Published in final edited form as:

Lancet HIV. 2018 July ; 5(7): e400–e404. doi:10.1016/S2352-3018(18)30093-6.

Dolutegravir for first-line antiretroviral therapy in low-income and middle-income countries: uncertainties and opportunities for implementation and research

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Declaration of interests: JD, PD and NG are investigators on the Simplified TREAtment and Monitoring of HIV (STREAM) study, a randomised trial of point-of-care viral load testing. Cepheid Inc. loaned the GeneXpert® instruments for this study at no cost. All other authors declare no competing interests.

Authorship statement: JD, RL and NG conceived and drafted the manuscript. PD, KN, TO, YP and SAK critically revised the manuscript. JD, RL, PD, KN, TO, YP, SAK and NG consented to publication.

Role of the funding source: Nil

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Summary

A new first-line antiretroviral therapy (ART) regimen containing dolutegravir is being rolled-out in low-income and middle-income countries (LMICs). Studies from predominantly high-income settings have found that dolutegravir-based regimens have superior efficacy, tolerability and durability compared with existing first-line regimens. However, several questions remain regarding the roll-out of dolutegravir in LMICs, where most people living with HIV are women of reproductive age, TB prevalence can be high, and access to viral load and HIV drug resistance testing is limited. Cohort studies suggest that dolutegravir is safe when initiated in pregnancy, but further data is required to determine the risk of adverse birth outcomes when dolutegravir is initiated pre-conception. Increasing access to viral load testing to monitor the effectiveness of dolutegravir remains crucial, but the optimal strategy to manage patients with viraemia is unclear. Furthermore, evidence demonstrating the effectiveness of dolutegravir when co-administered with tuberculosis treatment is scarce, particularly in programmatic settings in LMICs. Lastly, it is not known whether nucleoside reverse-transcriptase inhibitor resistance will affect the long-term efficacy of dolutegravir-based regimens in first-line, and potentially second-line ART. Clinical trials, cohorts and surveillance of HIV drug resistance will be required to answer these questions and to maximise the benefits of this new regimen.

Keywords

HIV; antiretroviral therapy; dolutegravir; viral load; adherence; resistance

Introduction

In September 2017 a breakthrough pricing agreement was reached to provide generic dolutegravir for HIV treatment in low- and middle-income countries (LMICs).[1] Combined with tenofovir disoproxil fumarate and lamivudine, this single pill, fixed-dose combination will cost approximately USD 75 per person per year,[1] and is likely to be cost effective when compared to current non-nucleoside reverse transcriptase inhibitor (NNRTI) first-line regimens.[2] Dolutegravir is an integrase strand transfer inhibitor (INSTI) with better tolerability, efficacy and durability than efavirenz.[3] The World Health Organization (WHO) supports transitioning to dolutegravir-based first-line regimens, particularly in regions where pre-treatment drug resistance to NNRTIs reaches 10%, such as Southern and Eastern Africa.[4,5] Brazil and Botswana have already introduced dolutegravir into their public health sectors, with countries including Malawi, Nigeria, Tanzania and South Africa planning to launch the fixed-dose combination in 2018.[6] While this could be a major improvement for HIV care in LMICs, specific key questions remain unanswered. Here, we outline uncertainties regarding safety in pregnancy, management of viraemia, tuberculosis (TB) drug interactions, immune reconstitution inflammatory syndrome (IRIS) and HIV drug resistance (HIVDR) which should be addressed during the roll-out of dolutegravir-based first-line ART in LMICs (Table 1).

Is dolutegravir safe in pregnancy and during breastfeeding?

Dolutegravir has a favourable safety profile amongst older children, adolescents and adults, but a key concern has been the lack of evidence to support use in pregnancy and breastfeeding. Data from small cohorts of pregnant women who conceived while receiving dolutegravir in Europe and North America showed no evidence of increased birth defects.[7,8] In Botswana, 1729 pregnant women who were initiated on dolutegravir-based ART (of whom 280 were initiated in the first trimester) had no increase in adverse foetal outcomes when compared to 4593 pregnant women who were initiated on efavirenz-based regimens.[9] However, more recent data from Botswana suggests a possible increased risk of neural tube defects in infants born to women who where initiated on dolutegravir prior to conception.[10,11] In this preliminary analysis, 0.94% (4/426) of women receiving dolutegravir gave birth to an infant with a neural tube defect, compared with 0.13% (14/11 173) of women receiving non-dolutegravir-based regimens. Full results are expected in 2019, and pending further data, WHO recommend that women of childbearing age receive alternative ART regimens with better evidence to support safe use in pregnancy.[10] With regard to efficacy, pharmacokinetic data from 29 pregnant women taking dolutegravir 50mg once daily found slightly lower maternal dolutegravir levels during the second and third trimesters, but this did not seem to impact greatly on viral outcomes or mother-to-child transmission.[12] Evidence from randomised clinical trials will be necessary to compare maternal and infant outcomes including safety, pharmacokinetics and virological efficacy between dolutegravir and other regimens.[13] Two large trials have recently begun, but are only enrolling ART naïve pregnant women in the second and third trimesters.[14,15] Therefore, surveillance of maternal and infant outcomes, particularly amongst women who conceive while receiving dolutegravir, will be important to confirm safety in pregnancy and whether dolutegravir can be recommended for use in women of child-bearing age..

Will the introduction of dolutegravir simplify the management of patients with viraemia?

The transition from efavirenz to a more efficacious dolutegravir-based first-line is hoped to increase levels of viral suppression in LMICs. However, ART stock outs, poor retention in care, funding constraints and increasing patient loads that pressurize healthcare systems may blunt the effectiveness of this new regimen. Expanding viral load coverage will therefore remain critical to monitor effectiveness of dolutegravir-based ART and to identify patients with viraemia who require intervention. However, the optimal strategy for viral load monitoring, particularly after detection of viraemia, will need to be reassessed, as some previous assumptions regarding management of treatment failure in adults will no longer be applicable.[16] In high-income settings, the emergence of HIV drug resistance (HIVDR) mutations against dolutegravir has been rare.[17,18] This contrasts sharply with current NNRTI-based first-line ART, where up to 89% of patients with first viraemia can have associated HIVDR mutations.[19,20] In LMICs, where HIVDR testing is not widely available, WHO recommends switching to second-line ART if viraemia persists for more than three months, despite adequate adherence. While effective in clinical trials,[21] these guidelines are often poorly implemented in public sector programmes, leading to ongoing viraemia,

morbidity and emergence and transmission of drug-resistant HIV.[4,22,23] The roll-out of first-line dolutegravir may allow simplification of these guidelines, as viraemia is likely to be caused by poor adherence in the absence of HIVDR, meaning switching from dolutegravir first-line to a second-line regimen should be greatly reduced. Instead, management of viraemia should shift from treating HIVDR to focus more intensely on improving adherence.

Does the dolutegravir roll-out provide an opportunity to re-evaluate adherence interventions?

Various adherence interventions have been evaluated in LMICs, but evidence demonstrating an effect on virological suppression is weak.[24] Adherence relies on a complex mix of medical, behavioural, social and structural factors,[25] which can be difficult to influence. Moreover, accurately measuring adherence is challenging.[26] While a suppressed viral load demonstrates good adherence to current first-line regimens, a high viral load could be caused by HIVDR, rather than contemporaneous poor adherence. For non-adherent patients on dolutegravir, the shorter half-life[27] when compared to efavirenz may result in faster viral rebound, while improved adherence should be reflected in a rapid return to viral suppression. Therefore, as dolutegravir use and viral load testing coverage increase, monitoring adherence, and response to adherence interventions, should become easier. This presents an important opportunity to develop and implement evidence-based adherence interventions to achieve early viral resuppression.[28] Point-of-care viral load testing may be particularly useful here to rapidly identify adherence problems, monitor the impact of counselling, and efficiently triage patients into differentiated care services.[29] Novel point-of-care adherence assays (e.g. measuring urine tenofovir levels) are being developed, and their potential as additional or alternative monitoring strategies should be evaluated as part of the dolutegravir roll-out.[30]

How should dolutegravir be used in the context of TB treatment and prevention?

Uncertainty remains regarding optimal dosing of dolutegravir when co-administered with rifamycins, key drugs in treating the large numbers of people co-infected with HIV and TB in LMICs. Rifampicin induces the liver enzymes uridine glucuronosyltransferase 1A1 and cytochrome P450 3A4, which increase dolutegravir metabolism and decrease drug levels.[31] Interim data from the INSPIRING trial suggest that doubling the dolutegravir dose to 50 mg twice daily when co-administered with rifampicin could be effective, safe and tolerable for patients co-infected with HIV and TB, although full 48 week outcomes are forthcoming.[32] Adjusting the dolutegravir dose may be challenging to implement in public sector programmes and would negate the benefits of a once daily regimen, meaning further work is needed to assess the clinical impact of rifampicin co-administered with once daily dolutegravir.[31] Some countries are therefore opting to continue efavirenz-based first-line ART in patients receiving TB treatment.[33] With regard to treatment of latent TB infection, results from the BRIEF-TB trial mean one month of daily isoniazid and rifapentine is being considered as an effective, safer and shorter alternative to isoniazid monotherapy.[34] However, issues around cost and appropriate co-formulations are unresolved, and a phase I

drug interaction study of dolutegravir and high dose, weekly isoniazid and rifapentine was stopped early due to serious toxicities.[35] The precise underlying mechanisms remain unclear, and whether this interaction persists at the lower, daily doses used in BRIEF-TB requires urgent assessment. In the interim, daily isoniazid preventative therapy is likely to remain the preferred option in countries that roll out dolutegravir, as other short course regimens contain rifampicin and would require dolutegravir dose adjustments.

Will dolutegravir be associated with increased risk of IRIS in LMICs?

Evidence from European cohort studies has suggested a possible increased risk of IRIS, particularly TB related, amongst patients initiated on INSTI-based regimens, compared to NNRTI or protease inhibitor (PI)-based regimens.[36–38] These findings were not replicated in a recent sub-analysis from REALITY, a multicentre, randomised, factorial trial of 1805 participants in Eastern and Southern Africa. This study enrolled ART naïve children and adults with CD4 counts less than 100 cells per μL, and demonstrated that 12 weeks of raltegravir intensification alongside standard ART initiation did not impact incidence or mortality of IRIS.[39] Data regarding dolutegravir-based ART is less conclusive. A meta-analysis of randomised controlled trials found no association between dolutegravir and IRIS when compared to NNRTI and PI-based regimens. However, these studies had only 13 cases of IRIS between them and may not be generalisable to LMICs as they excluded patients with CDC grade C disease.[40] Data from the Brazilian rollout reported only one case of IRIS amongst the first 26,070 ART naïve patients initiated on dolutegravir.[41] Whilst these emerging findings are reassuring, further data from randomised trials such as the ADVANCE study,[42] as well as cohort studies embedded in public sector programmes, will be important to establish the frequency of IRIS and its impact on mortality amongst patients receiving dolutegravir in LMICs.[43]

What impact will NRTI mutations have on dolutegravir-based regimens in LMICs, and what role will there be for HIVDR testing?

Recent evidence of dolutegravir resistance developing after use in monotherapy[44] means the long-term implications of combining dolutegravir with a significantly compromised NRTI backbone must be considered. This could occur more frequently in LMICs due to the paucity of HIVDR testing and incomplete viral load coverage. Firstly, adults with pretreatment drug resistance (particularly those with previous ART exposure) may have undetected NRTI mutations associated with reduced susceptibility to tenofovir and lamivudine.[23] Second, in Southern Africa, long delays in management of viraemia have been documented, which could allow emergence of NRTI resistance while on dolutegravir.[22,45] Third, several studies have reported high levels of K65R and M184V mutations amongst adults failing current first-line regimens in LMICs.[46] Therefore, if people are switched from tenofovir, emtricitabine and efavirenz, to tenofovir, lamivudine and dolutegravir without confirmation of viral suppression, there may be a higher risk of acquired dolutegravir HIVDR. Understanding the risks and benefits of such a strategy is a priority research question, as several ART programmes are not using viral load testing in the transition to dolutegravir-based first line ART.[33] While the advantages of dolutegravir might

justify this approach, programs should be supported in accelerating viral load roll out and implementing HIVDR surveillance systems to guide policy decisions.

Recent results from the DAWNING trial provide some evidence regarding the impact of NRTI resistance on dolutegravir-based regimens.[47] In DAWNING, patients failing first-line NNRTI-based ART were randomized to receive a dolutegravir- or protease inhibitor (PI)-based second-line regimen. In both the dolutegravir and PI arms, those with only one predicted active NRTI did better than those with two,[47] as has been seen in other studies of PI-based second-line regimens.[48–50] However, in all these studies, there were few patients who failed a tenofovir first-line regimen and then received tenofovir in their second-line regimen. Furthermore, confounding due to the difficulties of accurately measuring and controlling for poor adherence may explain some of these findings. In short, there is little high quality evidence demonstrating the long-term efficacy of dolutegravir alongside a compromised NRTI backbone.[51,52] Therefore, as dolutegravir is rolled out, HIVDR surveillance will be crucial to determine the incidence of both NRTI and dolutegravir HIVDR mutations, their impact on clinical outcomes and the need for, timing and cost-effectiveness of HIVDR testing in public sector programmes. This will require the development of INSTI HIVDR testing capacity in LMICs, and could be aided by new targeted HIVDR testing platforms or point-of-care resistance assays.[53] If found to be affordable and effective, these assays could be incorporated into algorithms to screen for and manage treatment failure on first-line dolutegravir, and guide selection of subsequent second-line regimens if necessary.

Should dolutegravir replace current first and second-line ART?

Several LMICs have prioritized ART naïve patients for initiation of dolutegravir based first-line ART, followed by transition of patients from NNRTI-based regimens to dolutegravir. While some patients may request to remain on effective NNRTI regimens, programmatic factors such as simplification of supply chain, ART tenders and training mean that transitioning the majority of stable patients to dolutegravir-based first-line should be encouraged, as long as concerns regarding safety in pregnancy have been addressed. There is also interest in dolutegravir to replace current second-line regimens, with the DAWNING trial demonstrating that a dolutegravir-based regimen was superior to a PI-based regimen amongst patients failing first-line NNRTI-based ART.[47] All participants in this study had at least one predicted fully active NRTI, with HIVDR testing used to select the second-line NRTI backbone, an approach which is not currently feasible in most LMICs. Despite this, results from DAWNING, coupled with significant cost savings,[54] have led some countries to consider dolutegravir as a replacement for current first- and second-line therapies.[55] Given the evidence currently available, in the absence of HIVDR testing it would seem prudent to ensure that patients with treatment failure on current tenofovir containing first-line ART are switched to zidovudine in a dolutegravir-based second-line regimen. In settings where viral load testing is unavailable, this would include patients with WHO clinical or immunological failure. Therefore, in the majority of cases, the tenofovir, lamivudine and dolutegravir fixed-dose combination could not be used for second-line ART.

Conclusion

In summary, the impending roll-out of dolutegravir as first-line ART has potential to be another important step in the evolution of HIV treatment programmes in LMICs. The superior durability of this INSTI should simplify treatment pathways, and coupled with increasing viral load coverage, presents an opportunity to focus on improving ART adherence to increase levels of viral suppression. Despite these benefits, a number of gaps in the evidence base must be addressed by researchers as part of the dolutegravir roll-out, in particular regarding safety in pregnancy. Using data from dolutegravir cohorts, clinical trials and HIVDR surveillance will allow health systems to maximize the potential benefits of this exciting new regimen.

Acknowledgments

JD, PD and NG are supported by the US National Institute of Health (AI124719-01). RL and TdO are supported by a South African Medical Research Council Flagship award (MRC-RFA-UFSP-01-2013/UKZN HIVEPI). The KwaZulu-Natal Research Innovation and Sequencing Platform (KRISP) is funded as a technology platform of the Technology Innovation Agency (TIA), an initiative of the Department of Science and Technology (DST).

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Table 1

Questions that need to be addressed in the roll-out of dolutegravir in low- and middle-income countries

Safety
• Is the use of dolutegravir in pregnancy associated with adverse birth outcomes?
• What is the frequency and impact of immune reconstitution inflammatory syndrome amongst severely immunocompromised patients who are initiated on dolutegravir in LMICs?
Monitoring effectiveness
• What is the optimal strategy for viral load and HIVDR testing to manage adults with viraemia on dolutegravir-based regimens?
• For patients with viraemia on dolutegravir, how can adherence support interventions be integrated with viral load monitoring to maximize virological re-suppression?
Drug interactions
• Will co-administration of dolutegravir and rifampicin in patients with HIV/TB impact on HIV treatment outcomes?
HIV drug resistance
• At what rate will dolutegravir HIV drug resistance mutations emerge in LMIC public sector programmes, and in which clinical scenarios?
• How will pretreatment or acquired NRTI drug resistance mutations impact on the efficacy of dolutegravir-based first or second-line regimens?
Implications for second-line ART
• If resistance to dolutegravir-based first-line occurs in LMICs, what will be the best second-line regimen and what is the optimal timing for regimen switch?
• For patients failing current NNRTI-based first-line ART, should dolutegravir be used in a second-line regimen?
Cost-effectiveness
• Will replacing current first- and/or second-line regimens with dolutegravir-based regimens prove cost-effective?
• How will the roll-out of dolutegravir impact the cost-effectiveness of viral load monitoring and HIV drug resistance testing?

ART – antiretroviral therapy, HIVDR – HIV drug resistance, LMIC – low- and middle-income country, NNRTI – non-nucleoside reverse transcriptase inhibitor, NRTI – nucleoside reverse transcriptase inhibitor