We would like to thank Slogrove and colleagues for the positive comments on our manuscript and for emphasizing the need to provide definitive evidence of the benefit of controlling maternal human immunodeficiency virus (HIV) infections for the health of infants born in low- and middle-income countries (LMIC), where the burden of HIV infection is highest [1]. We agree that the pathways leading to the vulnerability of HIV-exposed, uninfected (HEU) infants may not be identical in LMIC and in high-income countries (HIC), and that the potential role of specific factors has to be determined. As proposed by Slogrove and colleagues, the decreased risk of hospitalization observed in our study for those infections associated with the initiation of antiretroviral therapy (ART) before pregnancy may be offset by an increased risk of premature delivery in women living in LMIC [2]. On the other hand, contrary to HIC, women living with HIV in LMIC are encouraged to breastfeed. Although the evidence from HIC is less consistent [3], there is strong supportive evidence for a protective effect of breastfeeding on infectious morbidity in LMIC [4]. Through a diversity of immunological components, breastfeeding could reduce the immunological risk of severe infections after birth and thereby mitigate the impact of immune alterations induced by in utero exposure to maternal HIV infection. In our study, maternal and newborn immune activation predicted the risk of maternal hospitalization due to infection in infants born to mothers who initiated ART during pregnancy [5]. Immune activation is commonly observed in adults living in LMIC, independently of HIV infection [6]. Therefore, the potential for ART to correct immune activation in women living with HIV may be lower in LMIC as compared to HIC, and this could mitigate the impact of ART initiation before pregnancy on infants’ susceptibility to infectious diseases.

Although the vulnerability of HEU infants living in different settings could involve different factors, it is essential to recognize that this vulnerability is a global public health issue. An increased susceptibility of HEU infants to severe infections is observed in both LMIC and HIC, suggesting that common determinants are playing a critical role [7, 8]. Identifying these determinants has the potential to positively impact the health of HEU infants worldwide. To meet this challenge, researchers in HIC and LMIC should join efforts and integrate both intensive studies on relatively small study populations and larger studies that are powered to determine the impact of key environmental factors on clinical outcomes. Control of maternal HIV infection before pregnancy and progress in our understanding of the immunobiology of infant exposure to maternal HIV infection provide unprecedented opportunities to further improve the health of children born to HIV-infected mothers.

Note

Potential conflicts of interest. A. M.’s institution has received fees from GlaxoSmithKline Vaccines, outside the submitted work. G. A.’s institution has received grants from Gilead Sciences and the Bill and Melinda Gates Foundation (grant numbers OPP1032817, OPP1097381, and OPP114729). T. R. K.’s institution has received grants from the National Institute for Allergy and Infectious Diseases and the Canada Institutes for Health Research. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

**Does Tenofovir-containing First-line Antiretroviral Therapy Mitigate the Impact of Pretreatment Non-nucleoside Reverse Transcriptase Inhibitor Drug Resistance?**

To the Editor—In a human immunodeficiency virus treatment-as-prevention trial in South Africa, Derache et al [1] report the remarkable finding that the presence of non-nucleoside reverse transcriptase inhibitor (NNRTI)-associated pretreatment drug resistance (PDR) did not impair virological responses to fixed-dose tenofovir/efavirenz (Atripla). This is an important contrast with most past studies, which found that NNRTI-associated PDR was associated with a 2- to 3-fold increased risk of virological failure (VF) [2–9], although most patients in those studies received a thymidine analogue backbone (zidovudine/stavudine) with efavirenz or nevirapine [2, 3]. The authors attributed their finding to the better potency of efavirenz compared to nevirapine, and an Editorial Comment added the advantage of the similar half-lives of the Atripla components, making it less likely for resistance to emerge during missed doses [10].

In our previous analysis in the Pan-African Studies to Evaluate Resistance (PASER-M) cohort, we reported that patients with NNRTI-PDR had a > 2-fold increased risk of VF, compared to patients with a susceptible virus [4, 7]. Based on the hypothesis by Derache et al [1], we extended this to a stratified analysis by type of first-line regimen. We defined PDR as (1) an NNRTI, nucleoside reverse transcriptase inhibitor (NRTI), or dual-class NNRTI+NRTI resistance, based on the 2017 International Antiviral Society (IAS)-USA mutation list; or (2) a Stanford genotype susceptibility score (GSS; v8.7) <3 of the prescribed first-line regimen. We defined VF as a single viral load (VL) ≥ 50, 400, or 1000 cp/ml, measured at month 12. We assessed the association between PDR and VF using logistic regression, while adjusting for key confounders.

Of 2737 participants initiating first-line antiretroviral therapy (ART), 1941 had data on PDR and the 12 month VL. The median age was 37.0 years (interquartile range 31.7–43.1), 59.8% were women, and 56.4% had an overall mean adherence of ≥ 95% (as measured by visual analogue scale). Initial regimens contained either tenofovir and lamivudine/emtricitabine (xtc; 33%), with efavirenz (27.3%) or nevirapine (5.7%), or a non-NNRTI, thymidine analogue backbone and xtc (67%), with efavirenz (29.8%) or nevirapine (37.1%). In all, 1838 (94.7%) patients had no PDR, 79 (4.1%) had NNRTI-PDR only, 44 (2.3%) had NRTI-PDR, and 24 (1.2%) had dual-class NNRTI+NRTI-PDR. Only 84 (4.4%) patients initiated a first-line regimen with GSS < 3. VF was present in 335 (17.3%), 199 (10.3%), and 172 (8.9%) participants at VL thresholds ≥ 50, 400, and 1000 cp/ml, respectively.

Participants who had PDR defined as GSS < 3, NNRTI only, or dual-class NNRTI-NRTI who received non-tenofovir (xtc) with efavirenz or nevirapine had an increased risk of VF, compared to those without PDR. However, this risk was not increased for participants who received tenofovir (xtc)/efavirenz, whereas there was a borderline association for participants who received tenofovir (xtc)/nevirapine (Table 1). Participants with NNRTI-PDR only who received a tenofovir-containing regimen had an increased risk of VF at the VL threshold of ≥ 1000 cp/ml (with borderline statistical significance of P = .073), and the risk was not increased at the ≥ 50 and ≥ 400 cp/ml thresholds.

In conclusion, our analysis corroborates the finding that NNRTI-PDR may impact less on tenofovir (xtc)/efavirenz than on thymidine analogue-based regimens, especially with nevirapine. Nonetheless, it remains difficult to disentangle the possible beneficial effects of tenofovir, efavirenz, and fixed-dose combinations with similar drug half-lives. Given that 2 other studies have produced conflicting data [2, 3], it is premature to argue that Atripla is equally efficacious for patients with or without NNRTI-PDR.

**Notes**

**Author contributions.** T. F. R. dW. is the Pan-African Studies to Evaluate Resistance principal investigator. R. L. H. and T. F. R. dW. conceived the study. S. C. I. performed the statistical analysis. S. C. I. and R. L. H. drafted the manuscript. All authors provided valuable input to the interpretation of the data and critically reviewed the paper for important intellectual content. All authors reviewed and approved the final version of the manuscript.

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