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Short Communication

The Transition to Dolutegravir-Based Regimens in the Presence of High-Level Drug Resistance to Nucleotide Reverse Transcriptase Inhibitors: Does It Deserve More Attention?

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Introduction

Due to the increasing availability and major improvements in antiretroviral therapy (ART) over the past decade, survival and quality of life has dramatically improved in people living with HIV (PLHIV) [1-3]. Although ART has delivered remarkable benefits, it has been compromised by the development of HIV drug resistance (HIVDR), due to poor patient adherence and/or inconsistent drug supply [4]. The emergence of HIVDR constitutes one of the challenges to ART success and represents a serious emerging threat to the global scale-up of HIV treatment access. These challenges are more-pronounced in low-and-middle income countries (LMICs) where there is limited access to viral load (VL) testing and genotypic resistance testing is rarely performed [5].

In many LMICs including Zimbabwe, public health-based approaches to ART had been developed to simplify and streamline care using limited therapeutic options. The fixed dose combination of tenofovir disoproxil fumarate (TDF) and lamivudine (3TC) as nucleos(t)ide reverse transcriptase inhibitors (NRTIs), with efavirenz (EFV) as a non-NRTI (NNRTI) had been preferably used in first-line therapy [6]. However, high levels of acquired drug resistance to HIV reverse transcriptase (NRTI and NNRTI) have been described in Africa, amongst PLHIV failing NNRTI-based first-line therapy [7-12]. In the TenoRes study, TDF resistance was found to be highest in sub-Saharan Africa (57%) [13]. In Zimbabwe, high levels of pre-treatment and acquired HIVDR have recently been reported [14-17].

Due to the increasing prevalence of NNRTI associated mutations in naive and experienced individuals, the World Health Organization (WHO) recommended dolutegravir (DTG)-based ART as the preferred first-line regimen in these regions [18]. Recently, DTG has also been recommended by the WHO as a preferred component for second-line therapy [19]. The low-cost, fixed-dose combination of TDF, 3TC and DTG (TLD) has become available in several LMICs [20] and is expected to address the problems of HIVDR in these regions. By 2017, four African countries (Botswana, Kenya, Nigeria and Uganda) had included DTG as first-line ART option in their national guidelines [20]. As of July 2019, the Zimbabwe National ART guidelines had also been revised to include DTG in the preferred first-line ART for adults and adolescents [21]. However, as DTG is being given in combination with 2 NRTIs (TDF and 3TC), it is important to be vigilant about the possible effects of acquired NRTI resistance, specifically K65R (causing high level resistance to TDF) and M184V (causing high level resistance to 3TC) mutations in the TLD regimen. Both of these mutations reduce HIV-1 replication fitness [22].

Previous studies have reported challenges of scaling up DTG-based regimens in sub-Saharan Africa; with high levels of NRTI resistance affecting the potential effectiveness of DTG-based regimens [23-25]. In Zimbabwe, we recently reported high levels of NRTI (71%) and NNRTI (93%) among PLHIV failing a NNRTI-based first-line ART; with M184V and K65R mutations found in 65% and 34% respectively. In our study, only 58% of these participants had a predicted genotypic susceptibility score (corresponding to the number of 'active' drugs in the TLD regimen) of more than 2; suggesting that 42% with a genotypic susceptibility score of 2 or less were at risk for exposure to potential DTG functional monotherapy [23]. Similarly, in Togo, ART switch to a DTG-based regimen after VL failure (VL >1000 copies/ml) or blind switching without prior VL testing to a new DTG-based first line, estimated 31% and 47.6% of patients respectively to be potentially on functional DTG monotherapy [24]. Furthermore, a systematic review of the genetic mechanisms of DTG resistance concluded that the risk of functional monotherapy had implications for the use of DTG plus two NRTIs in NRTI-experienced persons in LMICs where VL monitoring is limited and genotypic resistance testing is not routinely available to guide therapy [26]. All these studies

concluded that clinical trials and/or observational studies would be urgently needed to quantify this risk and better comprehend the consequences of this switch of treatment in LMICs. There has not been clinical data to evaluate whether TLD would be effective in PLHIV with virologic failure on a first-line NNRTI-containing regimen harbouring NRTI resistance such as K65R and M184V. Clinical evidence to support switching PLHIV from TDF/3TC/EFV (TLE) with detectable or unknown VL levels directly to TLD is lacking.

Recently (2021), a large randomized study (NADIA) carried out in Kenya, Uganda and Zimbabwe has found that, DTG was effective in second-line treatment, even in the presence of high-level resistance to NRTIs included in the regimen [27]. Furthermore, the authors reported that, TDF and 3TC could be recycled in second-line treatment even in the presence of high-level resistance to the drugs, without compromising viral suppression when taking either DTG or darunavir/ritonavir [27]. These findings indeed support and cement the public health approach on ART in LMICs, which includes simplified monitoring, sparse VL and no resistance testing. However, it is critical to note that four people in the DTG arm developed resistance i.e. three high-level resistance and one intermediate-level resistance. This high-level DTG resistance found in the NADIA study is a concern and deserves more attention. Hence, more data on the risk of DTG resistance in long term use is needed, in case reduced antiviral pressure due to partial drug resistance might take longer for viral rebound to occur.

Furthermore, with the scale up of DTG in first-line ART in many LMICs, development of HIVDR to integrase strand transfer inhibitors (InSTIs) is likely to occur. Ensuring adequate VL and adherence monitoring should remain a priority as well as active monitoring and surveillance of HIVDR to InSTIs. Although genotypic resistance testing is limited in many resource limited settings [28,29]; low-cost, rapid and simplified point mutation assays previously developed and implemented in many LMICs [30-33] for HIVDR detection may contribute to expanding access to resistance testing for the clinical care of people on DTG-based regimens in these regions.

Conclusion

The adoption of dolutegravir in many LMICs is expected to minimize the emergence and transmission of this HIVDR problem. Although dolutegravir was shown to be effective in the presence of high-level resistance to NRTIs included in the regimen, it is critical to note that, its implementation in LMICs should be accompanied by an accelerated scaling up of access to VL monitoring.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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