Antiretroviral Therapy, Sexually Transmitted Infections, and Adverse Pregnancy Outcomes in South Africa

To the Editor—We read with interest the article by Theron et al [1] on their post hoc analysis of the Promoting Maternal and Infant Survival Everywhere (PROMISE) 1077BF/1077FF trials. They found an increased incidence of low-birth-weight (LBW) infants (<2500 g) and adverse pregnancy outcomes in women who conceived while on antiretroviral therapy (ART) compared with those who restarted ART after pregnancy was diagnosed. Their study adds an important data point to the limited, and sometimes contradictory, evidence regarding safety of ART in pregnancy and its relationship with adverse pregnancy outcomes [2].

We recently completed 2 studies on sexually transmitted infections (STIs) in pregnant women living with human immunodeficiency virus (HIV) in Pretoria [3] and Cape Town [4], South Africa. (Ethical approval for those studies was provided by the institutional review boards at the University of Cape Town's Faculty of Health Sciences Research Ethics Committee, University of Pretoria's Faculty of Health Sciences Research Ethics Committee, and the University of California, Los Angeles.

In both studies, we detected *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infection at the first antenatal care (ANC) visit. We examined the combined dataset of 416 women living with HIV with live births for the effect of ART at conception on birth outcomes. Overall, 190 (46%) women were on ART at the time of conception and 226 (54%) women initiated ART during pregnancy. There was no significant difference between these groups with regard to maternal age, gestational age at enrollment, gravidity, and ART regimen (mostly tenofovir disoproxil fumarate, emtricitabine, and efavirenz). The prevalence of STIs was high (30%); STIs were less common among women who conceived while on ART than those who initiated ART during pregnancy (25% vs 34%; $P = .063$); most likely this reflects increased engagement with healthcare.

ART at conception and STI at first ANC visit were not associated with LBW in our combined cohort (after adjustment for maternal age and gestational age at enrollment). After stratification by presence of an STI, there was a clear association of ART at conception with LBW infants among women with an STI detected at the first ANC visit (Table 1). This was not the case for women who tested STI-negative. In women with an STI, birthweight was significantly lower among those on ART at conception compared with those who initiated ART during pregnancy (3000 g vs 3140 g; $P = .034$). This association was absent in women without an STI (3060 g vs 3070 g; $P = .97$).

It is unclear why STIs may modify the effect of ART on birth weight. Methodological bias cannot be ruled out. Several pathogenic mechanisms may account for associations between ART and adverse pregnancy outcomes, including modulation of the Th1 to Th2 immune shift, which is associated with pregnancy, and changes in placental cytokine expression [5]. *Chlamydia trachomatis* and *N. gonorrhoeae* infection are associated with elevated genital tract cytokine concentrations and substantial changes in cytokine profile with upregulation of proinflammatory cytokines [6]. Possibly, combined alterations in cytokine expression related to ART and STIs might explain our observation.

Adverse pregnancy outcomes, STIs, and living with HIV are overlapping disease burdens in sub-Saharan Africa where the benefits of ART on maternal health and for prevention of

Table 1. Relationship Between Antiretroviral Therapy at Time of Conception and Low Birth Weight in Pregnant Women Living With Human Immunodeficiency Virus With and Without a Sexually Transmitted Infection in South Africa

Participant group	Time of ART Initiation	Low Birth Weight (n = 59)	Normal Birth Weight (n = 357)	OR (95% CI)	*P* Value
Total cohort	ART at conception	30 (16%)	160 (84%)	1.3 (.74–2.2)	.39
	ART initiated during pregnancy	29 (13%)	197 (87%)		
		Low Birth Weight (n = 19)	**Normal Birth Weight (n = 105)**	**OR (95% CI)**	***P* Value**
STI detected at first ANC visit[a]	ART at conception	12 (25%)	36 (75%)	3.3 (1.2–9.1)	.017
	ART initiated during pregnancy	7 (9.2%)	69 (91%)		
		Low Birth Weight (n = 40)	**Normal Birth Weight (n = 252)**	**OR (95% CI)**	***P* Value**
No STI detected at first ANC visit[a]	ART at conception	18 (13%)	124 (87%)	0.85 (.43–1.7)	.62
	ART initiated during pregnancy	22 (15%)	128 (85%)		

Data are presented as number with row proportion. Low birth weight is defined as <2500 g.

Abbreviations: ANC, antenatal care; ART, antiretroviral therapy; CI, confidence interval; OR, odds ratio; STI, sexually transmitted infection.

[a]The Xpert CT/NG assay was performed on vaginal swabs to detect *Chlamydia trachomatis* and *Neisseria gonorrhoea*; 94 women had a positive test for *C. trachomatis*, 9 for *N. gonorrhoeae*, and 21 for both.

mother-to-child transmission are unquestioned. We therefore agree with the authors that continuous monitoring of any adverse effects of ART on pregnancy outcomes is warranted. Future studies should explore the potential role of STIs and inflammatory pathway changes.

Notes

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Optimal Cycle Thresholds for Coronavirus Disease 2019 (COVID-19) Screening—Receiver Operating Characteristic (ROC)-Based Methods Highlight Between-Study Differences

To the Editor—Several articles in recent issues of *Clinical Infectious Diseases* have addressed questions regarding the role of cycle thresholds in the interpretation of molecular polymerase chain reaction (PCR)-based tests for coronavirus disease 2019 (COVID-19) [1–3]. The reason for this is that there is now a robust evidence base for the assertion that cycle thresholds are related to infectiousness, the development of an immune response, and symptom severity. However, translating this knowledge about significant relationships between cycle thresholds and relevant clinical outcomes into a specific threshold, for example, 27, 30, or 35, requires different analytic methods than the ones that have hitherto been used in the empirical literature. Specifically, we propose using receiver operating characteristic (ROC)-based methods [4, 5] to first determine empirically justified optimal cutoff scores for cycle thresholds and, second, to test their generality by comparing different studies.

To demonstrate the utility of this approach, we contacted the corresponding authors of the studies identified by Jefferson and colleagues [6] as reporting on the association between cycle thresholds and viral culture positivity. Of the 8 authors contacted, 2 responded and provided the necessary data [5, 6]. For 2 additional studies [7, 8] we were able to extract these data from the figures that showed the cycle threshold and viral culture positivity in the published articles. We then analyzed these data using the *cutpointr* [5] package for the open-source software R. Specifically, we plotted the distribution of cycle thresholds in culture positive and culture negative patients across studies, the ROC curve for the 4 studies, the cut points identified as optimal (criterion minimum 95% detection of virus-positive culture), and the out-of-bag estimation for the specificity at 95% sensitivity

As can be seen in Figure 1, there are marked differences between the studies. Most importantly the cycle threshold scores that are identified as optimal range from 26 (95%confidence interval [CI]: 22–32) [9] to 37 (95% CI: 34– 39) [7], whereas the other 2 studies provide optimal cut points of 29 (95% CI: 26–29) [8] and 31 (95% CI: 31–31) [2]. The confidence intervals indicate that estimation of optimal cut points is prone to random errors and that the differences between the studies are larger than what can simply be attributed to chance.

Although our analysis is limited by the poor data availability, our results already provide evidence for systematic differences in the optimal cycle thresholds. Therefore, great care is required when deciding which threshold should be used to determine whether a person is COVID-19 positive or negative. In addition, the width of the confidence intervals demonstrates that estimates of optimal cut points need to be based on very large samples. We believe that ROC-based methods are a valuable addition to the methodological toolkit because they allow formulating explicit criteria for what constitutes optimal cycle thresholds. Furthermore, although others have speculated before that it might not be possible to determine a universally