

Baseline HIV-1 drug resistance in Lusaka, Zambia. Preliminary results of the “PharmAccess African Studies to Evaluate Resistance” (PASER) cohort study

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Background

- The development of HIV-1 drug resistance (HIVDR) is a major challenge for the continued effectiveness of antiretroviral therapy (HAART). In resource-limited settings sub-optimal treatment conditions may result in exacerbated virological failure and subsequent emergence of HIVDR. The transmission of resistant viruses might compromise the future success of current first-line regimens.
- In Zambia, where HAART scale-up began in 2004, data on HIVDR transmission is limited.
- The objective of this preliminary analysis was to assess the extent and clinical impact of baseline HIVDR among adults accessing first-line HAART in Lusaka, Zambia.

Methods

- Baseline data from the “PASER-Monitoring” prospective cohort were analyzed. Study participants were chronically HIV-1 infected adults (≥ 18 yrs), who were eligible to initiate first-line HAART at 3 non-government HIV treatment centers in Lusaka, Zambia.
- Population-based nucleotide sequence analysis of the HIV-1 pol gene was performed on plasma (in-house assay). HIVDR mutations were designated using the International AIDS Society (IAS)–USA 2007 mutation list. HIV-1 subtypes were assessed using the REGA HIV-1 subtyping tool (v2.0).
- Response to therapy was determined by using the Stanford genotypic HIVDR interpretation algorithm (V4.3.6).

Results

- To date, 260 of 533 sequence results were available (Tables 2 and 3). HIV-1 subtype C was the predominant subtype (98%).
- Patients characteristics (Tables 1).

Table 1. Patient characteristics (n=533)

	Total ¹	ARV naive	ARV experienced ²
Patients – no. (%)	533	510 (96)	23 (4)
Age (years) – mean (SD)	37.9 (9.3)	38.0 (9.4)	35.5 (8.2)
Female sex – no. (%)	293 (55)	276 (54)	17 (74)
WHO clinical stage III/IV – no. (%)	300 (57)	285 (56)	15 (65)
CD4 count (cells/mm³) – median (IQR)	134 (73-203)	133 (68-198)	147 (83-212)
Initial HAART regimen – no. (%)			
TDF+FTC+EFV	260 (49)	252 (50)	8 (35)
d4T +3TC+NVP	78 (15)	76 (15)	2 (9)
ZDV+3TC+NVP	68 (13)	59 (12)	9 (39)
ABC+3TC+EFV	50 (9)	49 (10)	1 (4)
TDF+FTC+NVP	37 (7)	37 (7)	0 (0)
Other	40 (7)	37 (7)	3 (13)

ARV, antiretroviral drug; IQR, interquartile range; TDF, tenofovir; FTC, emtricitabine; EFV, efavirenz; 3TC, lamivudine; d4T, stavudine; ABC, abacavir ¹ Participants were recruited from 3 sizeable, free ART programs (1 NGO clinic, 1 mission hospital, and 1 private hospital) in Lusaka, Zambia ² Includes: previous HAART (14), single-dose NVP for pMTCT (3), ARVs unspecified (6), and unknown ARV history (5)

Conclusions

- Preliminary results demonstrated HIVDR mutations in 5.4% of chronically infected, ARV naive Zambian adults. HIVDR was generally limited to a single drug class, mostly NNRTIs (4.1%). At present, the standard first-line drug regimens seem to be effective for the large majority of patients.
- The initial response to the standard NNRTI-based therapy in Zambia may be compromised in the participants with baseline HIVDR
- The study design did not permit the accurate assessment of the current population prevalence of HIVDR transmission.
- Longitudinal studies will provide data on the clinical and HIVDR implications of TDF+FTC+EFV as the preferred first-line regimen in subtype C endemic Zambia.
- The PASER program aims at building capacity for the monitoring and surveillance of HIVDR in Africa by creating a network of clinics, laboratories and research centers.

Table 2. Major HIVDR mutations frequencies

	Total		ARV naive		ARV experienced	
	Number	% (CI)	Number	% (CI)	Number	% (CI)
Patients	260		242	93	18	7
Any mutation	16	6.2 (3.8-9.8)	13	5.4 (3.2-9.0)	3	16.7 (5.8-39.2)
NRTI-related					0	0
Any	2	0.8 (0.2-2.8)	2	0.8 (0.2-3.0)	0	0
K65R	1	0.4 (0.1-2.1)	1	0.4 (0.1-2.3)	0	0
M184V	1	0.4 (0.1-2.1)	1	0.4 (0.1-2.3)	0	0
NNRTI-related					0	0
Any	13	5.0 (2.9-8.4)	10	4.1 (2.3-7.4)	3	16.7 (5.8-39.2)
L100I	2	0.8 (0.2-2.8)	2	0.8 (0.2-3.0)	0	0
K103N	3	1.2 (0.4-3.3)	3	1.2 (0.4-3.6)	0	0
V106M	1	0.4 (0.1-2.1)	1	0.4 (0.1-2.3)	0	0
V108I	2	0.8 (0.2-2.8)	2	0.8 (0.2-3.0)	0	0
Y181C	5	1.9 (0.8-4.4)	3	1.2 (0.4-3.6)	2	11.1 (3.1-32.8)
G190S	1	0.4 (0.1-2.1)	1	0.4 (0.1-2.3)	0	0
G190A	2	0.8 (0.2-2.8)	1	0.4 (0.1-2.3)	1	5.6 (1.0-25.8)
PI-related						
Any	3	1.2 (0.4-3.3)	3	1.2 (0.4-3.6)	0	0
I50L	1	0.4 (0.1-2.1)	1	0.4 (0.1-2.3)	0	0
L90M	2	0.8 (0.2-2.8)	2	0.8 (0.2-3.0)	0	0
Multiclass (≥ 2 drug classes)						
NRTI+NNRTI	2	0.8 (0.2-2.8)	2	0.8 (0.2-3.0)	0	0

ARV, antiretroviral drug; CI, 95% confidence interval; NRTI, nucleos(t)ide reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors

Table 3. Patients (n=16) who had ≥ 1 major HIVDR mutations, with the predicted drug susceptibility and their actual initial HAART regimen.

	Mutations			Previous ARV (yr)	Predicted reduced susceptibility to ARV drugs ¹			Initial HAART regimen
	NRTI	NNRTI	PI		NRTI	PI	NNRTI	
1		Y181C		ZDV+3TC+NVP ('05-'06)			NVP (R); EFV (L)	d4T+3TC+EFV
2		K103N		None			NVP, EFV (R)	ABC+3TC+EFV
3		Y181C		ZDV+3TC+NVP ('06)			NVP (R); EFV (L)	d4T+3TC+EFV
4		L100I		None			NVP, EFV (I)	TDF+FTC+EFV
5	K65R	V108I, Y181C		None	d4T (R); ABC, ddI, FTC, 3TC, TDF (I)		NVP (R), EFV (I)	ABC+3TC+EFV
6		G190A		d4T+3TC+NVP ('05-'06)			NVP (R); EFV (I)	TDF+FTC+EFV
7		K103N		None			NVP, EFV (R)	d4T+3TC+EFV
8			I50L	None		ATV (I)		TDF+FTC+EFV
9		V108I		None			NVP, EFV (L)	3TC+d4T+NVP
10			L90M	None		SQV, NFV (I); IDV, FPV, ATV (L)		3TC+d4T+NVP
11			L90M	None		SQV, NFV (I); IDV, FPV, ATV (L); LPV (PL)		3TC+d4T+NVP
12		G190S		None			NVP, EFV (R)	3TC+d4T+EFV
13		K103N, Y181C		None			NVP, EFV (R)	3TC+d4T+NVP
14	M184V	V106M		None	3TC, FTC (R); ABC (PL)		NVP, EFV (R)	3TC+d4T+NVP
15		L100I		None			NVP, EFV (I)	3TC+d4T+NVP
16		Y181C, G190A		None			NVP, EFV (R)	3TC+d4T+NVP

¹ Susceptibility was predicted using the Stanford resistance interpretation algorithm (V4.3.6): high-level resistance (R), intermediate resistance (I), low-level resistance (L), potential low-level resistance (PL); NRTIs (7): abacavir (ABC), didanosine (ddI), emtricitabine (FTC), lamivudine (3TC), stavudine (d4T), tenofovir (TDF) and zidovudine (ZDV). NNRTIs (2): efavirenz (EFV) and nevirapine (NVP). PIs (8): atazanavir (ATV), fosamprenavir (FPV), indinavir (IDV), lopinavir (LPV), saquinavir/r (SQV), tipranavir (TPV), nelfinavir (NFV) and darunavir (DRV)

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