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Does tenofovir-containing first-line ART mitigate the impact of pretreatment NNRTI drug resistance?

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Dear Editor,

In an HIV treatment-as-prevention trial in South Africa, Durache et al[1] report the remarkable finding that the presence of NNRTI-associated pre-treatment drug-resistance (PDR) did not impair virological response to fixed-dose tenofovir/emtricitabine/efavirenz (Atripla). This is an important contrast with most past studies that found that NNRTI-associated PDR was associated with a 2-3-fold increased risk of virological failure (VF)[2–9], although most patients in those studies received a thymidine analogue backbone (zidovudine/stavudine), with efavirenz or nevirapine.[2,3] The authors attributed their finding to the better potency of efavirenz compared to nevirapine, and an Editorial Comment added the advantage of the similar half-lives of the Atripla components, making it less likely for resistance to emerge during missed doses.[10]

In our previous analysis in the Pan-African Studies to Evaluate Resistance (PASER-M) cohort, we reported that patients with NNRTI-PDR had a >2-fold increased risk of VF, compared to patients with susceptible virus[4,7]. Based on the hypothesis by Durache et al, we extended this to a stratified analysis by type of first-line regimen. We defined PDR as (1) NNRTI, NRTI or dual-class NNRTI+NRTI resistance, based on 2017-IAS-USA mutation list; (2) Stanford genotype susceptibility scores (GSS; v8.7) <3 of the prescribed first-line regimen. We defined VF as a single viral-load (VL) ≥50, 400 or 1000 cps/ml measured at month 12. We assessed the association between PDR and VF using logistic regression, while adjusting for key confounders.

Of 2,737 participants initiating first-line ART, 1,941 had data on PDR and 12 month VL. Median age was 37.0 years (IQR31.7-43.1), 59.8% were women, and 56.4% had an overall mean VAS adherence of ≥95%. Initial regimens contained tenofovir+lamivudine/emtricitabine (xtc) (33%), with efavirenz (27.3%) or nevirapine (5.7%), or a non-tenofovir, thymidine analogue backbone+xtc (67%), with efavirenz (29.8%) or nevirapine (37.1%). 1838 (94.7%) patients had no PDR, 79 (4.1%) had NNRTI-PDR only, 44 (2.3%) had NRTI-PDR and 24 (1.2%) had dual-class NNRTI+NRTI-PDR. 84 (4.4%) patients initiated a first-line regimen with GSS<3. VF was present in 335 (17.3%), 199 (10.3%) and 172 (8.9%) participants at VL≥50, 400 and 1000 cps/ml thresholds, respectively.

Participants who had PDR defined as GSS<3, NNRTI only, or dual-class NNRTI+NRTI who received non-tenofovir/xtc with efavirenz or nevirapine, had an increased risk of VF, compared to those without PDR. However, this risk was not increased for participants who received tenofovir/xtc/efavirenz, whereas there was a borderline association for participants who received tenofovir/xtc/nevirapine (Table 1). Participants with NNRTI-PDR only who received a tenofovir-

containing regimen had an increased risk of VF at the VL≥1000 cps/ml threshold (with borderline statistical significance p=0.073), and the risk was not increased at the ≥50 and ≥400 cps/ml thresholds.

In conclusion, our analysis corroborates the finding that NNRTI-PDR may impact less on tenofovir/xtc/efavirenz than on thymidine analogue-based regimens especially with nevirapine. Nonetheless, it remains difficult to disentangle the possible beneficial effects of tenofovir, efavirenz, and fixed-dose combinations with similar drug half-lives. Given that 2 other studies have produced conflicting data2,3, it is premature to argue that Atripla is equally efficacious for patients with or without NNRTI-PDR.

Competing interests

All authors declare that they have no conflict of interest.

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Authors' contributions

TFRW is the PASER principal investigator. RLH, TFRW and RP conceived the study. SCI perfomed the statistical analysis. SCI and RLH drafted the manuscript. All authors provided valuable input to interpretation of the data and critically reviewed the paper for important intellectual content. All authors reviewed and approved the final version of the manuscript.

References

1. Derache, A. *et al.* Impact of next generation sequencing defined HIV pre-treatment drug resistance on virological outcomes in the ANRS 12249 treatment as prevention trial. *Clin. Infect. Dis.* (2018). doi:10.1093/cid/ciy881

2. Kantor, R. *et al.* Pretreatment HIV Drug Resistance and HIV-1 Subtype C Are Independently Associated With Virologic Failure: Results From the Multinational PEARLS (ACTG A5175) Clinical Trial. *Clin. Infect. Dis.* **60,** 1541–1549 (2015).

3. Ávila-Ríos, S. *et al.* Pretreatment HIV-drug resistance in Mexico and its impact on the effectiveness of first-line antiretroviral therapy: a nationally representative 2015 WHO survey. *Lancet HIV* **3,** e579–e591 (2016).

4. Boender, T. S. *et al.* Pretreatment HIV drug resistance increases regimen switches in sub-Saharan Africa. *Clin. Infect. Dis.* **61,** 1749–1758 (2015).

5. Chung, M. H. *et al.* Oligonucleotide Ligation Assay Detects HIV Drug Resistance Associated with Virologic Failure among Antiretroviral-Naive Adults in Kenya. *J Acquir Immune Defic Syndr* (2014). at <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=25140907>

6. Cozzi-Lepri, A. *et al.* Low-frequency drug-resistant HIV-1 and risk of virological failure to first-line NNRTI-based ART: A multicohort European case-control study using centralized ultrasensitive 454 pyrosequencing. *J. Antimicrob. Chemother.* **70,** 930–940 (2015).

7. Hamers, R. L. *et al.* Effect of pretreatment HIV-1 drug resistance on immunological, virological, and drug-resistance outcomes of first-line antiretroviral treatment in sub-Saharan Africa: a multicentre cohort study. *Lancet Infect Dis* **12,** 307–317 (2012).

8. Kityo, C. *et al.* Pretreatment HIV drug resistance results in virological failure and accumulation of additional resistance mutations in Ugandan children. *J. Antimicrob. Chemother.* (2017). doi:10.1093/jac/dkx188

9. Wittkop, L. *et al.* Effect of transmitted drug resistance on virological and immunological response to initial combination antiretroviral therapy for HIV (EuroCoord-CHAIN joint

project): A European multicohort study. *Lancet Infect. Dis.* **11,** 363–371 (2011).

10. Shafer, R. W. & Frenkel, L. M. The clinical implications of pretreatment drug resistance -- a moving target. *Clin. Infect. Dis.* (2018). doi:10.1093/cid/ciy895

Table

Table 1: Effect of pre-treatment drug resistance on risk of virological failure up to 12 months of ART

Characteristic	N	No. of events	aOR (95%CI)	P-value	No. of events	aOR (95%CI)	P-value	No. of events	aOR (95%CI)	P-value
		VF≥50 cps/ml			VF≥400 cps/ml			VF≥1000 cps/ml		
TDF-containing ART	641	109			58			50		
GSS <3	30	7	1.56 (0.35-6.90)	0.560	5	2.31(0.36-14.73)	0.377	5	2.94 (0.56-15.35)	0.200
IAS NNRTI	31	8	1.82 (0.43-7.66)	0.412	6	2.91(0.56-15.15)	0.205	6	**3.76 (0.88-16.02)**	**0.073**
IAS NRTI	21	4	0.87 (0.29-2.62)	0.799	2	0.89 (0.22-3.36)	0.839	2	1.18 (0.34-4.14)	0.796
IAS NNRTI+NRTI	12	3	1.09 (0.23-5.12)	0.915	2	1.48 (0.35-6.32)	0.595	2	1.97 (0.54-7.22)	0.305
TDF/XTC/EFV	530	81			40			34		
GSS <3	22	4	1.40 (0.22-9.03)	0.725	3	2.81 (0.25-31.50)	0.437	3	3.72 (0.38-36.37)	0.259
IAS NNRTI	23	5	1.75 (0.32-9.43)	0.517	4	3.63 (0.46-28.31)	0.218	4	4.96 (0.70-35.08)	0.109
IAS NRTI	17	3	0.99 (0.20-4.90)	0.989	1	0.74 (0.05-9.90)	0.817	1	1.01 (0.08-12.75)	0.995
IAS NNRTI+NRTI	8	2	1.31 (0.09-18.58)	0.840	1	1.53 (0.72-32.62)	0.786	1	2.05 (0.11-38.95)	0.633
TDF/XTC/NVP	111	28			18			16		
GSS <3	8	3	1.69 (0.81-3.53)	0.160	2	1.68 (0.98-2.88)	0.059	2	**2.62 (1.01-6.75)**	**0.047**
IAS NNRTI	8	3	1.69 (0.81-3.53)	0.160	2	1.68 (0.98-2.88)	0.059	2	**2.62 (1.01-6.75)**	**0.047**
IAS NRTI	4	1	0.91 (0.31-2.67)	0.858	1	1.81 (0.65-5.07)	0.257	1	2.95 (0.70-12.46)	0.142
IAS NNRTI+NRTI	4	1	0.91 (0.31-2.67)	0.858	1	1.81 (0.65-5.07)	0.257	1	2.95 (0.70-12.46)	0.142
Non-TDF-containing ART	1299	226			141			122		
GSS <3	55	26	**4.93 (2.51-9.68)**	**<0.001**	19	**5.25 (2.00-14.07)**	**0.001**	18	**5.74 (2.13-15.51)**	**0.001**
IAS NNRTI	49	26	**6.53 (3.11-13.72)**	**<0.001**	20	**7.24 (3.00-17.43)**	**<0.001**	18	**6.97 (2.76-17.61)**	**<0.001**
IAS NRTI	24	6	1.42 (0.69-2.91)	0.340	4	1.52 (0.43-5.39)	0.515	4	1.78 (0.49-6.42)	0.380
IAS NNRTI+NRTI	13	5	3.04 (0.91-10.13)	0.070	4	**3.83 (1.24-11.87)**	**0.020**	4	**4.32 (1.44-12.94)**	**0.009**
Non-TDF/XTC/EFV	578	88			59			50		
GSS <3	17	7	**5.82 (1.96-17.27)**	**0.002**	6	**6.88 (1.75-27.08)**	**0.006**	5	**5.25 (1.53-17.99)**	**0.008**
IAS NNRTI	17	8	**6.79 (2.62-17.57)**	**<0.001**	6	**8.18 (2.69-24.84)**	**0.006**	5	**4.48 (1.20-16.72)**	**0.026**
IAS NRTI	7	1	0.84 (0.09-8.15)	0.890	1	1.09 (0.15-8.15)	0.930	1	1.17 (0.16-8.26)	0.878
IAS NNRTI+NRTI	3	1	1.78 (0.14-23.35)	0.661	1	1.93 (0.20-18.86)	0.571	1	1.86 (0.20-17.64)	0.590
Non-TDF/XTC/NVP	721	138			82			72		
GSS <3	38	19	**5.36 (1.90-15.11)**	**0.001**	13	**5.60 (1.15-27.29)**	**0.033**	13	**6.61 (1.40-31.34)**	**0.017**
IAS NNRTI	32	18	**7.37 (2.46-22.09)**	**<0.001**	13	**8.07 (1.79-36.29)**	**0.005**	13	**9.56 (2.26-40.51)**	**0.002**
IAS NRTI	17	5	1.78 (0.71-4.46)	0.219	3	1.85(0.43-8.03)	0.411	3	2.12 (0.47-9.65)	0.329
IAS NNRTI+NRTI	10	4	3.48 (0.73-16.54)	0.117	3	**4.81 (1.18-19.66)**	**0.029**	3	**5.47 (1.46-20.53)**	**0.012**

Abbreviations: aOR, adjusted odds ratio; EFV, efavirenz; XTC, lamivudine or emtricitabine; IAS, International Antiviral Society mutation list; GSS, genotypic sensitivity scores; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-NNRTI; NVP, nevirapine;

Odds ratios were adjusted for sex, type of initial NNRTI and NRTI, WHO clinical stage, BMI, calendar year of ART initiation, mean VAS adherence, and prior ARV exposure, pre-ART viral load and CD4 cell count.