

improved treatment monitoring and drug availability should narrow the gap between treatment failure and switching to second-line ART. The ultimate goal is to see improvements in the quality of life of children living with HIV and life expectancy similar to the general population in resource-limited settings, as has been achieved in adults living with HIV in Thailand.⁸

Stephen J Kerr, *Thanyawee Puthanakit

HIV-NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand (SJK, TP); and Research Affairs (SJK) and Department of Pediatrics (TP), Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
 thanyawee.p@chula.ac.th

We declare no competing interests.

1 The Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) Global Cohort Collaboration. Incidence of switching to second-line antiretroviral therapy and associated factors in children with HIV: an international cohort collaboration. *Lancet HIV* 2019; **6**: e105–15.

- 2 Wools-Kaloustian K, Marete I, Ayaya S, et al. Time to first-line ART failure and time to second-line ART switch in the leDEA pediatric cohort. *J Acquir Immune Defic Syndr* 2018; **78**: 221–30.
- 3 Dorward J, Drain PK, Garrett N. Point-of-care viral load testing and differentiated HIV care. *Lancet HIV* 2018; **5**: e8–9.
- 4 HHS Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Guidelines for the use of antiretroviral agents in pediatric HIV infection. AIDSinfo. <http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf> (accessed Nov 6, 2018).
- 5 Jesson J, Koumakpai S, Diagne NR, et al. Effect of age at antiretroviral therapy initiation on catch-up growth within the first 24 months among HIV-infected children in the leDEA west African pediatric cohort. *Pediatr Infect Dis J* 2015; **34**: e159–68.
- 6 Puthanakit T, Ananworanich J, Vonthanak S, et al. Cognitive function and neurodevelopmental outcomes in HIV-infected children older than 1 year of age randomized to early versus deferred antiretroviral therapy: the PREDICT neurodevelopmental study. *Pediatr Infect Dis J* 2013; **32**: 501–08.
- 7 Teeraananchai S, Kerr SJ, Puthanakit T, et al. Attrition and mortality of children receiving antiretroviral treatment through the universal coverage health program in Thailand. *J Pediatr* 2017; **188**: 210–16.
- 8 Teeraananchai S, Chaivooth S, Kerr SJ, et al. Life expectancy after initiation of combination antiretroviral therapy in Thailand. *Antivir Ther* 2017; **22**: 393–402.



Dolutegravir in sub-Saharan Africa: context is crucial

Published Online
 November 29, 2018
[http://dx.doi.org/10.1016/S2352-3018\(18\)30331-X](http://dx.doi.org/10.1016/S2352-3018(18)30331-X)
 See [Articles](#) page e116

A new, low-cost, generic, fixed-dose antiretroviral therapy (ART) combination containing tenofovir, lamivudine, and dolutegravir is being introduced in many countries in sub-Saharan Africa.¹ In *The Lancet HIV*, Andrew Phillips and colleagues² address two important concerns regarding the rollout of this regimen. First, what are the overall risks and benefits of use in women of child bearing potential, given that there is a possible increased risk of neural tube defects?³ Second, what are the risks of functional dolutegravir monotherapy in those who already have resistance to tenofovir and lamivudine⁴ if people on ART are transitioned to tenofovir, lamivudine, and dolutegravir without confirmation of viral suppression? The authors used the HIV Synthesis Model to compare policy scenarios in a hypothetical southern African population.² The model projected that a policy of tenofovir, lamivudine, and dolutegravir for all would give the best overall improvement in health outcomes, improved viral suppression, and slightly reduced mother-to-child HIV transmission, and would be cost-saving over a 20 year time horizon, when compared with continuing a policy of efavirenz-based first-line ART, or tenofovir, lamivudine, and dolutegravir dependent on confirmed viral suppression among those currently on ART, or tenofovir, lamivudine, and dolutegravir dependent

on women not wanting (more) children. Overall, the combined benefits of wider dolutegravir use would offset small increases in predicted neural tube defects.²

The authors went to great lengths to do extensive sensitivity analyses to support the robustness of their findings.² Nonetheless, as with all modelling studies, these projections depend on the assumptions used, and a key limitation of this analysis remains that there are substantial uncertainties in the evidence base for dolutegravir use in low-income and middle-income countries.^{5–7} Data from the NAMSAL trial⁸ in Cameroon raise questions on the effectiveness of dolutegravir in this setting. In ART-naive adults, dolutegravir did not show superior efficacy after 48 weeks compared with efavirenz 400 mg once daily.⁸ Among patients with a high pre-ART viral load (>500 000 copies per mL), less than 60% achieved viral suppression at less than 50 copies per mL.⁸ No dolutegravir-associated mutations were detected in three participants with viral load greater than 1000 copies per mL.⁸ However, information on mutational patterns of dolutegravir resistance and treatment outcomes in the context of HIV-1 non-B subtypes, and infrequent virological monitoring in low-income and middle-income countries, is scarce. Notably, in the present study,² the modelled sensitivity analyses in which dolutegravir potency was assumed to be equal

to that of efavirenz showed only marginal benefits of tenofovir, lamivudine, and dolutegravir for all compared with tenofovir, lamivudine, and dolutegravir dependent on confirmed viral suppression.² Therefore, expanded use of viral load and HIV drug resistance testing⁹ is warranted to evaluate the effect of persistent low-level viraemia¹⁰ and the emergence of resistance to dolutegravir-based regimens.

Whether dolutegravir is associated with an increased risk of neural tube defects is unknown. Ongoing surveillance in Botswana and worldwide will be crucial to better guide dolutegravir use in women of child bearing potential.³ Drug development pipelines should ensure that efficacy and safety are established among all populations in which drugs will be used, including pregnant women.⁵ Meanwhile, ART programmes should ensure access to reliable contraception for women and men to reduce unwanted pregnancies and the potential risk of neural tube defects. For women who want children, the model suggests that the benefits of dolutegravir should not be withheld because of the potential risk of neural tube defects in a child that has not yet been conceived.² However, some women might wish to remain on efavirenz-based regimens and, where possible, ART programmes should allow women to do so.

The modelled projections² provide guidance to policy makers as we await further scientific and operational data.^{3,5,11} But how should they be applied in the wide spectrum of different settings in sub-Saharan Africa? Populations, regulatory frameworks, human resources, ART supply chains, viral load testing, access to contraception, and prevalence of HIV drug resistance vary across the region. For example, in countries such as South Africa, in which laboratory services are more developed, a policy of tenofovir, lamivudine, and dolutegravir dependent on confirmed viral suppression could increase viral load testing and facilitate referral into more efficient models of differentiated HIV care.¹² These potential additional benefits were not accounted for in the model.² Therefore, although this study² provides important insights, tenofovir, lamivudine, and dolutegravir for all should not be implemented uniformly across the region. Instead, these findings should be interpreted and applied within different contexts and

in consultation with communities of people living with HIV to maximise the benefits of dolutegravir, while respecting the right to the best available treatment with the resources available.

*Jienchi Dorward, Raph L Hamers

Nuffield Department of Primary Care Health Sciences (JD) and Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine (RLH), University of Oxford, Oxford OX2 6GG, UK; Centre for the AIDS Programme of Research in South Africa (CAPRISA), University of KwaZulu-Natal, Durban, South Africa (JD); Eijkman-Oxford Clinical Research Unit, Eijkman Institute for Molecular Biology, and Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia (RLH); and Amsterdam Institute for Global Health and Development, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands (RLH)
jienchi.dorward@phc.ox.ac.uk

We declare no competing interests. JD is funded by the Wellcome Trust PhD Programme for Primary Care Clinicians (203921/Z/16/Z). RLH is funded by the Wellcome Trust.

Copyright 2018 © The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

- UNAIDS. New high-quality antiretroviral therapy to be launched in South Africa, Kenya and over 90 low-and middle-income countries at reduced price. Sept 21, 2017. http://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2017/september/20170921_TLD (accessed Nov 18, 2017).
- Phillips AN, Venter F, Havlir D, et al. Risks and benefits of dolutegravir-based antiretroviral drug regimens in sub-Saharan Africa: a modelling study. *Lancet HIV* 2018; published online Nov 29. [http://dx.doi.org/10.1016/S2352-3018\(18\)30317-5](http://dx.doi.org/10.1016/S2352-3018(18)30317-5).
- Zash R, Makhema J, Shapiro RL. Neural-tube defects with dolutegravir treatment from the time of conception. *N Engl J Med* 2018; **379**: 979–81.
- Gregson J, Tang M, Ndembu 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.
- Vitoria M, Hill A, Ford N, et al. The transition to dolutegravir and other new antiretrovirals in low-income and middle-income countries. *AIDS* 2018; **32**: 1551–61.
- Dorward J, Lessells R, Drain PK, et al. Dolutegravir for first-line antiretroviral therapy in low-income and middle-income countries: uncertainties and opportunities for implementation and research. *Lancet HIV* 2018; **5**: e400–04.
- Hamers RL, Rinke de Wit TF, Holmes CB. HIV drug resistance in low-income and middle-income countries. *Lancet HIV* 2018; **5**: e588–96.
- Cournil A, Kouanfack C, Eymard-Duvernay S, et al. Dolutegravir versus an efavirenz 400 mg based regimen for the initial treatment of HIV-infected patients in Cameroon: 48-week efficacy results of the NAMSAL ANRS 12313 trial. HIV Glasgow. Glasgow, Scotland, UK; Oct 28–31, 2018.
- Inzaule SC, Ondo P, Peter T, et al. Affordable HIV drug-resistance testing for monitoring of antiretroviral therapy in sub-Saharan Africa. *Lancet Infect Dis* 2016; **16**: e267–75.
- Hermans LE, Moorhouse M, Carmona S, et al. Effect of HIV-1 low-level viraemia during antiretroviral therapy on treatment outcomes in WHO-guided South African treatment programmes: a multicentre cohort study. *Lancet Infect Dis* 2018; **18**: 188–97.
- Venter WDF, Clayden P, Serenata C. The ADVANCE study: a groundbreaking trial to evaluate a candidate universal antiretroviral regimen. *Curr Opin HIV AIDS* 2017; **12**: 351–54.
- Phillips A, Shroufi A, Vojnov L, et al. Sustainable HIV treatment in Africa through viral-load-informed differentiated care. *Nature* 2015; **528**: 568–76.