

Favorable Long-term Outcomes of 2nd-line ART Despite Drug-Resistant HIV-1 in Sub-Saharan Africa

PASER-M cohort

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keywords

Drug Resistance

Second-line Antiretroviral Treatment

sub-Saharan Africa

background

- With the expansion of antiretroviral therapy (ART) in resource-limited settings, the number of people with treatment failure and need for 2nd-line regimens will increase.
- We assessed the long-term effectiveness of boosted protease inhibitor (bPI)-based 2nd-line ART in 13 African settings, in patients with and without extensive nucleoside reverse transcriptase inhibitor (NRTI) resistance mutations at the time of regimen switch.
- Additionally, we explored the accumulation of protease resistance mutations.

methodology

- In a prospective observational cohort, HIV-RNA and genotypic resistance testing was performed in adults who switched to bPI-based 2nd-line regimens at 13 clinical sites in Kenya, Nigeria, South Africa, Uganda, Zambia and Zimbabwe.
- Genotypic sensitivity score (GSS) was calculated using the Stanford algorithm.
- Associations between mutations present at the time of switch and virological failure (VF) after 12 or 24 months of ART were assessed using chi-square and Fisher's exact tests using Stata 12.

results

Figure 1 & Table 1

- Of 243 patients who started 2nd-line ART, 54% harbored drug resistant HIV with a GSS < 3, leading to a partially active 2nd-line regimen. After 12 and 24 months, 88% and 79% of patients were retained in care, respectively
- After 12 months, 29 out of 206 (14%) patients with available viral load (VL) had VF, compared to 27 out of 177 (15%) after 24 months (p=0.745).
- Of 29 patients with VF at 12 months, 10 (35%) also had VF at 24 months, 10 (35%) were re-suppressed, and the remainder was lost to follow-up, died or switched to 3rd-line ART.
- A partially active 2nd-line regimen at the time of switch was not significantly associated with VF at 12 or 24 months of follow-up (p=0.586 and p=0.897, respectively).
- At 12 and 24 months, 53% and 75% of patients with genotypic test results harbored drug resistant HIV, respectively.

Table 2

- Protease mutations increased over time and were present in 1 (6%) and 6 (30%; p=0.097) sequences after 12 and 24 months of bPI-based 2nd-line ART.
- There was no accumulation of thymidine analogue mutations (TAMs).
- Protease mutations were M46I (n=5), V82A (n=4), L76V (n=2) and I84V (n=1), and occurred in combination with NRTI mutations in all occasions (p=0.042).
- A partially active regimen at the time of switch was not significantly associated with protease resistance development (p=0.354).

conclusions

- **Favorable virological response to 2nd-line bPI-based ART was maintained over 2 years, despite extensive NRTI resistance at the time of switch.**
- **While still infrequent by month 24, increasing protease resistance over time may become a barrier to successful long-term bPI-based ART in resource-limited settings.**

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figure 1. Participants on second-line antiretroviral therapy after first-line failure

ART = antiretroviral therapy; LTFU = lost-to-follow-up; GSS = genotypic sensitivity score, calculated using the Stanford algorithm;
VL = viral load; VF = virological failure (viral load > 400 cps/ml)

	Fully active ART (GSS ≥ 3 or VL< 1000)	**Partially active ART** (GSS < 3)
Baseline **243 participants switched to 2nd-line ART**	109 participants	132 participants
10 (4%) deceased • 5 (2%) transfer out • 15 (6%) LTFU		
12 months **213 (88%) participants remained in care, on 2nd-line ART**	14 (16%) VF	15 (13%) VF
Cumulative: • 14 (6%) deceased • 9 (4%) transfer out • 24 (10%) LTFU • 4 (2%) switch to 3rd-line		
24 months **192 (79%) participants remained in care, on 2nd-line ART**	11 (15%) VF	16 (15%) VF

table 1. Population characteristics at second-line start, stratified by regimen activity

	Overall (n=241)	**% or IQR**	**Fully active ART (n=109)**	**% or IQR**	**Partially active ART (n=132)**	**% or IQR**	**P-value[a]**
Sex (female)	121	50.2	58	53.2	63	47.7	0.397
Median age (years)	40	38.8-41.1	39.9	38.3-41.6	40	38.4-41.6	0.979
WHO clinical stage							0.169
Stage 1 and 2	126	52.3	64	58.7	62	47.0	
Stage 3	76	31.5	31	28.4	45	34.1	
Stage 4	39	16.2	14	12.8	25	18.9	
Median CD4 cell count (cells/mm3)[b]	126	134-165	147	150-203	109	111-146	0.005
Median HIV-RNA (log_{10} copies/ml)	4.2	3.8-4.2	3.26	3.9-3.5	4.67	4.5-4.8	<0.001
Median duration of first-line regimen (months)[c]	15.4	1.5-26.3	14.1	3.2-23.0	16.1	1.5-28.6	0.045
ART regimen at failure[d]							<0.001
ZDV, 3TC, NNRTI	107	45.0	44	41.1	63	48.1	
D4T, 3TC, NNRTI	97	40.8	57	53.3	40	30.5	
TDF, FTC, NNRTI	24	10.1	3	2.8	21	16.0	
NNRTI-based, other	6	2.5	3	2.8	3	2.3	
Triple NRTI	4	1.7	0	0.0	4	3.1	
Second-line ART regimen							0.031
LPV/r + 2NRTI, incl 3TC/FTC	141	58.5	54	49.5	87	65.9	
LPV/r + 2NRTI, other	64	26.6	38	34.9	26	19.7	
LPV/r + 3NRTI	32	13.3	16	14.7	16	12.1	
Non prefered PI, double PI	4	1.7	1	0.9	3	3.3	
Criteria used for switch[e]							0.001
Clinico-immunological only	57	23.7	37	33.9	20	15.2	
Targeted viral load testing	184	76.4	72	66.6	112	84.9	
Country of origin							0.015
Uganda	78	32.4	27	24.8	51	38.6	
South Africa	61	25.3	34	31.2	27	20.5	
Kenya	36	14.9	22	20.2	14	10.6	
Nigeria	32	13.3	16	14.7	16	12.1	
Zambia	24	10.0	8	7.4	16	12.1	
Zimbabwe	10	4.2	2	1.8	8	6.1	

IQR, interquartile range; ART, antiretroviral treatment; ZDV, zidovudine; 3TC, lamivudine; D4T, stavudine; TDF, tenofovir; FTC, emtricitabine; LPV/r, lopinavir boosted with ritonavir, NNRTI / NRTI, non-/nucleoside reverse transcriptase inhibitor

[a] Categorical data were compared using the chi-square test; continuous were compared using the Wilcoxon rank-sum test.
[b] 238 observations.
[c] 236 observations.
[d] 238 observations.
[e] Clinico-immunological criteria for switch was defined as WHO clinical staging or CD4 counts only. Targeted viral load testing was defined as ART failure based on clinical and immunological information, confirmed with an HIV-RNA test.

table 2. HIV-1 drug resistance outcomes at baseline, 12 and 24 months

	Baseline		**12 months**		**24 months**	
HIV RNA results available	241		206		177	
Genotype resistance test results available	189		17		20	
Any drug resistance	164	87%	9	53%	15	75%
Median no of mutations/sequence [IQR]	4 [3-6]		1 [0-4]		3 [1-5]	
PI mutations	4	2%	1	6%	6	30%
NRTI mutations	158	84%	7	41%	12	60%
NNRTI mutations	156	83%	8	47%	10	50%
NRTI & NNRTI mutations	150	79%	6	35%	7	35%
NRTI & PI mutations	3	2%	1	6%	6	30%
NRTI & NNRTI & PI mutations	3	2%	1	6%	3	15%
Any thymidine analogue mutation (TAM)	98	52%	4	24%	8	40%
>=2 TAMs	69	37%	3	18%	6	30%
>=3 TAMs	43	23%	1	6%	3	15%
TAM only	0	0%	0	0%	1	5%
M184V only	1	1%	0	0%	0	0%
Any TAM & M184V/I	95	50%	3	18%	6	30%
>=2 NNRTI	74	39%	4	24%	4	20%
>=3 NNRTI	8	4%	2	12%	2	10%
PI mutations	**Baseline**		**12 months**		**24 months**	
M46I/L	1	1%	1	6%	5	25%
M54L	1	1%	0	0%	0	0%
Q58E	1	1%	0	0%	0	0%
L76V	0	0%	0	0%	2	10%
V82A	0	0%	1	6%	4	20%
I84V	1	1%	0	0%	1	5%

figure 2. PASER sites

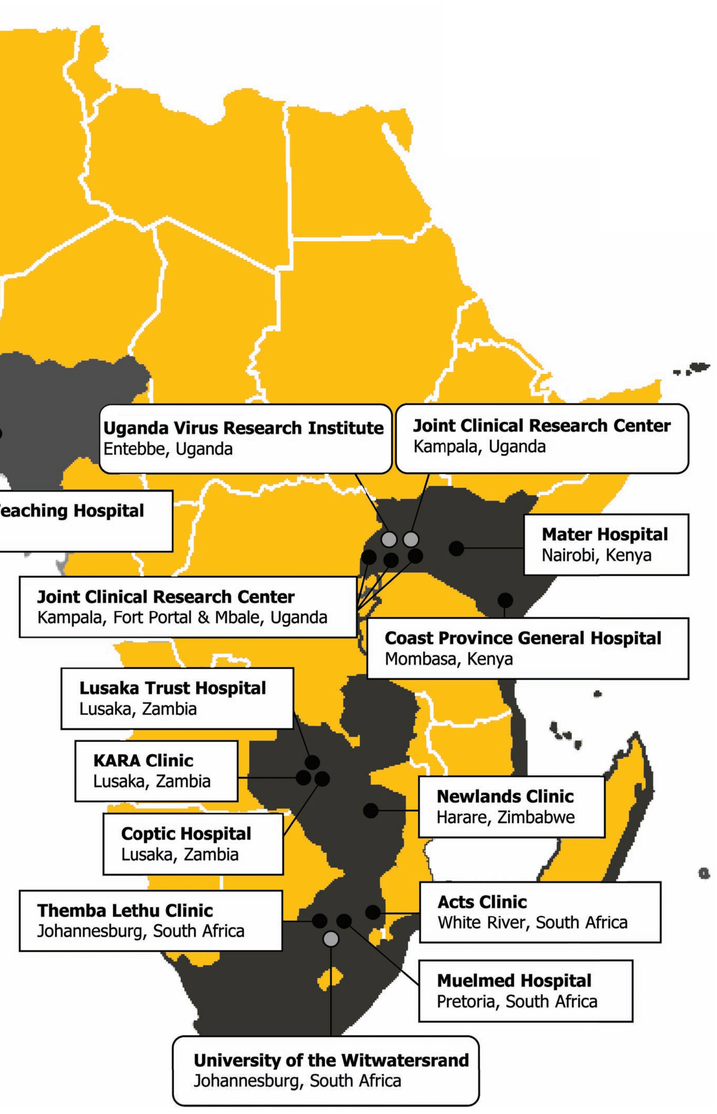
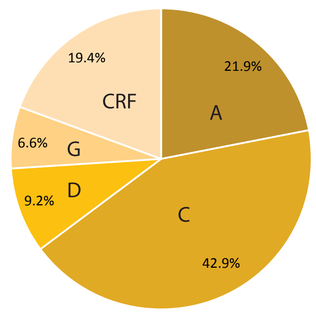


figure 3. HIV-1 Subtype

Determined using the Scueal algorithm



CRF = circulating recobinant form

affiliations

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K. Antiretroviral therapy: observational studies *Poster Session* **Number: P-K4** *Poster Category*