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Brief communication: virological outcomes and dolutegravir resistance mutations in HIV-infected patients: a multicenter retrospective cohort study in Mozambique

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Abstract

The global HIV epidemic remains a major public health challenge, with DTG playing a key role in ART regimens due to its efficacy and tolerability. This study evaluated virological outcomes and resistance mutations in patients on DTG in Mozambique through a retrospective cohort study in seven DREAM centers. Data from 29,601 patients (98.1% on DTG) revealed a virological suppression rate of 95% (27,622/29,051). Factors positively associated with suppression included age > 50, longer ART duration, and being female. Of 17 resistance tests, 8 showed major mutations, including G118R and E138K. Results highlight DTG's effectiveness and the need for resistance surveillance.

Keywords HIV, Drug resistance, Dolutegravir, Antiretroviral therapy, Africa

Introduction

An estimated 39.9 million people were living with HIV worldwide as of 2023 [1]. Antiretroviral therapy (ART) has been crucial in reducing morbidity and mortality associated with HIV [2]. Integrase strand transfer inhibitors (INSTIs) have become a cornerstone in HIV treatment and in 2018, the World Health Organization (WHO) endorsed Dolutegravir (DTG) as part of the preferred ART regimens, particularly in low- and middle-income countries, where the burden of HIV is disproportionately high [3, 4]. WHO reports that up to now 91% of reporting countries have adopted DTG-based ART as the preferred first-line treatment for adults and adolescents, 77% into second-line therapy, and 69% for infants and children [5].

In Mozambique approximately 2.4 million people live with the virus, with an ART coverage of 87.5% in 2023 according to UNAIDS [6]. DTG has been a key part of Mozambique's national HIV treatment strategy since its introduction into first-line ART regimens in 2019 [7].

Although DTG has proven highly effective in managing HIV, the emergence of resistance remains a growing concern, especially in resource-limited settings [5]. Recent studies from the field have reported higher-than-expected rates of DTG resistance, particularly in populations with previous exposure to antiretroviral therapy, highlighting challenges in real-world implementation [8, 9].

In Mozambique, where access to advanced diagnostic tools is often limited, data on drug resistance are sparse. We evaluated the prevalence of viral suppression among

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patients on DTG and to assess the emergence of drug resistance and we tied to identify key factors that may contribute to treatment failure, such as prior ART exposure, and time on treatment. Moreover, we report data on mutations detected in the small number of patients who were able to access resistance testing.

Methods

We conducted a retrospective cohort study across seven DREAM program centers in Mozambique, covering Maputo City (three centers), Maputo Province (one center), Sofala Province (two centers), and Zambezia Province (one center). These centers provide community-based healthcare focused on HIV treatment and ART [10].

Among the study population of HIV + patients in care in health centres in Mozambique, the study included only patients on ART for at least three months with recorded viral load (VL) results between July 1, 2022, and December 31, 2023. Data were extracted from routinely collected electronic medical records (EMR), encompassing demographics (age, sex), clinical variables (ART duration, time to VL testing), and geographical information. Age was treated as a categorical variable and grouped as 0–18, 18–25, 25–50, and > 50 years. This classification was chosen to include children and adolescents (a distinct group with unique clinical and social characteristics), young adults, adults, and older adults, ensuring meaningful comparisons across these demographic categories.

The primary endpoint was virological suppression, defined as VL < 1000 copies/mL. Patients with VL > 1000 copies/mL received enhanced adherence counseling and repeat VL testing after three months. Resistance testing was conducted on a subset of patients due to logistical constraints, highlighting systemic barriers to testing access in the region.

Resistance to DTG was evaluated using an in-house genotyping method. RNA was extracted, amplified via reverse transcription and nested PCR at the Zimpeto DREAM lab, and sequenced using the Sanger method at INQABA Biotechnical Industries, South Africa. Mutations were identified with DNAStar LASERGENE software and interpreted via the Stanford HIV Drug Resistance Database. Detailed methods are available in [11].

Data analysis was performed in R Studio (v 2023.09.1 + 494), with categorical variables summarized as frequencies and percentages and continuous variables as medians with IQR. Chi-square tests assessed associations, and logistic regression identified predictors of virological suppression (OR, 95% CI).

This study adhered to the Declaration of Helsinki and received ethical approval from Mozambique's CNBS (Ref: 430/CNBS/24, July 19, 2024). Anonymity and confidentiality were maintained, and informed consent was waived due to the retrospective nature of the data.

Results

The study population consisted in 30,906 PLWH in care in the selected centers during the study period; 29,601 patients met the inclusion criteria and were included in the study sample. Of these, 29,051 (n = 29,051) were on Dolutegravir-based therapy. Table 1 reports the general characteristics of the sample; the overall viral suppression rate among PLWH on DTG-based therapy was 95% (27,622/29,051).

As shown in Fig. 1, viral suppression rates varied by sex, age, location and time on ART. In the multivariate logistic regression analysis, Age, time on ART, sex, and geographical location were independently and significantly associated with viral suppression outcomes. Patients aged 50 years and above had higher odds of achieving viral suppression (OR: 2.45, 95% CI 1.85–3.26), as did those who had been on DTG therapy for more than five years (OR: 1.92, 95% CI 1.44–2.58). Male patients were slightly less likely to achieve suppression compared to female patients (OR: 0.85, 95% CI 0.75–0.97). Geographic differences were also observed, with patients in Quelimane City exhibiting lower odds of suppression compared to those in Machava (OR: 0.67, 95% CI 0.52–0.86).

Among patients with virological failure (viral load > 1000 copies/mL), 74 samples were sent for resistance testing. Of these, 17 underwent testing specifically for DTG resistance. Eight patients displayed major mutations conferring resistance to DTG, reflecting the complexity of emerging resistance patterns. The E138K mutation, detected in five patients, was frequently observed in combination with other mutations, such as G140A, S147G, and Q148R, which are associated with integrase strand transfer inhibitor resistance. Similarly, the G118R mutation, also found in five patients, appeared in varied combinations, including with E138K and additional substitutions like R263K, Q146P, T66A, and T66I. These combinations indicate an evolving resistance profile, with some patients harboring multiple mutations that potentially reduce the efficacy of DTG.

Notably, one patient exhibited the rare R263K mutation in isolation, a substitution linked to reduced DTG susceptibility. Another patient presented with the combination of G118R and E138A, while a third displayed a unique set of mutations (E138K, G140A, S147G, and Q148R).

Table 1 General characteristics of the study sample treated at clinical centers in Mozambique, comparing patients on Dolutegravir (DTG)-based therapy versus non-DTG-based therapy across age groups, sex, therapy durations, treatment sites, and viral suppression rates

Variable	Entire sample (n = 29601)		DTG-based regimen (n = 29051)		Non DTG-based regimen (n = 550)	
	N	Percentage	n	Percentage	n	Percentage
Age Group (0–18)	1916	6.4	1885	6.5	31	5.6
Age Group (18–25)	1847	6.2	1789	6.2	58	10.5
Age Group (25–50)	18,959	64.0	18,636	64.1	323	58.7
Age Group (> 50)	6879	23.2	6741	23.2	138	25.1
Sex (Female)	20,400	68.9	20,018	68.9	382	69.5
Sex (Male)	9201	31.1	9033	31.1	168	30.5
Time in therapy (0–1 year)	1834	6.2	1797	6.2	37	6.7
Time in therapy (1–5 years)	8357	28.2	8211	28.3	146	26.5
Time in therapy (> 5 years)	19,410	65.6	19,043	65.6	367	66.7
Centro (Beira)	4407	14.9	4308	14.8	99	18.0
Centro (Machava)	4301	14.5	4273	14.7	28	5.1
Centro (Manga Chingussura)	6911	23.3	6775	23.3	136	24.7
Centro (Maputo city)	5448	18.4	5355	18.4	93	16.9
Centro (Matola 2)	2650	9.0	2602	9.0	48	8.7
Centro (Quelimane)	3271	11.1	3229	11.1	42	7.6
Centro (Zimpeto)	2613	8.8	2509	8.6	104	18.9
DTG containing regimen	29,051	98.1				
Non-DTG regimen	550	1.9				
Viral suppression	28,180	95.2	27,697	95.3	483	87.8
No Viral suppression	1421	4.8	1354	4.7	67	12.2

Discussion

This study shows high rates of viral suppression (95%) among individuals on DTG-based ART at Mozambique's DREAM centers, with older age, longer duration on ART, and female sex linked with better outcomes. However, the detection of DTG resistance in 8 out of 17 patients tested for major mutations underscores the need for ongoing monitoring and surveillance. These findings align with global trends and reinforce the efficacy of DTG in achieving strong viral suppression across various clinical settings [12, 13]. Nevertheless, the emergence of resistance in Mozambique, as noted by WHO, calls for comprehensive resistance surveillance, particularly in populations with prior ART exposure or inconsistent adherence [5].

This study has several limitations. The small sample size for resistance testing restricts broader conclusions and highlights challenges in conducting such testing in resource-limited settings. The retrospective design limits causal inferences, and the focus on DREAM centers may affect the generalizability of findings. Additionally, the 18-month observation period does not allow evaluation of long-term trends in DTG efficacy or resistance.

Our results emphasize the importance of sustained viral load monitoring and resistance testing across Sub-Saharan Africa to optimize treatment outcomes. Surveillance systems, as many authors suggest, are critical for early detection of resistance and timely adaptation of treatment strategies [14]. Investments in reinforcing these networks are urgently needed in regions with growing ART programs.

Adherence strategies are critical to minimize DTG resistance. Tailored adherence strategies should prioritize subpopulations more susceptible to poor adherence, including individuals with prior ART exposure, adolescents, men, sex workers, and children. Evidence from targeted interventions has demonstrated that focused efforts can substantially enhance adherence and mitigate resistance risks in these vulnerable groups [15–19].

The rapid emergence of DTG resistance calls for more cautious public health strategies. Policymakers must avoid oversimplification and instead focus on differentiated services that account for the complexity of HIV [20]. Expanding resistance surveillance systems is particularly critical in regions with growing ART programs, enabling early detection and timely modification of treatment protocols. Furthermore, viral load testing and resistance monitoring must be fully integrated into national HIV

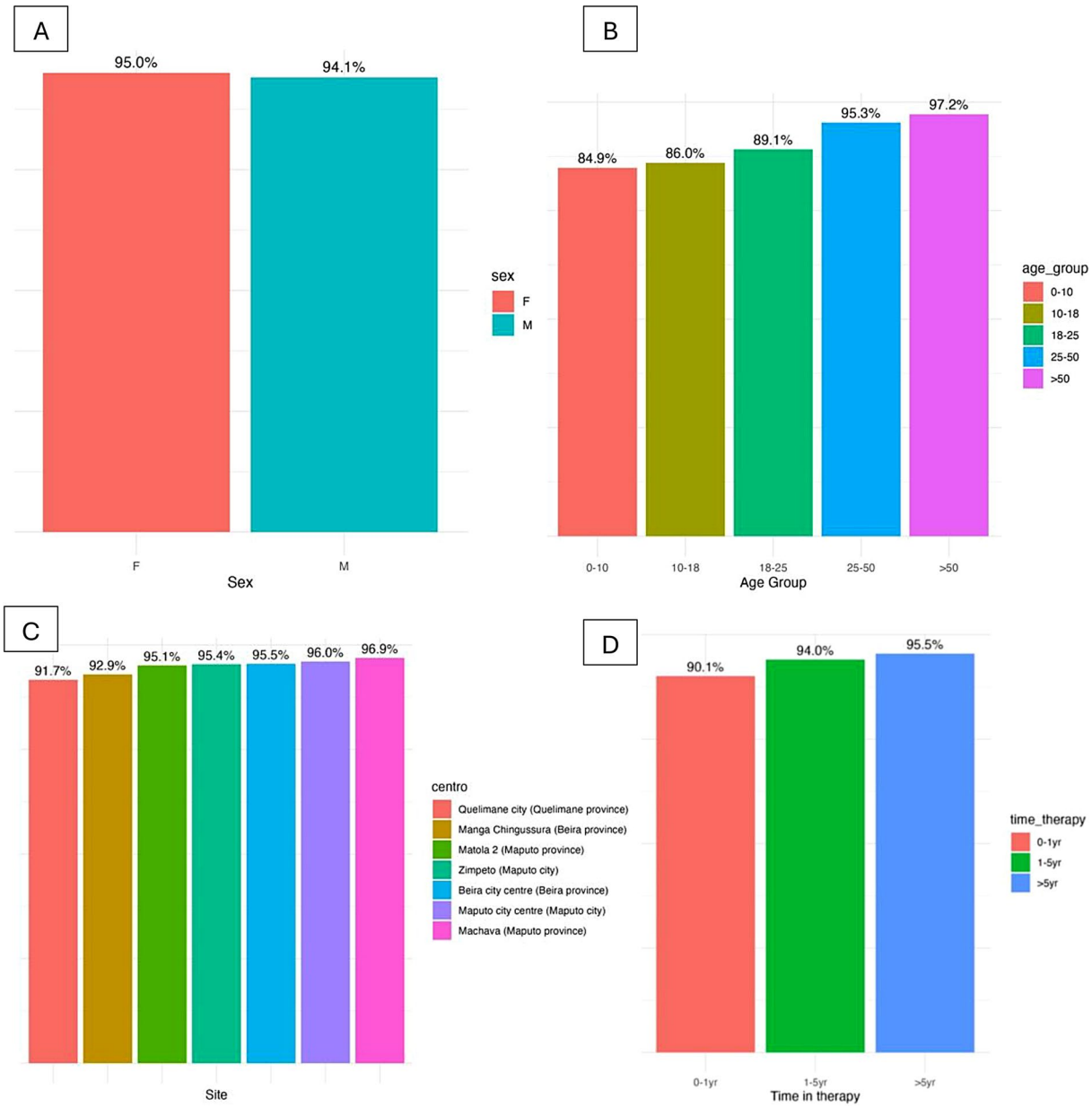

Fig. 1 Comparison of viral suppression rates among patients on Dolutegravir (DTG)-based therapy stratified by sex (**A** male vs female), by age group (**B** 0–18, 18–25, 25–50, > 50 years), by treatment sites (**C** Beira, Machava, Manga Chingussura, Maputo city, Matola 2, Quelimane, Zimpeto), and by duration of therapy (Panel **D**: 0–1 year, 1–5 years, > 5 years), based on data from multiple clinical centers in Mozambique

programs to adapt treatment strategies based on emerging resistance patterns.

In conclusion, while this study shows the effectiveness of DTG in Mozambique, with high rates of viral suppression, the increasing emergence of DTG resistance serves as a stark warning. With millions of people in Africa relying on DTG, the spread of resistance mutations poses a serious public health threat, also considering that new drugs and new drug classes are not at the horizon in Africa, therefore Dolutegravir efficacy needs to be preserved at best, since it represents the pillar of the current and perhaps future therapies. Urgent action is needed to rethink HIV care strategies in the region, focusing on differentiated service delivery, enhanced surveillance and resistance testing, digitalization, and effective patient tracking systems. Without prompt intervention, the significant progress in HIV management could be at risk.

In conclusion, this study highlights the high effectiveness of DTG-based antiretroviral therapy in Mozambique while emphasizing the urgent need for robust surveillance systems to monitor and address emerging drug resistance.

Declarations

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Author contributions
AMD conducted the analysis and drafted the manuscript.NM supervised data collection. SO reviewed the manuscript and provided insights into data interpretation. EU and MR managed the clinical data collection from patients. ZS supervised the laboratory data management. GG supervised data collection and reviewed the manuscript. FC conceptualized the study, supervised the analysis, and guided the interpretation of results.

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Availability of data and materials
The data that support the findings of this study are not openly available due to reasons of sensitivity, but are available from the corresponding author upon explicit and reasonable request.

Competing interests
The authors declare no competing interests.

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