Evaluation of HIV-1 Dolutegravir Resistance Patterns and Associated Clinical Factors in Cameroon

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BACKGROUND

- In low- and middle-income countries (LMICs), varying rates of emerging resistance to integrase inhibitors (INI) have been reported, but knowledge on INI mutational patterns and associated clinical factors remains limited.
- We herein evaluated INI-resistance and associated clinical factors among people with HIV (PWH) who failed dolutegravir (DTG)-based antiretroviral therapy (ART) in Cameroon, a country with a broad non-B HIV-1 diversity.

METHODS

- A cross-sectional study among PWH who failed (viral load [VL] ≥1000 copies/ml) DTG-containing regimens (without previous INI-exposure) from January 2020 to May 2025.
- Genotypic resistance test (GRT) including integrase was performed for all clinical samples.
- HIV Drug Resistance was interpreted using Stanford HIVdb.v.9.8 and phylogeny was performed for subtyping;
- Chi square/Fisher's and T Student tests were used to evaluate factors associated with resistance.

RESULTS

Population characteristics

- Overall, 65 PWH failing DTG-ART were included, with 50 still under DTG at the time of GRT (Group A), and 15 empirically transitioned to non-DTG-ART. Table 1 summarizes population characteristics.

Table 1: Socio demographic and clinical characteristics of the study population

Characteristics	Category	All participants, N = 65
Age in years	Median [IQR]	21 [17-44]
Age ranges, n (%)	0-18 years	27 (41.5%)
	≥19 years	38 (58.5%)
Sex, n (%)	Males	32 (49.2%)
	Females	33 (50.8%)
WHO clinical stage at diagnosis, n (%)	I/II	17 (26.2%)
	III/IV	18 (27.7%)
	Unknown	30 (46.2%)
Co-infection, n (%)	Tuberculosis	4 (6.5%)
	Others[a]	5 (7.7%)
	Undocumented	30 (46.2%)
Viral load at GRT (log copies/mL)	Median [IQR]	4.7 [3.8-5.2]
Last CD4 count before GRT (n=30), cells/mm^3	Median [IQR]	316 [200 – 567]
Overall duration on ART, years	Median [IQR]	8.7 [4.9 – 15.1]
Duration on INI-regimens, months	Median [IQR]	20.1 [12.2 – 33.7]
Regimen line at time of DTG failure, n (%)	First regimen	1 (1.5%)
	Second regimen	14 (21.5%)
	Third regimen or more	43 (66.2%)
	Unknown	7 (10.7)
ART-Regimen at the time of GRT	With DTG (A), n (%)	50 (76.9)
	Without DTG (B)[b], n (%)	15 (23.1)
Duration since DTG-withdrawal, months (n=15)	Median [IQR]	21.1 [11.3-34.3]
Adherence, n (%)	Good	21 (32.3)
	Poor	44 (67.7)
Viral clade, n (%)	CRF02_AG	36 (55.4%)
	Non CRF02_AG	29 (44.6%)

[a]Other co-infections: Atypical pneumonia (1), cryptococcal meningitis (1), HPV (1), Pneumocystosis (1), malaria (1). [b]2NRTI+NNRTI (2), 2NRTI+PI/r (13).

- ❖ About 1/3 patients who failed DTG-ART had an integrase resistance mutation
- ❖ Resistance only detected in those with DTG-pressure at the time of genotyping
- ❖ Three key clinical scenarios associated with DTG-resistance
  - ✓ *TB-coinfected individuals co-treated with rifampicin*
  - ✓ *Transition to DTG-ART from NNRTI-based first-line in the course of non-viral suppression*
  - ✓ *Use of DTG in third-line without considering genotypic resistance test for selecting ART-combination.*

Rates of Integrase Resistance

- Overall rate of integrase resistance was 29.2% (19/65).
- Integrase resistance was found exclusively in Group A (19/50 [38.0%] vs 0/15 [0%] in Group B; p=0.003).

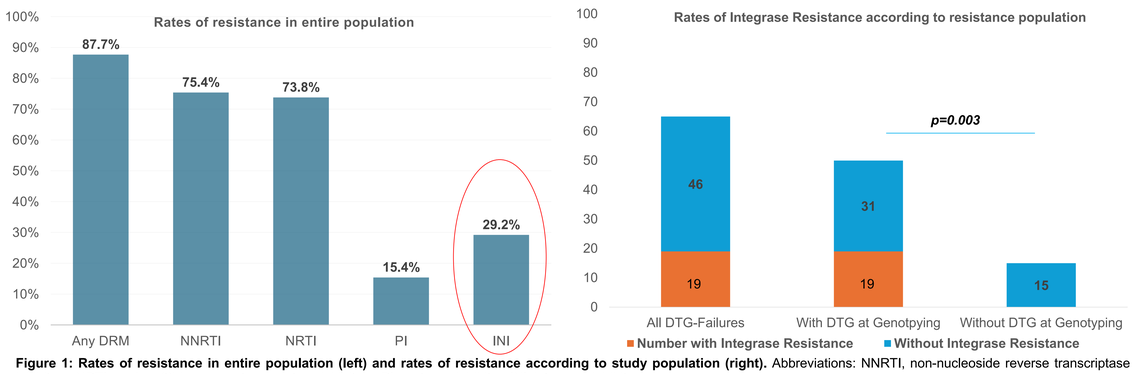


Figure 1: Rates of resistance in entire population (left) and rates of resistance according to study population (right). Abbreviations: NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleos(t)ide reverse transcriptase inhibitors; PI, protease inhibitor; INI, integrase inhibitor.

Determinants of integrase resistance (Group A)

- INI-resistance was higher in adults (≥19 vs <19 years: 58.6% *vs.* 41.3%, p<0.001), and with longer exposure to INI (34 [18-48] *vs.* 20 [11-33] months, p=0.046).
- Four PWH treated with rifampicin-containing regimens for tuberculosis all (100%) had INI-resistance.
- Individuals with INI-resistance had a higher rate of NRTI (100.0% *vs.* 58.1%, p<0.001) and NNRTI (94.7% *vs.* 61.3%, p=0.009) resistance, suggesting mono-functional DTG-ART.

Table 2: Linear regression model with outcome "Integrase Major Resistance" in the overall population of 65 individuals who failed dolutegravir (DTG)-based antiretroviral therapy (ART) in Cameroon.

Variable	Coefficient	95% Confidence	Limits	Std Error	F-test	P-value
Age in years (<19/≥19)	-0.237	-0.430	-0.043	0.097	6.009	**0.017**
Duration on INI	0.006	0.000	0.012	0.003	4.334	**0.042**
Adherence (Poor *vs.* Good)	0.058	-0.155	0.270	0.106	0.294	0.590
Coinfection TB (TB *vs.* others and unknown)	0.481	0.110	0.852	0.185	6.756	**0.012**
NRTI Major Resistance (Yes *vs.* No)	0.281	0.060	0.502	0.110	6.503	**0.014**
NNRTI Major Resistance (Yes *vs.* No)	0.173	-0.041	0.387	0.107	2.610	0.112
DTG pressure at time of failure (Yes *vs.* No)	0.275	0.057	0.493	0.109	6.385	**0.014**
Viral clade (Non-CRF02_AG *vs.* CRF02_AG)	0.037	-0.141	0.214	0.088	0.172	0.680

Significant p values are written in bold. Abbreviations: INI, Integrase inhibitors; NRTI, Neucleos(t)ide reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; TB, tuberculosis; DTG, Dolutegravir; GRT, genotypic resistance test.

Patterns of Integrase resistance

- G118R+≥1Resistance mutation (RM) was the most frequent pattern (57.9%), followed by R263K±1RM (26.3%).
- Despite no significant association between subtypes and INI RMs, CRF02_AG appeared more frequent in G118R+≥1RM pattern (n=11, 7 in CRF02_AG), while non-CRF02_AG appeared higher in patterns R263K±1RM (n=5, 4 in non-CRF02_AG).
- Overall, resistance scores appeared higher within AG recombinants as compared to other viral clades.

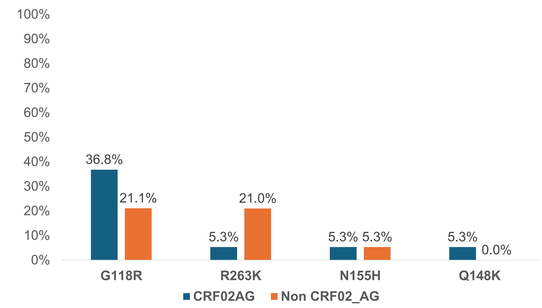


Figure 2: Signature mutational pathways observed with respect to viral clades.

CONCLUSIONS

- Among PWH failing DTG in this real-life setting, integrase resistance rate is consistent, reported in about 1/3 of the population, and higher in adults, with longer DTG-duration, NRTI-resistance and in TB co-treatment with rifampicin.
- Hence, prioritizing GRT-guided ART in these vulnerable PWH and promoting DTG-sparing ART with rifampicin-containing regimens would contribute to mitigating INI-resistance in LMIC.

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PLAIN LANGUAGE SUMMARY

In this real-world setting of Cameroon, a country with a broad non-B HIV-1 diversity, almost one out of three people with HIV who failed regimens containing dolutegravir had resistance to integrase inhibitors. This was more frequent in adults, with longer duration on dolutegravir, with pre-existing NRTI resistance, and in those receiving rifampicin for tuberculosis. Prioritizing genotyping in these vulnerable populations and using dolutegravir-sparing regimens alongside rifampicin could help in reducing emerging integrase resistance in low- and middle- income countries.