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EDITORIAL COMMENTARY

Outcomes Following Pregnancy Conception on Antiretroviral Therapy: A Call for More Data

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(See the Major Article by Hoffman et al on pages 273-9.)

Any discussion of the safety of maternal antiretroviral treatment (ART) in pregnancy must emphasize the remarkable benefits of ART for maternal health and for reducing mother-to-child transmission (MTCT) of human immunodeficiency virus (HIV). As an increasing number of women of childbearing potential conceive on a wide array of antiretroviral regimens in the universal treatment era, however, researchers have appropriately moved their focus from MTCT prevention to evaluating the impact of the timing and type of antiretroviral regimen on pregnancy outcomes (which include spontaneous abortion, stillbirth, preterm delivery, or low birth weight/small for gestational age).

Many studies have evaluated the association between ART initiation (and regimen) in pregnancy, and adverse pregnancy outcomes. Several studies have described pregnancy outcomes such as preterm delivery and low birth weight (or small for gestational age) among mothers who took ART from conception [1–7]. However, there is little published information regarding spontaneous abortion (pregnancy loss prior to 20 weeks' gestation) with ART from conception [5]. This situation has arisen in part because it is challenging to collect accurate information on early pregnancy events such as spontaneous abortion in women conceiving on ART.

We therefore commend Risa Hoffman and her colleagues for evaluating the combined rate of spontaneous abortion or stillbirth among women who became pregnant during follow-up in the Promoting Maternal and Infant Survival Everywhere (PROMISE) study, and describing these results in this issue of *Clinical Infectious Diseases*. Using prospectively collected data from the "HAART [highly active ART] Standard" component of PROMISE, the authors made inference regarding risk of pregnancy loss based on (1) whether women took ART during conception, and (2) whether women received protease inhibitor (PI)– or nonnucleoside reverse transcriptase inhibitor (NNRTI)–based regimens at conception. They found that women who had previously been randomized to continue (vs discontinue) ART postpartum had higher rates of the combined adverse pregnancy endpoint. In an "as-treated" analysis (which categorized women according to whether or not they actually received a 3-drug ART at the time of conception), the association trended in the same direction, but was not statistically significant. In women who had been previously randomized to continue ART, conceiving while taking an NNRTI (either efavirenz or rilpivirine) was associated with occurrence of spontaneous abortion or stillbirth compared with taking PI-based ART at the time of conception; this finding was not replicated among women in the other randomized arm, nor in both groups (all women) combined. An association between NNRTIs and spontaneous abortion has not been previously described, to our knowledge. A recently published study showed similar rates of spontaneous abortion or stillbirth in women conceiving on NNRTI- vs PI-based ART in a secondary analysis of pooled data from several AIDS Clinical Trials Group trials [5].

Hoffman et al conducted several additional analyses (modified intent-to-treat; crossovers removed; as-treated; and time-updated), to account for changes in ART use in the periconception period. These analyses were intended to address "crossover" of women between arms (ie, stopping ART in the continued ART arm and starting ART in the stop ART arm), as well as the initiation of ART after conception. As the authors acknowledge, these analyses have several inherent limitations. Although these data derived from follow-up of subjects who participated in a randomized study, they might be considered more observational in nature in that issues of selection bias, confounding, and nonadherence to the originally randomized treatment strategy arise in analysis. The second pregnancy experienced by women in the study occurred following randomization, and may have depended on behavior altered by randomization. Women crossed over from one study arm to another for different reasons: women who were randomized

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to continue ART postpartum but who stopped treatment (eg, due to nonadherence or challenges with ART access) and then conceived may well have been different in relevant ways from women who were randomized to stop ART postpartum but nonetheless started ART prior to conception (eg, due to HIV disease progression). Also noteworthy is that the primary analysis is based on ART status at conception, but in the discontinue ART arm, ART was primarily started after conception. In addition, the type of ART (in particular NNRTI vs PI) in this study varied by whether treatment was supplied by the study vs sourced locally (and therefore likely by timing of ART initiation during follow-up), and NNRTI use was much higher in the discontinue ART arm.

Confounding of assigned or realized treatment effects on pregnancy loss therefore can arise from (1) selection factors regarding who gets pregnant and timing of the pregnancy; (2) selective nonadherence to originally assigned treatment strategy; (3) type of ART used at and after conception; and (4) reasons for that differential use. Because of these challenges, we believe that the results presented in this article should be viewed as hypothesis generating, and should not lead—on their own—to conclusions regarding the risk of taking ART (or of particular regimens) at conception.

Even with a large database, developing or applying appropriate causal methods to simultaneously address all of the factors mentioned above would be challenging, and the small sample size of this study would render productive use of these methods unfeasible. Estimation of causal effects would require much larger databases that include the relevant information needed for causal modeling. Nonetheless, to investigate the impact of crossover on analyses of originally randomized treatment, it can be useful to compare key characteristics (especially factors associated with the outcomes of interest) of study participants who do vs do not follow the original assignment (and among women taking NNRTI- vs PI-based ART), so that readers can gain a general sense of the likely size and direction of potential biases.

Fortunately, data will be forthcoming regarding pregnancy outcomes by maternal antiretroviral use and regimen at conception, in >900 women who conceived in other components of the PROMISE study. When larger databases such as this are available, there are methods that might be particularly useful for analyses of such data. In particular, structural nested models and the associated method of G-estimation offer approaches to modeling and estimating the joint effects of a sequence of treatments or exposures [8, 9] such as arise in this study—with regard both to strategy of continuation of ART and the specific antiretrovirals used. Marginal structural models, another class of causal models, allow for adjustment of time-varying confounding; this confounding can arise even in follow-up of subjects from randomized studies, such as the one under discussion [10].

As information emerges suggesting that type and timing of ART during pregnancy may affect pregnancy outcomes, it is increasingly clear that key exposure and pregnancy outcomes data should be collected in women who take ART during pregnancy (including from conception). Randomized trials of ART regimens in pregnancy are rare, and interventional trials of different ART regimens from conception are not feasible. Only large sets of systematically collected, relatively high-quality observational data will permit use of statistical methods that help address all of the challenges to inference described above. Pregnant women living with HIV should be offered the safest and most effective ART for their health and that of their children, hence the moral imperative to develop—as rapidly as possible—databases of sufficient size and quality to guide their choices.

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