Supplementary Materials for "Population-level Viral Suppression among Pregnant and Post-partum Women in a Universal Test and Treat Trial"

Appendix: Further details on the statistical analysis.

The primary objective of this study is to determine whether universal "test and treat" improves viral suppression, beyond universal antiretroviral treatment (ART) eligibility, among peri-partum women living with HIV in rural East Africa. The secondary objective is to evaluate predictors of non-suppression among all women of reproductive age (15-45 years).

To accomplish these objectives, we will analyze data from the SEARCH Study (NCT:01864603), whose arms and main results have previously been published.[1] Briefly, in both the intervention and control arms, population-wide HIV testing was conducted at baseline (*t=0*) and three years later at study close (*t=3*). At the time of testing, women were asked to report current pregnancies or births within the last year, and persons living with HIV had their viral load measured. The intervention arm also offered interim annual testing (*t={1,2}*). Through linkage with clinic records, prior diagnoses and ART use were assessed. As in previous analyses,[3,5] we will assume complete measurement of prior diagnoses and ART use. Throughout, we define viral suppression at time *t* as HIV RNA level < 500 cps/ml.

Assessing HIV care outcomes and population-level suppression at year *t*

Using the above data, we will characterize the HIV care cascade (proportion of all persons living with HIV who are diagnosed; proportion of diagnosed who initiated ART, and proportion on ART who are virally suppressed) and population-level viral suppression (proportion of all persons living with HIV who are virally suppressed). The challenges in estimating these metrics are well-known.[2–5] Briefly, even in studies with high measurement coverage, such as SEARCH, we cannot assume that persons with known outcomes are representative of persons with missing outcomes. Instead, we need to adjust for differences in the characteristics of women with known versus unknown HIV status, and known versus unknown suppression status.

To accomplish this adjustment, we will use targeted maximum likelihood estimation (TMLE).[6] TMLE combines estimates of the outcome regression (e.g. conditional probability of viral suppression, given the adjustment set) with estimates of the propensity score (e.g. conditional probability of viral load testing, given the adjustment set). In doing so, TMLE achieves a number of desirable properties, including double robustness, efficiency, and valid statistical inference even when using data-adaptive algorithms. In secondary analyses, we will report unadjusted estimates, calculated as the number with the outcome divided by the number with the outcome measured.

We will estimate HIV care outcomes and population-level suppression at *t={0,3}* in both arms and *t={1,2}* in the intervention arm only (as interim testing was only conducted in the intervention arm).

Throughout, our primary analytic population is women reporting a current pregnancy or live birth in the prior year.

The secondary analytic population is all women of reproductive age (15-45 years at time *t*).

Accounting for clustering

To account for the dependence of individuals within a cluster, we will take a Two-Stage approach, appropriate for cluster randomized trials.[7] In Stage I, we will estimate HIV care outcomes and viral suppression in each community separately. As detailed in the previous section, Stage I provides an opportunity to control for potentially differential measurement on HIV status and viral suppression status. Then in Stage II, we will combine these community-specific estimates to obtain arm-specific endpoints and to assess the intervention effect. To do so, we will again use TMLE to provide an unbiased and more precise estimate of the intervention effect, while accounting for the pair-matched design and adaptively adjusting for the following community-level variables: baseline viral suppression and proportion of the community who are women aged 15-24 years.[7,8]

Assessing predictors of viral suppression at *t=3*

Among all women of reproductive age (15-45 years), we will evaluate risk factors for non-suppression at study close (*t=3*) within each arm separately. We will consider the following risk factors: age group, marital status, and pregnancy/live birth in the prior year. We will additionally adjust for study region. Adjusted relative risks will be obtained with TMLE, accounting for clustering by community.

Appendix References

1. Havlir DV, Balzer LB, Charlebois ED, et al. HIV Testing and Treatment with the Use of a Community Health Approach in Rural Africa. *New England Journal of Medicine*. 2019;381(3):219-229. doi:10.1056/NEJMoa1809866

2. Granich R, Gupta S, Hall I, Aberle-Grasse J, Hader S, Mermin J. Status and methodology of publicly available national HIV care continue and 90-90-90 targets: A systematic review. *PLoS Med*. 2017;14(4):e1002253. doi:doi:10.1371/ journal.pmed.1002253

3. Balzer LB, Schwab J, Laan MJ van der, Petersen ML. *Evaluation of Progress Towards the UNAIDS 90-90-90 HIV Care Cascade: A Description of Statistical Methods Used in an Interim Analysis of the Intervention Communities in the SEARCH Study*. University of California at Berkeley; 2017. http://biostats.bepress.com/ucbbiostat/paper357/.

4. Sabapathy K, Hensen B, Varsaneux O, Floyd S, Fidler S, Hayes R. The cascade of care following community-based detection of HIV in sub-Saharan Africa - A systematic review with 90-90-90 targets in sight. *PLoS ONE*. 2018;13(7):e0200737. doi:10.1371/journal.pone.0200737

5. Balzer LB, Ayieko J, Kwarisiima D, et al. *Far from MCAR: Obtaining Population-Level Estimates of HIV Viral Suppression*. medRxiv; 2019. https://www.medrxiv.org/content/10.1101/19012781v1.

6. van der Laan M, Rose S. *Targeted Learning: Causal Inference for Observational and Experimental Data*. New York Dordrecht Heidelberg London: Springer; 2011.

7. Balzer LB, Havlir DV, Schwab J, van der Laan MJ, Petersen ML, the SEARCH Collaboration. *Statistical Analysis Plan for SEARCH Phase I: Health Outcomes among Adults*. arXiv; 2018.

8. Balzer L, van der Laan MJ, Petersen M, SEARCH Collaboration. Adaptive Pre-specification in Randomized Trials With and Without Pair-Matching. *Statistics in Medicine*. 2016;35(10):4528-4545. doi:10.1002/sim.7023