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Title: Curbing the impact and rise of HIV drug resistance in low- and middle-income countries: the role of dolutegravir-containing regimens.

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Abstract: To improve virological suppression and address the emerging threat of HIV drug resistance (HIVDR), many low-and middle-income countries (LMIC) are moving away from non-nucleoside reverse transcriptase inhibitors (NNRTI) and transitioning to dolutegravir as part of a more affordable standard first- and second-line antiretroviral therapy (ART). Whereas this transition may blunt the impact of rising NNRTI resistance and yield improved ART outcomes, it also presents new challenges. First, current safety concerns for dolutegravir use in women of child-bearing potential require alternative solutions in face of the high levels of resistance to NNRTIs. Second, pre-existing resistance to the co-administered nucleoside reverse transcriptase inhibitors might reduce effectiveness and durability of dolutegravir, particularly where access to viral load tests to monitor treatment outcomes is limited. Third, there is inadequate information on the genetic correlates of resistance to dolutegravir, particularly in patients infected with HIV-1 non-B subtypes. Finally, clinical management of patients with confirmed virological failure on a dolutegravir-based regimen can pose challenges due to uncertainty of whether dolutegravir resistance has actually developed and switching is needed or whether only interventions to improve adherence (without switching) is sufficient. These considerations should be addressed to consolidate expected gains from widespread introduction of dolutegravir in LMIC.

1 **Viewpoint**

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3 **Curbing the impact and rise of HIV drug resistance in low- and middle-income**  
4 **countries: the role of dolutegravir-containing regimens.**

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**Abstract (word count 199, max 200)**

To improve virological suppression and address the emerging threat of HIV drug resistance (HIVDR), many low-and middle-income countries (LMIC) are moving away from non-nucleoside reverse transcriptase inhibitors (NNRTI) and transitioning to dolutegravir as part of a more affordable standard first- and second-line antiretroviral therapy (ART). Whereas this transition may blunt the impact of rising NNRTI resistance and yield improved ART outcomes, it also presents new challenges. First, current safety concerns for dolutegravir use in women of child-bearing potential require alternative solutions in face of the high levels of resistance to NNRTIs. Second, pre-existing resistance to the co-administered nucleoside reverse transcriptase inhibitors might reduce effectiveness and durability of dolutegravir, particularly where access to viral load tests to monitor treatment outcomes is limited. Third, there is inadequate information on the genetic correlates of resistance to dolutegravir, particularly in patients infected with HIV-1 non-B subtypes. Finally, clinical management of patients with confirmed virological failure on a dolutegravir-based regimen can pose challenges due to uncertainty of whether dolutegravir resistance has actually developed and switching is needed or whether only interventions to improve adherence(without switching) is sufficient. These considerations should be addressed to consolidate expected gains from widespread introduction of dolutegravir in LMIC.

## Introduction

The past decade has witnessed an unprecedented scale-up of access to life-saving antiretroviral treatment (ART) for persons infected with HIV-1, which has dramatically reduced infectiousness and improved health and life expectancy of millions of people.<sup>1</sup> The widely adopted public health approach to ART, recommended by the World Health Organization (WHO), has been largely based on using in first line ART a backbone of two nucleoside reverse transcriptase inhibitors (NRTI) in combination with a companion non-nucleoside reverse transcriptase inhibitor (NNRTI), either efavirenz (EFV) /or nevirapine (NVP). However, evidence is emerging globally that HIV variants resistant to NNRTIs are on the rise in populations initiating ART, so-called pretreatment HIV drug resistance (PDR).<sup>2-5</sup> Recent WHO global report on HIV drug resistance (HIVDR) suggest that in several low-and middle-income countries (LMIC) over 1 in 10 HIV-infected patients initiating ART have PDR to EFV and/or NVP.<sup>5</sup> PDR is associated with poor virological outcomes, impaired immune recovery, reduced durability of NNRTI-based regimens, and increased mortality in both adults and children.<sup>6-10</sup> The rise in PDR has been forecasted to drive a significant increase in mortality, HIV incidence and overall ART programmatic costs, if changes to HIV treatment regimens are not made.<sup>11</sup> To respond to the threat of PDR, in July 2017 WHO issued guidelines recommending the use of a non-NNRTI-based ART regimen in countries with levels of resistance to NNRTI  $\geq 10\%$ .<sup>12</sup>

Since 2014, dolutegravir (DTG), a second-generation strand transfer inhibitor (INSTI), has been increasingly used as part of first-line regimens in high-income settings<sup>13,14</sup> because of its favorable efficacy and toxicity profile. In LMIC, where until recently its use remained restricted due to high costs, a new low-cost generic fixed-dose combination of tenofovir disoproxil fumarate, lamivudine, and DTG 300/300/50 mg ("TLD") has been made available at an affordable price. Since September 2017, 92 LMICs are licensed through the Medicines Patent Pool to obtain TLD at a median price of US \$75 per person per year.<sup>15</sup> This is comparable or even lower than current NNRTI-based ART<sup>15</sup>. Due to this benefits, WHO in July 2018, issued guidelines recommending the use of DTG in first and second-line treatment; this approach also offers an effective public health intervention to respond to the high levels of pretreatment NNRTI resistance observed in LMICs.<sup>16</sup> The US President's Emergency Plan For AIDS Relief (PEPFAR) also initiated accelerated access of TLD in all HIV-infected patients<sup>17</sup> in PEPFAR-supported countries to maximize its benefits and minimize programmatic logistics for provision of multiple drugs.

Despite the optimistic perspectives, there are some notes of caution to heed if DTG would be positioned as the single overall 'solution' to the rise in HIVDR in LMIC. In this Personal View, we aim to discuss the public health opportunities and potential challenges of the expanded use of DTG-based ART in LMIC with an emphasis on HIVDR. To this end, we review available data and knowledge gaps on its resistance profile, in the context of the public health approach to ART, and highlight the reasons for the continuous need for a solid HIVDR surveillance and prevention framework and stringent therapeutic monitoring strategies.

## **Dolutegravir efficacy, safety and tolerability**

Due to its tolerability and low rates of discontinuation, DTG has been shown to have a superior efficacy to efavirenz, atazanavir, and darunavir when used in first-line ART, and is non-inferior to the first generation INSTI raltegravir.<sup>18–22</sup> In addition, DTG is reportedly a more potent second-line therapy compared to ritonavir-boosted lopinavir when used with at least one fully-active NRTI drug<sup>23</sup>. A twice-daily dosage was demonstrated effective in INSTI experienced patients with minimal resistance to DTG<sup>24,25</sup>, indicating its potential for use in salvage therapy. Recently, DTG dual therapy with lamivudine was shown to be a promising strategy when used as maintenance therapy in patients with viral suppression<sup>26</sup>. In addition DTG was non-inferior to triple-drug ART when used in combination with lamivudine as dual-therapy first-line regimen, in antiretroviral-naïve patients with a plasma viral load (VL) of  $\leq 500,000$  cps/ml and without pre-existing HIV resistance.<sup>27</sup> Initial speculations that DTG could be used as mono-therapy were refuted by studies that showed an increased risk of virological failure (VF), combined with the emergence of INSTI-resistance.<sup>28,29</sup> In addition to a high efficacy, DTG has a good tolerability,<sup>30</sup> and a higher genetic barrier to emerging resistance. Moreover, DTG has become increasingly affordable in fixed dose combinations (FDC).<sup>15</sup>

## **Safety concerns potentially limits DTG use in specific populations**

A recent report from Botswana highlighted potential safety concerns related to an increased risk of neural tube defects in infants born to women who were taking DTG at the time of conception.<sup>31</sup> Following this, the recent WHO interim guidelines recommend the use of DTG in women of child bearing potential when a consistent and reliable contraception is assured and indicate EFV as a safe and effective alternative option in first-line ART.<sup>16</sup> In sub-Saharan Africa, the population of women of reproductive age comprise 60-70% of people living with HIV, and access to effective contraception is limited.<sup>32</sup>

Ironically, the 2017 WHO report showed that PDR to NNRTI is typically high in this population, having exceeded a prevalence of 10% in 8 of the 11 countries surveyed, and being nearly two times higher in women than in men.<sup>12</sup> This suggests that alternative regimens may be needed for women, pending further confirmation of observed safety concerns.

In addition to the above, a recent meta-analysis of data from four clinical trials showed significantly high rates of adverse events and treatment discontinuation in patients switched from other regimens to DTG.<sup>33</sup> Overall these findings highlight the need for enhanced pharmacovigilance and the provision of alternative ART, when rolling out DTG in LMICs.

## Limited information on DTG resistance mutation patterns

To date, most patients who accessed DTG are from high-income settings infected with HIV-1 subtype B. In these settings, among treatment-naïve patients only two cases of possible DTG resistance have been reported to date. The first case was a late presenter with high viremia who started on tenofovir, emtricitabine, DTG and experienced viral rebound within two weeks of treatment with a transient Met184Ile RT mutation detected at ~3 weeks, and a Gln148Lys INSTI mutation at 5 weeks.<sup>34</sup> Of note, baseline INSTI resistance testing was not done, and it is possible that the Gln148Lys was already transmitted during infection. Subsequently, the patient maintained viral suppression with an optimized background regimen rilpivirine, tenofovir and emtricitabine. The second case was a patient enrolled in the ACTG5353 study assessing the efficacy of DTG plus 3TC dual combination in treatment-naïve individuals.<sup>35</sup> The patient achieved viral suppression by 4 weeks of treatment, but experienced VF by week 8 with Met184Val RT and Arg263Lys INSTI mutations being detected at 16 weeks.

In treatment-experienced but INSTI-naïve patients, a few additional cases have been reported to experience VF with DTG resistance mutations.<sup>36,37</sup> In particular, the Arg263Lys INSTI mutation has been reported in 4 patients (2 in subtype B and 2 in C), Asn155His INSTI mutation in two patients infected with a non-B subtype virus, Gly118Arg in two patients (1 subtype B and 1 C), and Glu138Glu/Lys and His51His/Tyr in one patient infected with subtype C virus. Patients failing on DTG mono-therapy were shown to further select for the Gln148His/Arg/Lys INSTI mutations accompanied by compensatory mutations leading to intermediate- to high-level DTG resistance.<sup>38</sup>

Among INSTI-experienced patients, the Gln148 mutation together with 2 or more accessory mutations significantly impairs DTG efficacy,<sup>24,39,40</sup> although the use of a twice-daily DTG dosage can significantly improve treatment response in patients with fewer mutations.<sup>24,25</sup>

There is limited information on the patterns of DTG resistance in non-B subtypes, although available data suggest the possibility of HIV-1 subtype influencing the mutational patterns of INSTI resistance.<sup>37,41–44</sup> *In vitro* studies have shown that the Arg263Lys INSTI mutation is mainly selected in viral isolates from subtype B and Gly118Arg in non-B subtypes.<sup>42,45</sup> Selection of Gly118Arg is possibly influenced by the presence of a rare polymorphism with a low genetic barrier<sup>45</sup> which could be particularly common in patients infected with subtype A.<sup>46</sup> This could result in differential sub-type specific DTG-associated resistance prevalence *in vivo*, as has been observed with high prevalence of the Lys65Arg mutation associated with tenofovir resistance in subtype C.<sup>47,48</sup>

## **DTG replacement risks among patients with NRTI resistance**

Resistance to the NRTI backbone is very common among patients with VF on NNRTI-based first-line ART in LMIC. In the TenoRes study, a large systematic review covering 1926 patients in 36 countries globally, 57% have documented tenofovir resistance and of those with tenofovir resistance, 83% have also resistance to emtricitabine and lamivudine.<sup>48</sup> This suggests that the majority of people failing first-line EFV-based ART carries a virus with reduced susceptibilities to both tenofovir and lamivudine. As a consequence, if patients are switched from a first- or second-line regimen to a DTG-based regimen while maintaining the same tenofovir-based NRTI backbone, there is a risk that those patients with VF could be exposed to a functional DTG monotherapy. Recent studies evaluating DTG mono-therapy in maintenance strategies have reported INSTI resistance in 50-82% of patients with VF.<sup>38,49</sup> Therefore, these data support an approach of DTG replacements be performed only when virological suppression is confirmed.

Recent data from the DAWNING study comparing DTG with ritonavir-boosted lopinavir in patients failing first-line NNRTI-based ART demonstrated high efficacy of 84% among patients with less than 2 fully active NRTIs. This suggests adequate residual NRTI activity when at least one NRTI remained unaffected by resistance mutations.<sup>50</sup> Such findings are similar to what has been reported with PI-based regimens.<sup>51</sup> Further analysis however showed a reduced efficacy of 76% for patients maintained on NRTI drugs used in first-line ART compared to 87% for those who were switched to newer NRTIs according to the WHO recommendation.<sup>52</sup> This suggests the need for optimization of the NRTI backbone when DTG is used in second-line as also recommended in the recent WHO guidelines.<sup>16</sup>

To mitigate the risk of DTG resistance, in patients currently on ART with unknown VL who are switched to DTG-based ART while maintaining the same NRTI backbone, PEPFAR recommends that ART programs should closely monitor treatment response using a VL test within 3-6 months of switching.<sup>17,53</sup> In LMIC this approach can be challenging, since many ART programs currently do not provide universal access to routine virological monitoring. As of July 2018, only 50% of the patients on ART in LMIC were estimated to have received at least one VL test in the past year.<sup>54</sup> In another report on 7 African countries, substantial differences were observed with respect to access to VL testing for ART patients: from 91% in Namibia, to 5% in Tanzania.<sup>55</sup> WHO has recommended prudence in doing a blind switch to DTG in the absence of VL testing and the need for close monitoring of treatment outcomes including VL and drug resistance using well-designed cohorts or national representative surveys.<sup>16</sup>

It is worth noting that, even in settings where VL testing would be routinely used, the WHO-recommended VL cut-off of 1,000 copies/ml to trigger a regimen switch could be associated with the risk of accumulation of HIVDR.<sup>38,43,56,57</sup>

While the transition to DTG will re-set the resistance clock, the programmatic challenges in HIV treatment delivery documented in LMIC (e.g. drug stock out, poor

retention, suboptimal adherence, etc.) that are associated with resistance emergence will not disappear in the presence of DTG. Therefore, higher rates of VF and the potential for HIVDR might be expected in LMIC compared to that observed in controlled trial or well-monitored settings.<sup>34–37,58</sup>

Finally, in the absence of individualized resistance testing to optimize selection of the NRTI backbone, it remains unclear how a WHO recommended optimized NRTI backbone may impact on the durability of DTG-based therapy. Further research is clearly needed to monitor the durability of DTG-based ART and resistance patterns across the different subpopulations in LMIC and the impact of NRTI resistance on a DTG-containing regimen.

### **Change to DTG warrants optimal switching strategy**

The WHO switching algorithm currently recommends the use of a confirmed VL>1,000 c/ml to trigger a change in regimen from NNRTI to the more costly ritonavir boosted protease inhibitors (bPI)-based second line ART.<sup>57</sup> Approximately 10-30% of people on NNRTI-based ART have a VL>1,000 c/ml 12 months after ART initiation.<sup>5,59</sup> Among those failures, between 70 to 90% harbor high-level NNRTI resistant variants<sup>5,48</sup>, warranting a need for timely switch to second-line ART if they remain unsuppressed after enhanced adherence intervention. Moreover, the resistance prevalence in patients failing EFV-based ART have prompted considerations around the use of a single VL test to prompt the switch to second line ART.<sup>60</sup> On the contrary data from clinical trials indicate that of the 10-18% of patients who initiated first-line DTG-based ART experiencing VF within 48 weeks of treatment,<sup>18–23</sup> most do not harbor any resistance to either the INSTI or NRTI backbone.<sup>18–23</sup>

This difference in resistance prevalence prompts considerations on the appropriateness of applying the current switching guidelines for managing treatment failure on a NNRTI-containing regimen to patients experiencing VF on a TLD regimen. Therefore, studies will be needed to determine the appropriate switching algorithm to manage patients failing TLD regimen in LMIC settings. A better understanding on the frequency of VF in patients on first-line TLD regimen, on the levels of resistance to the cytosine analogues, tenofovir, and DTG components of the regimen, and on the probability to re-suppress after intensive adherence counseling, will be required to optimize the management of VF in regions where routine genotypic resistance testing is not available.

Where possible and feasible, individualized resistance tests could help to optimize the composition of the NRTI background and help preventing premature and unnecessary switches to more costly PI-based regimens. It is worth noting that countries like Botswana and Brazil have policies recommending the use of individual resistance testing to guide the clinical management of patients with VF on DTG-based regimens.<sup>61</sup>



## **Rational antiretroviral drug sequencing**

Optimal drug sequencing strategies in patients experiencing treatment failure while on DTG are critical, given the limited drug options in many LMIC. The previous WHO-recommended sequencing approach of ART regimens in adults and adolescents included a standard first-line regimen of a preferred NNRTI (EFV) with a dual NRTI-backbone, followed by a second-line regimen of a ritonavir-boosted PI (either atazanavir or lopinavir) with 1 or 2 unused or recycled NRTIs, and followed by third-line regimen of an INSTI combined with ritonavir-boosted darunavir with or without 1 or 2 optimized NRTIs. In the 2018 interim WHO guidelines, the alternative sequencing approach involves the use of a DTG-based first-line regimen, followed by a bPI-based second-line, and ritonavir-boosted darunavir in third-line, with recycled DTG and 1 or 2 NRTIs, preferably optimized based on resistance test.<sup>16</sup> While DTG is likely to have residual activity when recycled with fully active DRV-r in third-line, further research is still warranted to assess the efficacy of this approach.

It is generally expected that the use of DTG in first-line would lead to fewer cases of treatment failure and reduce the need for next-lines of treatment. In short, the use of DTG-based first-line regimens may reduce the available sequential treatment lines but may increase the durability of first line and brings focus to the potential need for individualized resistance testing as part of treatment monitoring on the medium-longer term.

## **The continued necessity for population-based resistance surveillance in LMICs**

Independent of the timeliness and success of introduction of DTG in LMICs, continued resistance surveillance remains indicated (**Table**). First, HIVDR is one of the markers of the quality of care of HIV programs. There is a continuous need to monitor critical gaps within HIV programs that facilitate the occurrence of resistance. These include quality indicators such as VL suppression rates, drug stock outs, patient uptake and retention, pharmacy pick-up rates, as included in the WHO-defined early warning indicators for HIVDR.<sup>57</sup> Monitoring these quality indicators, as part of programme monitoring and evaluation efforts, will continue to provide important information at the programmatic and clinic level ART that help identifying ART quality gaps to be addressed to curb wide-scale emergence of resistance.

The implementation of nationally representative surveys of population-level HIV drug resistance both in untreated and treated populations will be important to provide up-to-date information to guide, and if needed accelerate transition plans from NNRTI-based first-line and to monitor any future emergence of DTG resistance. These surveys will continue documenting NRTI resistance, especially in patients failing NRTI-based pre-exposure prophylaxis. Finally, such surveys can also inform on optimum individual management of patients failing DTG-based treatment including the possible role of resistance tests to guide treatment switches.

### **Access to affordable viral load and HIV drug resistance testing**

To support the proposed monitoring strategies and maximize the gains of DTG-based regimen, there is the need to support current efforts for universal access to routine VL tests. Strategies to improve VL testing have previously been reviewed, with a strong emphasis on using point-of-care tests for increasing decentralized access, use of dried blood spots specimens, creating demand by increasing treatment literacy among the communities and addressing gaps in the VL testing cascade to ensure efficient uses of resources.<sup>62,63</sup>

Equally, the need for HIVDR tests for both individualized patient management and population-based surveillance is expected to increase during the DTG era. A number of HIVDR genotyping technologies are becoming increasingly affordable, as reviewed elsewhere.<sup>64,65</sup> Increased political will and investments are needed to actualize affordable HIVDR testing in LMICs.

### **Conclusion and future directions**

As the therapeutic landscape for ART in LMICs changes dramatically, with potential for more efficacious and durable therapy based on DTG, a similar transition needs to be made to improve on the monitoring framework to ensure sustained optimal treatment outcomes. There is a paucity of data on DTG resistance in the context of the WHO public health approach to ART, with limited access to virological monitoring and among circulating non-B subtypes. We caution that focusing on medical-technical solutions alone risks complacency, whilst curbing resistance requires a multi-faceted approach. There is an urgent need for implementing a framework for the systematic and standardized monitoring of patients on DTG-based treatment, in order to determine new mutation patterns not previously observed or well-understood as well as the magnitude of DTG-associated resistance development in LMIC.

### **Authors' contributions**

SCI, RLH, TFRW conceptualized the paper. SCI drafted the manuscript, with assistance from RLH and TFRW. All authors reviewed and contributed to subsequent drafts for important intellectual content, and approved the final manuscript.

### **Disclaimer**

The views expressed in this review are those of the authors and may not necessarily reflect those of the institutions for which they work.

### **Conflicts of interest**

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**Table: Resistance assessment needs in the era of dolutegravir-based antiretroviral therapy in low- and middle-income countries**

	Rationale	Strategy		Public-health action
		Population-based DRT	Individual-level DRT	
NRTI resistance	Possible impact on dolutegravir efficacy	a. PDR survey in patients initiating or re-initiating ART b. PDR surveillance in patients failing on tenofovir -based PrEP c. HIVDR surveillance in children <18 months	Patients with virological failure switching to dolutegravir-based treatment	-Perform viral load testing before switching to dolutegravir based regimen -If virological failure is detected, optimize use of the most effective NRTI backbone
Dolutegravir resistance	Possible increased frequency of dolutegravir resistance in non-B subtypes	a. Pretreatment drug resistance to detect transmitted resistance to integrase-inhibitor based regimens b. Acquired drug resistance to assess prevalence and patterns of dolutegravir resistance in failing patients	Patients with virological failure, to prevent unnecessary switches and optimize next-line of treatment	Determine and plan for alternative regimens and effective drug sequencing strategies
NNRTI resistance	Potential for NNRTI use in specific populations i.e. a) countries with limited access to low-cost dolutegravir based regimen b) Women of child-bearing	a. Pretreatment drug resistance to determine the prevalence of NNRTI resistance in adults b. HIVDR surveillance in children <18 months	PDR in patients more at risk of having NNRTI resistance or in all patients based on the prevalence of NNRTI resistance in countries not able to switch all patients to non-NNRTI based regimen	-Accelerate transition to dolutegravir based first-line regimen -Assess cost-effectiveness of switching to dolutegravir -based first-line in countries without access to generic low-cost



	potential in LMICs when effective and reliable contraceptives is not assured c) For children in countries with limited access to alternative pediatric treatment			dolutegravir -Accelerate transition to non-NNRTI-based pediatric treatment and in women of reproductive age who are not able to access effective and reliable contraceptives
bPI-resistance	Need to preserve treatment options	-PDR survey in patients initiating or re-initiating bPI-based ART -Acquired drug resistance in patients on bPI based regimens	Patients with virological failure, to prevent unnecessary switches and optimize next-line of treatment	-Determine optimum sequencing strategies, preserve treatment options and optimize third-line regimen

ART=antiretroviral therapy; bPI=ritonavir boosted protease inhibitors; DRT= drug resistance test; HIVDR= HIV drug resistance; LMICs = low- and middle-income countries; NRTI= nucleoside reverse transcriptase inhibitors; NNRTI= non-NRTI; PDR=pretreatment drug resistance; PrEP=pre exposure prophylaxis