OPEN

Quantifiable Plasma Tenofovir Among South African Women Using Daily Oral Pre-exposure Prophylaxis During the ECHO Trial

Ivana Beesham, MBChB,[a] Leila E. Mansoor, BPharm, PhD,[b] Dvora L. Joseph Davey, PhD,[c,d] Thesla Palanee-Phillips, PhD,[e] Jenni Smit, BPharm, MSc, PhD,[a] Khatija Ahmed, MBChB, MMed (Micro), FcPath (Micro),[f,g] Pearl Selepe, MBChB,[h] Cheryl Louw, MBChB,[i,j] Mandisa Singata-Madliki, Dip Gen Nursing, MBA, PhD,[k] Philip Kotze, MBChB, MMed,[l] Renee Heffron, MPH, PhD,[m] Urvi M. Parikh, MD, PhD,[n] Lubbe Wiesner, PhD,[o] Helen Rees, MB BChir, MA (CANTAB), MRCGP, DCH, DRCOG,[e] Jared M. Baeten, MD, PhD,[p,q] and Mags Beksinska, MSc, PhD[a]

Background: HIV endpoint–driven clinical trials provide oral pre-exposure prophylaxis (PrEP) as HIV prevention standard of care. We evaluated quantifiable plasma tenofovir among South African women who used oral PrEP during the Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial.

Methods: ECHO, a randomized trial conducted in 4 African countries between 2015 and 2018, assessed HIV incidence among HIV-uninfected women, aged 16–35 years, randomized to 1 of 3 contraceptives. Oral PrEP was offered onsite as part of the HIV prevention package at the South African trial sites. We measured tenofovir in plasma samples collected at the final trial visit among women reporting ongoing PrEP use. We used bivariate and multivariate logistical regression to assess demographic and sexual risk factors associated with plasma tenofovir quantification.

Received for publication February 17, 2022; accepted May 16, 2022.

From the [a]MatCH Research Unit (MRU), Department of Obstetrics and Gynaecology, Faculty of Health Sciences, University of the Witwatersrand, Durban, South Africa; [b]Centre for AIDS Programme of Research in South Africa (CAPRISA), University of KwaZulu-Natal, Durban, South Africa; [c]Division of Epidemiology and Biostatistics, School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa; [d]Department of Epidemiology, Fielding School of Public Health, University of California Los Angeles, Los Angeles, CA; [e]Wits Reproductive Health and HIV Institute (Wits RHI), Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [f]Setshaba Research Centre, Soshanguve, South Africa; [g]Department of Medical Microbiology, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa; [h]The Aurum Institute, Klerksdorp, South Africa; [i]Madibeng Centre for Research, Brits, South Africa; [j]Department of Family Medicine, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa; [k]Effective Care Research Unit, Universities of the Witwatersrand and Fort Hare and Eastern Cape Department of Health, East London, South Africa; [l]Qhakaza Mbokodo Research Clinic, Ladysmith, South Africa; [m]Department of Global Health and Department of Epidemiology, University of Washington, Seattle, WA; [n]Department of Medicine, Division of Infectious Diseases, University of Pittsburgh School of Medicine, Pittsburgh, PA; [o]Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa; [p]Department of Global Health, Department of Epidemiology, Department of Medicine, University of Washington, Seattle, WA; and [q]Gilead Sciences, Foster City, CA.

This work and the Evidence for Contraceptive Options and HIV Outcomes (ECHO) study were made possible by the combined generous support of the Bill & Melinda Gates Foundation (Grant OPP1032115), the American people through the United States Agency for International Development (Grants AID-OAA-A-15–00045; AID-OAA-A-15-0031), the Swedish International Development Cooperation Agency (Grant 2017/762965–0), the South Africa Medical Research Council, and the United Nations Population Fund. Contraceptive supplies were donated by the Government of South Africa and US Agency for International Development. IB received funding from the South African Medical Research Council (SAMRC) Clinician Researcher MD PhD Development Programme. The contents of this paper are solely the responsibility of the authors and do not necessarily reflect the views, decisions, or policies of the institutions with which they are affiliated, the ECHO trial funders, the SAMRC, or the supporting governments. The University of Cape Town Clinical PK Laboratory is supported in part through the Adult Clinical Trial Group (ACTG), the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health under award numbers UM1 AI068634, UM1 AI068636, and UM1 AI106701; as well as the Infant Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT), funding provided by National Institute of Allergy and Infectious Diseases (U01 AI068632), the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and National Institute of Mental Health grant AI068632.

The authors have no conflicts of interest to disclose.

I.B. conceptualized the study and drafted the initial manuscript. I.B. analyzed the data under the supervision of D.J.D. M.B., L.E.M., J.M.B., and D.J.D. reviewed and revised the first drafts. L.W. was involved in the testing and analysis of samples. I.B., L.E.M., D.J.D., T.P., J.S., K.A., P.S., C.L., M.S., P.K., R.H., L.W., U.M.P., H.R., J.M.B., and M.B. have read the manuscript, provided critical review, and approved the final version.

Access to data from the ECHO study may be requested through submission of a research concept to icrc@uw.edu. The concept must include the research question, data requested, analytic methods, and steps taken to ensure ethical use of the data. Access will be granted if the concept is evaluated to have scientific merit and if sufficient data protections are in place. As of the time of publication, data access applications are in process with the governing institutional review boards of the ECHO study to make deidentified data publicly available.

Correspondence to: Ivana Beesham, MBChB, MatCH Research Unit (MRU), Department of Obstetrics and Gynaecology, Faculty of Health Sciences, University of the Witwatersrand, 40 Dr AB Xuma Street, Commercial City Building, 11th Floor, Suite 1112, Durban 4001, South Africa (e-mail: i_beesham@yahoo.com).

Results: Of 260 women included, 52% were ≤24 years and 22% had *Chlamydia trachomatis* at enrollment. At PrEP initiation, 68% reported inconsistent/nonuse of condoms. The median duration of PrEP use was 90 days (IQR: 83–104). Tenofovir was quantified in 36% (n = 94) of samples. Women >24 years had twice the odds of having tenofovir quantified vs younger women (OR = 2.12; 95% confidence interval = 1.27 to 3.56). Women who reported inconsistent/nonuse of condoms had lower odds of tenofovir quantification (age-adjusted OR = 0.47; 95% confidence interval = 0.26 to 0.83).

Conclusions: Over a third of women initiating PrEP and reporting ongoing use at the final trial visit had evidence of recent drug exposure. Clinical trials may serve as an entry point for PrEP initiation among women at substantial risk for HIV infection with referral to local facilities for ongoing access at trial end.

Clinical trial number: NCT02550067.

Key Words: HIV prevention, women, plasma tenofovir, oral PrEP, clinical trials, Africa

(*J Acquir Immune Defic Syndr* 2022;91:26–30)

INTRODUCTION

In 2020, 63% of new HIV infections in sub-Saharan Africa occurred in women and girls[1] and 140,000 South African women aged 15–49 years acquired HIV,[2] highlighting an urgent need for HIV prevention options in this setting. Oral pre-exposure prophylaxis (PrEP) containing tenofovir disoproxil fumarate (TDF) is recommended by the World Health Organization (WHO) as an HIV prevention option for persons at substantial risk of HIV[3] and is approved for use in South Africa (SA).[4] Adherence to oral PrEP is important for adequate levels of protection against HIV acquisition. Subjective measures of adherence such as participant self-report may be subject to bias and lead to an overestimation of adherence,[5] whereas objective measures provide greater accuracy. Adherence to oral PrEP as measured by plasma tenofovir has varied in studies.[6] In studies enrolling African women using oral TDF/emtricitabine (FTC), plasma tenofovir was quantified in 29% of samples in the VOICE trial,[7] in <40% of samples in the FEM-PrEP study,[8] and in 68% of samples in HPTN 067.[9]

Although several trials have assessed adherence to oral PrEP using plasma tenofovir,[7–9] data on adherence to oral PrEP where oral PrEP was offered as part of the HIV prevention package in a trial are lacking. The objective of this analysis was to evaluate the frequency and factors associated with the quantification of plasma tenofovir among women from SA who elected to use daily oral PrEP (hereafter referred to as PrEP) as part of the HIV prevention package in the Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial.[10]

METHODS

ECHO Trial Procedures

The design, procedures, and outcomes, including the integration of PrEP in the ECHO Trial (Clinicaltrials.gov NCT02550067), have been previously described.[10,11] In brief, the ECHO Trial, conducted between 2015 and 2018, assessed HIV incidence among HIV-uninfected women, aged 16–35 years, who were randomized to 1 of 3 contraceptives (intramuscularly injected depot medroxyprogesterone acetate, the copper intrauterine device, or levonorgestrel implant). Testing for sexually transmitted infections (STIs; *Chlamydia trachomatis* and *Neisseria gonorrhoeae*) was conducted at enrollment and exit. Follow-up was quarterly for 12–18 months.

PrEP Access and On-Site Availability

Initially, PrEP access during the trial was through referral to off-site facilities where PrEP was available. During the latter 8 months of the trial (March to October 2018), daily oral PrEP containing TDF/FTC was provided on-site by trial staff at the SA trial sites. All eligible women remaining in study follow-up were offered PrEP as an additional HIV prevention option. PrEP was dispensed for a month at initiation, and subsequently, 3-monthly supplies were provided. Eligibility criteria for on-site PrEP initiation included having at least 1 month of follow-up remaining in the trial.

Data Collection

Demographic data (age, education, marital status, cohabitation with partner, income, and partner support) were collected at enrollment. Sexual risk behaviors were collected at the PrEP initiation visit. Demographics, sexual risk behaviors, and PrEP use dates were collected with standardized questionnaires in face-to-face interviews by trained study staff and recorded using case report forms. To ascertain PrEP use, women were asked at each study follow-up visit whether they had used PrEP since their previous visit, and if PrEP was used, start and stop dates were recorded. Where PrEP was provided on-site, clinicians documented dates of use. Additional adherence data, such as pill counts and on/off-site PrEP dispensation, were not collected as PrEP was provided as standard of care, not as a research component of the trial.

Sample Collection and Testing

For this analysis, we retrospectively tested stored plasma samples that were collected at the final ECHO study visit for women reporting ongoing PrEP use at this visit. This analysis is limited to women enrolled at 8 SA trial sites (Brits, Durban, East London, Edendale, Johannesburg, Klerksdorp, Ladysmith, and Soshanguve) who had initiated oral PrEP, reported ongoing use at the final study visit, and provided consent to long-term sample storage and testing. We included women who initiated PrEP on-site at the trial sites and women who obtained PrEP off-site. Samples collected from women at study sites were processed and then transported to a central laboratory (BARC; Bio Analytical Research Corporation) in Johannesburg, SA, where the samples were stored in freezers at −80°C. Samples were then transported to the University of Cape Town (UCT) for tenofovir testing. Tenofovir in plasma was analyzed with a validated liquid chromatography tandem mass spectrometry assay developed at the Division of Clinical Pharmacology, UCT.[12] Quantification of tenofovir above 10 ng/mL was defined as quantifiable. Quantifiable plasma tenofovir indicates recent PrEP use over a few days.[13,14]

Statistical Methods

Bivariate logistical regression was used to evaluate participant characteristics associated with quantifiable tenofovir at the final trial visit. Each factor significant at $P \leq 0.05$ in a bivariate model was then adjusted for age in independent models. Results are presented as crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) and P values. All statistical analyses were conducted using Stata v14.1.[15]

Ethics

Women signed written informed consent to participate in the ECHO Trial, which included consent for sample storage and future research testing. Approval for the additional tenofovir testing was obtained from the University of the Witwatersrand Human Research Ethics Committee (reference M191155).

RESULTS

In total, 465 women initiated PrEP at the 8 SA trial sites and 260 (56%) plasma samples from the final study visit were tested for tenofovir. The remaining 205 women did not have tenofovir testing performed because of declining long-term sample storage (n = 19) or not using PrEP at the final study visit (n = 186). Among the 260 women who had samples available for testing, approximately half were ≤24 years (n = 136, 52%) and most were unmarried (n = 253, 97%) and unemployed (n = 215, 83%) (Table 1). About 1 in 5 women (n = 56, 22%) had *C. trachomatis* and more than two-thirds reported inconsistent or nonuse of condoms (n = 178, 68%). The median duration of PrEP use was 90 days (IQR: 83–104 days).

Tenofovir was quantified in over a third of samples (n = 94, 36%). Older women (>24 years) had double the odds of having tenofovir quantified compared with younger women [odds ratio (OR) = 2.12; 95% confidence interval (CI): 1.27 to 3.56]. Women who reported inconsistent or nonuse of condoms had lower odds of having tenofovir quantified compared with women who reported always using condoms (adjusted OR = 0.47; 95% CI: 0.26 to 0.83). Similarly, women who reported not using a condom at last sex had reduced odds of having tenofovir quantified compared with those who reported using a condom at last sex (adjusted OR = 0.50, 95% CI: 0.29 to 0.86). Women who had >1 sex partner in the past 3 months had higher odds of quantifiable tenofovir (OR = 2.70, 95% CI = 0.99 to 7.36), although not statistically significant when adjusted for age (adjusted OR = 2.44; 95% CI = 0.88 to 6.75).

DISCUSSION

In this analysis, we found that tenofovir was quantified in over a third of SA women who reported PrEP use at the final study visit in the ECHO Trial. Women >24 years and those who reported multiple sex partners had a greater likelihood of having tenofovir quantified, whereas women who used condoms inconsistently or did not use condoms had a reduced likelihood of having tenofovir quantified. The novelty of this study includes that PrEP was provided as part of an HIV prevention package and integrated with contraceptive provision and care.

The proportion of women with quantifiable tenofovir in our study was similar to the VOICE trial that enrolled women from 3 African countries, where tenofovir was quantified in around a third of samples[7]; however, women in our study were younger (18–35 vs. 18–45 years) and from SA only. Furthermore, the VOICE trial was a blinded, placebo-controlled trial of an unproven product, whereas PrEP in ECHO was of a now recommended intervention. Quantifiable tenofovir in our study was lower than HPTN 067 that enrolled women from Cape Town, SA, where tenofovir was quantified in just over two-thirds of samples, but in HPTN 067, women were directly observed dosing for 5 weeks and thereafter assigned to either daily or nondaily oral PrEP regimens.[9] Although we measured plasma tenofovir in the ECHO Trial, other studies have measured tenofovir-diphosphate (TFV-DP) in dried blood spots (DBS),[16,17] which has a half-life of 17 days and provides a measure of adherence over weeks.[18] In HPTN 082 that enrolled women from 2 African countries, TFV-DP in DBS was quantified in 84% of women at month 3 and 57% at month 6,[16] and a PrEP implementation study that enrolled women from maternal child health and family planning clinics in Kenya found TFV-DP in DBS quantified in 61% of samples at a median of 5 weeks after PrEP initiation.[17]

An additional consideration when evaluating adherence to PrEP is the "effective use of PrEP" which takes into account that some PrEP users might have periods or "seasons" of risk and therefore will require PrEP during these times and use might not be continuous.[19] Despite only about a third of women having quantifiable tenofovir in our study, among all women who had initiated PrEP in the ECHO Trial, only 2 had seroconverted at an incidence rate of 1.0 per 100 person-years compared with 3.81 per 100 person-years in the overall study.[10] Furthermore, HIV incidence in ECHO dropped by about 50% after on-site access to PrEP.[20] We found that 40% of women discontinued PrEP before the final visit in our study, and this was consistent with findings from a large systematic review and meta-analysis where about a third discontinued PrEP within the first month.[21]

In our study and the VOICE trial, older age was associated with quantifiable tenofovir.[7] The VOICE trial also found that being married and earning an income were associated with quantifiable tenofovir; however, when adjusting for age, we did not find similar associations. Age ≥24 years was also associated with quantifiable TFV-DP in DBS in a real-world PrEP implementation program in Kenya.[17] Notably, we found that women who used condoms inconsistently or did not use condoms were less likely to have tenofovir quantified, and this reflects the complex interplay of condom use with factors such as HIV risk perception and partner risk.

Our study has some limitations. Plasma tenofovir provides an indication of PrEP use over the previous few days; therefore, biomarkers such as TFV-DP that measure longer-term adherence to PrEP would have been useful to assess longer-term PrEP use. It is also possible that even among women with quantifiable tenofovir at the final visit, PrEP use might not have been consistent. PrEP was introduced relatively late in the ECHO Trial, and testing was conducted at 1 time point and not

TABLE 1. Participant Characteristics and Factors Associated With Quantifiable Tenofovir Among Oral PrEP Users in the ECHO Trial

Variable	Total, N	Tenofovir Quantified, N (%)	Tenofovir Not Quantified, N (%)	OR, 95% CI	*P*	OR, 95% CI (Adjusted for Age)	*P* (Adjusted for Age)
Baseline participant characteristics (at enrollment into the ECHO trial)							
Age							
18-24	136	38 (27.9)	98 (72.1)	Ref			
25-35	124	56 (45.2)	68 (54.8)	2.12 (1.27 to 3.56)	**0.004**		
Marital status							
Never married	253	88 (34.8)	165 (65.2)	Ref			
Married/previously married	7	6 (85.7)	1 (14.3)	11.25 (1.33 to 94.93)	**0.03**	8.04 (0.94 to 68.92)	0.06
Does not live with partner/no partner	224	82 (36.6)	142 (63.4)	Ref			
Lives with partner	36	12 (33.3)	24 (66.7)	0.87 (0.41 to 1.82)	0.70		
Partner provides financial/material support							
No/no partner	164	59 (36.0)	105 (64.0)	Ref			
Yes	96	35 (36.5)	61 (63.5)	1.02 (0.60 to 1.72)	0.94		
Does not earn own income	215	72 (33.5)	143 (66.5)	Ref			
Earns own income	45	22 (48.9)	23 (51.1)	1.90 (0.99 to 3.64)	**0.05**	1.71 (0.88 to 3.31)	0.11
Education*							
Secondary (any)	222	84 (37.8)	138 (62.2)	Ref			
Postsecondary	37	9 (24.3)	28 (75.7)	0.53 (0.24 to 1.17)	0.12		
Sexually transmitted infections							
Chlamydia trachomatis not detected	204	77 (37.7)	127 (62.3)	Ref			
C. trachomatis detected	56	17 (30.4)	39 (69.6)	0.72 (0.38 to 1.36)	0.31		
Neisseria gonorrhoeae not detected	246	89 (36.2)	157 (63.8)	Ref			
Neisseria gonorrhoeae detected	14	5 (35.7)	9 (64.3)	0.98 (0.32 to 3.01)	0.97		
Participant characteristics at PrEP initiation visit†‡							
Number of sex partners in the past 3 mo							
0/1	243	84 (34.6)	159 (65.4)	Ref			
≥2	17	10 (58.8)	7 (41.2)	2.70 (0.99 to 7.36)	**0.05**	2.44 (0.88 to 6.75)	0.09
No new sex partner/no partner	245	85 (34.7)	160 (65.3)	Ref			
New sex partner	15	9 (60.0)	6 (40.0)	2.82 (0.97 to 8.20)	0.06		
Condom use in the past 3 months§							
Always used condoms	69	33 (47.8)	36 (52.2)	Ref			
Did not use/inconsistent use	178	55 (30.9)	123 (69.1)	0.49 (0.28 to 0.86)	**0.01**	0.47 (0.26 to 0.83)	**0.01**
Condom use at last vaginal sex§							
Yes	121	52 (43.0)	69 (57.0)	Ref			
No, had condomless sex	126	36 (28.6)	90 (71.4)	0.53 (0.31 to 0.90)	**0.02**	0.50 (0.29 to 0.86)	**0.01**
HIV status of primary sex partner							
Negative/unknown	248	88 (35.5)	160 (64.5)	Ref			
Positive	9	4 (44.4)	5 (55.6)	1.45 (0.38 to 5.56)	0.58		
Do you feel your primary sex partner had sex with anyone else beside you in the past 3 months?							
No/do not know	225	76 (33.8)	149 (66.2)	Ref			
Yes	32	16 (50.0)	16 (50.0)	1.96 (0.93 to 4.13)	0.08		

Bold values = P ≤ 0.05
*One woman reported no school education.
†Three women reported not having a primary sex partner over the past 3 months
‡None of the women reported having anal sex over the past 3 months
§Thirteen women had no sex partner/did not have vaginal sex.

prospectively. Some studies have shown that adherence to PrEP might change over time, aligning with relationship dynamics and life situations. Although we recorded dates of PrEP use, we did not collect additional adherence data on patterns of PrEP use, including reasons for not taking or discontinuing PrEP. As more clinical trials and rollout programs begin to provide oral PrEP onsite as part of HIV prevention standard of care, additional research is needed to explore patterns of PrEP use, including the use of PrEP during periods of risk, barriers to PrEP adherence, and linkage of study participants to publicly available PrEP sources at trial completion. Finally, longer-acting PrEP agents such as injectables, rings, and implants might address some barriers to oral PrEP adherence.

CONCLUSIONS

We found that over a third of South African women who initiated PrEP as an HIV prevention option during the ECHO Trial and reported ongoing PrEP use at the final trial visit had evidence of recent use on testing. Younger women and those who reported inconsistent or nonuse of condoms had lower odds of having tenofovir quantified. Clinical trials can potentially be used as an entry point for PrEP initiation among persons at substantial risk for HIV infection with referral for continuing PrEP access to local facilities on trial termination.

ACKNOWLEDGMENTS

The authors thank the women who participated in the ECHO Trial, and the authors are grateful to those who advocated for PrEP provision during the study including the community advisory boards and the ECHO study team.

REFERENCES

1. UNAIDS. *Fact Sheet: 2021*. Available at: https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf. Accessed July 26, 2021.
2. UNAIDS. *Country Fact Sheet, South Africa: 2020*. Available at: https://www.unaids.org/en/regionscountries/countries/southafrica. Accessed July 26, 2021.
3. World Health Organization. *Guideline on when to Start Antiretroviral Therapy and on Pre-exposure Prophylaxis for HIV*; 2015. Available at: https://www.who.int/hiv/pub/prep/policy-brief-prep-2015/en/. Accessed December 9, 2020.
4. Medicines Control Council (MCC) & Department of Health, South Africa. *Press Release: Medicines Control Council Approves Fixed-Dose Combination of Tenofovir Disoproxyl Fumarate and Emtricitabine for Pre-exposure Prophylaxis of HIV*; 2015. Available at: https://www.sahpra.org.za/wp-content/uploads/2020/01/6614b94510.11_Media_release_ARV_FDC_PrEP_Nov15_v1.pdf. Accessed July 29, 2021.
5. Haberer JE. Current concepts for PrEP adherence in the PrEP revolution: from clinical trials to routine practice. *Curr Opin HIV AIDS*. 2016;11:10–17.
6. Sheth AN, Rolle CP, Gandhi M. HIV pre-exposure prophylaxis for women. *J Virus Erad*. 2016;2:149–155.
7. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *N Engl J Med.* 2015;372:509–518.
8. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med.* 2012;367:411–422.
9. Bekker LG, Roux S, Sebastien E, et al. Daily and non-daily pre-exposure prophylaxis in African women (HPTN 067/ADAPT Cape Town Trial): a randomised, open-label, phase 2 trial. *Lancet HIV*. 2018;5:e68–e78.
10. Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial Consortium. HIV incidence among women using intramuscular depot medroxyprogesterone acetate, a copper intrauterine device, or a levonorgestrel implant for contraception: a randomised, multicentre, open-label trial [published correction appears in Lancet. 2019 Jul 27; 394(10195):302]. *Lancet*. 2019;394:303–313.
11. Beesham I, Welch JD, Heffron R, et al. Integrating oral PrEP delivery among African women in a large HIV endpoint-driven clinical trial. *J Int AIDS Soc.* 2020;23:e25491.
12. Phillips TK, Sinxadi P, Abrams EJ, et al. A comparison of plasma efavirenz and tenofovir, dried blood spot tenofovir-diphosphate, and self-reported adherence to predict virologic suppression among South African women. *J Acquir Immune Defic Syndr.* 2019;81:311–318.
13. Spinelli MA, Haberer JE, Chai PR, et al. Approaches to objectively measure antiretroviral medication adherence and drive adherence interventions. *Curr HIV/AIDS Rep.* 2020;17:301–314.
14. Hendrix CW, Andrade A, Bumpus NN, et al. Dose frequency ranging pharmacokinetic study of tenofovir-emtricitabine after directly observed dosing in healthy volunteers to establish adherence benchmarks (HPTN 066). *AIDS Res Hum Retroviruses*. 2016;32:32–43.
15. *StataCorp*. College Station, TX: StataCorp LP. Available at: http://www.stata.com. Accessed June 30, 2021.
16. Celum C, Hosek S, Tsholwana M, et al. PrEP uptake, persistence, adherence, and effect of retrospective drug level feedback on PrEP adherence among young women in southern Africa: results from HPTN 082, a randomized controlled trial. *PLoS Med.* 2021;18:e1003670.
17. Pintye J, Kinuthia J, Abuna F, et al. Frequency and predictors of tenofovir-diphosphate detection among young Kenyan women in a real-world pre-exposure prophylaxis implementation program. *Clin Infect Dis.* 2020;71:e509–e512.
18. Anderson PL, Liu AY, Castillo-Mancilla JR, et al. Intracellular tenofovir-diphosphate and emtricitabine-triphosphate in dried blood spots following directly observed therapy. *Antimicrob Agents Chemother*. 2017;62:e01710–17.
19. AVAC. *Defining and Measuring the Effective Use of PrEP: Think Tank Meeting Report. June 18- 19, 2019*. Available at: https://www.avac.org/resource/defining-and-measuring-effective-use-prep-think-tank-meeting-report. Accessed July 26, 2021.
20. Donnell D, Beesham I, Welch JD, et al. Incorporating oral PrEP into standard prevention services for South African women: a nested interrupted time-series study. *Lancet HIV*. 2021;8:e495–e501.
21. Stankevitz K, Grant H, Lloyd J, et al. Oral preexposure prophylaxis continuation, measurement and reporting. *AIDS*. 2020;34:1801–1811.