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

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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.

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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 deidentified data publicly available.

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INTRODUCTION

In 2020, 63% of new HIV infections in sub-Saharan Africa occurred in women and girls and 140,000 South African women aged 15–49 years acquired HIV, 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 infection with referral to local facilities for ongoing access at trial end. 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.

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. Quantification of tenofovir above 10 ng/mL was defined as quantifiable. Quantifiable plasma tenofovir indicates recent PrEP use over a few days.
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 samples7; 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...
| Variable                                                                 | Total, N | Tenofovir Quantified, N (%) | Tenofovir Not Quantified, N (%) | OR, 95% CI                      | P (Adjusted for Age) | 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/formerly 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 on site 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.

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