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

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

Jienchi Dorward, Richard Lessells, Paul K Drain, Kogieleum Naidoo, Tulio de Oliveira, Yogan Pillay, Salim S Abdool Karim, Nigel Garrett

A new first-line antiretroviral therapy (ART) regimen containing dolutegravir is being rolled out in low-income and middle-income countries (LMICs). In studies from predominantly high-income settings, dolutegravir-based regimens had superior efficacy, tolerability, and durability compared with existing first-line regimens. However, several questions remain about the roll out of dolutegravir in LMICs, where most people with HIV are women of reproductive age, tuberculosis prevalence can be high, and access to viral load and HIV drug resistance testing is limited. Findings from cohort studies suggest that dolutegravir is safe when initiated in pregnancy, but more data are needed to determine the risk of adverse birth outcomes when dolutegravir-based regimens are initiated before conception. Increasing access to viral load testing to monitor the effectiveness of dolutegravir remains crucial, but the best strategy to manage patients with viraemia is unclear. Furthermore, evidence to support the effectiveness of dolutegravir when given with tuberculosis treatment is scarce, particularly in programmatic settings in LMICs. Lastly, whether nucleoside reverse transcriptase inhibitor resistance will affect the long-term efficacy of dolutegravir-based regimens in first-line, and potentially second-line, ART is unknown. Clinical trials, cohorts, and surveillance of HIV drug resistance will be necessary to answer these questions and to maximise the benefits of this new regimen.

Lancet HIV 2018

Published Online
June 5, 2018
http://dx.doi.org/10.1016/S2352-3018(18)30093-6

Centre for the AIDS Programme of Research in South Africa (J Dorward MBChB, K Naidoo PhD, Prof T de Oliveira PhD, Prof S S Abdool Karim PhD, N Garrett MBBS), **KwaZulu-Natal Research and Innovation Sequencing Platform (KRISP)** (R Lessells PhD, Prof T de Oliveira), **and CAPRISA-MRC HIV-TB Pathogenesis and Treatment Research Unit** (K Naidoo, Prof S S Abdool Karim), **Doris Duke Medical Research Institute, Nelson R Mandela School of Medicine, and Discipline of Public Health Medicine, School of Nursing and Public Health** (K Naidoo, N Garrett), **University of KwaZulu-Natal, Durban, South Africa; Department of Global Health, Schools of Medicine and Public Health** (P K Drain MD), **Department of Medicine, School of Medicine** (P K Drain), **and Department of Epidemiology, School of Public Health** (P K Drain), **University of Washington, Seattle, WA, USA; National Department of Health, Pretoria, South Africa** (Y Pillay PhD); **and Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA** (Prof S S Abdool Karim)

Correspondence to:
Dr Jienchi Dorward, CAPRISA, Doris Duke Medical Research Institute, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Congella 4013, South Africa
jienchi.dorward@caprisa.org

Introduction

In September, 2017, a breakthrough pricing agreement to provide generic dolutegravir for HIV treatment in low-income and middle-income countries (LMICs) was reached.[1] Tenofovir disoproxil fumarate, lamivudine, and dolutegravir as a single-pill, fixed-dose combination will cost about US$75 per person per year[1] and is likely to be cost-effective compared with existing first-line regimens containing non-nucleoside reverse transcriptase inhibitors (NNRTIs).[2] Dolutegravir is an integrase strand transfer inhibitor (INSTI) with better tolerability, efficacy, and durability than efavirenz.[3] WHO supports transitioning to dolutegravir-based first-line regimens, particularly in regions where pretreatment drug resistance to NNRTIs reaches 10%, such as southern and eastern Africa.[4,5] Dolutegravir has already been introduced in public health sectors in Brazil and Botswana, and Malawi, Nigeria, Tanzania, and South Africa plan to launch the fixed-dose combination in 2018.[6] Although this could be a major improvement for HIV care in LMICs, specific key questions remain unanswered. In this Viewpoint, we outline uncertainties in safety during pregnancy, management of viraemia, tuberculosis drug interactions, immune reconstitution inflammatory syndrome (IRIS), and HIV drug resistance, which should be addressed during the roll out of dolutegravir-based first-line antiretroviral therapy (ART) in LMICs (panel).

Dolutegravir during pregnancy and breastfeeding

Dolutegravir has a favourable safety profile in older children, adolescents, and adults, but a key concern has been the lack of evidence to support its use during pregnancy and breastfeeding. In studies of small cohorts of pregnant women in Europe and North America who conceived while receiving dolutegravir, no evidence was found of increased birth defects.[7,8] In Botswana, 1729 pregnant women who were initiated on dolutegravir-based ART during pregnancy (of whom 280 were initiated in the first trimester) had no increase in adverse fetal outcomes when compared with 4593 pregnant women who were initiated on efavirenz-based regimens.[9] However, more recent data from Botswana suggest a possible increased risk of neural tube defects in infants born to women who where initiated on dolutegravir before conception. In this preliminary analysis, four (0·94%) of 426 women receiving dolutegravir gave birth to an infant with a neural tube defect, compared with 14 (0·13%) of 11173 women receiving non-dolutegravir-based regimens.[10,11] 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 respect to efficacy, pharmacokinetic data from 29 pregnant women taking dolutegravir 50 mg once daily showed slightly lower concentrations of dolutegravir in the mother during the second and third trimesters, but this did not seem to affect viral outcomes or mother-to-child transmission substantially.[12] Evidence from randomised clinical trials will be necessary to compare maternal and infant outcomes such as safety, pharmacokinetics, and virological efficacy of dolutegravir and other regimens.[13] Two large trials (NCT03048422; NCT03249181) have recently begun but are only enrolling ART-naive pregnant women in the second and third trimesters. Surveillance of maternal and infant outcomes, particularly in women who conceive while receiving dolutegravir, will therefore be important to confirm safety in pregnancy and whether dolutegravir can be recommended for use in women of childbearing age.

***Panel*: Questions that need to be addressed in the roll out of dolutegravir in LMICs**

Safety
- Is the use of dolutegravir in pregnancy associated with adverse birth outcomes?
- What is the frequency and impact of immune reconstitution inflammatory syndrome in severely immunocompromised patients who are initiated on dolutegravir in LMICs?

Monitoring effectiveness
- What is the optimal strategy for viral load and HIV drug resistance 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 maximise virological resuppression?

Drug interactions
- Will coadministration of dolutegravir and rifampicin in patients with HIV and tuberculosis affect 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 mutations that confer resistance to nucleoside reverse transcriptase inhibitors affect the efficacy of dolutegravir-based first-line or second-line regimens?

Implications for second-line ART
- If resistance to dolutegravir-based first-line ART occurs in LMICs, what will be the best second-line regimen and what is the optimal timing for regimen switch?
- For patients who have treatment failure with non-nucleoside reverse transcriptase inhibitor first-line ART, should dolutegravir be used in a second-line regimen?

Cost-effectiveness
- Will replacing current first-line or second-line regimens, or both, with dolutegravir-based regimens be cost-effective?
- How will the roll out of dolutegravir affect the cost-effectiveness of viral load monitoring and HIV drug resistance testing?

LMICs=low-income and middle-income countries. ART=antiretroviral therapy.

Management of patients with viraemia

The transition from efavirenz to a more efficacious dolutegravir-based first-line ART in LMICs is expected to increase levels of viral suppression. However, ART stock-outs, poor retention in care, funding constraints, and increasing numbers of patients that pressurise health-care systems might blunt the effectiveness of this new drug regimen. Expanding viral load coverage will therefore remain crucial to monitor the effectiveness of dolutegravir-based ART and to identify patients with viraemia who need intervention. However, the optimal strategy for viral load monitoring, particularly after detection of viraemia, will need to be reassessed because some previous assumptions about the management of treatment failure in adults will no longer be applicable.[14] In high-income settings, the development of HIV drug resistance in patients receiving dolutegravir has been rare.[15,16] By contrast, in patients receiving first-line ART containing NNRTIs, up to 89% with first viraemia can have mutations associated with HIV drug resistance.[17,18] In LMICs, where drug resistance testing is not widely available, WHO recommends switching to second-line ART if viraemia persists for more than 3 months, despite adequate adherence. Although effective in clinical trials,[19] these guidelines are often poorly implemented in public sector programmes, leading to ongoing viraemia, morbidity, and the emergence and transmission of drug-resistant HIV.[4,20,21] The roll out of first-line dolutegravir could allow these guidelines to be simplified because viraemia is likely to be caused by poor adherence rather than HIV drug resistance, meaning that the number of patients switching from first-line dolutegravir to a second-line regimen should be greatly reduced. Instead, management of viraemia should shift from treating HIV drug resistance to improving adherence.

Adherence interventions

Various adherence interventions have been assessed in LMICs, but evidence of an effect on virological suppression is weak.[22] Adherence relies on a complex combination of medical, behavioural, social, and structural factors[23] that can be difficult to influence. Moreover, accurately measuring adherence is challenging.[24] For patients receiving NNRTI-based first-line ART, a suppressed viral load suggests good adherence, but a high viral load could be caused by HIV drug resistance rather than contemporaneous poor adherence. In patients who do not adhere to their dolutegravir treatment, the short half-life[25] of dolutegravir compared with efavirenz could result in faster viral rebound, whereas improved adherence should be reflected in a rapid return to viral suppression. As dolutegravir use and viral load testing coverage increase, monitoring adherence and response to adherence interventions should therefore become easier. This presents an important opportunity to develop and implement evidence-based adherence interventions to achieve early viral resuppression.[26] In this context, point-of-care viral load testing might be particularly useful to identify adherence problems rapidly, to monitor the effect of counselling, and to triage patients efficiently into differentiated care services.[27] Novel point-of-care adherence assays (eg, measuring urine tenofovir concentrations) are being developed, and their potential as additional or alternative monitoring strategies should be assessed as part of dolutegravir roll out.[28]

Tuberculosis treatment and prevention

Uncertainty still surrounds the optimal dosing of dolutegravir when coadministered with rifampicin, a key drug in treating the large numbers of people co-infected with HIV and *Mycobacterium tuberculosis* in LMICs. Rifampicin induces the liver enzymes uridine glucu-ronosyltransferase 1A1 and cytochrome P450 3A4, which increase dolutegravir metabolism and decrease circulating drug concentrations.[29] Interim data from the INSPIRING trial[30] suggest that doubling the dolutegravir dose to 50 mg twice daily when given with rifampicin could be effective, safe, and tolerable for patients with

 Published online June 5, 2018 http://dx.doi.org/10.1016/S2352-3018(18)30093-6

HIV and tuberculosis, although full outcomes at 48 weeks are forthcoming. Adjusting the dolutegravir dose might be challenging in public sector programmes and would negate the benefits of a once-daily regimen, meaning that further work is needed to assess the clinical effect of rifampicin co-administered with once-daily dolutegravir.[29] Some countries are therefore opting to continue first-line efavirenz-based ART in patients receiving tuberculosis treatment.[31] For latent tuberculosis, results from the BRIEF-TB trial[32] mean that 1 month of daily isoniazid plus rifapentine is being considered as an effective, safe, and short alternative to isoniazid monotherapy. However, issues with cost and appropriate co-formulations are unresolved, and a phase 1 drug interaction study of dolutegravir and high-dose, weekly isoniazid plus rifapentine was stopped early because of serious toxic effects.[33] The precise underlying mechanisms remain unclear, and whether this interaction persists at the low, daily doses used in BRIEF-TB[32] needs urgent assessment. In the interim, preventive therapy with daily isoniazid is likely to remain the preferred option in countries that roll out dolutegravir because other short-course regimens contain rifampicin and would need dolutegravir dose adjustments.

IRIS

Evidence from European cohort studies has suggested a higher risk of IRIS, particularly tuberculosis-related IRIS, in patients taking INSTIs than in patients receiving NNRTI or protease inhibitor (PI)-based regimens.[34–36] However, these findings were not replicated in a subanalysis of the multicentre, randomised, factorial REALITY trial,[37] which included 1805 ART-naive children and adults in eastern and southern Africa who had CD4 counts less than 100 cells per µL. 12 weeks of raltegravir intensification alongside standard ART initiation did not affect the incidence or mortality of IRIS. With respect to dolutegravir-based ART, no association between dolutegravir and IRIS was found in a meta-analysis[38] of randomised controlled trials; however, these studies had only 13 cases of IRIS between them and might not be generalisable to LMICs because they excluded patients with US Centers for Disease Control and Prevention grade C disease. During the Brazilian roll out, only one case of IRIS was reported in the first 26 070 ART-naive patients who were initiated on dolutegravir.[39] Although these emerging findings are reassuring, further data from randomised trials such as the ADVANCE study[40] and from cohort studies embedded in public sector programmes will be important to establish the incidence of IRIS and its effect on mortality in patients receiving dolutegravir in LMICs.[41]

HIV drug resistance and resistance testing

Recent evidence of dolutegravir resistance developing after use in monotherapy[42] means that the long-term implications of combining dolutegravir with a substantially compromised nucleoside reverse transcriptase inhibitor (NRTI) backbone must be considered. In LMICs, the paucity of drug resistance testing and incomplete viral load coverage could lead to functional dolutegravir monotherapy in several situations. First, adults with pretreatment drug resistance (particularly those with previous ART exposure) might have undetected NRTI mutations associated with reduced susceptibility to tenofovir and lamivudine.[21] Second, in southern Africa, long delays in management of viraemia have been documented, which could allow NRTI resistance to emerge in patients taking dolutegravir.[20,43] Third, several accounts exist of high prevalences of Lys65Arg and Met184Val mutations in adults living in LMICs who have virological failure with NNRTI-based first-line ART.[44] People who switch from a combination of tenofovir, emtricitabine, and efavirenz to a combination of tenofovir, lamivudine, and dolutegravir without confirmation of viral suppression might therefore be at increased risk of acquired HIV drug resistance to dolutegravir. Understanding the risks and benefits of such a strategy is a high-priority research question because several ART programmes are not using viral load testing in the transition to dolutegravir-based first-line ART.[31] Although the advantages of dolutegravir might justify this approach, programmes should be supported in accelerating roll out of viral load testing and implementing HIV drug resistance surveillance systems to guide policy decisions.

Results from the DAWNING trial[45] suggest that dolutegravir-based regimens can be efficacious in the presence of NRTI resistance. Patients receiving first-line NNRTI-based ART and who had virological failure were randomly assigned to receive either a dolutegravir-based or a PI-based second-line regimen. In both the dolutegravir and PI groups, patients with only one predicted active NRTI did better than those patients with two predicted active NRTIs,[45] which confirms findings from other studies of PI-based second-line regimens.[46–48] However, in all these studies, the number of patients who received a tenofovir-based first-line regimen and then received tenofovir in their second-line regimen was low. Furthermore, confounding because of difficulties of accurately measuring and controlling for poor adherence might explain some of these findings. In short, little high-quality evidence supports the long-term efficacy of dolutegravir alongside a compromised NRTI backbone.[49,50] As dolutegravir is rolled out, surveillance of HIV drug resistance will therefore be crucial to determine the incidence of resistance to both NRTIs and dolutegravir, the effect on clinical outcomes, and the need for, timing, and cost-effectiveness of HIV drug resistance testing in public sector programmes. LMICs will need to develop the capacity to test for INSTI drug resistance and could be aided by new and targeted HIV drug resistance testing platforms or point-of-care resistance assays.[51] If affordable and effective, these assays could be incorporated into algorithms to screen

for and manage treatment failure in patients taking first-line dolutegravir and to guide selection of subsequent second-line regimens, if necessary.

Replacing first-line and second-line ART

In several LMICs, priority for initiation of dolutegravir-based first-line ART has been given to ART-naive patients, followed by patients taking NNRTI-based first-line regimens. Although some patients might request to remain on effective NNRTI regimens, programmatic factors (such as simplification of supply chain, ART tenders, and training) mean that transitioning most stable patients to dolutegravir-based ART should be encouraged, as long as concerns with safety in pregnancy have been addressed. There is also interest in replacing existing second-line regimens with dolutegravir. In the DAWNING trial,[45] a dolutegravir-based regimen was superior to a PI-based regimen in patients who had virological failure with first-line NNRTI-based ART. All participants in this study had at least one predicted fully active NRTI, with HIV drug resistance testing used to select the second-line NRTI backbone; however, this approach is not feasible in most LMICs at present. Nevertheless, results from DAWNING, coupled with substantial cost savings,[52] have led some countries to consider dolutegravir as a replacement for both first-line and second-line ART.[53] In view of the existing evidence, and until HIV drug resistance testing becomes available, it would seem prudent to ensure that patients who have treatment failure with 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 strategy would include patients with WHO-defined clinical or immunological failure. In most cases, the fixed-dose combination of tenofovir, lamivudine, and dolutegravir could therefore not be used for second-line ART.

Conclusion

The roll out of dolutegravir as first-line ART has potential to become another important step in the evolution of HIV treatment programmes in LMICs. The superior durability of this INSTI should simplify treatment pathways and, when coupled with increasing viral load coverage, present an opportunity to focus on improving ART adherence and increasing levels of viral suppression. Despite these benefits, several 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 HIV drug resistance surveillance will allow health systems to maximise the potential benefits of this exciting new regimen.

Contributors

JD, RL, and NG conceived and drafted the manuscript. PKD, KN, TdO, YP, and SSAK critically revised the manuscript. JD, RL, PKD, KN, TO, YP, SSAK, and NG consented to publication.

Declaration of interests

JD, PKD, 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 loaned the GeneXpert instruments for this study at no cost. All other authors declare no competing interests.

Acknowledgments

JD, PKD, 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, an initiative of the Department of Science and Technology.

References

1 UNAIDS. New high-quality antiretroviral therapy to be launched in South Africa, Kenya and over 90 low- and middle-income countries at reduced price. 2017. http://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2017/september/20170921_TLD (accessed Nov 17, 2017).

2 Phillips AN, Cambiano V, Nakagawa F, et al. Cost-effectiveness of public-health policy options in the presence of pretreatment NNRTI drug resistance in sub-Saharan Africa: a modelling study. *Lancet HIV* 2018; **5:** e146–54.

3 Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir–lamivudine for the treatment of HIV-1 infection. *N Engl J Med* 2013; **369:** 1807–18.

4 WHO. HIV drug resistance report 2017. July, 2017. http://www.who.int/hiv/pub/drugresistance/hivdr-report-2017/en/ (accessed April 11, 2018).

5 WHO. The public health response to pretreatment HIV drug resistance. July, 2017 http://apps.who.int/iris/bitstream/10665/255880/1/9789241550055-eng.pdf?ua=1 (accessed April 11, 2018).

6 USAID Global Health Supply Chain Program—Procurement and Supply Management. The dolutegravir opportunity: managing supply chain risk for the introduction of a new antiretroviral (ARV) medicine. Oct 19, 2017. https://www.ghsupplychain.org/sites/default/files/2017-10/HIV-AIDS TLD 1 pager.pdf (accessed Feb 6, 2018).

7 Thorne C, Favarato G, Peters H, et al. Pregnancy and neonatal outcomes following prenatal exposure to dolutegravir. 9th IAS Conference on HIV Science; Paris, France; July 23–26, 2017. Abstract 4549.

8 Vannappagari V, Albano J, Ragone L, et al. Dolutegravir use during pregnancy and birth outcomes: data from the Antiretroviral Pregnancy Registry (APR). 9th IAS Conference on HIV Science. Paris, France; July 23–26, 2017. Abstract 68.

9 Zash R, Jacobson DL, Diseko M, et al. Comparative safety of dolutegravir-based or efavirenz-based antiretroviral treatment started during pregnancy in Botswana: an observational study. *Lancet Glob Health*; in press.

10 WHO. Statement on DTG. May 18, 2018. http://www.who.int/medicines/publications/drugalerts/Statement_on_DTG_18May_2018final.pdf?ua=1 (accessed May 18, 2018).

11 PEPFAR. Statement on potential safety issue affecting women living with HIV using dolutegravir at the time of conception. May 18, 2018. https://www.pepfar.gov/press/releases/282221.htm (accessed May 21, 2018).

12 Mulligan N, Best BM, Wang J, et al. Dolutegravir pharmacokinetics in pregnant and postpartum women living with HIV. *AIDS* 2018; **32:** 729–37.

13 Slogrove AL, Clayden P, Abrams EJ. Toward a universal antiretroviral regimen: special considerations of pregnancy and breast feeding. *Curr Opin HIV AIDS* 2017; **12:** 359–68.

14 Barnabas RV, Revill P, Tan N, Phillips A. Cost-effectiveness of routine viral load monitoring in low- and middle-income countries: a systematic review. *J Int AIDS Soc* 2017; **20:** 50–61.

15 Anstett K, Brenner B, Mesplede T, Wainberg MA. HIV drug resistance against strand transfer integrase inhibitors. *Retrovirology* 2017; **14:** 36.

16 Lepik KJ, Harrigan PR, Yip B, et al. Emergent drug resistance with integrase strand transfer inhibitor-based regimens. *AIDS* 2017; **31:** 1425–34.

17 Hunt GM, Dokubo EK, Takuva S, et al. Rates of virological suppression and drug resistance in adult HIV-1-positive patients attending primary healthcare facilities in South Africa. *J Antimicrob Chemother* 2017; **72:** 3141–48.

18 Boender TS, Kityo CM, Boerma RS, et al. Accumulation of HIV-1 drug resistance after continued virological failure on first-line ART in adults and children in sub-Saharan Africa. *J Antimicrob Chemother* 2016; **71:** 2918–27.

19 Paton NI, Kityo C, Hoppe A, et al. Assessment of second-line antiretroviral regimens for HIV therapy in Africa. *N Engl J Med* 2014; **371:** 234–47.

20 Murphy RA, Court R, Maartens G, Sunpath H. Second-line antiretroviral therapy in sub-Saharan Africa: it's time to mind the gaps. *AIDS Res Hum Retroviruses* 2017; **33:** 1181–84.

21 Gupta RK, Gregson J, Parkin N, et al. HIV-1 drug resistance before initiation or re-initiation of first-line antiretroviral therapy in low-income and middle-income countries: a systematic review and meta-regression analysis. *Lancet Infect Dis* 2017; **18:** 346–55.

22 Kanters S, Park JJH, Chan K, et al. Interventions to improve adherence to antiretroviral therapy: a systematic review and network meta-analysis. *Lancet HIV* 2017; **4:** e31–40.

23 Heestermans T, Browne JL, Aitken SC, Vervoort SC, Klipstein-Grobusch K. Determinants of adherence to antiretroviral therapy among HIV-positive adults in sub-Saharan Africa: a systematic review. *BMJ Glob Heal* 2016; **1:** e000125.

24 Haberer JE. Actionable adherence monitoring to optimise intervention. *Lancet HIV* 2017; **4:** e5–6.

25 Cottrell ML, Hadzic T, Kashuba ADM. Clinical pharmacokinetic, pharmacodynamic and drug-interaction profile of the integrase inhibitor dolutegravir. *Clin Pharmacokinet* 2013; **52:** 981–94.

26 Bonner K, Mezochow A, Roberts T, Ford N, Cohn J. Viral load monitoring as a tool to reinforce adherence: a systematic review. *J Acquir Immune Defic Syndr* 2013; **64:** 74–78.

27 Dorward J, Drain PK, Garrett N. Point-of-care viral load testing and differentiated HIV care. *Lancet HIV* 2018; **5:** e8–9.

28 Cressey TR, Siriprakaisil O, Klinbuayaem V, et al. A randomized clinical pharmacokinetic trial of tenofovir in blood, plasma and urine in adults with perfect, moderate and low PrEP adherence: the TARGET study. *BMC Infect Dis* 2017; **17:** 496.

29 Maartens G, Boffito M, Flexner CW. Compatibility of next-generation first-line antiretrovirals with rifampicin-based antituberculosis therapy in resource limited settings. *Curr Opin HIV AIDS* 2017; **12:** 355–58.

30 Dooley K, Kaplan R, Mwelase N, et al. Safety and efficacy of dolutegravir-based ART in TB/HIV coinfected adults at week 24. Conference on Retroviruses and Opportunistic Infections. Boston, MA, USA; March 4–7, 2018. Abstract 33.

31 WHO. Transition to new antiretroviral drugs in HIV programmes: clinical and programmatic considerations. July, 2017. http://apps.who.int/iris/bitstream/10665/255887/1/WHO-HIV-2017.23-eng.pdf?ua=1 (accessed Feb 7, 2018).

32 Swindells S, Ramchandani R, Gupta A, et al. One month of rifapentine/isoniazid to prevent TB in people with HIV: BRIEF-TB/A5279. Conference on Retroviruses and Opportunistic Infections; Boston, MA, USA; March 4–7, 2018. Abstract 5279.

33 Brooks KM, George JM, Pau AK, et al. Cytokine-mediated systemic adverse drug reactions in a drug–drug interaction study of dolutegravir with once-weekly isoniazid and rifapentine. *Clin Infect Dis* 2018; published online Feb 3. DOI:10.1093/cid/ciy082.

34 Wijting I, Rokx C, Wit F, et al. Integrase inhibitors are an independent risk factor for IRIS: an ATHENA cohort study. Conference on Retroviruses and Opportunistic Infections; Seattle, WA, USA. Feb 13–16, 2017. Abstract 731.

35 Dutertre M, Cuzin L, Demonchy E, et al. Initiation of antiretroviral therapy containing integrase inhibitors increases the risk of iris requiring hospitalization. *J Acquir Immune Defic Syndr* 2017; **76:** e23–26.

36 Psichogiou M, Basoulis D, Tsikala-Vafea M, Vlachos S, Kapelios CJ, Daikos GL. Integrase strand transfer inhibitors and the emergence of immune reconstitution inflammatory syndrome (IRIS). *Curr HIV Res* 2017; **15:** 405–10.

37 Gibb D, Szubert A, Chidziva E, et al. Impact of raltegravir intensification of first-line ART on IRIS in the REALITY trial. Conference on Retroviruses and Opportunistic Infections; Boston, MA, USA; March 4–7, 2018. Abstract 23.

38 Hill AM, Mitchell N, Hughes S, Pozniak AL. Risks of cardiovascular or central nervous system adverse events and immune reconstitution inflammatory syndrome, for dolutegravir versus other antiretrovirals. *Curr Opin HIV AIDS* 2018; **13:** 102–11.

39 Batista C, Meireles M, Fonseca F, et al. Safety profile of dolutegravir: real-life data of large scale implementation in Brazil. Conference on Retroviruses and Opportunistic Infections; Boston, MA, USA; March 4–7, 2018. Abstract 494.

40 Venter WDF, Clayden P, Serenata C. The ADVANCE study. *Curr Opin HIV AIDS* 2017; **12:** 351–54.

41 Jibril H. Enhanced ARV monitoring in countries: Botswana. 9th IAS Conference on HIV Science; Paris, France; July 23–26, 2017: Abstract 4610.

42 Wijting I, Rokx C, Boucher C, et al. Dolutegravir as maintenance monotherapy for HIV (DOMONO): a phase 2, randomised non-inferiority trial. *Lancet HIV* 2017; **4:** e547–54.

43 Manasa J, Lessells RJ, Skingsley A, et al. High-levels of acquired drug resistance in adult patients failing first-line antiretroviral therapy in a rural HIV treatment programme in KwaZulu-Natal, South Africa. *PLoS One* 2013; **8:** e72152.

44 Gregson J, Tang M, Ndembi N, et al. Global epidemiology of drug resistance after failure of WHO recommended first-line regimens for adult HIV-1 infection: a multicentre retrospective cohort study. *Lancet Infect Dis* 2016; **16:** 565–75.

45 Aboud M, Kaplan R, Lombaard J, et al. Superior efficacy of dolutegravir (DTG) plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) compared with lopinavir/ritonavir (LPV/RTV) plus 2 NRTIs in second-line treatment: interim data from the DAWNING study. In: 9th IAS Conference on HIV Science; Paris, France; July 23–26, 2017. Abstract 5613.

46 Boyd MA, Moore CL, Molina JM, et al. Baseline HIV-1 resistance, virological outcomes, and emergent resistance in the SECOND-LINE trial: an exploratory analysis. *Lancet HIV* 2015; **2:** 42–51.

47 La Rosa A, Harrison L, Taiwo B, et al. Raltegravir in second-line antiretroviral therapy in resource- limited settings (SELECT): a randomised, phase 3, non-inferiority study. *Lancet HIV* 2016; **3:** e247–58.

48 Paton NI, Kityo C, Thompson J, et al. Nucleoside reverse-transcriptase inhibitor cross-resistance and outcomes from second-line antiretroviral therapy in the public health approach: an observational analysis within the randomised, open-label, EARNEST trial. *Lancet HIV* 2017; **4:** e341–48.

49 Sörstedt E, Carlander C, Flamholc L, et al. Effect of dolutegravir in combination with nucleoside reverse transcriptase inhibitors on people living with HIV who have pre-existing nucleoside reverse transcriptase inhibitor mutations. *Int J Antimicrob Agents* 2018; **51:** 733–38.

50 Demarest J, Underwood M, St. Clair M, Dorey D, Brown D, Zolopa A. Short communication: dolutegravir-based regimens are active in integrase strand transfer inhibitor-naive patients with nucleoside reverse transcriptase inhibitor resistance. *AIDS Res Hum Retroviruses* 2018; **34:** 343–46.

51 Duarte HA, Panpradist N, Beck IA, et al. Current status of point-of-care testing for human immunodeficiency virus drug resistance. *J Infect Dis* 2017; **216:** S824–28.

52 Phillips A, Venter F, Apollo T, et al. Cost-effectiveness of the introduction of dolutegravir in first or second-line ART regimens in sub-Saharan Africa. 9th IAS Conference on HIV Science; Paris, France; July 23–26, 2017. Abstract 1604.

53 Hill AM, Venter F. The unexpected success of NRTIs in second-line treatment. *Lancet Infect Dis* 2018; **18:** 3–5.