Forum on the risks of preconception dolutegravir exposure

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FAQs for Dolutegravir & Women of Childbearing Potential: Interim Considerations

Dolutegravir (DTG) is an integrase inhibitor offering many advantages for people living with HIV. World Health Organization (WHO) currently recommends DTG-based regimens as first-line antiretroviral therapy (ART) (primarily as a fixed-dose combination of tenofovir [TDF]/lamivudine [3TC]/DTG) for people living with HIV [1]. However, recent data from a birth outcomes surveillance study in Botswana identified a possible concern regarding the use of DTG in women of childbearing potential. Preliminary data from this study suggest that periconceptional use of DTG may cause a small (under 1%) but significantly increased risk of neural tube defects (NTDs) in infants compared to the risk in women receiving non-DTG regimens or HIV-negative women. In May 2018, these preliminary findings led WHO, European Medicines Agency (EMA), the U.S. Food and Drug Administration (FDA), and some other organizations and guideline panels to issue a drug safety caution about the use of DTG in this population [2-7] pending further evidence from Botswana and other studies that is anticipated in April/May of 2019. The purpose of a drug safety caution is to identify evidence of a specific risk, rather than to contextualize that potential risk against relative benefits.

These FAQs are designed to help provide that context, and to support public health and clinical decision-making bodies as they balance the current potential concerns about the use of DTG in women of childbearing potential against its known benefits.

1. **What are the advantages of a DTG-based ART regimen over an efavirenz (EFV)-based ART regimen?**

   a. In the SINGLE study, which compared a DTG-based to an efavirenz (EFV)-based ART regimen[8"]:

      i. The DTG-based regimen was better tolerated than the EFV-based regimen, with lower reported discontinuation rates due to adverse events (4% vs. 14%).

      ii. The DTG-based regimen had better rates of viral suppression (HIV RNA <50 copies/mL) than the EFV-based regimen, which persisted through week 144 of therapy. This difference was driven by a lower rate of drug discontinuation due to adverse effects with DTG than with EFV-based ART.

      iii. CD4 cell count increase was greater with the DTG-based than EFV-based regimen.

   b. Similar improved tolerability with DTG has been observed in studies comparing DTG to darunavir-ritonavir, atazanavir-ritonavir, and raltegravir-based ART [9-12]

   c. Viral load decrease is much more rapid with integrase inhibitor-based regimens such as DTG compared to regimens with drugs from other antiretroviral drug classes, including non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs such as EFV. This effect can be important for some populations, including women who become infected while pregnant or who first present in late pregnancy and need rapid viral suppression in order to decrease maternal to child transmission. [13]

   d. Integrase inhibitors have a higher barrier to drug resistance than NNRTI drugs [14], so patients are less likely to develop HIV drug resistance, and thus less likely to transmit drug-resistant HIV infection to their infants or pass on drug-resistant strains to sexual partners. In areas where rates of transmitted NNRTI resistance are already high (10% or higher), DTG-based ART is expected to achieve virologic suppression better than

EFV-based ART [15] A 2017 WHO report found that half of the 11 surveyed countries had levels of NNRTI pretreatment resistance above 10 percent. [16]

e. DTG-based regimens are expected to be active against HIV-2 infections [17] which may coexist with HIV-1 infection in West and Central Africa. Current EFV-based regimens are not fully active against HIV-2. [18]

f. DTG is also expected to play an important role as a second-line therapy for patients who fail first-line therapy with NNRTI-based ART [19-21], as DTG is better tolerated and less expensive than the previously recommended protease inhibitor-based second-line regimens.

g. Further evidence about the relative effects of DTG compared to low-dose (400 mg) EFV-based ART as first line regimens in an African setting will be provided by the NAMSAL trial, which will be presented in late October at the HIV Drug Therapy Glasgow 2018 meeting.

h. The cost of DTG-based regimens is currently similar to or lower than EFV-based regimens. It is expected that as manufacturing capacity and competition increases, the cost for DTG-based regimens may drop further [https://clintonhealthaccess.org/2018-hiv-market-report/].

2. **What are the data about periconceptional use of DTG and neural tube defects that led to the caution about its use in women of childbearing potential?**

a. In 2014, with support from the US National Institute of Child Health and Human Development, the Tsepamo study was launched in Botswana to assess the risk of NTDs (such as spina bifida or anencephaly) with periconceptional EFV use, based on data in monkeys suggesting in utero EFV exposure might be associated with central nervous system defects. When DTG-based ART was implemented as the preferred first-line ART in Botswana in 2016, the use of this regimen before and during pregnancy was also captured through the surveillance system. The study involved assessment of all births, including live births and stillbirths, to HIV-positive and HIV-negative women at eight maternity sites, covering 45% of births occurring in Botswana. All infants at these sites underwent surface examination by trained nurse midwives for external birth defects, including NTDs. Drug exposures before and during pregnancy were recorded by review of the mother's antenatal care records.

b. In preparation for the WHO guidelines development meeting in May 2018, the Tsepamo investigators were asked to conduct an interim analysis of their findings related to birth outcomes with DTG use before and during pregnancy. This interim analysis revealed an unexpected increased risk of NTDs among infants born to women who were receiving DTG-based regimens at the time of conception (4/426, 0.94%, 95% CI 0.37-2.4%), but not in those receiving non-DTG ART regimens at the time of conception (14/11,300, 0.12%, 95% CI 0.07-0.21%) [22]. The increased risk was also present in comparison to the rate of NTDs among HIV-negative women (61/66,057, 0.09%, 95% CI 0.07-0.12%).

c. The Tsepamo study data were updated on May 1, 2018 to now include 596 births to women receiving DTG regimens at conception. No additional NTDs were reported in women receiving DTG at conception, bringing the interim reported rate to 4/596, 0.67% (95% CI 0.26-1.7%). [23]

d. The four defects reported after periconceptional DTG exposure include one case each of anencephaly, lumbosacral meningomyelocele (also referred to as spina bifida), iniencephaly, and frontonasal encephalocele. Anencephaly and meningomyelocele reflect failure of closure of the embryonic neural tube in the first 4 weeks of gestation and are always classified as NTDs; however,

iniencephaly and encephalocele are thought by some experts to occur soon after neural tube closure and thus might have a different pathogenesis. Sparse data exist to determine if this distinction in pathogenesis is embryologically correct or to conclude whether these types of birth defects have similar or dissimilar risk factors. In the Tsepamo study all four defects were considered to be NTDs and analyzed as a group.

e. The geographic occurrence of the defects in Botswana, as well as potential confounding maternal factors were examined, but no specific patterns were detected.

3. **What additional data are being collected and when will an answer about the potential risk of NTDs with periconceptional use of DTG be available?**

a. Although the currently known data from the Tsepamo study are concerning, it is possible that the observed increase in NTDs reflects random clustering of a relatively rare event. If more NTD cases are seen with periconceptional DTG use, the signal may be confirmed, with a clearer estimate of magnitude. Many more exposures without defects are needed to rule out an increase of NTDs, because the background prevalence of NTDs is very low (about 0.1%); it is estimated that approximately 2,000 preconception exposures are needed to be able to rule out a 3-fold increase in a defect with a background prevalence of 0.1%. [24].

b. The Tsepamo study has expanded from 8 to 18 sites, covering 72% of births in Botswana. The next in-depth assessment of the Tsepamo study will occur in April, 2019; approximately 1,200 women with preconception DTG exposure are expected to have delivered at Tsepamo sites by that time.

c. Birth defect surveillance in Botswana has also been expanded at sites outside of the Tsepamo study by the Botswana Ministry of Health with support from US Centers for Disease Control and Prevention. With this expanded surveillance added to the existing Tsepamo program, birth defect data collection will cover over 90% of births in Botswana by November 2018.

d. DTG has been implemented on a more limited basis in several other countries, including Kenya, Uganda, Brazil and Ukraine. Pregnancies occurring among women on DTG in these countries are being tracked. However, data outside of the Tsepamo study from Botswana and other countries will need to be assessed carefully to assure that the full denominator of exposures has been included, and that a biased sample is not obtained because of differential reporting of infants with adverse birth outcomes. Understanding the background population rate of birth defects in each country is also important to aid in interpretation.

e. The Antiretroviral Pregnancy Registry, an international registry supported by antiretroviral drug manufacturers and administered by an independent Advisory Board, contains limited numbers of cases of DTG-exposed pregnancies to date. As of the 31 January 2018 cutoff, 161 cases with any first trimester exposure to DTG had been reported, with five birth defects reported. Of these, 121 had exposure at conception and 40 initiated exposure later in the first trimester. Among those cases, no NTDs or central nervous system defects were identified. Data reported through 31 July 2018 are currently under review and will be reported as soon as possible, most likely in December, 2018.

f. Databases relying on passive retrospective reporting of NTD cases after birth of the infant will not have the utility to add to the current data, due to potential selectivity bias and lack of denominators.

g. In the US, which has been implementing DTG since approval in 2013, an effort is underway to match state birth defect registries with HIV-exposed birth registries to identify birth defects by timing and category of ARV exposure. Data from this effort are expected in late 2018 or early 2019.

h. Surveillance of all births for defects similar to the Tsepamo study has been implemented at several facilities in Uganda and Malawi, covering over 60,000 births/year. These programs will provide additional data on the safety of DTG and other antiretroviral agents as they are implemented in these countries.

i. Two academic groups have modelled outcomes in women and children with implementation of DTG vs EFV-based ART in women of childbearing potential. [25,26] These models are undergoing peer review and being refined. Both models indicate that providing DTG-based ART for all HIV-positive women, including those of childbearing potential, resulted in lower mortality than providing them with EFV-based ART, and that the reduction in mortality significantly exceeded the potential increase in neonatal mortality should the increased risk of an NTD be confirmed.

4. **What are the contraceptive options that should be offered to women of child-bearing potential, including those who want to take DTG regimens?**

a. Concerns about potential teratogenic effects of ARVs underscore the critical importance of women's access to contraception.

b. Women should have access to a full range of contraceptive options to allow them to plan pregnancies when they desire, regardless of their HIV status or their choice of ART regimen. Contraceptive options include condoms, injectable agents such as Depo-Provera and Sayana Press, oral contraceptive pills, and long-acting agents such as implants and intrauterine devices. Access to a range of options is important, as it is correlated with an increase in contraceptive use among women seeking it. [27] Ideally the full range of options would be available in the ART clinic, but if not, counseling should be provided and referrals should be facilitated for women to access their desired method. Reducing the unmet need for family planning should be promoted as part of quality HIV and healthcare services.

c. Metabolic pathways and limited pharmacokinetic data do not suggest a significant interaction between DTG regimens and hormonal contraceptives that would affect contraceptive efficacy [28].

d. Women should be counseled about potential risks of NTDs with DTG use at conception and provided with contraceptives as desired. However, after appropriate risk/benefit counseling, use of contraception should not be a requirement for women to have access to DTG-based regimens. Women's specific risk of pregnancy may be low or they may have side effects from another ART regimen that could lead them to discontinue treatment. ART discontinuation is the least desirable outcome, as it would endanger the woman's own health as well as increase the risk of transmission of HIV to their sexual partner or their child should they become pregnant.

5. **Values and Preferences**

Women living with HIV (WLHIV) have strongly expressed the importance of ensuring a woman's right to make her own informed choice among ART regimen options. A forum of women living with HIV organized by AfroCAB in Kigali, Rwanda in July 2018 provided narrative evidence of the enhanced tolerability of DTG over EFV, and emphasized the importance of WLHIV being involved in discussions and decisions regarding their

treatment. [29] Women from that forum called for countries to ensure availability of DTG-based ART for all HIV-positive individuals, regardless of gender or reproductive capability, allowing women to make a choice regarding use of DTG after receiving counseling regarding benefits and potential risks. They also strongly called for integration of sexual and reproductive health services into HIV care for all WLHIV, regardless of which ART regimen they choose. https://www.projectinform.org/hiv-news/ias2018-communique-of-the-kigali-dolutegravir-stakeholder-meeting-of-african-women-living-with-hiv-hosted-by-afrocab/

6. **What is the bottom line?**

   a. It is important to recognize that the background rate of NTDs in the absence of DTG (and in the general population) is not zero; 1 in every 1000 births may be expected to have an NTD. Given the current estimate of risk from the Tsepamo study, preconception DTG may increase this risk from the background rate of 1 infant with an NTD per 1000 births to 7 per 1000 births.

   b. While the global community hopes that the expected data described above will lead to a definitive answer regarding the risk of periconceptional use of DTG, it is possible that uncertainty and the cautionary guidance regarding DTG for women of child bearing potential may persist beyond April/May 2019.

   c. As evidence emerges, clinical and public health decision-making about choice of ART regimen for women who may become pregnant will need to balance potential risks of DTG against its potential benefits. Consideration of risk should include current lack of certainty of the risk of an NTD with preconception DTG exposure. Consideration of benefits should include the rapid decline in viral load and excellent viral efficacy of DTG along with its better tolerability profile. In addition, a high geographic prevalence of NNRTI resistance would make an EFV-based ART regimen significantly less effective in treating HIV and preventing transmission. Poorly treated maternal HIV could affect a woman's health, her quality of life, and could lead to other negative birth outcomes such prematurity and an HIV positive baby.

   d. WHO has affirmed the importance of a woman-centered approach to DTG. Women will need support to weigh the risks and benefits in the context of their lives, including their own risks of pregnancy and side effects experienced on other regimens. Even if some increase in risk of NTDs is confirmed, it may be reasonable for individual women to choose DTG, including women who are unable to access, or choose not to use, hormonal or other long-acting contraception.

Note: This document will be updated as new data become available.

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ABOUT THE FORUM

Over the past few years, through the efforts of multiple stakeholders and government leadership, antiretroviral regimens containing dolutegravir (DTG) have become accessible to the vast majority of persons living with HIV (PLHIV) throughout the world. Plans to transition most PLHIV to DTG-containing regimens has brought with them the promise of a more efficacious, safe and durable regimen for individuals as well as the achievement of epidemic control through community levels of viral suppression. In response to data from the Tsepamo birth defect surveillance study in Botswana, suggesting that periconceptional use of DTG may be associated with a small (under 1%) but significantly increased risk of neural tube defects (NTDs) in infants compared to the risk in women receiving non-DTG regimens or among HIV-negative women, HIV treatment guidelines groups from around the world have made recommendations on the potential safety risks of preconception DTG exposure. This advice is dependent on further data becoming available. Unless these data are collected swiftly, comprehensively, and in an epidemiologically robust manner the decision to roll out DTG-based antiretroviral therapy (ART) or not on a global basis could be delayed and/or limited. Using this as an example, the IAS convened a high-level group of experts to gather and discuss data quality, data interpretation and appropriate messaging of the risks and benefits of administering ART such as DTG to HIV-infected women of child-bearing age. This effort should be considered complimentary to other efforts presently being undertaken by the WHO Advisory Committee on the Safety of Medical Products, the WHO guidelines processes, other regulatory agencies, and drug manufacturers. It will be an academic exercise whose outputs and process might be applied to any drug used in pregnancy and inform regulators responsible for pharmacovigilance.

Forum Participants

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