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Methodological considerations in evaluating pregnancy outcomes in women living with HIV

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In the January 2019 issue of this journal, Dadabhai and colleagues presented an analysis of birth outcomes, including preterm birth (PTB), low birth weight and small for gestational age (SGA) among infants born to women living with HIV (WLHIV) on antiretroviral therapy (ART) compared to women without HIV, enrolled in the Pregnancy Outcomes and Infant Survival in the Era of Universal HAART in Africa (POISE) study[1]. This comparison is crucial to understand whether the previously observed disparity in birth outcomes between women with and without HIV is being narrowed by maternal ART[2]. In POISE, WLHIV were included if they were on antiretroviral therapy (ART) for at least one week prior to delivery and had a delivery CD4 count ≥350 cells/mm^3. Women were enrolled in the maternity ward either just before or after delivery, at one teaching hospital and four major health centers in Blantyre Malawi during 2016 and 2017. Of 5423 women approached, 614 WLHIV and 685 women without HIV were ultimately enrolled. Within the cohort of infants born to enrolled women there was no difference in PTB, low birth weight or SGA by

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This work has not previously been presented

maternal HIV status and the paper concludes that “ART use has reduced the high rates of adverse pregnancy outcomes among HIV-infected women”[1].

The authors considered the possibility of selection bias and thought it unlikely to be present or at least not to be differential between women with and without HIV. However, the methodology used for participant selection is likely to preferentially exclude women with adverse birth outcomes, particularly severe outcomes. Women approached postpartum whose newborns were acutely ill or who died shortly after birth (often due to severe prematurity) may have been less likely to enroll in a 1-year prospective study of infant survival and may also not have been readily accessible for recruitment. For the same reasons, women approached before delivery in preterm labor, or with serious pregnancy complications, may have been less inclined to enroll and less accessible. Evidence for this type of selection bias is seen in the POISE study population, as the lowest birth weight of enrolled infants was 1.9kg and the minimum gestational age was 34 weeks, highlighting the fact that no infant with very low birthweight (<1.5kg) or born very preterm was included. Even though lower enrollment with severe outcomes may have occurred regardless of maternal HIV-infection status, the included study population is no longer representative of the entire population. If PTB and lower birth weights occur more frequently in the newborns of WLHIV then selection bias in the POISE study sample would lead to a bias towards the null in the comparison of PTB and low birth weight between WLHIV and women without HIV. Interestingly, the POISE study did find differences in some of the SGA outcomes by HIV status. SGA, which is associated with less immediate morbidity than very PTB or very low birthweight among neonates, may therefore be less susceptible to selection bias.

Recent studies from Botswana and South Africa have indeed shown that compared to women without HIV, WLHIV and on ART have an increased risk of adverse birth outcomes, particularly PTB[3,4]. There are important methodological differences between these studies and POISE. The Tsepamo study in Botswana reported increased risk of PTB (aRR 1.18; 95% CI 1.12,1.25) and SGA (aRR 1.30; 95% CI 1.23,1.38) among women on efavirenz-based ART compared with women without HIV[3]. Like POISE, Tsepamo collected maternal pregnancy and birth outcome data shortly after delivery but in Botswana the data were abstracted on all consecutive deliveries at eight government hospitals[3]. By including all deliveries at the study facilities and not a selected sample as in POISE, the risk of selection bias was minimized. The South African study, that enrolled pregnant women at their first antenatal care visit, observed double the odds of PTB in WLHIV initiating ART during pregnancy compared to women without HIV (aOR 2.03; 95% CI 1.33–3.10)[4]. Antenatal enrolment well before the end of pregnancy with prospective follow-up for complete outcome ascertainment guards against non-inclusion of women with worse birth outcomes.

The likely selection bias introduced by the design of the POISE study and conducted in a single African country should not provide stakeholders with definitive reassurance or causal evidence that maternal ART has mitigated adverse pregnancy outcomes among WLHIV in sub-Saharan Africa.

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