Assessing the risk of dolutegravir for women of childbearing potential

Data from May 2018 from Botswana have suggested a potential increased risk of neural tube defects (NTDs) in infants born to women with periconception exposure to the antiretroviral drug dolutegravir.[1,2] Among 426 women exposed to dolutegravir at conception, four infants with NTDs were identified, giving a proportion of 0·94% compared with 0·10% in infants of women exposed to other antiretroviral drugs at conception.[2] Prevalence of NTDs in sub-Saharan Africa among live births in general is estimated at 0·10%, and about 0·15% without folic acid fortification.[3,4] Importantly, the Botswana surveillance study found no evidence of an increased risk of adverse birth outcomes, such as stillbirths, among women who initiated dolutegravir during pregnancy—ie, 8 weeks after conception.[5]

After these data were reported, WHO issued a drug safety alert advising against dolutegravir use in women of childbearing potential and committed to update guidance as more information becomes available. WHO has called for strengthened pharmacovigilance and monitoring of birth outcomes, and additional data will be made available from the Botswana study and other programmes in the coming months. As data accumulate, it will be important to confidently assess whether a given number of dolutegravir exposures and NTDs represents a level of risk that is greater than chance. One proposed approach is shown in the accompanying figure, which illustrates the lower bound of the 95% CI for the proportion of NTDs for different numbers of dolutegravir conception exposures and NTD events, compared with the expected proportion of 0·10% in women exposed to other antiretrovirals at conception. For example, the current proportion of NTDs among infants of women exposed to dolutegravir at conception is four in 426 (0·94%); the lower limit of the respective one-sided 95% CI for this proportion is 0·32%, represented by a solid black dot in the figure. This proportion is higher than the expected 0·10% expected in the general population in sub-Saharan Africa, suggesting that the findings cannot be explained by chance alone. As data on further exposures and cases of NTDs accumulate, one can recalculate the lower confidence limit and assess how close this limit is to the background NTD risk of 0·10%, or to different background risks: for instance, another 1000 cases without further diagnosed NTDs, as shown by the red triangle in the graph, would result in the lower limit of the CI crossing the background proportion, indicating that the risk associated with dolutegravir exposure might be no different to that in infants born to women exposed to other antiretroviral drugs (given the background rate, one new NTD can be expected per 1000 live births).

Reliable ascertainment of both numerators and denominators will be essential. For numerators, although reliable diagnosis of NTDs is relatively straightforward, the optimal approach would be diagnosis with the investigator blinded to exposure status by use of prospectively collected data, and including other adverse birth outcomes such as stillbirths, fetal loss, and terminations due to congenital anomalies, as was done in the Botswana surveillance programme. For the denominators, all dolutegravir exposures must be captured within a given cohort, and timing of exposure

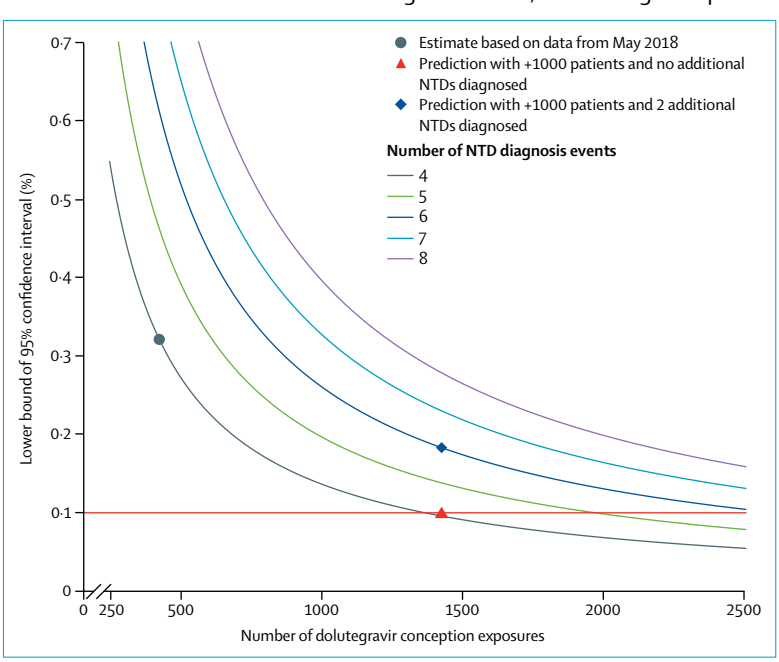

Figure: **Lower confidence bound for the proportion of NTDs by number of dolutegravir conception exposures and number of NTDs**
If there are a further 1000 exposures, that is 1426 in total, with no further cases of NTDs, the lower 95% confidence limit would cross the expected background risk of 0·10%, indicating that the risk associated with dolutegravir exposure might be no different to that in infants born to women exposed to other antiretroviral drugs. In contrast, if a further two cases are found within the 1000 additional exposures, the lower confidence limit for the proportion of NTDs would remain well above the background proportion of 0·10%, albeit lower than estimates suggested by the data from Botswana (blue circle). The calculated one-sided interval expresses the 95% CI with respect to the lower limit because we are interested in whether the lower limit crosses the assumed background proportion of 0·10%. The upper bound of the CI will always be 1.[6] NTD=neural tube defect.

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(periconception) reliably assessed. A minimal assessment of potentially important confounders (eg, folate use) would be desirable. Although case reports and case series will not be informative, relatively small cohorts (eg, 20 exposures) could be pooled with other studies in a so-called living meta-analysis approach, whereby estimates are constantly updated as new data become available.[7] Without an established mechanism of action, surveillance should include periconception exposure to other integrase inhibitors to establish if any increased NTD risk is a drug class effect.

A proactive, collaborative approach is needed to provide clarity regarding the risk of dolutegravir as soon as possible. Another antiretroviral drug, efavirenz, had been contraindicated in pregnancy since 2006 after several retrospective case reports suggested an association with NTDs. Retrospective reports are not reliable for establishing risk; it took 8 years before enough data had accumulated to convince the WHO guideline panel that evidence of fetal harm was sufficiently limited and the benefits of efavirenz for pregnant women outweighed potential harms. During this delay, women with HIV in low-income and middle-income countries wishing to conceive were usually switched to nevirapine, a drug associated with greater viral failure compared with efavirenz and adverse drug reactions including serious and sometimes fatal hypersensitivity reactions.

The global HIV and sexual and reproductive health community have an unprecedented opportunity to collaborate in assessing periconception dolutegravir risk as rapidly as possible. We cannot afford to delay confirmation of whether women with HIV who wish to conceive can take dolutegravir—a drug that is superior to other antiretrovirals in virtually every other regard.

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