Dolutegravir in sub-Saharan Africa: context is crucial

Lancet HIV 2018
Published Online
November 29, 2018
http://dx.doi.org/10.1016/S2352-3018(18)30331-X
See Online/Articles
http://dx.doi.org/10.1016/S2352-3018(18)30317-5

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 colleagues[2] 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 lamivudine[4] 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 trial[8] 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 testing[9] is warranted to evaluate the effect of persistent low-level viraemia[10] 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 projections[2] 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 study[2] 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.

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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.

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