Resistance to first-line ART and a role for dolutegravir

In view of increasing prevalence of HIV pretreatment drug resistance to non-nucleoside reverse transcriptase inhibitor (NNRTI) in sub-Saharan Africa, Andrew Phillips and colleagues[1] present a convincing case in The Lancet HIV for the cost saving and cost-effectiveness of transitioning from a NNRTI-based first-line antiretroviral treatment (ART) regimen to a dolutegravir-based ART regimen in this setting. This is particularly important because proposed reductions in US foreign aid to sub-Saharan Africa will probably increase pressure on national programmes to address both the costs and effectiveness of HIV strategies.[2]

By contrast with funding cutbacks, a recent announcement[3] of a 30% reduction of the annual treatment price of fixed-dose generic dolutegravir regimen to US$75 is encouraging. However, rapid changes in both funding and drug pricing highlights a challenge for modelling studies because regimen costs are subject to market forces and international lobbying, making 20 year projections implausible.

The authors' individual-based simulation model projected cost saving and cost-effectiveness of several strategies in which dolutegravir was used as first-line treatment instead of efavirenz. The authors however did not consider dolutegravir as a second-line option or the potential effect of a cost reduction in pretreatment drug resistance testing to guide first-line treatment choices. In a recent study[4] of dolutegravir and two nucleoside reverse transcriptase inhibitors (NRTIs) compared with a WHO-recommended protease inhibitor ritonavir-boosted lopinavir and two NRTIs as second-line treatments, dolutegravir was superior to the protease inhibitor. This indicates that dolutegravir potentially has an important place as a second-line regimen in resource-limited settings where costs of protease inhibitors are prohibitive. The cost advantage of a cost-effective, first-line NNRTI-based regimen, followed by a cost-effective, dolutegravir-based second-line regimen could be substantial, and the potential savings on the diminished use of protease inhibitors could possibly offset the cost of pretreatment drug resistance testing to guide treatment choice in first line.

Although we agree that first-line ART strategy should change in view of increasing mortality because of pretreatment NNRTI drug resistance, and we note that the decrease in the annual cost of dolutegravir make it a very desirable first-line option, we see several challenges. The authors do comment on some of these, namely that not enough evidence exists to guide dolutegravir use in pregnancy and tuberculosis and the possibility of increased risk of immune response inflammatory syndrome (IRIS), particularly in individuals with low CD4 cell counts,[5] but they do not seem to consider these factors as caveats for use in first-line therapy. Pregnancy, tuberculosis, and IRIS are common in patients receiving ART in sub-Saharan Africa, and ongoing trials are testing dolutegravir in pregnant women and in patients with tuberculosis, but outcomes of these are not yet known.[6-8]

In response to the paucity of evidence to guide dolutegravir use in all patients, the introduction of first-line dolutegravir could be restricted to selected patient groups, but this would mean a transition to individualised treatment regimens as opposed to a public health approach of standardised first-line and second-line regimens. With large numbers of patients in sub-Saharan Africa needing effective ART, restricted budgets, and decreasing international funding, new strategies are urgently required to guide both cost-effective first-line and second-line ART to meet WHO's 90-90-90 targets in the region.

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3 Clinton Health Access Initiative. ARV market report. Sept 28, 2017. https://clintonhealthaccess.org/content/uploads/2017/09/2017-ARV-Market-Report_Final.pdf (accessed Oct 4, 2017).

4 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. IAS 2017; Paris, France; July 23–26, 2017. Abstract TUAB0105LB.

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7   Clayden P, HIV i-Base. Fit for purpose. Antiretroviral treatment optimisation for adults and children. July, 2017. http://i-base.info/htb/32022#4 (accessed Oct 4, 2017).

8   ClinicalTrials.gov. ADVANCE study of DTG + TAF + FTC vs DTG + TDF + FTC and EFV + TDF+FTC in first-line antiretroviral therapy (ADVANCE). April 20, 2017. http://clinicaltrials.gov/show/NCT03122262 (accessed Oct 4, 2017).