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Circulating resistance to first-line HIV drug regimens in sub-Saharan Africa: A sheep in wolf's clothing?

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Pre-treatment HIV drug resistance (PDR) is increasing in sub-Saharan Africa (SSA), driven by increasing resistance to non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs¹. This has led the WHO to recommend that countries with a population prevalence of NNRTIs resistance >10% adopt alternate first-line regimens, or consider pre-therapy drug resistance testing to guide selection of antiretroviral therapy (ART)^{1,2}. In response, many countries in SSA are now rolling out dolutegravir-based first-line ART. These recommendations rely on the theoretical basis that efavirenz (EFV) efficacy is significantly curtailed in the presence of NNRTI resistance and that drug resistance testing prior to initiation of EFV-based ART enables selection of more efficacious regimens, respectively. Yet, for these theories to be true and support guideline changes, various criteria must be met: 1) EFV efficacy must be significantly reduced in the face of circulating NNRTI resistance; 2) PDR must be of sufficient prevalence that testing for it will have population-level effects on viral suppression and 3) pre-treatment drug resistance testing for selection of optimal regimens will improve outcomes. Yet, clinical data in support of these theories are either contradicting or altogether lacking.

In this issue of *Lancet HIV*, Chung and colleagues³ attempt to resolve the latter two of these criteria by evaluating whether using an oligonucleotide assay (OLA) to detect genotypic drug resistance to NNRTIs at codons K103N, Y181C, G190A, and to lamivudine at M184V, could improve virologic suppression after initiation of NNRTI-based ART in Kenya. The investigators randomized 991 participants to either standard of care without pre-ART resistance testing or use of the OLA assay to tailor ART regimen selection. They found no significant difference in virological failure between the OLA-guided therapy arm (8.5%) and the standard of care arm (9.7%) after 12 months on ART. Amongst the 9.4% of individuals with PDR, as defined by the presence of pre-specified OLA-detected mutations, virologic failure was lower in the OLA-guided therapy arm (14%) than the SOC arm (50%). Nonetheless, PDR testing was not found to be beneficial in the overall cohort. A few limitations include the open-label nature of the study and lack of evaluation of the clinical impact of other nucleoside reverse transcriptase inhibitor PDR except the M184V. For example, the presence of the H208Y and T215Y mutations may lead to hyper-susceptibility to NNRTIs⁴

There were two main reasons why pre-treatment resistance testing did not appear to demonstrate improvements in virologic outcomes in this study. First, although HIV drug resistance reduces treatment efficacy, this study reinforces that it by no means abrogates it. Approximately 48% of individuals in the SOC arm with PDR (2% cut-off) achieved virologic suppression at 12 months. Second, PDR was not significantly common to make testing for it to improve outcomes on a population level. Indeed, these results highlight that, unless PDR is exceptionally common, testing for it is unlikely to significantly impact care (Table).

This study will not resolve the ongoing debates about selection of optimal first-line ART regimens in areas with a high prevalence of circulating resistance. It does add to a growing number of studies demonstrating high efficacy with EFV-based ART in such areas. The findings from this study is similar to another in rural South Africa, with high virological suppression (95%), despite the presence of NNRTI PDR (8.8%)⁵. Similarly, in the ADVANCE study, EFV achieved similar suppression rates as dolutegravir as first-line ART, without pre-therapy resistance testing, and notably achieved >95% in the per-protocol analysis⁶. These data stand in contrast to modelling studies, which generally apply lower virologic suppression rates with EFV in the face of NNRTI resistance, and partly informed the WHO guidelines^{7,8}.

In summary, this well-designed randomized study by Chung et al, provides a significant advance for the field by helping to clarify the limited role for PDR testing at the population level in low-resource settings, even in areas with high prevalence of circulating drug resistance. It also adds important data to the debate about optimal first-line regimens in resource-limited settings where programmatic guidelines and relatively limited treatment options drive the vast majority of regimen decision making. Although beyond the scope of this review, additional data on the possible side effects and toxicity of dolutegravir, including neural tube defects⁹ and weight gain⁶, add to the complexity around the optimal choice of first-line regimens in the region. Thus, while dolutegravir maintains many advantages over efavirenz in terms of potency, costs of generic production, and side effect profiles¹⁰ its advantage in terms of management in individuals with drug resistance remains to be fully clarified.

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Table. Case base scenario for number needed to treat for 12 months according to pre-treatment drug resistance (PDR) prevalence observed in OLA (0.0975) and SOC (0.0769) arms in Chung et al. and simulations at different levels of PDR prevalence

	OLA arm			Standard of care arm			
Case base	PDR prevalence 0.0975			PDR prevalence 0.0769			
	N	Virologic failure (VF)	Probability of VF	N	VF	Probability of VF	Absolute diff. in prob. of VF
Total	400	34	0.08500	403	39	0.09677	0.01177
Wild type	361	28	0.07756	372	24	0.06452	
2-9%	4	1	0.25000	5	2	0.40000	
10%+	35	5	0.14286	26	13	0.50000	
PDR	39	6	0.15385	31	15	0.48387	
Simulations	PDR prevalence			PDR prevalence			
	0.10		0.08519	0.10		0.10645	0.02126
	0.15		0.08900	0.15		0.12741	0.03841
	0.20		0.09281	0.20		0.14839	0.05558
	0.25		0.09663	0.25		0.16935	0.07272
	0.30		0.10044	0.30		0.19032	0.08988
							47.0
							26.0
							18.0
							13.8
							11.1

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	0.15		0.08900	0.15		0.12741	0.03841 26.0
	0.20		0.09281	0.20		0.14839	0.05558 18.0
	0.25		0.09663	0.25		0.16935	0.07272 13.8
	0.30		0.10044	0.30		0.19032	0.08988 11.1

Explanatory notes:

Table 2 of the manuscript represents the base case scenario with probability of virologic failure (VF) in the OLA arm being 34/400 (0.085) and in the SOC arm 39/403 (0.097) at a pre-treatment drug resistance (PDR) prevalence of 39/400 (0.0975) and 31/403 (0.0769) respectively. The number needed to treat (reciprocal of the absolute difference in VF) to prevent one case of VF in the OLA arm will be 84.9.

We computed the probability of VF in both arms at different simulations of PDR prevalence as follows:

OLA arm: $\text{PDR prevalence} \times \text{Prob. of VF in those with PDR} + (\text{Wild-type prevalence} \times \text{Prob. of VF in those with wild-type virus})$

SOC arm: $\text{PDR prevalence} \times \text{Prob. of VF in those with PDR} + (\text{wild-type prevalence} \times \text{Prob. of VF in those with wild-type virus})$

We estimated the number needed to treat by the reciprocal of the absolute difference in prob. of VF from both arms.