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Research Article

Prevalence of Dolutegravir Resistance Among Adults Receiving Dolutegravir-based Antiretroviral Therapy with Virological Failure in Cuba

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Abstract

Background: In late 2018, Cuba incorporated Dolutegravir, a second-generation integrase inhibitor (INSTI), into its first-line antiretroviral treatment regimens. Monitoring HIV-1 drug resistance in patients with virological failure is critical for optimizing HIV care and treatment outcomes. This study assessed the prevalence of INSTI resistance among adults experiencing virological failure while receiving Dolutegravir-based ART in Cuba. Methods: Cross-sectional analysis using programmatic data from eight healthcare facilities, representing approximately 78% of adults receiving ART in Cuba. Adults (≥18 years) receiving all individuals receiving a Dolutegravir-based ART, who presented a confirmed virological failure (two consecutive viral loads >1000 copies/mL at least three months apart) between June 2022 and December 2024, were included. Demographic and clinical data were extracted from standardized laboratory requisition forms. Blood specimens were collected for HIV drug resistance and tested by Sanger sequencing, with resistance predicted using the Stanford HIVdb tool. Results: Among 110 eligible adults, 9 (8.2%) showed INSTI resistance-associated mutations, but only 6 had high level of resistance to Dolutegravir. Acquired HIV-1 drug resistance of any type was identified in 50.0% of patients (95% CI, 40 3–59 7). Additionally, 28.2% (95% CI, 20.6–37.2) carried mutations associated with resistance to non-nucleoside reverse transcriptase inhibitors and 18 2% (95%

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CI, 11.5-26.7) to nucleoside reverse transcriptase inhibitors. Two patients (1.8%) were found to have multidrug-resistant virus. Conclusions: The low prevalence of Dolutegravir resistance among patients with virological failure suggests that poor adherence, rather than antiviral resistance, may be the primary contributor to unsuppressed viral load in this population. These findings underscore the need to strengthen adherence support, alongside continued surveillance to promptly detect emerging resistance.

Keywords

Acquired Resistance, Dolutegravir, HIV, Cuba

1. Introduction

The implementation of antiretroviral therapy (ART) has significantly reduced morbidity and mortality in people living with HIV (PLHIV) [1]. However, the emergence and transmission of HIV drug resistance [2] threaten the effectiveness of current and future treatments and ultimately hinder progress toward the goal of ending HIV/AIDS as a public health threat by 2030 [3].

The World Health Organization (WHO) recommends that countries establish surveillance systems to monitor HIV drug resistance in both people initiating and those receiving ART. The main purpose of this is to minimize the emergence of drug resistance, preserve the effectiveness of first- and second-line therapies, and improve the quality of life of PLHIV [4].

ART was introduced in Cuba in 2001 using generic first- and second-line antiretroviral drugs (ARVs) produced by the national biopharmaceutical industry, benefiting over 28,000 PLHIV by December 2024 (MEDISYS VIH, 2025). However, a 2017 national survey of pre-treatment HIV resistance in the untreated population [5] identified a high prevalence of HIV resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs), which constituted the basis of first-line ART regimens at the time. In response, Dolutegravir (DTG), a second-generation integrase strand transfer inhibitor (INSTI), was introduced as part of the first-line –and second-line ART at the end of 2018.

Globally, the transition to DTG-based regimens has improved the overall HIV-1 viral suppression at the population level [6]. However, recent data from ART programs in sub-Saharan Africa have documented rising levels of HIV drug resistance among patients failing DTG-containing regimens [7], highlighting the need for systematic, periodic, and representative surveillance of HIV drug resistance among those receiving DTG-containing ART [8].

HIV genotyping for the integrase gene was incorporated into laboratory protocols in Cuba in 2019, constituting an essential tool in the detection of HIV resistance to INSTIs in PLHIV with virological failure [9]. The objective of this study was to assess the prevalence of INSTI, in particular DTG resistance, among adults receiving DTG-based antiretroviral therapy with virological failure in Cuba.

2. Materials and Methods

2.1. Study Design and Patient Population

A cross-sectional analysis was conducted based on programmatic data collected from eight provinces, which represent approximately 78% of adults receiving ART nationally (MEDISYS VIH, 2025). The study period spanned from June 2022 to December 2024. The study population included adults (≥18 years) receiving DTG-based ART, whether as first- or second-line treatment, with confirmed virological failure, defined as two consecutive viral load measurements above 1000 copies/mL at least three months apart. Eligibility was limited to individuals for whom the treating physician had requested HIV drug resistance testing as part of routine clinical care. All eligible patients were included, resulting in a census of cases meeting study criteria. This approach ensured that the analysis reflected the real-world implementation of HIV care and drug resistance monitoring within the national ART program. Demographic and clinical data were extracted from standardized laboratory requisition forms submitted with the samples [9].

2.2. Ethical Considerations

This study was reviewed and approved by the Council of Research of AIDS Research Laboratory (CC-LISIDA-22-0007). Ethical procedures were carried out in accordance with the requirements and standards of the Ministry of Public Health of the Republic of Cuba and the Ministry of Science, Technology, and Environment (CITMA), which incorporate the principles outlined in the Declaration of Helsinki. This study was conducted with ethical clearance by the research on Human Subjects (Medical) Committee at the AIDS Research Laboratory, Cuba (CE-LISIDA-22-005). Informed consent was obtained from each individual prior to participating in the study.

2.3. Laboratory Procedures

Whole blood (10 mL) was collected in EDTA tubes by venipuncture. Plasma was separated for HIV-1 viral load

quantification and drug resistance testing. Viral load was measured using either the COBAS AmpliPrep/COBAS TaqMan HIV-1 test v2 0 or the Cobas HIV-1 test on the Cobas 4800 platform (Roche Molecular Diagnostics, Branchburg, NJ, USA), following the manufacturer's instructions. Plasma specimens with a viral load >1000 copies/mL were shipped for genotyping testing to the AIDS Research Laboratory (LISIDA) in Cuba, a WHO-designated national laboratory for HIV drug resistance surveillance.

HIV viral RNA was extracted from 1 mL of plasma using the QIAamp Viral RNA mini kit (QIAGEN, Valencia, CA, USA). The protease (PR), reverse transcriptase (RT), and integrase (IN) regions were amplified using an in-house procedure [10, 11]. Sequencing was performed with GenomeLab™ DTCS QuickStart kit chemistry (Beckman Coulter, USA) on a CEQ™ 8800 genetic analyzer (Beckman Coulter, USA), and sequences were assembled using RECall software. Sequence quality control was assessed using the WHO HIVDR tool (http://pssm.cfenet.ubc.ca/who_qc).

HIV-1 subtyping was determined using the REGA HIV-1 subtyping tool v 3 0 (http://dbpartners.stanford.edu:8080/RegaSubtyping/stanford-hiv/typingtool/) and confirmed by phylogenetic analysis.

Resistance levels to nucleoside reverse transcriptase inhibitors (NRTIs), NNRTIs, protease inhibitors (PIs), and INSTIs were determined using HIVdb version 9.8 from the Stanford University HIV ARV Resistance Database (http://hivdb.stanford.edu).

2.4. Statistical Analysis

Statistical analysis was performed using GraphPad Prism 10 software (San Diego, CA, USA). Group comparisons for categorical variables were conducted using Fisher's or chi-square tests, as appropriate. Ninety-five percent confidence intervals for prevalence estimates were calculated using the modified Wald method.

3. Results

3.1. Clinical and Epidemiological Characteristics of the Study Population

Between June 2022 and December 2024, 110 patients receiving DTG-based ART were classified as having virological failure. Most of the patients participating in the study were male (74.5%), and 61.8% were men who have sex with men. 57.3% of PLHIV had received two or more ART regimens, and 82.7% were receiving tenofovir (TDF), lamivudine (3TC) or emtricitabine (FTC) and Dolutegravir (DTG). The predominant HIV subtype in the 110 patients studied was CRF19_cpx (27.3%), followed by CRF20_BG (22.7%) (Table 1).

Table 1. *Epidemiological, clinical, and virological characteristics of the 110 Cuban patients studied in the period 2022-2024.*

Characteristic	
Gender, n (%)	
Male	82 (74.5)
Female	28 (25.5)
Sexual Orientation, n (%)	
MSM	68 (61.8)
Heterosexual	42 (38.2)
Mean Age, years (IQR)	37 (18-73)
<25 years, n (%)	15 (13.6)
≥25 years, n (%)	95 (86.4)
Origin, n (%)	
Havana	47 (42.7)
Matanzas	21 (19.1)
Mayabeque	17 (15.5)
Granma	10 (9.1)
Santiago de Cuba	6 (5.5)
Guantanamo	5 (4.5)
Villa Clara	2 (1.8)
Camaguey	2 (1.8)
Median HIV-1 viral load, RNA copies/mL (IQR) (log10 RNA copies/mL)	4.74 log10 (3.13 log10-7.65 log10)
VL <4 log10, n (%)	28 (25.5)
VL≥4log10 but <5log10, n (%)	38 (34.5)
VL≥5log10, n (%)	44 (40)
Number of ART regimens received, n (%)	
1	47 (42.7)
2	41 (37.3)
3 or more	22 (20)
Current combination of ART used, n (%)	
3TC + TDF + DTG (as TLD)	56 (50.9)
TDF + FTC + DTG	35 (31.8)
3TC + AZT + DTG	12 (10.9)
3TC + ABC + DTG	2 (1.8)
TDF + ATV/r + DTG	2 (1.8)
3TC + DTG	2 (1.8)
DRV/r + DTG	1 (0.9)
Subtype, n (%)	
CRF19_cpx (A1, D, G)	30 (27.3)

Characteristic	
CRF20_BG	25 (22.7)
CRF18_cpx (A1, F, G, H y K)	20 (18.4)
CRF24_BG	18 (16.4)
B	15 (13.6)
C	2 (1.8)

3TC: lamivudine; ABC: abacavir ART: Antiretroviral therapy, AZT: zidovudine, ATV/r: atazanavir/ritonavir, DRV/r: darunavir/ritonavir, DTG: Dolutegravir, FTC: emtricitabine, IQR: interquartile range, MSM: Men who have sex with men; n: number, TDF: tenofovir; TLD: tenofovir + lamivudine + Dolutegravir combination tablet; VL: viral load

3.2. Prevalence of HIV Drug Resistance

Fifty percent of the PLHIV studied presented at least one mutation associated with HIV resistance to ARVs. 28.2% presented resistance to an NNRTI, 8.2% of patients presented a mutation associated with INSTIs and 6.4% presented mutations associated with resistance to PIs. Only 1.8%patients presented multidrug-resistant viruses (resistant to all four ARV families) (Table 2).

The most frequent mutations were K103N/S (19.1%) associated with NNRTIs and M184V (10.9%), which confers a high level of resistance to 3TC/FTC. For INSTI, the most frequent mutations were E138K/A/T, common non-polymorphic accessory resistance mutations selected in patients receiving RAL, EVG, CAB, and DTG, but that alone do not reduce INSTI susceptibility.

Table 3 shows the clinical characteristics and the profile of mutations associated with HIV resistance to ARVs in Cuban patients with DTG resistance.

Table 2. *Prevalence of HIV drug resistance by drug family in the 110 Cuban patients receiving DTG and virological failure according to the ART regimen received.*

ARV	All			1 ART regimen received			>1 ART regimen received		
	N=110	%	95% CI	N=47	%	95% CI	N=63	%	95% CI
NRTI									
Any	20	18 3	11 5-26 7	1	2 1	0 1-11 3	19	30 2	19 2-43 0
ABC	15	13 6	7 8-21 5	1	2 1	0 1-11 3	14	22 2	12 7-34 5
3TC/FTC	15	13 6	7 8-21 5	1	2 1	0 1-11 3	14	22 2	12 7-34 5
TDF	7	6 4	2 6-12 7	0	0 0	0 0-7 5	7	11 1	4 6-21 6
AZT	15	13 6	2 6-12 7	1	2.1	0 1-11 3	14	22 2	12 7-34 2
NNRTI									
EFV or NVP	45	40 9	3 6-50 7	2	4 3	0 5-14 5	43	68 3	55 3-79 4
DOR	11	10 0	5 1-17 2	1	2.1	0 1-11 3	11	17 5	9 1-29 1
EFV	42	38 2	29 1-47 9	2	4 3	0 5-14 5	40	63 5	50 4-75 3
ETR	18	16 3	9 9-24 6	1	2.1	0 1-11 3	17	26 9	16 6-39 7
NVP	44	40 0	30 8-49 8	2	4 3	0 5-14 5	42	66 7	53 7-78 0
RPV	27	24 5	16 8-36 7	1	2.1	0 1-11 3	26	41 3	29 0-54 4
PI/r									
ATV/r, DRV/r or LPV/r	7	6 4	2 6-12 7	0	0 0	0 0-7 5	7	11 1	4 6-21 6
ATV/r	6	5 5	2 0-11 5	0	0 0	0 0-7 5	6	9 5	3 6-19 6
DRV/r	4	3 6	1 0-9 0	0	0 0	0 0-7 5	4	6 3	1 8-15 5
LPV/r	4	3 6	1 0-9 0	0	0 0	0 0-7 5	4	6 3	1 8-15 5
INSTI									

ARV	All			1 ART regimen received			>1 ART regimen received		
	N=110	%	95% CI	N=47	%	95% CI	N=63	%	95% CI
Any	9	8 2	3 8-14 9	1	2.1	0 1-11 3	8	12 7	5 6-23 5
BIC	8	7 3	3 2-13 8	1	2.1	0 1-11 3	7	11 1	4 6-21 6
CAB	9	8 2	3 8-14 9	1	2.1	0 1-11 3	8	12 7	5 6-23 5
DTG	9	8 2	3 8-14 9	1	2.1	0 1-11 3	8	12 7	5 6-23 5
EVG	9	8 2	3 8-14 9	1	2.1	0 1-11 3	8	12 7	5 6-23 5
RAL	2	1 8	0 2-6 4	0	0 0	0 0-7 5	2	3 2	0 4-11 0

CI: confidence interval., PI: Protease inhibitors; NRTI: Nucleoside reverse transcriptase inhibitors; NNRTI: Non-nucleoside reverse transcriptase inhibitors; INSTI: Integrase inhibitors. ATV/r: Atazanavir/ritonavir; LPV/r: Lopinavir/ritonavir; DRV/r: Darunavir/ritonavir; ABC: Abacavir; AZT: Zidovudine; 3TC: Lamivudine; FTC: Emtricitabine; TDF: tenofovir; DOR: doravirine; EFV: efavirenz; ETR: etravirine; NVP: nevirapine; RPV: rilpivirine; BIC: bictegravir; CAB: cabotegravir; DTG: Dolutegravir; EVG: evitegravir; RAL: raltegravir.

Table 3. *Clinical and genotypic characteristics of Cuban patients with DTG resistance.*

Code	Age	Gender	VL (cp/mL)	Subtype	Actual ART	Previous ARV	Time with viral replication after incorporating DTG (days)[a]	INSTI Mutations	Predicted DTG resistance[b]
LIS-15	52	M	55 400	B	3TC+TDF+ DTG	AZT, 3TC, EFV, NVP, FTC, TDF	420	G140S, Q148H, N155H	High
LIS-16	43	M	18 600	CRF20_BG	3TC+TDF+ DTG	None	330	E138K	Low
LIS-20	39	M	29 800	CRF20_BG	3TC+TDF+ DTG	AZT, 3TC, NVP	513	R263K	Intermediate
LIS-29	58	F	19 000	B	FTC+TDF+ DTG	AZT, 3TC, NVP, IDV/r, LPV/r, TDF, FTC, TDF	425	S230R	Low
MAT-02	22	M	16 6000	CRF18_cpx	FTC+TDF+ DTG	3TC, AZT, NVP, EFV	307	G118R, E138K	High
MAT-06	49	M	7 810	CRF20_BG	3TC+TDF+ DTG	3TC, AZT, NVP, EFV	552	E92Q, E138K, N155H	High
VIL-06	61	M	76 600	C	TDF+ATV/r + DTG	3TC, AZT, NVP, EFV	598	T66A, G118R, E138K	High
HAB-22	55	M	542 600	CRF18_cpx	3TC+TDF+ DTG	3TC, AZT, NVP, EFV	282	E138A, G140A, Q148R	High
HAB-24	58	F	142 000	CRF19_cpx	3TC+TDF+ DTG	3TC, AZT, NVP, EFV	442	N155H	High

VL: viral load, cp/mL: copies/mL, M: male, F: Female, 3TC: lamivudine, TDF: tenofovir, DTG: Dolutegravir, FTC: emtricitabine, ATV/r: atazanavir/ritonavir, AZT: zidovudine, NVP: nevirapine, IDV/r: indinavir/ritonavir, LPV/r: lopinavir/ritonavir. Mutations highlighted in black confer high levels of resistance to DTG

a-This corresponds to number of days from the first detectable viral load after the introduction of DTG into ART regimens until the resistance test was performed

b-The resistance level is based on the Stanford HIVdbv 9 8

4. Discussion

This study shows the frequency of HIV-1 resistance to ARVs in a group of Cuban PLHIV with FV criteria three years after the introduction of DTG in first-line ART in Cuba. Fifty percent of the PLHIV studied presented at least one resistance-associated mutation, with the NNRTI family (included in the first-line regimen in Cuba from 2001 to 2018) being the most frequent. The most common mutations detected in this ARV family were K103N and G190A, associated with a decreased susceptibility to EFV and NVP. Previous studies conducted in Cuba on treated populations had already shown high levels of HIV-1 resistance to these drugs [12, 13], and the national survey of pre-treatment HIV-1 resistance to ARVs conducted in 2017 indicated a prevalence of NNRTI of 23.4% among naïve individuals [5]. The constant selection pressure on HIV due to suboptimal ARV concentrations over time, resulting from suboptimal adherence or intolerance, coupled with the low genetic barrier of NNRTIs, are factors that could contribute to the increase in resistance to these drugs [14-16]. Since 2018, Cuba has gradually replaced EFV and NVP with DTG (integrase inhibitor).

Despite the efficacy of DTG [6], the prevalence of resistance to this drug in the present study was 8.2%; a similar value to that obtained in a study conducted in Malawi, but lower than the values described in Mozambique [8]. Overall, this number indicates that most individuals on DTG-based regimens that are failing ARVs do not exhibit resistance to DTG, however, the prevalence is higher than anticipated based on clinical trials, and similar to or lower than other experiences [8]. In a study conducted in Cuba between January 2017 and January 2019, which involved patients infected with viruses resistant to at least one member of the antiretroviral families (NRTI, NNRTI, PI), primary resistance to DTG was not detected [16].

Several factors may facilitate the emergence of DTG-associated mutations, including late diagnosis, late presentation to care services, suboptimal treatment adherence, and drug-drug interactions [14, 17]. The emergence of HIV resistance is context-dependent, and its management requires the collaboration of all health system stakeholders, along with civil society [14].

Rapid and timely identification of virological failure, followed by HIV genotypic drug resistance testing and subsequent adjustment of treatments, would prevent prolonged viremia during exposure to DTG, which may facilitate the progressive accumulation of DTG resistance mutations. In the present study, patients with INSTI resistance had detectable viremia for more than 200 days before accessing HIV drug resistance testing, a result similar to that described in a study in Malawi [18]. Systematic monitoring of viral load and timely action by the physicians providing comprehensive care to PLHIV will optimize the management of virological failure and prevent the development of HIV resistance to ARVs. A sequence corresponding to a patient without previous ART (LIS-16) presented low resistance to DTG, due to the presence of the E138K mutation (accessory), which by itself does not reduce sensitivity to INSTIs, but in combination with other mutations, particularly at position 148 of the integrase enzyme, can reduce susceptibility to this family of ARVs.

The results illustrate the high prevalence of the CRF18_cpx and CRF19_cpx variants and BG recombinants (CRF20_BG and CRF24_BG) in the Cuban HIV-positive population, a trend observed by various authors in previous studies on the Cuban HIV-positive population [5, 19, 20]. Some of these (CRF19_cpx) were associated with rapid progression [19], however, there was no association with frequency of resistance.

One limitation of this study is that the observed proportion of DTG resistance may not be extrapolated to the Cuban population receiving DTG with virological failure, because not all provinces in the country were represented. Conducting a national survey of acquired HIV resistance, following the recommendations issued by the World Health Organization regarding representativeness criteria [4], will contribute to understanding the landscape of HIV resistance to antiretrovirals five years after the introduction of DTG in ART regimens in Cuba.

The availability of genotyping for routine care and the patient-centered model of care to support adherence in our country could also contribute to preventing the increase in the levels of acquired resistance detected in this study and its transmission. One in 10 individuals failing DTG could benefit from continuing the use of this drug. Close follow-up of these cases, as well as the early switching of cases with documented resistance might be needed to improve viral suppression and contribute to meeting the goals set by UNAIDS for 2030.

5. Conclusions

In conclusion, the presence of ART-resistant variants in individuals receiving DTG-based regimens highlights the need to maintain and strengthen resistance surveillance and implement high-impact interventions to curb the rise in resistance to first-line regimens, primarily DTG. Implementing a systems approach through a holistic view of the HIV drug resistance phenomenon and the interconnectedness of medical, social, and systemic factors, would ensure treatment success and, therefore, contribute to the elimination of HIV as a health problem by 2030.

Abbreviations

ART	Antiretroviral Therapy
PLHIV	People Living with HIV
HIV	Human Immunodeficiency Virus
AIDS	Acquired Immunodeficiency Syndrome
WHO	World Health Organization

ARVs	Antiretroviral drug
NNRTI	Non Nucleoside Reverse Transcriptase Inhibitor
DTG	Dolutegravir
INSTI	Integrase Strand Transfer Inhibitor
CITMA	Ministery of Science, Technology and Enviroment
PR	Protease
RT	Reverse Transcriptase
IN	Integrase
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PI	Protease Inhibitor
TDF	Tenofovir
3TC	Lamivudine
FTC	Emtricitabine
MSM	Men Who Sex with Men
ABC	Abacavir
AZT	Zidovudine
IQR	Interquartile Range
TLD	Tenofovir + Lamivudine + Dolutegravir Combination Tablet
VL	Viral Load
ATV/r	Atazanavir/Ritonavir
DRV/r	Darunavir/Ritonavir
LPV/r	Lopinavir/Ritonavir
DOR	Doravirine
EFV	Efavirenz
ETR	Etravirine
NVP	Nevirapine
RPV	Rilpivirine
BIC	Bictegravir
CAB	Cabotegravir
BIC	Bictegravir
EVG	Evitegravir
RAL	Raltegravir

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Data Availability Statement

These proposals will be reviewed and must be approved by the National HIV Program of the Ministry of Health and the senior investigators. Eventually, a data access agreement must be signed.

Conflicts of Interest

The authors declare no conflicts of interest.

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Biography

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