HIV Drug Resistance and Viral Outcomes after 2nd-line Antiretroviral Failure in Kenya

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BACKGROUND

- The number of people living with HIV (PLWH) who have failed 1st- and 2nd-line antiretroviral treatment (ART) is increasing in low- and middle-income countries (LMICs).
- Program data on HIV drug resistance and clinical outcomes after 2nd-line failure in LMICs are limited, yet can inform care, particularly with better ART access and options.
- We examined resistance upon 2nd-line failure and subsequent viral outcomes in a large HIV treatment program, the Academic Model Providing Access to Healthcare (AMPATH) in western Kenya.

METHODS

- ***Study design***: retrospective cohort
- ***Setting***: HIV Drug Resistance Clinic at Moi Teaching and Referral Hospital in western Kenya, which served as a regional referral clinic for PLWH with 2nd-line failure and those on 3rd line ART. In this setting, guideline-recommended 1st line was efavirenz- or nevirapine-based; 2nd-line was atazanavir/ritonavir (ATV/r) or lopinavir/ritonavir (LPV/r) based; 3rd line was raltegravir, darunavir/ritonavir, or dolutegravir based, with or without etravirine.
- ***Eligibility criteria***:
  - Enrolled in HIV care at AMPATH
  - Failed 2nd line ART according to Kenya HIV treatment guidelines (i.e., ≥2 consecutive viral loads ≥1000 copies/mL despite adherence interventions)
  - Had a HIV genotype performed during 2nd-line failure and prior to decision on subsequent regimen.
  - Age ≥3 years at the time of genotyping
- ***Analysis***:

Outcomes: Composite outcome of viral non-suppression (≥1000 copies/mL) 3-18 months post-genotyping; loss to follow-up (LTFU, missing the last scheduled visit by >90 days prior to the 18-month anniversary for each patient); and death prior to database closure on March 1, 2022.

Analytic methods:

- The data were summarized using frequencies and proportions for categorical variables and medians and interquartile ranges (IQR) for continuous variables.
- HIVdb v9.0 (hivdb.stanford.edu) used for drug resistance analyses.
- Comparisons between individual characteristics were made using Chi-square and Wilcoxon rank-sum tests.

RESULTS

Characteristics at genotyping

- Of 187 PLWH (54% female; median age 41 years; median 3.5 and 4.1 years on 1st- and 2nd-line), 59% were on lopinavir/ritonavir and 41% on atazanavir/ritonavir-based regimens (Figure 1, Table 1).
- Overall, 171 (91%) had any resistance: 17% mono-, 36% dual-, 38% triple-class; 79% to NRTIs; 81% NNRTIs; and 47% to PIs - 54% of those on atazanavir/ritonavir; 27% on lopinavir/ritonavir (Table 2, Figures 2 and 3).
- Of those 171, 25% had intermediate-high predicted resistance to darunavir/ritonavir (8 upon atazanavir/ritonavir and 10 upon lopinavir/ritonavir failure; p=0.75).

Figure 1. Eligibility flow diagram.

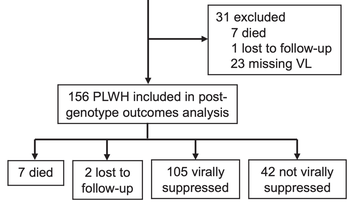


Table 1. Characteristics of PLWH at the time of genotyping.

Characteristic	Total N=187 n (%)
Female	101 (54)
Age, median years (IQR)	41 (27-49)
Age 3-14 years	17 (9)
Age ≥15 years	170 (91)
Year of genotype	
2011-2016	84 (45)
2017-2021	103 (55)
CD4 count at ART initiation, median cells/mm^3 (IQR)	112 (40-182)
Total years on ART, median (IQR)	8.8 (6.7-10.9)
Years on 1st-line ART, median (IQR)	3.5 (2.4-6.1)
Years on 2nd-line ART, median (IQR)	4.1 (2.6-6.0)
NNRTI exposure pre-genotype	
EFV	71 (40)
NVP	149 (83)
EFV and NVP	41 (23)
PI exposure pre-genotype	
ATV/r	76 (41)
LPV/r	143 (77)
ATV/r and LPV/r	32 (17)
PI base at genotype	
ATV/r	76 (41)
LPV/r	111 (59)

Table 2. Genotype results.

Characteristic	Total n=187 n (%)
Subtype (n=83)	
A	67 (81)
C	8 (10)
D	7 (8)
G	1 (1)
Total resistance (Level ≥2/5)	
NRTI total	148 (79)
NNRTI total	151 (81)
PI major total	82 (44)
PI major + accessory total	87 (47)
Resistance category	
None	16 (9)
NRTI only	9 (5)
NNRTI only	22 (12)
PI only	1 (1)
NRTI / NNRTI only	58 (30)
NRTI / PI only	10 (5)
NNRTI / PI only	0 (0)
NRTI / NNRTI / PI	71 (38)
Total resistance (Level ≥2/5)	73 (39)
ATV/r	73 (39)
LPV/r	66 (35)
DRV/r	45 (25)
RPV	126 (67)
ETR	126 (67)
Any resistance to any component of ART regimen at genotyping	146 (78)

Characteristics after genotyping

- Among 156 PLWH included in the post-genotype analysis, the antiretroviral base was not switched for 69 (44%) patients, 16 (10%) switched within 2nd-class (i.e., 2 from ATV/r to LPV/r, and 14 from LPV/r to ATV/r), and 71 (46%) switched to 3rd line.
- The most common 3rd-line antiretroviral bases were DTG (44%; 27/31 patients on DTG were on TDF+3TC+DTG), DTG + DRV/r (35%), and RAL (8.4%).
- The composite outcome occurred in 51 (33%) PLWH overall, comprised of 42 cases of viral non-suppression, 7 deaths, and 2 cases of LTFU (Figure 1).
- Death (1.4% vs. 7.1%, p=0.13) and viral non-suppression (11% vs. 40%, p<0.001) were lower among those who switched to 3rd-line compared to those who did not.

Figure 3. Frequency of HIV-1 drug resistance mutations in 187 PLWH with genotypes following failure of 2nd-line ART.

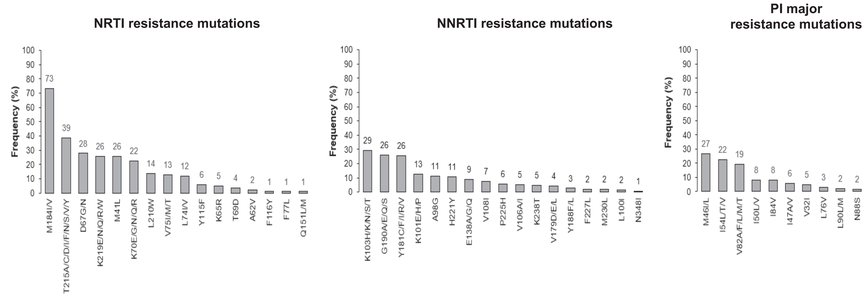
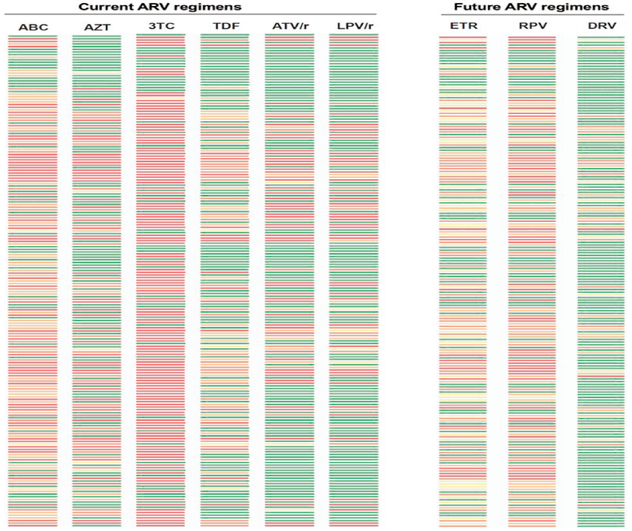


Figure 2. Predicted drug resistance to current and future regimens.

The figure demonstrates detailed information (one row per patient) of one of 5 predicted levels of drug resistance according to Stanford Database scores, to current regimens (left panel) and future regimens (right panel). Resistance levels are color-coded based on the legend on the left of the panels.



ABC, abacavir; AZT, zidovudine; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate; ATV/r, atazanavir/ritonavir; LPV/r, lopinavir/ritonavir; ETR, etravirine; RPV, rilpivirine; DRV, darunavir

DISCUSSION

- PLWH with 2nd-line failure in Kenya exhibited extensive resistance across multiple parameters, highlighting the vulnerability of this population enrolled in routine care in a resource-constrained setting.
- Major PI resistance was high (44%) compared to prior reports and included 25% with predicted intermediate to high DRV/r resistance, a key component of guideline-recommended 3rd-line ART in LMICs.
- Viral non-suppression and death were lower among those who were on 3rd-line ART at the time of the post-genotype outcome compared to those who were not, potentially supporting the early effectiveness of guideline-recommended 3rd-line regimens for this population.
- Future research will determine predictors of post-genotype viral suppression and other adverse outcomes, and assess the real-world impact of national HIV treatment guidelines on the management and outcomes of patients with 2nd-line failure.

Acknowledgements

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