Dolutegravir (DTG) resistance among ART-experienced viremic patients in Kenya receiving DTG-based ART

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BACKGROUND

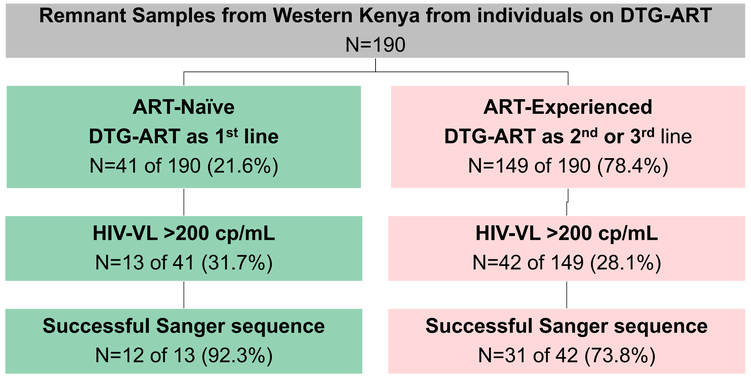
- Kenya rolled out dolutegravir-based antiretroviral therapy (DTG-ART) in 2017, as 1st and 2nd line treatment for people living with HIV (PLHIV).
- HIV drug resistance (HIVDR) data among PLHIV with detectable viremia on DTG-ART is limited, especially from LMIC settings.
- We assessed the frequency and patterns of HIV drug resistance mutations (HIV-DRM) in PLHIV with detectable viremia (single viral load measurement of >200 cp/mL) on DTG-ART between January and March 2023 from national HIV treatment clinics in the nine counties in Western Kenya.

METHODS

- **Samples**: 190 remnant plasma samples from PLHIV on DTG-ART were received out of the expected calculated sample size of 622 based on the Cyclical Acquired HIVDR (CADRE)[1] surveillance program, from the nine Western Kenya counties (accounts for 73.8% of Kenya HIV burden).
- **Demographic Data:** obtained anonymized data from the National HIV viral load (HIV-VL) testing program.
- **HIVDR Genotyping:** performed at the National Genomics and Molecular Surveillance Laboratory, Nairobi, on samples with load HIV-VL >200 cp/mL
  - Gene regions: HIV-1 protease, reverse transcriptase and integrase
  - Assay: HIVDR Genotyping by Sanger sequencing
  - HIV-DRMs and ARV resistance interpretation were determined using the Stanford HIV Drug Resistance database (v 9.5.1).
- **Statistical analysis**: Fisher's exact and Student's t-test using R statistical software were used to compare the age, gender, treatment duration, and HIV viral loads for ART-naïve individuals initiated on DTG-ART as 1st line ART to those who were ART-experienced and switched to DTG-ART.

[1]Monitoring Emerging HIVDR in Sub-Saharan Africa in the Era of Dolutegravir. Da Silva et al. JID. 225(3). 2022

Figure: Consort diagram



Prevalence of INSTI resistance mutations among viremic ART-experienced PLHIV in Kenya was 22.6%.

Table 1: Demographics and detail of ART-naïve and ART-experienced individuals

	ART-Naïve DTG-ART as 1st line N=41	ART-Experienced DTG-ART as 2nd or 3rd line N=149	Total N=190	p-value
Median Age in years (IQR)	30 (27, 40)	24 (16, 40)	28 (17, 40)	0.130
Female (%) **Male (%)**	25 (61%) 16 (39%)	86 (42%) 63 (58%)	111 (58%) 79 (42%)	0.725
Time on ART (yrs) Median (IQR)	1.5 (1.2, 2.2)	7.5 (5.4, 10.2)	6.1 (3.1, 9.7)	<0.001
Time on ART (yrs) prior to DTG- ART Median (IQR)	-	5.2 (3.3, 7.6)	-	-
Time on DTG (yrs) Median (IQR)	1.5 (1.2, 2.2)	2.1 (1.8, 3.1)	2.1 (1.5, 2.9)	0.001
Status of HIV-VL within 3 months prior to DTG initiation				
VL not available	-	93 (62%)	-	-
HIV VL ≤200 cp/ml	-	26 (17%)	-	-
HIV VL >200 cp/ml	-	30 (20%)	-	-
Current HIV-VL				
HIV VL ≤200 cp/ml	28 (68%)	107 (72%)	135 (71%)	0.699
HIV VL >200 cp/ml	13 (32%)	42 (28%)	55 (29%)	
Successful DR sequencing	N=12	N=31	N=43	
# with INSTI DRM	1 (8.3%)	7 (22.6%)	8 (18.6%)	-

Table 2: Demographics and DR results of individuals with INSTI DR mutations

	Age	Sex	ART Experienced	Duration on DTG-ART (yrs)	Previous ART regimens (~ yrs)	HIV-VL <6m before DTG-ART (cp/ml)	Current HIV - VL (cp/mL)	HIV-1 Subtype	INSTI DRMs	DTG resistance interpretation	Reverse Transcriptase DRMs (*TAMS)
1	60	M	Yes	4	AZT/3TC/EFV (9)	88,027	1,030	A1	Major: E138K Acc: None	Potential low-level	NRTI: M184V NNRTI: A98G, K103N, P225PH
2	69	F	Yes	3.1	TDF/3TC/EFV (7) AZT/3TC/LPV/r (4)	3,079	5,726	A1	Major: E138K, G140A, Q148KN Acc: S230R	High-level	NRTI: D67G*, S68G, K70R, M184V, T215F*, K219Q* NNRTI: K101H, V106I, Y188L
3	60	M	Yes	3.3	TDF/3TC/EFV (4)	202,000	93,486	A1	Major: E138K, G140A, S147G, Q148R Acc: T97A	High-level	NRTI: D67HN*, K70R, V75VM, M184V, T215FI*, K219E* NNRTI: K103N, V108I
4	48	M	Yes	3.3	D4T/3TC/NVP (8) TDF/3TC/NVP (2) TDF/3TC/EFV (2)	Not Done	2,054	A1	Major: E138K, G140A, S147G, Q148R Acc: None	High-level	NRTI: M41L*, M184V, T215Y* NNRTI: A98G, K101E, G190A
5	45	F	Yes	2.3	TDF/3TC/EFV (7)	54,135	502	A1	Major: T66I, G118R, E138K Acc: L74M	High-level	NRTI:M41L*, S68G, M184V, L210LW*,T215F* NNRTI: A98G, K103N, E138A, K238T
6	30	F	Yes	1.8	TDF/3TC/EFV (2)	194,000	88,926	C	Major: T66I, G118R, E138K Acc: G149A	High-level	NRTI: K65R, S68N, Y115F, M184V NNRTI: K101E, V106M, E138A, V179IT, G190A
7	37	F	Yes	3.1	D4T/3TC/NVP (5) TDF/3TC/LPV/r (5) TDF/3TC/ATV/r (3)	Not Done	2,012	A1	Major: E138EK S147G, N155H Acc: L74LFS, E157Q	Intermediate	NRTI: S68G, M184V, T215F* NNRTI: A98G, K103N
8	42	F	No	1.4	None	-	296	A1	Major: R263K Acc: E157Q	Intermediate	NRTI: K70Q, M184V

Abbreviations: AZT-Azidothymidine; 3TC-Lamivudine; EFV- efavirenz; TDF- Tenofovir Disoproxil Fumarate; LPV/r- Lopinavir/Ritonavir; D4T-Stavudine; NVP-Nevirapine; EFV-Efavirenz; ATV/r- Atazanavir/Ritonavir; NRTI- Nucleoside Reverse Transcriptase Inhibitor; NNRTI- Non-Nucleoside Reverse Transcriptase Inhibitor; Acc- Accessory; TAMS- Thymidine Analogue Mutations

RESULTS

- **ART-naïve vs ART-experienced (Table 1):**
  - No difference in age and gender, and approximately 70% had suppressed HIV-VL (≤ 200 cp/mL) on DTG-ART in the two groups.
  - ART naïve PLHIV had shorter duration on DTG-ART (median 1.5 yrs), compared to ART-experienced (median 2.1yrs).
- **Genotyping and Resistance Mutations (Table 2):**
  - **ART-experienced (DTG-ART as 2nd or 3rd line)**: 7 of 31 (23%) had HIV-1 integrase strand transfer inhibitor (INSTI) resistance mutations and 5 individuals had predicted high-level resistance to DTG.
  - **ART-naïve (DTG-ART as 1st line):** 1 of 12 (8%) had INSTI DRMs predicted to confer intermediate resistance to DTG.
  - All 8 with INSTI mutations harbored additional NRTI and/or NNRTI mutations.

CONCLUSIONS

- **Frequency of INSTI HIVDR was high (22.6%) in viremic ART-experienced PLHIV on DTG-based ART used as 2nd or 3rd line and lower (8.3%) in ART-naïve adults using DTG for 1st-line, suggesting the risk of developing DTG DRMs may be higher in those with a background of pre-existing mutations.**
- This study emphasizes the importance of viral load and HIVDR monitoring in PLHIV on DTG-based ART.
- **Limitations**: A small sample size and use of a convenience sample limits the determination of DTG DRMs in viremic PLHIV on a population level.

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