Study examines effect on pregnancy of receiving antiretroviral therapy for preventing HIV

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Among heterosexual African couples in which the male was HIV positive and the female was not, receipt of antiretroviral pre-exposure preventive (PrEP) therapy did not result in significant differences in pregnancy incidence, birth outcomes, and infant growth compared to females who received placebo, according to a study in the July 23/30 issue of *JAMA*, a theme issue on HIV/AIDS. The authors note that these findings do not provide a definitive conclusion regarding the safety of PrEP therapy prior to pregnancy. The issue is being released early to coincide with the International AIDS Conference.

Antiretroviral pre-exposure prophylaxis as daily oral tenofovir disoproxil fumarate (TDF) and co-formulated emtricitabine/tenofovir disoproxil fumarate (FTC+TDF) has been demonstrated to be efficacious for the prevention of human immunodeficiency virus (HIV) acquisition in diverse populations. PrEP could be an important component of safer conception strategies for women at risk for HIV infection, including those in HIV-serodiscordant couples (i.e., in which only one member is HIV infected), but the effect on pregnancy outcomes is not well defined, according to background information in the article.

Nelly R. Mugo, M.B.Ch.B., M.P.H., of the Kenya Medical Research Institute, Nairobi, Kenya, and University of Washington, Seattle, and colleagues conducted further follow-up of the Partners PrEP Study, a randomized, placebo-controlled trial of PrEP for HIV prevention among

HIV-serodiscordant couples conducted between July 2008 and June 2013. For this analysis, which included 1,785 couples in Kenya and Uganda, the researchers assessed pregnancy incidence and outcomes among women using PrEP during the periconception period. Females had been randomized to daily oral TDF (n = 598), combination FTC+TDF (n = 566), or placebo (n = 621) through July 2011, when PrEP demonstrated efficacy for HIV prevention. Thereafter, participants continued receiving active PrEP without placebo.

A total of 431 pregnancies occurred. The researchers found that pregnancy incidence did not differ significantly by study group, and that there was no statistically significant association between women receiving PrEP and those receiving placebo and the occurrence of pregnancy losses, which was 42.5 percent for women receiving FTC+TDF, 32.3 percent for those receiving placebo, and 27.7 percent for those receiving TDF alone. After July 2011 (when the placebo group was discontinued), the frequency of pregnancy loss was 37.5 percent for FTC+TDF and 36.7 percent for TDF alone.

Occurrence of preterm birth, congenital anomalies, kidney function and growth throughout the first year of life did not differ significantly for infants born to women who received PrEP vs placebo.

The authors write that for some outcomes, including pregnancy loss, preterm birth, congenital anomalies, and infant mortality, confidence intervals were wide (suggesting uncertainty in the result and the need for more data), including both a null effect and potential harm, and thus definitive statements about safety of PrEP in the periconception period cannot be made.

"These results should be discussed with HIV-uninfected women receiving PrEP who are considering becoming pregnant."

Bradley M. Mathers, M.B.Ch.B., M.D., and David A. Cooper, M.D., D.Sc., of the University of New South Wales, Sydney, Australia, comment on the findings of this study in an accompanying editorial.

"… it appears (from the magnitude and asymmetry of the confidence intervals) that there may be a signal suggesting potential harm as pregnancy loss based on the emtricitabine/tenofovir vs placebo comparison (absolute difference ending in pregnancy loss of 10.2 percent) and on the post hoc emtricitabine/tenofovir vs tenofovir alone comparison (absolute difference ending in pregnancy loss of 9.2 percent)."

"These intriguing findings reported by Mugo et al provide important information from one of the largest studies of exposure to these nucleoside analogues in HIV-negative persons and therefore must be considered carefully. Tenofovir and emtricitabine are both category B drugs, but this signal suggesting a possible association with pregnancy loss has not to date appeared in studies of HIV-infected persons, suggesting that this observation deserves evaluation in future studies. Moreover, the nucleosides were stopped according to the trial protocol no later than 6 weeks into the pregnancy, albeit this period is highly sensitive to subsequent adverse pregnancy outcomes, but exposure to these drugs may be longer in the real-world setting."

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