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High Levels of Pre-Treatment HIV Drug Resistance in Zimbabwe: Is this a Threat to HIV/AIDS Control?

Vinie Kouamou*, Alan M McGregor

Unit of Internal Medicine, Faculty of Medicine and Health Sciences, University of Zimbabwe, Harare, Zimbabwe

*Correspondence should be addressed to Vinie Kouamou; kvinie2005@yahoo.fr

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Zimbabwe is one of the countries in Southern Africa most affected by the Human Immunodeficiency Virus (HIV) epidemic. The country has the third highest HIV prevalence (12.5% among 15-49 years) in the region, with an estimated 1.4 million people living with HIV (PLHIV) to date [1]. New infections (35,000) and AIDS-related deaths (20,000) in all ages were recently (2020) updated [1]. However, Zimbabwe has made enormous strides in scaling up access to HIV testing and treating. Consequently, the progress made towards the Joint United Nations Programme on HIV/AIDS (UNAIDS) 90-90-90 targets set for 2020 has been remarkably successful. Ninety percent of PLHIV were aware of their status, 94% of those diagnosed were on antiretroviral therapy (ART) and 86% of PLHIV on ART were virally suppressed [1]. In many resource-limited settings (RLS) including Zimbabwe; reduced adherence, limited access to viral load (VL) monitoring and HIV drug resistance mutation (DRM) analysis, make managing HIV more difficult. These factors contribute to virologic failure and the emergence of ART resistance [2,3]. Drug resistance is a serious threat to the global scale-up of HIV treatment particularly in many RLS with limited ART treatment options.

Pre-treatment HIV drug resistance (PDR), referring to resistance that is detected among ART-naive people initiating ART or people with previous ART drug exposure initiating or reinitiating first-line ART contributes to increasing rates of virologic failure and further accumulation of HIV DRMs [4-6]. Moderate levels (5%-10%) of HIV DRMs to non-nucleoside reverse transcriptase inhibitors (NNRTI) in ART-naive patients, as specified by the WHO classification [7] have previously been reported in Zimbabwe [8,9]. Similarly, the 2017 WHO report on HIV DRMs, showed that the prevalence of NNRTI resistance has reached a critical level (>10%) in three (Namibia, Uganda and Zimbabwe) of the four African countries which reported data to WHO between 2014-2016 [7]. This observed prevalence was nearly three times higher among people re-initiating first-line ART, reporting previous exposure to ART drugs, than among ART-drug–naive people: 21.1% (95%CI 15.0–28.9) versus 7.8 (6.3–9.6), $p \leq 0.0001$.

In a cross-sectional study conducted between October 2018 and February 2020 among adults (≥ 18 years old) initiating or re-initiating first-line ART at Parirenyatwa Hospital HIV ART treatment clinic, a tertiary level setting, in Harare, Zimbabwe; we showed that among 120 participants enrolled in the study, any PDR was present in 31% (95% CI: 22.5–39.6) and PDR to any NNRTIs and to [efavirenz/nevirapine (EFV/NVP)] was found in 29% and 17%, respectively [10]. These findings provide evidence of a considerable annual rise in PDR in Zimbabwe driven primarily by NNRTI-resistance. As previously reported in the 2017 WHO report; in our study, we also found that PDR to NNRTIs (EFV/NVP) was more than six times higher among people with previous ART exposure than ART-naive people: 63% versus 10%, $p<0.001$. Although limitations of our study included the small sample size and the fact that the results were not representative of PDR at the national level, these findings emphasize the critical need for national ART programmes to improve strategies for the retention of PLHIV on ART, so as to reduce the rate of HIV-infected people who default from care, as they significantly contribute to the increasing PDR prevalence, as shown in this study. A thorough evaluation of previous ART drug history is needed before ART re-initiation.

To address the rising levels of PDR, as per the WHO recommendations [7], as of July 2019, the Zimbabwe National guidelines were revised to include the use of dolutegravir (DTG) as preferred first-line ART for adults and adolescents [11]. The adoption of the low-cost generic formulation [tenofovir disoproxil fumarate (TDF)/ lamivudine/DTG (TLD)] is expected to address the rising

levels of PDR, and may minimize the emergence and transmission of HIV DRMs [12]. However, it is important to bear in mind two critical points that need to be considered carefully so as to avoid exposure to potential functional DTG monotherapy in TLD. The strategies to introduce TLD in the country need to consider;

- The possible effects of prior acquired nucleotide reverse transcriptase inhibitor (NRTI) resistance, specifically K65R and M184V mutations in the TLD regimen.

- The possible effect of NNRTI PDR on the efficacy of DTG among PLHIV initiating or re-initiating on TLD.

Previous studies in Africa demonstrated high rates (>90%) of acquired drug resistance to the HIV reverse transcriptase (NRTI and NNRTI), amongst HIV-infected individuals failing NNRTI-based first-line ART [13-15]. In the TenoRes study, the prevalence of tenofovir resistance was highest in sub-Saharan Africa (57%) [16]. In Zimbabwe, we recently demonstrated high rates of acquired drug resistance (94%) among adolescents and young adults failing NNRTI-based first-line ART [17]. In this study, a total genotypic susceptibility score (number of 'active' drugs in a regimen) of 2 or less risked DTG functional monotherapy in 42% of first-line failures switching to TLD.

Similarly, in a recent systematic review of the genetic mechanisms of DTG resistance, Rhee et al. identified the risk of functional monotherapy, with implications for the use of DTG + 2 NRTIs in NRTI-experienced people in LMICs [18]. This suggests that a fully active NRTI backbone may be needed to sustain effectiveness of first-line DTG-based regimens. Although, to date, no available clinical trial studies have looked into the possible impact of NRTI resistance on the efficacy of DTG in TLD, these reported observations call for caution in the implementation of TLD in many LMICs. Therefore, it is important to reinforce VL monitoring, enhanced adherence counseling and, when possible, genotype resistance testing in RLS, to assess virologic failure among PLHIV switching to TLD. Furthermore, an alternative DTG-based regimen containing zidovudine instead of TDF may well optimize virologic suppression in this population.

The second critical point that needs to be considered, with the introduction of TLD in many LMICs including Zimbabwe, is the effect of NNRTI PDR on the efficacy of DTG among PLHIV initiating or re-initiating first-line ART containing DTG. Previous studies have well documented the contribution of NNRTI PDR to virologic failure among people initiating NNRTI- based regimens [4,19,20]. It is important to note that the most recent (2020) findings from a randomized controlled trial in South Africa (the ADVANCE study) show that, NNRTI resistance before treatment initiation, is significantly associated with failure of a DTG containing first-line regimen [21]. Although the biological and behavioral explanations for these observations were not well defined, this observation is a warning for national programmes and may have multiple public health implications for many LMICs including Zimbabwe, which are switching to DTG-based ART. As we have recently reported, high levels of PDR (31%) and NNRTI (29%) and NNRTI (EFV/NVP; 17%) drug resistance were observed amongst adults initiating or re-initiating first-line ART in Zimbabwe [10]. These people were very likely initiated or re-initiated on a first-line ART regimen containing DTG. However, there is no data yet on the efficacy of DTG in the context of high circulating NNRTI PDR in Zimbabwe. It will be important in the future to assess this effect of NNRTI PDR on the efficacy of DTG in such people.

This observation from the ADVANCE study provides us with important data that the Zimbabwe National ART policy makers need to take into consideration during the switch to first-line DTG-based regimens which include; reinforcing adequate VL monitoring with DTG-based regimens and adherence counselling amongst those failing, and encouraging the implementation of rapid and low-cost genotype resistance testing in the country as we have recently reported [22]. Genotype resistance testing could mitigate switching to functional DTG monotherapy that may further limit ART options in LMICs.

High rates of acquired and PDR, driven mostly by resistance to NNRTIs (EFV and NVP) have been reported in recent studies in Zimbabwe. The introduction of TLD, with a high genetic barrier to resistance in LMICs, may optimize long-term ART treatment success. However, this should be accompanied by frequent VL monitoring to avoid functional DTG monotherapy and further limit ART options in these regions. Rapid and low-cost genotype resistance testing could mitigate switching to potentially ineffective, functional DTG monotherapy.

Dedication

This communication is dedicated to the memory of our late collaborator, co-author and friend David Katzenstein, who died in Harare, Zimbabwe on January 25th, 2021 of Covid-19, with affection, respect and deep gratitude.

Conflict of Interest

The authors have no conflict of interest to declare.

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