# In-utero ART exposure and the need for pharmacovigilance

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In 2016, the PROMISE trial demonstrated the remarkable efficacy of antiretroviral treatment (ART) during pregnancy and breastfeeding to reduce perinatal and postnatal transmission in Africa—from 37% in the absence of treatment[1] to 1·1% at age 18 months—and to provide clinical benefit to the mother.[2–4] ART use by pregnant women living with HIV has resulted in a paradigm shift in the paediatric HIV epidemic in the past 20 years, with a striking 80% decrease in new infant infections, down from 590 000 in 1998 to 120 000 in 2016.[5,6] Universal ART has improved the survival of people living with HIV, and with consistent viral suppression, can also eliminate the risk of sexual transmission.[7] However, although the benefits of treatment are clear, the crucial need for pharmacovigilance to assess for potential adverse effects of new agents, particularly on pregnancy outcome, birth defects, and exposed infants, has been relatively neglected.

In *The Lancet Global Health*, Rebecca Zash and colleagues report preliminary results from a carefully conceived and well conducted birth surveillance programme in Botswana that was designed to fill a major gap in the evaluation of safety of antiretroviral drugs in pregnancy.[8] The Tsepamo study was developed following the rollout of lifelong ART for all pregnant women living with HIV (the so-called option B+) using efavirenz, tenofovir, and emtricitabine or lamivudine; although there had been experience with this regimen in pregnancy, residual concerns remained related to efavirenz and birth defects. Although voluntary registries and cohort studies can give information on birth outcomes, screening of all livebirth and stillbirth outcomes in HIV-uninfected and HIV-positive women at sentinel sites offers an unbiased and comparative evaluation of adverse pregnancy outcomes.

Plans to implement a more potent and better tolerated treatment regimen with the integrase inhibitor dolutegravir have begun in many low-resource countries. The Tsepamo birth surveillance programme, covering approximately 45% of births in Botswana with broad geographical representation, has enabled a careful, real-time evaluation of the potential effects of this change on pregnancy outcomes as Botswana transitioned to dolutegravir from efavirenz-based treatment for adults.[8] Three important outcomes are described. First, initiation of efavirenz-based therapy during pregnancy was shown to be safe: only one major congenital abnormality, skeletal dysplasia, was observed among 395 first-trimester exposures—a prevalence of 0·25%. Second, the risk profile of dolutegravir-based therapy when started during pregnancy was similar to that of efavirenz. Third, adverse pregnancy outcomes among women living with HIV continue to be elevated compared with HIV-uninfected women, despite ART. Further investigation is needed to determine whether these persistent adverse events are secondary to HIV infection (eg, residual inflammation) or to potential effects of ART. In all, these data are very reassuring regarding the use of both regimens when initiated during pregnancy.

However, the authors note that this analysis only evaluated effects of in-utero exposure when starting antiretroviral drugs during pregnancy and did not evaluate the crucial issue of preconception drug exposure. The first 2·5 weeks after fertilisation are generally not sensitive to teratogens. However, both the central nervous and cardiac systems begin development by about day 17 after fertilisation. The neural tube, the basis of the nervous system, closes by day 28–30 post fertilisation.[9] This crucial developmental period is very sensitive to potential teratogens, including drugs, which can result in serious neural tube defects, such as anencephaly and meningomyelocele, and occurs prior to recognition of pregnancy. Thus, the greatest risk for serious defects is not in women first starting drugs during pregnancy, but rather women who conceive while receiving the drug.

The Tsepamo study combines collection of detailed information on maternal characteristics, including the dates of ART initiation and concomitant medication for HIV-positive women, with universal surface evaluation of all births at eight sentinel maternity wards, and hence can discriminate exposures that started preconception from those that started during pregnancy. The study's inclusion of evaluation of stillborn infants is important because limiting evaluation to livebirths can underestimate the rate of neural tube and other birth defects.[10] The study has recently identified a potential signal of birth defects with preconception exposure to dolutegravir (but not with preconception exposure to efavirenz).[11] This signal will

require further evaluation to substantiate the accuracy of the observation, and more data should be available from women who have already had preconception exposure and will deliver in the next 9 months. In the interim, WHO has issued an alert stating that although pregnant women who are taking dolutegravir should not stop their therapy, women wishing to conceive should use an efavirenz–based regimen.[11] Dolutegravir can be considered in women with childbearing age in cases where consistent contraception can be assured.[11]

This recent finding illustrates the importance of having a pharmacovigilance system in place as new drugs are introduced into the adult population to enable evaluation of potential effects of drug exposure prior to recognition of pregnancy in women of childbearing age. The Tsepamo study provides a model of a such a programme; in Uganda and Malawi, similar programmes have been put into place through funding from the US President's Emergency Plan for AIDS Relief. The study by Zash and colleagues reminds us that although ART has great benefits, including prevention of perinatal transmission and saving mothers' lives, surveillance systems to enable early detection of signals of potential adverse effects are needed to assess safety of new drugs in pregnancy and women of childbearing age.

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I declare no competing interests.



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