 Python Software Foundation, Amsterdam, Netherlands). The adherence calculation (CMA5) was performed using R software version 4.1.3 (2022 The R Foundation for Statistical Computing). Statistical analyses were performed using the Statistical Package for Social Science for Windows (SPSS) version 29.0.

Results

We identified 202,607 individuals in SICLOM who initiated ART from January 1, 2017, to December 2019 in Brazil, of which 167,438 individuals used a

regimen containing TDF/3TC/DTG. Among these, 1,050 (0.63%) had a record of genotyping, of which 430 (40.9%) underwent the test 12 weeks after starting ART (Figure 1). The mean DTG use time between the date of the first ART dispensing and the record of the genotyping test was 399 days (SD = 216 days).

Approximately half (50.9%) of the 430 individuals included in the study were male, with a mean age of 33.80 years (SD = 10.62 years).

DTG resistance was observed in 7.0% ($n = 30$) of the study population. Among the HIV subtypes identified, the highest proportion was subtype B ($n = 24$), followed by subtype F1 ($n = 3$) and subtype C ($n = 3$). The isolated patterns of major and accessory mutations associated with IN resistance are presented in Figure 2.

The G118R mutation, associated with a great impact on DTG susceptibility, was identified in only one individual. One individual's Q148R mutation was identified in association with the primary mutation G140S or E138A. Four individuals' Q148HR+G140S combination was observed, with the additional presence of A124 T or L101I in all of them. The accessory INSTI mutations L101I and T124A were found together in eight individuals, two with the primary mutation R263K. The E157Q mutation selected in individuals who received RAL was found in association with the R263K mutation in one individual. The accessory mutation T97A was found in association with the primary mutation N155H in two individuals, and one individual had an association with the primary mutations E138A, G140S, and Q148H.

When assessing viral resistance levels to DTG, five individuals had high-level resistance, 11 had intermediate resistance, 10 had potential low-level resistance, and four were considered susceptible (Table 1). Individuals with optimal adherence had higher proportions of intermediate ($n = 11$) and high-level ($n = 4$) resistance to DTG (data not shown in the table).

The results of the viral resistance analyses by ARV class showed that 1.9% of individuals had resistance to the INSTI+NRTI classes, 0.7% to the INSTI+NNRTI classes, 6.5% to the NRTI+NNRTI class, and 1.2% to both INSTI+NRTI+NNRTI classes (data not shown in the table). Twelve (40.0%) of these 30 individuals with resistance to DTG had resistance to the NRTI class and seven (23.3%) to the NNRTI class. A lower proportion of PLWHA with resistance to DTG had full susceptibility to NRTI and NNRTI when compared to those without any resistance (Table 2).

The characteristics of the studied population by the presence of DTG resistance mutation are then shown

Table 1. Descriptive analysis of individuals with intermediate and high levels of viral resistance based on genotyping records ($n = 16$).

Patient	HIV Viral Subtype	Integrase RAM (major)	Integrase RAM (accessory)	GSS	Time to Failure (days)[a]	Viral Load (RNA-HIV-1)[a]	CD4+ T cell count[a]	Additional ARV regimen used prior to GRT
1	B	G140S Q148R	A124D, D10E	IR	210	6.954	182	**RAL**/TDF+3TC
2	B	E138K S147G Q148R	D10E, T66 K/T	HLR	188	1.159.914	107	**RAL**/TDF+3TC
3	B	E92Q N155H	A124T, L101I	IR	342	1.085.035	310	**RAL**/TDF+3TC
4	B	G140S Q148H	A124T, L101I, D10E	HLR	516	81.315	310	**RAL**/TDF+3TC
5	C	G140A Q148R	E157Q, A124N, L101I, D10E	IR	242	173	457	**RAL**/3TC/ABC
6	B	R263K	A49C, E157Q, A124T, L101I, D10E	IR	546	403.296	58	TDF+3TC/DRV/RTV/ETV
7	B	T66K	D10E	HLR	117	791.570	285	**RAL**/TDF+3TC
8	C	E92Q N155H	L101I, A124Q, D10E	IR	162	491.838	37	1stTDF+3TC+EFZ 2nd **RAL**/TDF+3TC
9	B	E138A G140S Q148H	L74LM, T97A, A128T, D10E	HLR	884	18.834	262	1st**RAL**/TDF+3TC 2nd 3TC+TDF/DTG
10	F1	E92Q N155H	L101I, D10E	IR	284	5.060	967	DRV/RTV/**RAL**
11	B	R263K	A124T, L101I, D10E	IR	109	2.179.283	88	3TC/ABC/DTG
12	C	G118R E138A	A124T, L101I, D10E	HLR	567	134.214	223	DTG/3TC+ZDV
13	B	R263K	A49G, D10E	IR	408	113.349	15	**RAL**/TDF+3TC
14	B	R263K	A124T, D10E	IR	231	150.770	15	–
15	B	E138K Q148R	A124T, L101I	IR	99	1.093	365	–
16	F1	R263K	L101I, D10E	IR	366	248.861	34	TDF+3TC+EFZ

[a]Mean. High-level resistance (HLR), Intermediate resistance (IR), raltegravir (RAL), darunavir (DRV), dolutegravir (DTG), lamivudine (3TC), tenofovir (TDF), abacavir (ABC), ritonavir (RTV, zidovudine (ZDV), etravirine (ETV), Genotype Resistence Testing (GRT).

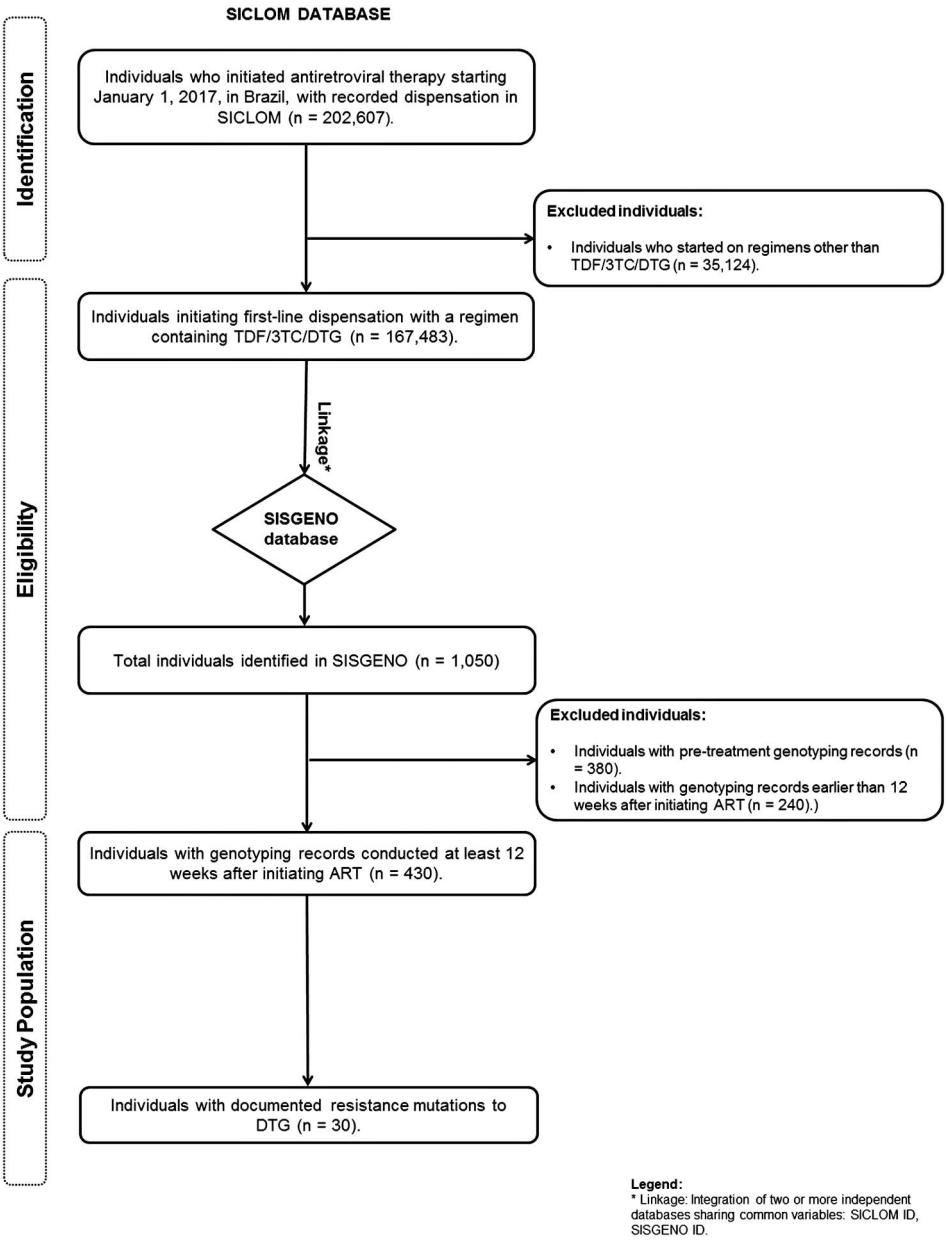

Figure 1. Eligibility flowchart of individuals included in the study. Brazil, 2017–2019.

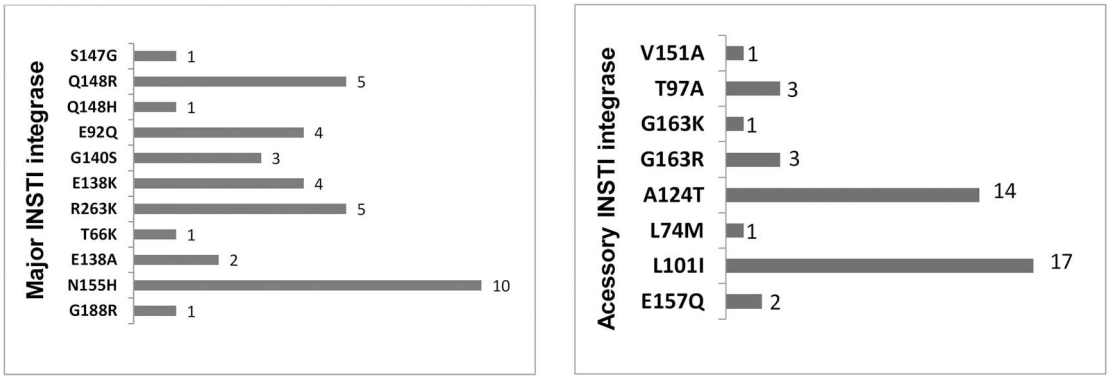

Figure 2. Description of major and accessory mutations associated with INSTI resistance mutation ($n = 30$).

Table 2. Resistance levels to NRTI and NNRTI based on dolutegravir susceptibility ($n = 430$).

Resistance Level	Individuals without resistance DTG $n = 400$ (%)	Individuals with resistance to DTG $n = 30$ (%)
NRTI Resistance Level		
Intermediate resistance	8 (0,9)	2 (1,4)
Low-level resistance	40 (7,3)	9 (16,0)
Potentially low-level resistance	1 (0)	1 (0,4)
Susceptible	351 (84,3)	18 (42,2)
NNRTI Resistance Level		
High-level resistance	15 (2,2)	3 (2,9)
Intermediate resistance	14 (2,0)	3 (2,9)
Low-level resistance	11(1,5)	1 (0,4)
Potentially low-level resistance	5 (0,5)	0
Susceptible	355 (85,4)	23 (59,6)

Nucleoside Reverse Transcriptase Inhibitors (NRTIs); Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs).

in Table 3. An average of 1.71 ± 0.881 additional regimens used and a record of switching due to TB were observed for 12.1% of the study population (data not shown in the table). Individuals with resistance to DTG, when compared with individuals without resistance, were male (76.7% vs. 49.0%, $p = 0.03$), white (46.7% vs. 30.8%, $p < 0.001$) with HIV-VL > 100,000 copies/mL on the date of first ART dispensing (20.0% vs. 15.5%; $p = 0.039$). These data were missing for approximately half of the study population. When genotyping, the groups were homogeneous for HIV-VL and CD4+ T cell count.

There was a record of the need to change the ART regimen for 305 individuals (70.9%). Among the individuals who needed to change the ART regimen, 130 (30.2%) used RAL after the need for change. This RAL use was higher in the group of individuals with

Table 3. Sociodemographic characteristics of people living with HIV/AIDS initiating a DTG-based regimen according to the presence or absence of resistance to this drug ($n = 430$).

Characteristic	Total ($n = 430$) n (%)	Without DTG Resistance ($n = 400$) n (%)	With DTG Resistance ($n = 30$) n (%)	valor-p
Sociodemographic characteristics				
Sex				
Male	219 (50,9)	196 (49,0)	23 (76,7)	**0,003**
Female	211(49,1)	204 (51,0)	7 (23,3)	
Age group (years)				
≤19	28 (6,5)	27 (6,8)	1 (3,3)	0,271
20–24	69 (16,0)	67 (16,8)	2 (6,7)	
25–29	71 (16,5)	64 (16,0)	7 (23,3)	
30–39	134 (31,2)	121 (30,3)	13 (43,3)	
≥40	128 (29,8)	121 (30,3)	7 (23,3)	
Region of residence				
Southeast	146 (34,0)	134 (33,5)	12 (40,0)	0,92
South	110 (25,6)	102 (25,5)	8 (26,7)	
Northeast	89 (20,7)	84 (21,0)	5 (16,7)	
Midwest	43 (10,0)	40 (10,0)	3 (10,0)	
North	42 (9,8)	40 (10,0)	2 (6,7)	
Education (years)				
Illiterate/none	10 (2,3)	10 (2,5)	0	0,096
1–7	105 (24,4)	99 (24,8)	6 (20,0)	
8–11	112 (26,0)	109 (27,3)	3 (10,0)	
12 ≥	34 (7,9)	31 (7,8)	3 (10,0)	
Missing	169 (39,3)	151 (37,8)	18 (60,0)	
Race/skin color [a]				
White	137 (31,9)	123 (30,8)	17 (46,7)	**< 0,001**
Brown	167 (38,8)	157 (39,3)	10 (33,3)	
Black	51 (11,9)	51 (12,8)	0	
Asian	3 (0,7)	3 (0,8)	0	
Indigenous	2 (0,5)	0	2 (6,7)	
Missing	70 (16,3)	67 (16.5)	4 (13,3)	
Marital status				
Single	163(37,9)	152 (38,0)	11 (36,7)	0,974
Married	35 (8,1)	33 (8,3)	2 (6,7)	
Divorced	14 (3,3)	14 (3,5)	0	
Living common law	21(4,9)	20 (5,0)	1 (3,3)	
Missing	197 (45,8)	181 (45,3)	16 (53,3)	
HIV Viral Load at first ART dispensing (copies/mL)				
>100.000	68 (15,8)	62 (15,5)	6 (20,0)	**0,039**
≤100.000	149 (34,7)	145 (36,3)	4 (13,3)	
Missing	213 (49,5)	193 (48,3)	20 (66,7)	
CD4+ T cell count at first ART dispensing (cell/μL)				
>200	137 (31,9)	132 (33,0)	5 (16,7)	0,18

(*Continued*)

Table 3. Continued.

Characteristic	Total ($n = 430$) n (%)	Without DTG Resistance ($n = 400$) n (%)	With DTG Resistance ($n = 30$) n (%)	valor-p
≤200	95 (22,1)	87 (21,8)	8 (26,7)	
Missing	198 (46.0)	181 (45,3)	17 (56,7)	
Treatment-related characteristics				
Adverse drug reactions				
Yes	33 (7,7)	30 (7,5)	3 (10,0)	0,62
No	397 (92,3)	370 (92,5)	27 (90,0)	
Adherence to antiretroviral therapy				
Ideal ≥ 80%	235 (54,7)	212 (47,0)	23 (76,7)	**<0,001**
Non-ideal < 80%	195 (45,3)	188 (53,0)	7 (23,3)	
Adherence in the three months before the date of genotyping				
Ideal ≥ 80%	66 (15,3)	59 (14,7)	7 (23,3)	0,208
Non-ideal < 80%	364 (84,7)	341 (85,3)	23 (76,7)	
Use of raltegravir after switching				
Yes	130 (30,2)	112 (28,0)	18 (60,0)	**<0,001**
No	300 (69,8)	288 (72,0)	12 (40,0)	
Need to switch ART.				
Yes	305 (70,9)	277 (69,3)	28 (93,3)	**0,005**
No	125 (29,1)	123 (30,8)	2 (6,7)	
NRTI Resistance				
Yes	71 (16,5)	58 (14,5)	13 (43,3)	**<0,001**
No	359 (83,5)	342 (85,5)	17 (56,7)	
NNRTI Resistance				
Yes	81 (18,8)	73 (18,3)	8 (26,7)	**0,027**
No	349 (81,2)	327 (81,8)	22 (73,3)	
Imunovirological characteristics				
HIV viral load at genotyping (copies/mL)				
>500	173 (40,2)	163 (40,8)	10 (33,3)	0,716
≤500	15 (5,3)	14 (3,5)	1 (3,3)	
Missing	242 (56,3)	223 (58,8)	19 (63,3)	
CD4+ T cell count at genotyping (cells/μL)				
>200	156 (36,3)	149 (37,3)	7 (23,3)	0,304
≤200	76 (17,7)	70 (17,5)	6 (20,0)	
Missing	198 (46,0)	181 (45,3)	17 (56,7)	

Significant values are denoted in **bold** ($p < 0.05$). DTG: Dolutegravir; NRTI: Nucleoside Reverse Transcriptase Inhibitors; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitors.

[a]In Brazil, the terms "race" and "skin colour" are widely used interchangeably, reflecting the specific characteristics of a country with great diversity and racial mixing. Since "race/skin color" is the terminology used in the Siclom information system, it is impossible to determine whether the classification refers exclusively to one concept or the other.

DTG resistance (60%) than the group of individuals without resistance (28.0%) ($p < 0.001$). Both the presence of resistance records for the NRTI class (43.3%) and the NNRTI class (26.7%) were higher for individuals with resistance to DTG (14.5% vs. 18.3%, respectively; $p < 0.05$). More than half of the individuals had ideal adherence to ART (54.7%). Individuals with resistance to DTG had a higher proportion of ideal adherence (76.7% vs. 23.0%) ($p < 0.001$).

Discussion

In this real-life study of PLWHA starting antiretroviral therapy in Brazil, which underwent genotyping after starting treatment, we observed a proportion of 7.0% of primary or accessory viral resistance mutations to DTG. The most common primary mutations were N155H, followed by R263K, Q148R, E138K, E92Q, E138A, G140S, Q148H, and S147G. Half of the individuals had DTG high/intermediate resistance levels. Individuals with resistance to DTG were male, white, had an HIV-VL count > 100,000 copies/mL on the date of the first ART dispensing, with ideal adherence, used raltegravir in a regimen after the first-line regimen, with a need to change the ART regimen and with resistance to the NRTI and NNRTI classes.

Varying proportions of viral resistance to DTG were found in the literature (De Salazar et al., 2023; Loosli et al., 2023; Marcelin et al., 2021; Paton et al., 2022; Underwood et al., 2022). The proportion of 7.0% of resistance to DTG found in the present study was similar to the prevalence of 6.0% in a multicohort global study assessing individuals failing a DTG-containing ART (Loosli et al., 2023). In the DTG RESIST study, at least one major or accessory INSTI viral resistance mutations was identified in 86 (14.0%) of 599 PLWHA with genotypic resistance testing. Viral resistance to DTG per the Stanford algorithm was detected in 36 (6.0%) of them. In this study, resistance to DTG was assessed two weeks after initiation and up to two months after

discontinuing any DTG-based regimen. The authors included individuals previously exposed to other INSTIs, unlike our sample, which consisted of ART-naïve individuals. Our proportion was slightly lower than the prevalence of 8.0% found by Marcelin et al. in a French study including both treatment-naïve and treatment-experienced individuals with virologic failure on INSTI-containing regimens (Marcelin et al., 2021). The difference in the proportion of DTG resistance found between the two studies can probably be explained by the heterogeneous samples since DTG RESIST included individuals from different geographic areas and previous exposure to other INSTIs.

Most of the 30 individuals with viral resistance to DTG were infected with HIV-1 subtype B, which can recombine with other subtypes (Diaz et al., 2023). Subtype B is highly prevalent in Brazil, exceeding 70.0%. The R263K mutation selected by subtype B and the G188R mutation selected by subtype C were identified as two mutational pathways that result in high levels of resistance to DTG (Quashie et al., 2015). These mutations may reduce the activity of ARVs when used in combination with DTG at higher levels (Gil et al., 2022; Loosli et al., 2023; Paton et al., 2022).

We found more primary mutations N155H and R263K in individuals who initiated ART, pointing to a significant resistance pathway. Resistance to R263K is the primary mutation associated with DTG resistance in treatment-naïve individuals (Loosli et al., 2023). The N155H mutation combined with the R263K mutation increases the level of resistance and the virus replicative capacity (Anstett et al., 2015; Malet et al., 2018), as observed with the R263K mutation combined with G118R (Xiao et al., 2023). Similarly, the R263K mutation combined with the *in vivo* accumulation of mutations E138K, G140S, S147G, and Q148R decreases susceptibility to DTG and may confer high-level viral resistance to the drug (Ndashimye et al., 2020; Zhang et al., 2018). The R263K-E157Q combination was found in an individual with high viremia and low LT-CD4+ count, producing high-level resistance to DTG. The accessory mutation E157Q with R263K increases enzymatic activity, viral replication capacity, and resistance to DTG (Buzon-Martin et al., 2024).

In this study, all individuals had accessory and primary mutations in association, with a significant contribution of accessory mutations. An example is the primary mutations Q148H and G140S, which synergistically reduce susceptibility to DTG when associated with the accessory mutation T97A (Huik et al., 2022). According to the Stanford algorithm, there is evidence of high-level viral resistance to DTG, and administering DTG twice daily is recommended in this case (Liu & Shafer, 2006). This combination of mutations was found in one individual in the present study. The most frequent accessory mutations identified, L101I and A124 T, indicate a possible *in vitro* resistance pathway to DTG in INI-naïve individuals in Brazil (Diaz et al., 2023).

In the present study, the use of raltegravir after the need for switching was associated with the emergence of viral resistance to DTG. Nine of the 16 individuals with intermediate mutations and high-level resistance used RAL in the post-switch regimen in combination with TDF+3TC ($n = 7$), ABC ($n = 1$), and DRV/RTV ($n = 1$) in the present study. Significant nonpolymorphic intermediate and high-level resistance mutations commonly selected in individuals receiving RAL (E157R, T66K, E92Q, N155H, G140A/S, Q148R) were found in individuals with DTG resistance mutations. The N155H and Q148H/R mutations represent the principal pathways for RAL resistance (Gil et al., 2022). The Q148R mutation is associated with high-level resistance to RAL *in vivo* and *in vitro* (Anstett et al., 2015), and N155H reduces RAL susceptibility by approximately 10- and 30-fold (Liu & Shafer, 2006). At the time of data collection, Brazilian guidelines recommended RAL as a therapeutic option for HIV/TB coinfection in pregnant women. RAL has a lower genetic barrier than DTG, and a possible change may increase the drug's susceptibility to the emergence of resistance.

When comparing the groups of individuals with and without DTG resistance, we observed statistically significant differences regarding sociodemographic, treatment-related, and clinical variables. The higher proportion of men with DTG resistance found in this study aligns with the study by Loosli et al. (2023), which reported male gender as a risk factor for developing DTG resistance. Regarding self-reported skin color, compared with the Morbidity and Mortality Weekly Report (MMWR) of the United States, social conditions and racial/ethnic identity impact PLWHA's health indicators (Dailey, 2022). In Brazil, lower schooling levels and yellow, Indigenous, Black, and brown skin colors reflect the social determinants of access to health for PLWHA (Ministério da Saúde, 2022b).

The associations we found with DTG resistance and resistance to the NRTI class align with other studies (Loosli et al., 2023; WHO, 2024). However, the NADIA study did not identify evidence that resistance to the NRTI class could impact the efficacy of the first-line DTG-containing regimen (Paton et al., 2022).

When comparing our study with the DTG RESIST study (Loosli et al., 2023), both confirmed DTG resistance with previous resistance testing. Mutations in the NRTI class leave the DTG unprotected and may reflect adherence problems. When comparing adherence among individuals with resistance, most individuals in our study showed ideal adherence ($p < 0.001$). A possible explanation for the lower proportion of mutations in individuals with non-ideal adherence is that there is no selective pressure for the emergence of resistance if the individual stops taking the medication (Lepik et al., 2017; Loosli et al., 2023; Paton et al., 2022).

We observed an association between HIV-VL on the date of first ART dispensing and resistance to DTG. Notably, half of the population in this study did not have this data, which may limit this result's significance. However, another study (Loosli et al., 2023) reported weak and statistically non-significant evidence (OR 1.19, CI 0.76–1.85) of an association between HIV-VL and resistance to DTG.

This study has limitations regarding (1) the use of administrative data with incomplete information, especially regarding clinical variables, and (2) the indirect method of analyzing adherence through pharmacy dispensing records. Although indirect, this method is consolidated for analyzing adherence (Dima & Dediu, 2017; Vollmer et al., 2012). (3) Given the dataset's nature (i.e., population-based), it is impossible to determine whether all individuals with virological failure underwent genotypic resistance testing nor to determine the number of genotypic resistance tests that failed to amplify. The study's strength is the adoption of large Brazilian representative databases on viral resistance to DTG. It is the first real-life study in the country to explore this resistance and its impact on adherence to ART and how it can influence public health policies globally.

Conclusion

A significant proportion (7.0%) of viral resistance mutations were found in individuals starting treatment with DTG-containing regimens who had viremia after starting ART and underwent genotyping. Half of the individuals had high/intermediate DTG resistance levels. The most common primary mutations were N155H, followed by R263K, Q148R, E138K, E92Q, E138A, G140S, Q148H and S147G.

Close monitoring of the incidence and pattern of DTG mutations is important, considering that this antiretroviral is part of the preferred treatment for HIV in Brazil. Expanding the use of this drug in the first-line regimen reinforces the incentive for pharmacoepidemiological surveillance of DTG. Given their potential to contribute substantially to the global understanding of HIV drug resistance, we recommend studies investigating the risk factors associated with mutations in the public health context.

Disclosure statement

No potential conflict of interest was reported by the authors.

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