

Decision-Making in a Time of Uncertainty: Dolutegravir for Reproductive-Age Women

Plans for a global dolutegravir-based antiretroviral therapy (ART) rollout were unexpectedly disrupted in May 2018 by preliminary results from the Botswana Tsepamo birth surveillance study that showed a higher-than-expected rate of neural tube defects (NTDs) in infants born to women receiving dolutegravir-based ART (0.94%) than in those receiving efavirenz-based ART (0.05%) at conception (1). These data brought into sharp focus the complexity of decision-making regarding treatment for pregnant women, the lack of data on new drugs in pregnancy, and the need for improved pharmacovigilance systems to evaluate safety when broadly introducing new drugs into populations that include women of child-bearing potential.

The advantages of dolutegravir-based over current efavirenz-based ART include more rapid viral suppression, better tolerability, and potency against nonnucleoside reverse transcriptase inhibitor-resistant virus, an issue of major importance in settings of high HIV burden (2, 3). After the preliminary Tsepamo results, public health policy discussions focused on the potential risk for NTDs with dolutegravir-based ART. Interim World Health Organization (WHO) guidance recommended dolutegravir as a preferred first- and second-line ART regimen, with a caution regarding use in women of child-bearing potential (4). Several countries responded by restricting dolutegravir to men and to women beyond reproductive age; this was rapidly followed by objections from women living with HIV, advocating for autonomy over health decisions, access to family planning, and the right to dolutegravir-based ART (5).

Providing women of child-bearing potential with access to effective ART while ensuring fetal safety if pregnancy occurs requires a careful balancing of risks and benefits to both the woman and her fetus. Although teratogenicity is an important consideration when providing treatment to women of child-bearing potential, ART decisions require consideration of other factors, such as maternal health, side effects that may affect treatment adherence, fertility and desire for pregnancy, prevention of perinatal and sexual transmission, and the local prevalence of drug resistance. In their current article in *Annals*, Dugdale and colleagues (6) provide an elegant model that explores 3 ART policies for women of child-bearing potential—efavirenz for all, dolutegravir for all, and the WHO approach of using efavirenz without and dolutegravir with contraception—and the outcomes of maternal and child deaths, sexual and perinatal transmission, and NTDs. Their model uses the July 2018 Tsepamo data on NTD risk (0.05% with efavirenz and 0.67% with dolutegravir), a range of possible efavirenz efficacies, and age-stratified fertility rates (7). While we await definitive data to

refute or confirm the preliminary Tsepamo findings, this well-designed model allows examination of various outcomes across a range of potential NTD rates.

Although models are limited by the assumptions required to construct them, they allow for consideration of several scenarios through sensitivity analyses. Dugdale and colleagues (6) varied several parameters to explore a range of possible outcomes in their model. In the end, they found that regardless of inputs, dolutegravir for all outperformed other scenarios, resulting in the smallest number of deaths among women and the fewest HIV transmission events, with the tradeoff of slightly more pediatric deaths. This outcome did not change despite sensitivity analyses varying the NTD rate beyond the 95% confidence intervals in the Tsepamo study, up to a rate of 1.5%, and the use of efficacy data from a Cameroon trial showing the 48-week efficacy of dolutegravir to be equal to that of low-dose efavirenz (8).

This model was designed for South Africa but used a conservative estimate of long-acting contraceptive use (24% to 40%) and varied fertility rates in the sensitivity analysis. Using a fertility rate similar to that of Tanzania and Uganda, the authors found that dolutegravir-for-all outcomes remained favorable as long as the NTD rate was 0.8% or lower. In multivariate analyses, the dolutegravir-for-all model resulted in more children alive and HIV-free as long as the dolutegravir-associated NTD risk was lower than 1.0%, regardless of fertility rates or the number of women starting ART annually.

Both the dolutegravir-for-all strategy and the WHO approach of dolutegravir with contraception for women of child-bearing age seem better than the efavirenz-for-all strategy. Although the WHO approach calls for women of child-bearing potential to make an informed choice regarding their ART regimen, implementing this policy may be difficult in many settings. Simplicity has been the key to success of many ART programs in resource-limited settings, and offering a choice of either efavirenz or dolutegravir for women of child-bearing potential adds a layer of complexity to the supply chain with regard to forecasting supply, ensuring the availability of buffer stock, and avoiding drug expirations. The WHO approach also may present challenges in the setting of widespread scale-up of differentiated models of care, such as community ART groups and adherence clubs, given that they often are based on a “one-size-fits-all” ART regimen.

Salient to the discussion of any of these strategies, women continue to confront substantial barriers to family planning services. Antiretroviral therapy programs face challenges, including lack of provider time to address family planning service delivery, insufficient space to co-locate or integrate family planning into the ART visit, and interruptions in the supply chain for fam-

ily planning medications and supplies. Although strong political will and accompanying funding have led to important gains toward the UNAIDS (Joint United Nations Programme on HIV and AIDS) 90-90-90 goals, family planning coverage remains extremely low. Funds from the U.S. President's Emergency Plan for AIDS Relief cannot be used to procure contraception (other than condoms), and little attention is given to contraception as an indicator for measuring program success (9). According to some estimates, scaling up family planning might prevent one third of maternal deaths by allowing women to delay motherhood and to avoid unintended pregnancies and subsequent abortions (10). Regardless of whether dolutegravir remains associated with higher NTD rates, this recent chapter in the history of the HIV epidemic has highlighted an urgent need to strengthen family planning within HIV service delivery models so that women have convenient and reliable access to contraception.

Finally, proactively evaluating the safety of periconceptional ART will require innovative strategies, such as the development of large observational cohorts with wide geographic diversity and carefully planned clinical trials that include women of child-bearing potential and that continue to follow those who conceive while receiving therapy. The Dugdale model may help guide policymakers in critically balancing benefits and risks as they make decisions regarding national ART policy. Moving forward, context-specific discussions must occur among all stakeholders, including women living with HIV, who have the highest stake in policy decisions.

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References

- Zash R, Makhema J, Shapiro RL. Neural-tube defects with dolutegravir treatment from the time of conception [Letter]. *N Engl J Med.* 2018;379:979-981. [PMID: 30037297] doi:10.1056/NEJMc1807653
- Hamers RL, Rinke de Wit TF, Holmes CB. HIV drug resistance in low-income and middle-income countries. *Lancet HIV.* 2018;5:e588-e596. [PMID: 30193863] doi:10.1016/S2352-3018(18)30173-5
- Dorward J, Lessells R, Drain PK, Naidoo K, de Oliveira T, Pillay Y, 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-e404. [PMID: 29884404] doi:10.1016/S2352-3018(18)30093-6
- World Health Organization. HIV/AIDS. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV. Interim guidance. Accessed at www.who.int/hiv/pub/guidelines/ARV2018update/en/ on 19 February 2019.
- Nakkazi E. Changes to dolutegravir policy in several African countries. *Lancet.* 2018;392:199. [PMID: 30043745] doi:10.1016/S0140-6736(18)31641-6
- Dugdale CM, Ciaranello AL, Bekker LG, Stern ME, Myer L, Wood R, et al. Risks and benefits of dolutegravir- and efavirenz-based strategies for South African women with HIV of child-bearing potential. A modeling study. *Ann Intern Med.* 2019. [Epub ahead of print]. doi: 10.7326/M18-3358.
- Zash R. Surveillance for neural tube defects following antiretroviral exposure from conception. Presented at 22nd International AIDS Conference, Amsterdam, the Netherlands, 23-27 July 2018.
- Cournil A, Kouanfack C, Eymard-Duvernay S, Lem S, Mpoudi-Ngole M, Omgba P, et al. Dolutegravir versus an efavirenz 400 mg-based regimen for the initial treatment of HIV-infected patients in Cameroon: 48 week efficacy of the NAMSAL ANRS 12312 trial. *HIV Drug Therapy 2018* [Abstract]. *J Int AIDS Soc.* 2018;21(Suppl 8):16. Abstract no. O342.
- Sherwood J, Sharp A, Honermann B, Horrigan C, Chatterjee M, Jones A, et al. Mapping the impact of the expanded Mexico City Policy for HIV/ family planning service integration in PEPFAR-supported countries: a risk index. *BMC Public Health.* 2018;18:1116. [PMID: 30208876] doi:10.1186/s12889-018-6008-2
- Chola L, McGee S, Tugendhaft A, Buchmann E, Hofman K. Scaling up family planning to reduce maternal and child mortality: the potential costs and benefits of modern contraceptive use in south africa. *PLoS One.* 2015;10:e0130077. [PMID: 26076482] doi:10.1371/journal.pone.0130077

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