HHS Public Access

Author manuscript

Lancet Infect Dis. Author manuscript; available in PMC 2021 March 15.

Published in final edited form as:

Lancet Infect Dis. 2019 July ; 19(7): e246–e252. doi:10.1016/S1473-3099(18)30710-2.

Curbing the rise of HIV drug resistance in low-income 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, many low-income and middle-income countries are moving away from non-nucleoside reverse transcriptase inhibitors (NNRTI) and transitioning to dolutegravir as part of a more affordable and standardised antiretroviral therapy (ART). Although this transition could decrease the effect of rising NNRTI resistance and yield improved ART outcomes, it also presents new challenges. First, current safety concerns for dolutegravir use in women of childbearing potential require alternative solutions. Second, pre-existing resistance to the co-administered nucleoside reverse transcriptase inhibitors might reduce effectiveness and durability of dolutegravir, particularly if there is scarce access to viral load tests to monitor treatment outcomes. 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 because of uncertainty around whether dolutegravir resistance has actually developed and switching is needed, or whether only interventions to improve adherence without switching are sufficient. These considerations should

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Contributors

SCI and RLH contributed equally and share first authorship. SCI, RLH, and TFRdW conceptualised the paper. SCI and RLH drafted the manuscript, with input from TFRdW. All authors reviewed and contributed to subsequent drafts for important intellectual content, and approved the final manuscript.

Declaration of interests

RWS has received grants from Gilead Sciences, Vela Diagnostics, and InSilixa; and personal fees from ViiV and Abbott Diagnostics, all outside the submitted work. RLH has received a research grant from Gilead Sciences, outside the submitted work. All other authors declare no competing interests. The views expressed in this Personal View are those of the authors and do not necessarily reflect those of the institutions for which they work.

be addressed to consolidate expected gains from widespread introduction of dolutegravir in low-income and middle-income countries.

Introduction

In the past 15 years there has been an unprecedented scale-up of access to life-saving antiretroviral treatment (ART) for people infected with HIV-1, which has substantially reduced infections and improved health and life expectancy of millions of people.[1] The widely adopted public health approach to ART, recommended by WHO, has been largely based on the use of a first-line ART regimen, which comprises two nucleoside reverse transcriptase inhibitors (NRTIs) and a non-nucleoside reverse-transcriptase inhibitor (NNRTI), either efavirenz or nevirapine. However, global evidence shows that HIV variants resistant to NNRTIs are on the rise in populations initiating ART, so-called pretreatment HIV drug resistance.[2–5] A WHO global report on HIV drug resistance suggests that in several low-income and middle-income countries (LMICs) over one in ten HIV infected patients initiating ART have pretreatment HIV drug resistance to efavirenz and nevirapine.[5] This resistance is associated with poor virological outcomes, impaired immune recovery, reduced durability of NNRTI-based regimens, and increased mortality in adults and children.[6–10] If changes to HIV treatment regimens are not made, then the rise in pretreatment HIV drug resistance could lead to an increase in mortality, HIV incidence, and overall ART programmatic costs.[11] To respond to the threat of resistance, in July, 2017, WHO issued guidelines that recommend the use of alternative non-NNRTI-containing first-line ART regimen in countries with levels of pretreatment resistance to NNRTI of 10% or more.[12]

Since 2014, dolutegravir, a second generation integrase strand transfer inhibitor (INSTI), has been increasingly used as part of first-line regimens in high-income settings[13,14] because of its favourable efficacy and toxicity profile. The use of the drug has been scarce in LMICs because of high costs; however, a new low-cost generic fixed-dose combination of 300 mg tenofovir disoproxil fumarate, 300 mg lamivudine, and 50 mg dolutegravir (TLD) is now available at an affordable price. Since September, 2017, 92 LMICs have been licensed through the Medicines Patent Pool to obtain TLD at a median price of US$75 per person per year.[15] This price is similar to or even lower than current NNRTI-based ART.[15] Because of the benefits of efficacy, safety, and affordability, in July, 2018, WHO issued guidelines recommending the use of dolutegravir in first-line and second-line treatment; this approach offers a public health intervention to respond to the high levels of pretreatment NNRTI resistance observed in LMICs.[16] The US President's Emergency Plan For AIDS Relief (PEPFAR) initiated accelerated access of TLD in all HIV-infected patients[17] in countries that are supported by PEPFAR to maximise its benefits and minimise programmatic logistics for provision of multiple drugs.

Despite the optimistic perspectives, there are some notes of caution to heed if dolutegravir would be positioned as the only overall solution to the rise in HIV drug resistance in LMICs. In this Personal View, we aim to discuss the public health opportunities and potential challenges of the expanded use of dolutegravir-based ART in LMIC with an emphasis on HIV drug resistance. 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 HIV drug resistance surveillance and prevention framework and stringent therapeutic monitoring strategies.

Dolutegravir efficacy, safety, and tolerability

Dolutegravir 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.[18–22] Additionally, dolutegravir is a more potent second-line therapy than ritonavir-boosted lopinavir when used with at least one fully-active NRTI drug.[23] A twice daily dose was shown effective in INSTI experienced patients with minimal resistance to dolutegravir,[24,25] indicating its potential for use in salvage therapy. Dolutegravir dual therapy with lamivudine was shown to be a promising strategy when used as maintenance therapy in patients with viral suppression.[26] The drug was non-inferior to triple-drug ART when used in combination with lamivudine as dual-therapy in first-line regimen, in antiretroviral-naive patients with a plasma viral load of 500 000 copies per mL or less and without pre-existing HIV drug resistance.[27] Initial speculations that dolutegravir could be used as monotherapy were refuted by studies that showed an increased risk of virological failure, combined with the emergence of INSTI resis tance.[28–30]

Safety concerns potentially limit dolutegravir use in specific populations

A report from Botswana highlighted potential safety concerns related to an increased risk of neural tube defects in infants born to women who conceived when they were taking dolutegravir.[31] Subsequently, WHO interim guidelines recommend the use of dolutegravir in women of childbearing potential when a consistent and reliable contraception is used, and indicate efavirenz as a safe and effective alternative option in first-line ART.[16] 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 scarce.[32]

The 2017 WHO report showed that pretreatment HIV drug resistance to NNRTI is typically high in women with HIV: resistance exceeded a prevalence of 10% in eight of the 11 countries surveyed, and was nearly two times higher in women than in men.[12] These data suggest that alternative regimens could be needed for women pending confirmation of the observed safety concerns.

In addition, a 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 dolutegravir.[33] Overall these findings highlight the need for enhanced pharmacovigilance and the provision of alternative drug regimens, when dolutegravir is rolled out in LMICs.

Limited information on dolutegravir resistance mutation patterns

To date, most patients who accessed dolutegravir are from high-income settings and are infected with HIV-1 subtype B. In treatment-naive patients from these settings, only two cases of possible dolutegravir resistance have been reported. The first patient was a late presenter with high viraemia who started on tenofovir, emtricitabine, dolutegravir, and had

viral rebound within 2 weeks of treatment with a transient Met184Ile reverse transcriptase (RT) mutation detected at around 3 weeks, and a Gln148Lys INSTI mutation at 5 weeks.[34] Baseline INSTI resistance testing was not done, and it is possible that Gln148Lys was already transmitted during HIV infection. The second patient was enrolled in the ACTG5353 study that assessed the efficacy of dolutegravir and lamivudine dual combination in treatment-naive individuals.[35] The patient achieved viral suppression by 4 weeks of treatment, but had virological failure by week 8 with Met184Val RT and Arg263Lys INSTI mutations being detected at 16 weeks.

Few treatment-experienced but INSTI-naive patients have experienced virological failure with dolutegravir resistance mutations.[36,37] In particular, the Arg263Lys INSTI mutation has been reported in four patients (two in subtype B and two in subtype C), Asn155His INSTI mutation in two patients infected with a non-B subtype virus, Gly118Arg in two patients (one subtype B and one subtype C), and Glu138Glu/Lys and His51His/Tyr in one patient infected with subtype C virus. Patients not responding to dolutegravir monotherapy were shown to further select for the Gln148His/Arg/Lys INSTI mutations accompanied by compensatory mutations that lead to intermediate-level to high-level dolutegravir resistance.[38]

In INSTI-experienced patients, the Gln148 mutation together with two or more accessory mutations significantly impairs dolutegravir efficacy,[24,39,40] although the use of a twice-daily dolutegravir dose can substantially improve treatment response in patients with fewer mutations.[24,25]

There is a scarcity of information on the patterns of dolutegravir resistance in non-B subtypes, although available data suggest the possibility of HIV-1 subtype influencing the mutational patterns of INSTI resistance.[37,41–44] Studies in vitro have shown that the Arg263Lys INSTI mutation is mainly present in viral isolates from subtype B and Gly118Arg in non-B sub types.[42,45] Selection of Gly118Arg is possibly influenced by the presence of a rare polymorphism with a low genetic barrier,[45] which could be particularly common in patients infected with subtype A.[46] This could result in differential prevalence and patterns of dolutegravir resistance between the HIV-1 subtypes. A similar phenomenon has been observed for the Lys65Arg RT mutation, associated with tenofovir resistance, which has been shown to be more prevalent in HIV-1 subtype C than in other subtypes.[47,48]

Dolutegravir replacement risks among patients with NRTI resistance

Resistance to the NRTI backbone is very common among patients with virological failure on NNRTI-based first-line ART in LMICs. In a systematic review[48] that included 1926 patients from 36 countries, 57% of patients had tenofovir resistance and of those with tenofovir resistance, 83% also had resistance to emtricitabine and lamivudine. This finding suggests that most people with virological failure to first-line efavirenz-based ART carry a virus with reduced susceptilibity to tenofovir and lamivudine. As a consequence, if patients are switched from a first-line or second-line regimen to a dolutegravir-based regimen while maintaining the same tenofovir-based NRTI backbone, there is a risk that patients with virological failure could be exposed to a functional dolutegravir monotherapy. Studies that

evaluated dolutegravir monotherapy in maintenance strategies reported INSTI resistance in 50–82% of patients with virological failure.[38,49] Therefore, these data support dolutegravir replacement only when virological suppression is confirmed.

Data from the DAWNING study[50] that compared dolutegravir with ritonavir-boosted lopinavir in patients with virological failure to first-line NNRTI-based ART showed 84% efficacy in patients with less than two fully active NRTIs. This finding suggests adequate residual NRTI activity when at least one NRTI remained unaffected by resistance mutations. These findings are similar to what has been reported with protease inhibitors (PI)-based regimens.[51] However, further analysis showed a reduced efficacy of 76% for patients maintained on NRTI drugs used in first-line ART compared with 87% for those who were switched to newer NRTIs according to WHO recommendation.[52] This suggests the need for optimisation of the NRTI backbone when dolutegravir is used in second-line treatment as recommended in recent WHO guidelines.[16]

To mitigate the risk of dolutegravir resistance in patients on ART with unknown viral load who are switched to dolutegravir-based ART while maintaining the same NRTI backbone, PEPFAR recommends that ART programmes should closely monitor treatment response using a viral load test 3–6 months after switching.[17,53] In LMICs this approach can be challenging because many ART programmes do not provide universal access to routine virological monitoring. As of July, 2018, only 50% of the patients on ART in LMICs were estimated to have received at least one viral load test in the past year.[54] In another report on seven African countries, substantial differences were observed in access to viral load testing for ART patients (eg, from 91% in Namibia to 5% in Tanzania).[55] WHO recommends prudence in doing a blind switch to dolutegravir in the absence of viral load testing and highlights the need for close monitoring of treatment outcomes including viral load and drug resistance by the use of well-designed cohorts or national representative surveys.[16]

It is worth noting that, even in settings where viral load testing would be routinely used, WHO recommends the use of a viral load cut-off of 1000 copies per mL to trigger a regimen switch. Such a high cut-off could be associated with the risk of accumulation of HIV drug resistance due to ongoing low-level viral replication.[38,43,56,57]

Although the transition to dolutegravir will reset the resistance clock, the programmatic challenges in the delivery of HIV treatment in LMICs that are associated with resistance emergence (eg, drug stock out, poor retention, and suboptimal adherence) will not disappear with the introduction of dolutegravir. Therefore, higher rates of virological failure and the potential for HIV drug resistance might be expected in LMICs than in clinical trials or well-monitored settings.[34–37,58]

Finally, without individualised resistance testing to optimise selection of the NRTI backbone, it remains unclear how a WHO recommended optimised NRTI backbone could affect the durability of dolutegravir-based therapy. Further research is clearly needed to monitor the durability of dolutegravir-based ART and resistance patterns across the different subpopulations in LMICs and the effect of NRTI resistance on a dolutegravircontaining regimen.

Change to dolutegravir warrants optimal switching strategy

The WHO switching algorithm recommends the use of a confirmed viral load greater than 1000 copies per mL to trigger a change in regimen from NNRTI to the more costly ritonavir-boosted, protease inhibitor-based secondline ART.[57] Approximately 10–30% of people on PI-based ART have a viral load greater than 1000 copies per mL 12 months after ART initiation.[5,59] Among those patients with treatment failure, 70–90% have high-level NNRTI resistant variants,[5,48] which warrants the need for a timely switch to second-line ART if they remain unsuppressed after enhanced adherence intervention. The high resistance prevalence in patients with virological failure on efavirenz-based ART have prompted considerations about the use of a single viral load test to prompt the switch to second-line ART.[60] However, data from clinical trials showed that most of the patients who initiated firstline dolutegravir-based ART and had virological failure within 48 weeks of treatment did not harbour any resistance to either the INSTI or NRTI backbone.[18–23]

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 virological failure on a TLD regimen. Therefore, studies will be needed to determine the appropriate switching algorithm to manage patients not responding to TLD in LMICs. To optimise the management of virological failure in regions where routine genotypic resistance testing is not available, a better understanding will be needed on the frequency of virological failure in patients on first-line TLD regimen; the levels of resistance to the cytosine analogues, tenofovir, and dolutegravir components of the regimen; and on the probability to re-suppress after intensive adherence counselling.

Where possible and feasible, individualised resistance tests could help to optimise the composition of the NRTI background and help with the prevention of premature and unnecessary switches to more costly PI-based regimens. Countries like Botswana and Brazil have policies that recommend the use of individual resistance testing to guide the clinical management of patients with virological failure on dolutegravir-based regimens.[61]

Rational antiretroviral drug sequencing

Optimal drug sequencing strategies in patients experiencing treatment failure when on dolutegravir are essential because of the scarce drug options in many LMICs. The previous WHO-recommended sequencing approach of ART regimens in adults and adolescents included a standard first-line regimen of a preferred NNRTI (efavirenz) with a dual NRTI-backbone, followed by a second-line regimen of a ritonavir-boosted PI (atazanavir or lopinavir) with one or two unused or recycled NRTIs, and followed by third-line regimen of an INSTI combined with ritonavir-boosted darunavir with or without one or two optimised NRTIs. In the 2018 interim WHO guidelines, the alternative sequencing approach involves the use of a dolutegravir-based first-line regimen, followed by a ritonavir-boosted PI-based second-line, and ritonavir-boosted darunavir in third-line, with recycled dolutegravir and one or two NRTIs, preferably optimised on the basis of a resistance test.[16] Although dolutegravir is likely to have residual activity when recycled with fully active ritonavir-boosted darunavir

in third-line treatment, further research is still warranted to assess the efficacy of this approach.

It is generally expected that the use of dolutegravir in first-line treatment would lead to fewer cases of treatment failure and reduce the need for further treatment. In short, the use of dolutegravir-based first-line regimens could reduce the available sequential treatment lines but might increase the durability of first-line regimens and bring focus to the potential need for individualised resistance testing as part of treatment monitoring in the medium to longer terms.

The continued necessity for population-based resistance surveillance in LMICs

Independent of the timeliness and success of introduction of dolutegravir in LMICs, routine surveillance of HIV drug resistance needs to be continued (table). First, HIV drug resistance is one of the markers of the quality of ART programmes. WHO[57] recommends monitoring a set of early warning indicators associated with emergence of HIV drug resistance, which include viral load on so-called early warning indicators for HIV drug resistance, such as viral load suppression rates, drug stockouts, patient retention, and pharmacy drug pickup rates. Monitoring these quality indicators will continue to provide important information at the programmatic and clinic level that helps to identify quality gaps that need to be addressed to curb wide-scale emergence of resistance.

The implementation of surveys that are nationally representative of population-level HIV drug resistance in untreated and treated populations will be important to provide up-to-date information to guide and monitor any future emergence of dolutegravir resistance, and if needed accelerate transition plans from NNRTI-based first-line treatments. These surveys will continue to document NRTI resistance, including in patients failing NRTI-based pre-exposure prophylaxis. Finally, such surveys could inform on optimal individual management of patients not responding to dolutegravir-based treatment, including the possible role of resistance tests to guide treatment switches.

Access to affordable viral load and HIV drug resistance testing

To enable the proposed monitoring strategies and maximise the gains of dolutegravir-based regimens, there is a need to support current efforts for universal access to routine viral load tests. Strategies to improve viral load testing have previously been reviewed, with a strong emphasis on using point-of-care tests to increase decentralised access, use of dried blood spots specimens, create demand by increasing treatment literacy among communities, and address gaps in the viral load testing cascade to ensure efficient uses of resources.[62,63]

Equally, the need for HIV drug resistance tests for both individualised patient management and populationbased surveillance is expected to increase during the dolutegravir era. Various HIV drug resistance genotyping technologies are becoming increasingly affordable.[64,65] Increased political will and investments are needed to ensure affordable HIV drug resistance 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 dolutegravir, a similar transition needs to be made to improve the monitoring framework to ensure sustained and optimal treatment outcomes. There is a paucity of data on dolutegravir resistance in the context of WHO's public health approach to ART, limited access to virological monitoring, and circulating HIV-1 non-B subtypes. We caution that focusing on medical-technical solutions alone risks complacency. Curbing HIV drug resistance requires a multifaceted approach. There is an urgent need for the implementation of a framework for the systematic and standardised monitoring of patients on dolutegravirbased treatment. It is also important to determine new mutation patterns not previously observed or well understood and the magnitude of dolutegravir-associated resistance development in LMICs.

Acknowledgments

We thank the participants of the Joep Lange Institute meetings in Amsterdam on Sept 6–7, 2017, and The Hague on March 19–20, 2018, and the participants of the WHO HIVResNet meeting held in Johannesburg, South Africa on Nov 9–10, 2017, for all their contributions and deliberations towards this topic.

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Table:

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

	Rationale	Population-based DRT strategy	Individual-level DRT strategy	Public health action
NRTI resistance	Possible effect on dolutegravir efficacy	PDR survey in patients initiating or re-initiating ART; PDR surveillance in patients failing on tenofovir-based PrEP; HIV drug resistance surveillance in children aged <18 months	Patients with virological failure switching to dolutegravir-based treatment	Determine the need for optimising NRTI backbone
Dolutegravir resistance	Possible increased frequency of dolutegravir resistance in non-B subtypes	PDR to detect transmitted resistance to integrase-inhibitor based regimens; acquired drug resistance to assess prevalence and patterns of dolutegravir resistance in failing patients	Patients with virological failure, to prevent unnecessary switches and optimise next-line of treatment	Determine and plan for alternative regimens and effective drug sequencing strategies
NNRTI resistance	Potential for NNRTI use in specific populations: countries with inadequate access to low-cost dolutegravir-based regimen, women of childbearing potential in LMICs when effective and reliable contraceptives are not assured, and for children in countries with scarce access to alternative paediatric treatment	Pretreatment drug resistance to determine the prevalence of NNRTI resistance in adults; HIV drug resistance surveillance in children aged <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 regimen in countries without access to generic low-cost dolutegravir; accelerate transition to non-NNRTI-based paediatric treatment and in women of reproductive age who are not able to access effective and reliable contraceptives
PI-resistance	Need to preserve treatment options	PDR survey in patients initiating or re-initiating PI-based ART; acquired drug resistance in patients on PI-based regimens	Patients with virological failure, to prevent unnecessary switches and optimise next-line of treatment	Determine optimum sequencing strategies, preserve treatment options, and optimise third-line regimen

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