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Pre-exposure Prophylaxis Recent Adherence With Real-Time Adherence Feedback and Partner Human Immunodeficiency Virus Self-Testing: A Pilot Trial Among Postpartum Women

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Background. Pre-exposure prophylaxis (PrEP) is safe and effective in postpartum women. Human immunodeficiency virus self-testing (HIVST) for male partners combined with biofeedback counseling through real-time adherence measures may improve PrEP use among postpartum women.

Methods. Between August 2020 and April 2021, we randomized postpartum women who initiated PrEP in pregnancy 1:1 to the intervention group (HIVST + biofeedback counseling after urine tenofovir test) or to standard of care ([SOC] facility-based human immunodeficiency virus [HIV] tests and routine counseling without biofeedback). The outcomes of interest were PrEP adherence in the past 48–72 hours via urine tenofovir tests and partner HIV testing, measured 1-month after randomization. Secondary outcomes included the proportion of partners who tested for HIV and the discrepancy between self-reported PrEP adherence and urine tenofovir result.

Results. We enrolled 106 women (median age = 26 years). At enrollment, 72% of women reported missing <2 doses in the past 7 days; 36% of women had tenofovir present in her urine. One month after enrollment, 62% (n = 33) of women in the intervention arm had tenofovir present in their urine compared to 34% (n = 18) in SOC (risk ratio [RR] = 1.83; 95% confidence interval [CI] = 1.19–2.82; $P = .001$). Two thirds of women in the intervention arm reported that her partner tested for HIV (66%; n = 35), compared to 17% (n = 9) in SOC (RR = 3.89; 95% CI = 2.08–7.27; $P < .001$). Self-reported PrEP adherence (took PrEP >5 of last week) with no tenofovir in urine test was lower in the intervention group (17% vs 46%; RR = 0.33; 95% CI = 0.17–0.67; $P = .03$). No social or clinical adverse events were reported in the intervention arm.

Conclusions. The HIVST for partners and biofeedback counseling increased levels of recent PrEP adherence, pointing to the importance of these interventions to support PrEP use in this population.

Keywords. adherence; breastfeeding; pre-exposure prophylaxis; pregnant; South Africa.

Over half of human immunodeficiency virus (HIV) infections globally occur among cisgender women [1], and the risk of HIV acquisition nearly doubles during periods of pregnancy and postpartum due to biological and behavioral factors [2–4]. Few primary HIV prevention interventions exist for the majority of pregnant or breastfeeding cisgender women (PBFW) who initially test negative for HIV in antenatal care (ANC). With adequate adherence, oral pre-exposure prophylaxis (PrEP) is highly effective for HIV prevention and is safe and feasible for use in PBFW without HIV to prevent HIV acquisition during pregnancy and the postpartum period [5]. Despite its potential value for HIV prevention, PrEP adherence is low in many settings [6–10], including in PBFW [11].

Preliminary findings from our study with PBFW in South Africa show high levels of PrEP initiation (>90% of eligible women starting PrEP) but low levels of continuation and adherence on PrEP (<60% of women who initiated PrEP continued and were adherent in the postpartum period) [12]. Given the high HIV incidence among PBFW and risk of infant HIV acquisition, new intervention strategies are urgently needed to improve adherence among PBFW at risk for HIV [13–15]. Primary barriers to daily oral PrEP among PBFW include low perceived risk of infection and couple dynamics, suboptimal counseling

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and adherence strategies, and facility-level barriers to PrEP access [14, 15]. Cisgender women often have limited knowledge about their sexual partner's serostatus, and many underestimate the likelihood that their partner is infected with HIV [12, 16], and others report needing permission from their partner to use PrEP and fear disclosing to their partner that they are taking PrEP [16]. The PrEP use in PBFW requires monthly or bimonthly facility visits with HIV testing throughout the duration of PrEP use, and PrEP consultations are likely the only reason women visit the clinic once postpartum, adding substantial burden [16]. Furthermore, standard PrEP counseling is based on self-reported adherence, which may overreport true drug adherence [17–21], rather than focusing on addressing barriers to daily PrEP use (and promoting condom use when not adherent) to protect the individual [21]. Empowering cisgender women to monitor their own HIV testing and increase knowledge of their partner's serostatus using HIV self-testing (HIVST) could alleviate the need for multiple clinical visits while improving HIV risk perception, disclosure, and partner support for daily PrEP taking.

The PrEP adherence counseling based on recent real-time adherence levels may improve adherence to daily PrEP. Direct feedback to clients of real-time PrEP levels is difficult and expensive to do with standard blood testing because of the need for laboratory personnel and specialized equipment, but it may improve daily oral PrEP adherence [22–25]. Ongoing studies have demonstrated the potential importance of real-time adherence counseling on PrEP [22, 26]. A recently developed immunoassay using urine measures tenofovir (TFV) and is sensitive (96%) and specific (100%) when compared with plasma levels [21, 22, 27–29]. The urine assay shows TFV concentrations if PrEP is taken in the past 48–72 hours and is processed within 10–15 minutes, enabling providers to adapt counseling messages immediately [21, 29], potentially increasing motivation for adherence.

We conducted a randomized control pilot trial to test the impact of a combined intervention (HIVST for PrEP users and male partners, and real-time adherence biofeedback) on recent PrEP adherence among postpartum women who took PrEP during pregnancy compared with standard of care (SOC) in Cape Town, South Africa.

METHODS

Study Procedures

This pilot study (ClinicalTrials.gov Identifier NCT04897737) was designed as a parallel-arm, randomized, control trial embedded within an ongoing parent study, PrEP-PP (PrEP in Pregnant and Postpartum women), that observed postpartum cisgender women for 1 month after study enrollment. The PrEP-PP is an open prospective cohort that enrolls consenting, pregnant, HIV-uninfected cisgender adolescent girls and women (age >16 years) at the first ANC visit and follows participants through 12-month postdelivery at a single public health clinic in Cape Town, South Africa [12].

Between August 2020 and April 2021, trained study staff recruited cisgender women from the PrEP-PP cohort for the pilot study. Eligibility criteria included having given birth to a live infant in the preceding 4–24 weeks, documented HIV-negative status in the study on the date of screening [30], initiating PrEP in the recently completed pregnancy, and reported having at least 1 sexual partner. Women were randomized in 1:1 to the combination intervention arm (n = 53) or SOC arm (n = 53) through a series of opaque envelopes kept secure by the study coordinator; random assignments were generated by the principal investigator using a computer program.

Standard of Care

Cisgender women received the SOC national PrEP services including HIV counseling and testing at the facility by a trained HIV counselor, face-to-face counseling that is based on self-reported adherence, and HIV testing referral slips to invite male sex partners for HIV testing. Participants gave a urine sample for the tenofovir test to evaluate recent PrEP adherence, but without feedback on the test result, nor was additional counseling provided in the SOC group, although both groups were told that their urine was being tested for PrEP adherence monitoring. Participants were asked to return at 1 month for a pilot study follow-up survey, although participants on PrEP received a 3-month prescription for PrEP in line with national SOC (meaning the 1 month follow-up visit was not tied to PrEP services).

Intervention

Based on the Ickovics' and Meisler's [31] conceptual framework for clinical care and formative work [12], we hypothesized that a combination intervention with HIVST for PrEP users and male partners, combined with biofeedback counseling through real-time adherence measures, would improve recent PrEP adherence compared with SOC (Supplemental Figure 1). The intervention package included provision of the following: (1) HIVST kits (OraQuick ADVANCE HIV I/II self-testing kits; OraSure Technologies, Bethlehem, PA) were distributed to enrolled women for her own use and 1 test for each of her reported male sex partners, along with instructions on how to use and interpret the results; (2) counselors asked participants to confirm her partners' HIVST result within 1 month after enrollment by either sending a picture of the HIVST test kit or bringing the used HIVST kit to study staff, and if the result was reactive, participants received confirmatory HIV testing and linkage to HIV care (and if the participant's test was reactive, PrEP would be immediately stopped); and (3) PrEP adherence biofeedback counseling using the UrSure/OraSure [21, 29] test, which provides feedback on recent adherence within 10–15

minutes (control line present = at least 1 dose of PrEP in the previous 48 hours; control and test lines present = no dose in the previous 48 hours).

Follow-up

Women enrolled to either arm were asked to return in 1 month to have additional HIV testing, adherence counseling and UrSure/OraSure urine tenofovir testing for recent PrEP adherence (in the past 48–72 hours), and to complete a brief questionnaire. If participants did not return, they were offered a phone interview for the questionnaire. If the participant did not return, the follow-up urine tenofovir result was recorded as missing. Loss to follow up was defined as not returning to the study clinic, and not able to contact participant telephonically, for >90 days after the substudy enrollment.

Measures

Questionnaires were conducted at baseline and follow-up visit for all participants and included items on the following: (1) demographic information, (2) partner HIV testing, (3) sexual behaviors, (4) intimate partner violence (IPV) (using the World Health Organization IPV scale [32]), (5) PrEP adherence according to self-report (7- and 30-day recall), and (6) the acceptability of the intervention (in the intervention group) using a Likert scale stratified by their intervention outcome.

The primary outcome was recent PrEP adherence measured through point-of-care tenofovir detection in urine (reflecting adherence in past 48–72 hours). Secondary outcomes included the following: (1) proportion of sexual partners who tested for HIV within the 1-month study follow-up period based on reporting by the participant, confirmed with SMS/WhatsApp picture or return of used HIVST for intervention arm participants or by self-report from participant in the control arm, and (2) discrepancy between self-reported PrEP adherence urine tenofovir measure of recent PrEP adherence.

Data Analysis

We examined baseline demographic and behavioral characteristics by study arm using medians and interquartile ranges (IQRs) for continuous variables and frequencies and proportions for categorical variables. Wilcoxon rank-sum (for continuous variables), χ^2, and Fisher's exact tests (for categorical variables) were used to explore the characteristics by study arm. We also analyzed differences in participants retained versus lost to follow up. All statistical tests were 2-sided at $\alpha = .05$.

All analyses were by intention-to-treat. In the case of missing outcomes for participants who did not return for the follow-up visit, we assigned outcome values of the following: poor PrEP adherence (TFV undetected) and partner not tested for HIV. We constructed univariate Poisson regression models with robust standard errors to examine the predictors of outcomes of interests. Model results are presented as crude risk ratios (RRs) and risk differences (RDs) with 95% confidence intervals (CIs). All statistical analyses were conducted with STATA v.15 (StataCorp LLC, College Station, TX).

Patient Consent Statement

Written informed consent was attained by all participants. The study was approved by the University of Cape Town Human Research Ethics Committee and the University of California Los Angeles Institutional Review Board and conforms to standards currently applied in South Africa.

RESULTS

We screened 176 postpartum cisgender women who were enrolled in the PrEP-PP study; 38 (22%) declined study participation, whereas 32 (18%) were ineligible (most commonly because they did not report having a current partner or partner was out of town). We enrolled 106 postpartum women (60% of women screened) in the pilot study and randomized 1:1 to intervention and SOC arm. Overall, 48 of 53 women randomized to the intervention group and 52 of 53 women randomized to the SOC group returned for follow up at 1 month (91% and 98%, respectively) (Figure 1).

The median age was 26 years (IQR = 23–31 years), and women were 2 median months' postpartum (IQR = 1–6 months). Half of women had some secondary school education (n = 56; 53%) and 75% were unemployed. Most women were unmarried or non-cohabitating with their partner (56%) (Table 1). Overall, 85% reported they knew their partner's serostatus. Approximately half of women reported having sex since giving birth (48%), and 76% of those reported having condomless sex at last sex. Overall, 72% of women reported missing 0–1 PrEP doses in the past week, and 28% reported missing 2 or more doses. There was no difference in self-reported PrEP adherence at baseline by arm.

Using urine assays as a biomarker for baseline tenofovir levels, 36% (n = 68) of women had tenofovir present in their urine. Overall, almost half (43%; n = 46) had discrepant results, meaning that they reported recent strong PrEP adherence (missing <2 doses in the past week) but did not have tenofovir in her urine for the same time frame (Table 2). Women who did not return for follow up (n = 6) tended to be older, and none had tenofovir present in their urine at baseline compared to those retained ($P < .05$; data not shown).

Outcomes

Median follow up was 3 weeks (IQR = 3–7 weeks). Overall, 62% (n = 33) of the intervention arm and 34% (n = 18) of the SOC arm had tenofovir present in their urine using urine assays, with nearly double the relative risk of a positive tenofovir result for the intervention arm (RR = 1.83; 95% CI = 1.19–2.82; $P = .001$). The RD between the intervention and SOC groups

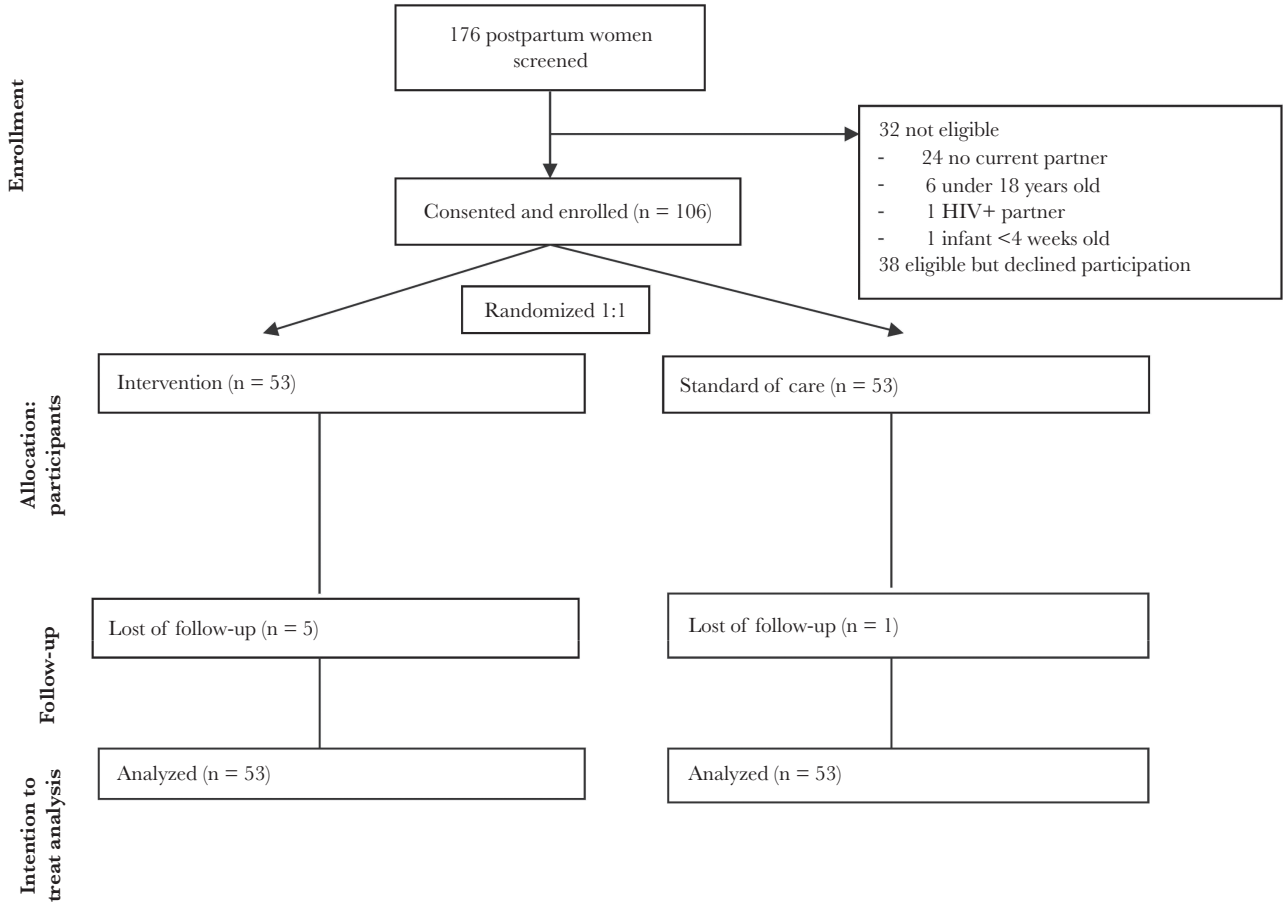

Figure 1. Consort diagram. Participant flow of women screened, enrolled, and randomized in the postpartum adherence study, Cape Town, South Africa, August 2020–April 2021. HIV, human immunodeficiency virus.

for recent PrEP adherence was 28.3% (95% CI = 10.06–46.55; $P = .001$) (Figure 2).

Overall, 66% (n = 35) of partners in the intervention and 17% (n = 9) of partners in the SOC arm tested for HIV. Women in the intervention group had an almost 4-fold increase of reporting her partner had tested for HIV compared to the SOC group (RR = 3.89; 95% CI = 2.08–7.27; $P < .001$). The risk difference (RD) between women in the intervention versus SOC was 49% (95% CI = 32.8–65.3; $P < .001$). Among those whose partners tested, most women reported testing with their partner—83% (n = 29 of 35 partners tested) in the intervention arm and 69% (n = 6 of 9 tested) in the SOC arm. In each arm, 1 partner tested positive for HIV (8.6% positivity rate for intervention arm, 11% positivity rate for SOC arm).

The proportion of women with a discrepant adherence result (self-reported recent PrEP adherence with no TFV in urine test) was significantly lower in the intervention group (n = 8; 17%) compared to the SOC group (n = 24; 46%) (RR = 0.33; 95% CI = 0.17–0.67; $P = .03$). In the intervention group, 77% (n = 41) of women reported being adherent in the past week, versus 81% in the SOC group (RR = 1.06; 95% CI = 0.89–1.26; $P = .06$). Postpartum sexual activity was the same in intervention (43%) versus SOC (53%) at follow up (RR = 0.82; 95% CI = 0.55–1.23; $P = .34$). In addition, 35% of women reported that they greatly improved their PrEP adherence after the intervention.

Acceptability

At follow up, 46 women in the intervention arm reported that they used the HIVST to test themselves (96%) and 42 gave a HIVST kit to their partner (87%). Most of those who distributed a HIVST kit (93%) demonstrated how to use the kit to their partner. One woman said she pressured her partner to test; this participant was the only one to report that testing caused conflict in her relationship. The majority of women said that their partner used the HIVST (66% overall and 83% of those who gave their partner the test). Most women reported that the HIVST was not difficult (91%) and that they felt comfortable distributing and demonstrating HIVST kits to their sexual partners. Almost all women whose partner tested (91%) brought in the HIVST or sent in a photo of the test. Of the women who reported that her partner tested, 82% said that they were very satisfied with the partner HIVST kits and counseling on their

Table 1. Baseline Socio-Demographic Factors by Study Arm Postpartum Women (N = 106) in Cape Town, South Africa, August 2020–April 2021

Socio-demographic factors	Total (N = 106, %)	Intervention (n = 53, %)	SOC (n = 53, %)	*P* Value
Age (median, IQR)	26 (23–31)	26 (23–31)	26 (23–31)	.91
Postpartum age, months (median, IQR)	2 (1–6)	2 (1–6)	2 (1–6)	.81
Time since PrEP start (weeks, median, IQR)	25 (13–47)	26 (23–57)	24 (13–37)	.17
Education				
Primary	56 (53%)	26 (49%)	30 (57%)	.44
Secondary or higher	50 (47%)	27 (51%)	23 (43%)	
Employment Status				
Full-time	18 (17%)	7 (13%)	11 (21%)	.66
Part-time	7 (7%)	3 (6%)	4 (8%)	
Self-employed	1 (1%)	1 (2%)	0 (0%)	
Not employed	79 (75%)	41 (79%)	38 (72%)	
Prior Pregnancies (no.)				
1	38 (36%)	16 (30%)	22 (42%)	.46
2–3	56 (53%)	30 (57%)	26 (49%)	
4+	12 (11%)	7 (13%)	5 (9%)	
Relationship Status				
No relationship	1 (1%)	1 (2%)	0 (0%)	.70
Married	14 (13%)	8 (15%)	6 (11%)	
Cohabiting	32 (30%)	14 (26%)	18 (34%)	
Not cohabiting	59 (56%)	30 (57%)	29 (55%)	
Partner's Education				
Primary	32 (33%)	14 (29%)	18 (37%)	.39
Secondary or higher	66 (67%)	35 (71%)	31 (63%)	
Partner Employed				
Full-time	50 (47%)	24 (45%)	26 (49%)	.44
Part-time	26 (25%)	11 (21%)	15 (28%)	
Self-employed	2 (2%)	1 (2%)	1 (2%)	
Not employed	27 (25%)	17 (32%)	10 (19%)	
Unknown	1 (1%)	0 (0%)	1 (2%)	

Abbreviations: IQR, interquartile range; PrEP, pre-exposure prophylaxis; SOC, standard of care.

Table 2. Baseline HIV Risk Factors by Study Arm Postpartum Women (N = 106) in Cape Town, South Africa, August 2020–April 2021

HIV risk factors	Total (N = 106)	Total (%)	Intervention (n = 53)	Intervention (%)	SOC (n = 53)	SOC (%)	*P* Value
Partner HIV Status							
HIV negative	89	84%	46	87%	43	81%	.42
HIV positive	1	1%	1	2%	0	0%	
Unknown	16	15%	6	11%	10	19%	
Condom Use at Last Sex							
Condomless sex	81	76%	40	75%	41	77%	.82
Condom used	25	24%	13	25%	12	23%	
No. of Sex Partners in Past Year							
0–1 partner	99	93%	49	92%	50	94%	1.00
	7	7%	4	8%	3	6%	
No. Days Missed PrEP in Last 7 Days							
0–1	76	72%	40	75%	36	68%	.46
2–3	10	9%	3	6%	7	13%	
3–4	20	19%	10	19%	10	19%	
No. Days Missed PrEP in Last 30 Days							
0–3	64	60%	36	68%	28	53%	.41
4–7	17	16%	7	13%	10	19%	
8–11	4	4%	1	2%	3	6%	
	21	20%	9	17%	12	23%	
TFV in Urine TFV Test							
TFV absent	68	64%	34	64%	34	64%	1.00
TFV present	38	36%	19	36%	19	36%	

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; PrEP, pre-exposure prophylaxis; SOC, standard of care; TFV, tenofovir.

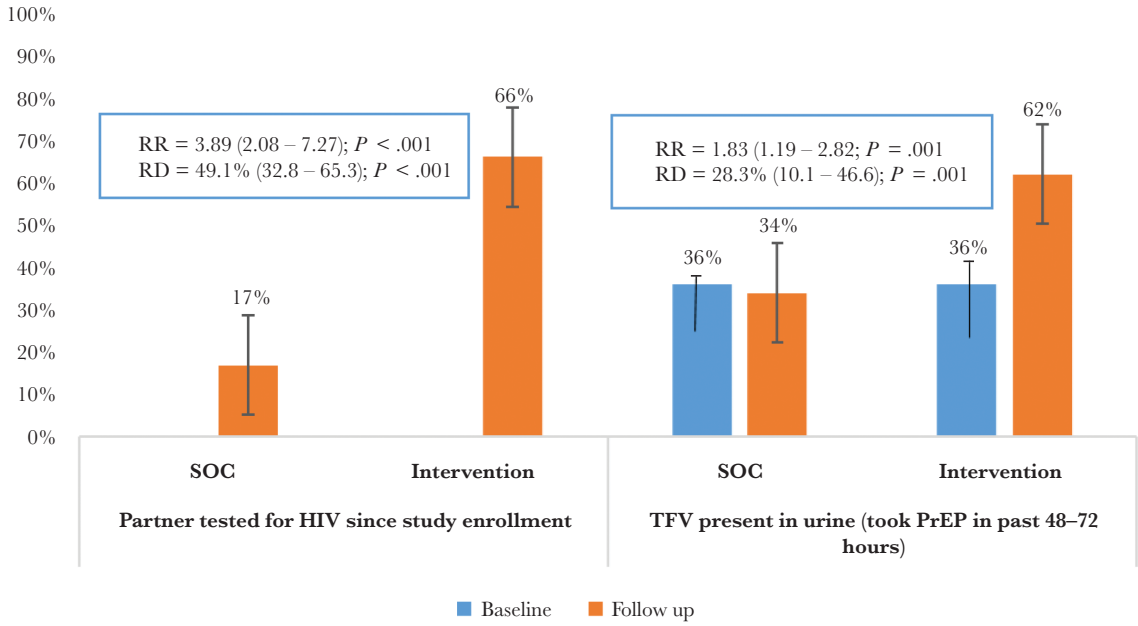

Figure 2. Results from randomized control trail of male partner human immunodeficiency virus (HIV) testing and urine tenofovir (TFV) testing with self-reported pre-exposure prophylaxis (PrEP) adherence results postpartum women (N = 106) in Cape Town, South Africa, August 2020–April 2021. RD, risk difference; RR, risk ratio; SOC, standard of care.

use. Women whose partners did not test were less satisfied with the HIVST intervention (50% reported that they were very satisfied) (Table 3).

Women reported that the urine TFV test took 4–7 minutes for 96% of women. All women said that they understood the results, and 98% said they would like to get the test again in the future. However, 5 women stated that the result was not as they expected, all of whom had received a negative tenofovir urine test result, but reported taking PrEP in the last week (so expected a TFV-positive result), indicative of missing PrEP in the past 48–72 hours. Among participants without tenofovir detected, 64% were very satisfied or satisfied (Supplementary Table 1).

DISCUSSION

This study is one of the first to evaluate the impact on PrEP adherence and continuation after HIVST and adherence biofeedback counseling among postpartum cisgender women using PrEP. Our pilot trial of a combination intervention (HIVST for PrEP users and their partners plus biofeedback counseling) demonstrated that recent adherence was almost double that of the standard of care among postpartum women on PrEP in South Africa (62% vs 34%). Similarly, partner testing occurred 4 times as frequent in the intervention versus SOC arm (66% vs 17%). The majority of women in the intervention arm tested together with their partner, giving them an opportunity to discuss their HIV status together as a couple. Postpartum women in the intervention arm reported high levels of satisfaction with both biofeedback counseling and HIVST.

These findings are important for the field of PrEP among postpartum and breastfeeding women who may be more at risk of poor PrEP adherence [12]. In our parent study, PrEP-PP, there are noticeable drop-offs in clinic visits, PrEP collection, and adherence in postpartum women, mostly because they are no longer attending the clinic for ANC and most women do not know their partner's serostatus and have limited partner communication about HIV and PrEP [16]. Postpartum visits at 1 week and 6 weeks after birth are part of the standard of care in South Africa and provide an opportunity for contraception and HIV prevention interventions. Our study called, texted women reminders for the study visits, as well as provided flexible hours to attend the study visits [33]. The HIVST and biofeedback counseling used in our combined intervention may address these barriers through several complementary mechanisms, although further research is needed to fully understand "how" and "why" the combination intervention was effective in this pilot. First, HIVST for PrEP users may facilitate women monitoring her own status and therefore increase agency and ownership over her own care [34], while simultaneously reducing PrEP clinical visit time. At the same time, urine assays used for immediate biofeedback counseling may confront consequences of poor adherence. Women may not really believe missing doses would have an impact. Counseling on results of the biomarker may confront them with the consequence of not taking the medication as having no drug in their system. When combined with a client-centered approach, we hypothesize that biofeedback counseling may improve counseling on barriers to daily PrEP use,

Table 3. Results From HIV Self-Testing in Women Who Returned for Postpartum Intervention Arm in Cape Town, South Africa, August 2020–April 2021 (n = 48 Women Who Returned for Follow-up Visit)

	N (%)
Gave Partner HIVST	
No	6 (13%)
Yes	42 (87%)
No. Partners Given Test	
0	6 (13%)
1	42 (87%)
Demonstrated How to Use HIVST to Partner[a]	
No	3 (7%)
Yes	39 (93%)
Pressured Partner to Test	
No	47 (98%)
Yes	1 (2%)
Partner Used HIVST[a]	
No	7 (17%)
Yes	35 (83%)
Tested Together With Partner[a]	
No	6 (17%)
Yes	29 (83%)
Test Result[b]	
HIV-negative	34 (97%)
HIV-positive	1 (3%)
Participant Used HIVST	
No	2 (4%)
Yes	46 (96%)
Difficulty Testing[c]	
Not difficult	42 (91%)
Little difficult	2 (4%)
Difficult	0 (0%)
Very difficult	2 (4%)
Brought in HIVST to Study Staff[c]	
No	14 (30%)
Yes	32 (70%)
Did the Test Cause Conflict?[b]	
No	34 (97%)
Yes	1 (3%)

Abbreviations: HIV, human immunodeficiency virus; HIVST, oral HIV self-test kit; PrEP, pre-exposure prophylaxis; TFV, tenofovir.

[a]n = 42 who gave a partner an HIVST.

[b]n = 35 partners who used the HIVST.

[c]n = 46 participants who used the HIVST.

resulting in greater patient understanding about adherence and strategies to address barriers to care, as well as improve patient-provider relationships because both work together to improve PrEP adherence and continuation. For adherent clients, visual positive feedback may promote sustained adherence, especially when coupled with a negative HIVST result. In other recent trials that provided drug feedback to PrEP users, acceptability was high [24, 35, 36]. Finally, HIVST for sex partners increases knowledge of partner status and therefore risk of HIV acquisition, and this may promote increased communication about HIV and PrEP within couples, facilitating partners who may not attend health facilities to engage with HIV services postpartum.

More importantly, the urine tenofovir testing in our intervention was provided in a context of ongoing counseling and supportive nonjudgmental approaches for PrEP clients. Counselors were trained to interpret the urine test results with their participants so that they could review the results and the implications together. If the test was negative, indicating that the participant missed PrEP dosing in the past 48–72 hours, the counselor worked with clients to develop alternative prevention plans, including the use of condoms consistently until the client has taken PrEP again for 7 days, in addition to developing strategies to adhere to daily oral PrEP in the future. This technique was meant to remove judgment of the participant and moved the conversation into troubleshooting how best to improve daily adherence, including daily reminders, PrEP disclosure to family members, and the importance of condom use if PrEP was not taken daily. This is similar to a recent study of the dapivirine ring (HOPE study; MTN-025), which evaluated client-centered adherence counseling and found that reframing discussions from an "adherence" to "protection" perspective encouraged adherence among consistent users [35].

In parallel, partner disclosure, encouragement to take PrEP due to partner disclosure, and HIVST have improved PrEP adherence in prior studies [12, 37, 38]. Secondary HIVST distribution to sex partners may improve disclosure of PrEP use and adherence. Our study did not find any reports of intimate partner violence after testing. One woman reported "conflict" after testing with her partner who did not initially want to test. This result is in line with prior studies that show minimal adverse events, including intimate partner violence, were associated with HIVST distribution by female partners [39–42]. Of note, the 2 women in our study who had partners diagnosed with HIV did not report IPV or any conflict after testing.

Findings are similar to recent work focused on use of retrospective feedback (not point-of-care) pharmacokinetic results to improve adherence counseling among non-PBFW using PrEP. In the 3P study in Cape Town young women, participants received retrospective feedback about PrEP drug levels at months 1–3 and showed high levels of adherence; yet only 8% and 5% in the incentive and SOC groups had detectable drug levels at 12 months. Women in the VOICE trial in southern Africa were interviewed poststudy and shown their PrEP adherence patterns. This disclosure showed that providing objective results stimulated discussions regarding adherence, and women suggested that real-time drug monitoring could improve adherence [18, 19]. Prior studies have demonstrated the importance of adherence counseling on PrEP and simplified PrEP collection for optimal PrEP use [22, 26].

Discrepancies between self-report and biomarker results for recent adherence were significantly lower among women in the intervention arm compared to SOC arm (17% versus 46%), suggesting that biomedical measures of adherence encouraged honesty and transparency between patient and provider regarding adherence concerns. More importantly, providers were trained (1) to communicate biofeedback results in a nonjudgmental manner and (2) to use client-centered approaches to adherence education when there is discrepancy between self-report and biomarker adherence results. Almost all women in the intervention arm reported that the biofeedback result was as they expected (89%) and desired to keep receiving biofeedback counseling (including the urine assay test). However, women with discrepant results were less satisfied with the intervention and more likely to be nonadherent (did not have tenofovir in their urine). Overall, satisfaction with the combination intervention in women in the study was high.

We identified that women who were lost to follow up were older and had no TFV levels in the baseline evaluation. These women may struggle to adhere to study visits and PrEP, and they may be more vulnerable than those who remained in the study. Additional interventions may be needed for pregnant and postpartum women who have difficulties with adherence and PrEP continuation, including differentiated care or community-based delivery models.

Limitations of this study include the short follow-up period (only 1 month) and modest sample size fundamental to a pilot study. Barriers for PrEP persistence and adherence may be more challenging in more prolonged periods, and more time is needed to establish whether the intervention is effective over a longer period of time. The study was within another cohort study so is not integrated into standard postnatal or PrEP services. The differential loss to follow up may affect the acceptability of the intervention because we do not know why the women in the intervention group did not return, and we inferred that they were not adherent to PrEP to mitigate the potential bias in follow up. As a result, the intervention may not be as efficacious to those participants struggling to adhere to PrEP. Furthermore, we are unable to determine which intervention, HIVST, biofeedback or both, impacted on women's adherence, a common concern in combination interventions. The study was unblinded so participants may improve their adherence because of social desirability.

CONCLUSIONS

We found that a combination intervention with HIVST for PrEP users and their partners plus adherence biofeedback counseling using urine tenofovir testing improved recent PrEP adherence in postpartum women. Adherence was almost double that of the standard of care in postpartum women on PrEP, and partner testing occurred 4 times as frequent in the intervention versus SOC arm. These preliminary results suggest that simple combination interventions may be highly effective in improving PrEP adherence in this population, and more research is needed to understand the mechanisms of action, scalability, and longer term effect of the intervention.

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Author contributions. D. L. J. D. designed the study, analyzed data, wrote the manuscript, and approved final submission. K. D. designed the study, reviewed the manuscript, and approved final submission. R. M. cleaned and analyzed the data, reviewed the manuscript, and approved final submission. D. N. analyzed data, reviewed the manuscript, and approved final submission. N. M. oversaw study implementation, reviewed the manuscript, and approved final submission. L.-G. B. designed the study, reviewed the manuscript, and approved final submission. P. M. G. designed the study, reviewed the manuscript, and approved final submission. T. J. C. designed the study, reviewed the manuscript, and approved final submission. L. M. designed the study, reviewed data and manuscript drafts, and approved final submission.

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References

1. Graybill LA, Kasaro M, Freeborn K, et al. Incident HIV among pregnant and breast-feeding women in sub-Saharan Africa: a systematic review and meta-analysis. AIDS **2020**; 34:761–76.
2. Thomson KA, Hughes J, Baeten JM, et al. Increased risk of HIV acquisition among women throughout pregnancy and during the postpartum period: a prospective per-coital-act analysis among women with HIV-infected partners. J Infect Dis **2018**; 218:16–25.
3. Joseph Davey DL, Nyemba DC, Gomba Y, et al. Prevalence and correlates of sexually transmitted infections in pregnancy in HIV-infected and- uninfected women in Cape Town, South Africa. PLoS One **2019**; 14:e0218349.
4. Joseph Davey D, Farley E, Gomba Y, et al. Sexual risk during pregnancy and postpartum periods among HIV-infected and -uninfected South African women: implications for primary and secondary HIV prevention interventions. PLoS One **2018**; 13:e0192982.
5. Van de Perre P, Goga A, Ngandu N, et al. Eliminating postnatal HIV transmission in high incidence areas: need for complementary biomedical interventions. Lancet **2021**; 397:1316–24.
6. Velloza J, Khoza N, Scorgie F, et al. The influence of HIV-related stigma on PrEP disclosure and adherence among adolescent girls and young women in HPTN 082: a qualitative study. J Int AIDS Soc **2020**; 23:e25463.
7. Scorgie F, Khoza N, Baron D, et al. Disclosure of PrEP use by young women in South Africa and Tanzania: qualitative findings from a demonstration project. Cult Health Sex **2021**; 23:257–72.
8. Janes H, Corey L, Ramjee G, et al. Weighing the evidence of efficacy of oral PrEP for HIV prevention in women in Southern Africa. AIDS Res Hum Retroviruses **2018**; 34:645–56.
9. Thomson KA, Baeten JM, Mugo NR, et al. Tenofovir-based oral preexposure prophylaxis prevents HIV infection among women. Curr Opin HIV AIDS **2016**; 11:18–26.
10. Corneli A, Perry B, McKenna K, et al. Participants' explanations for nonadherence in the FEM-PrEP clinical trial. J Acquir Immune Defic Syndr **2016**; 71:452–61.
11. Kinuthia J, Pintye J, Abuna F, et al. Pre-exposure prophylaxis uptake and early continuation among pregnant and post-partum women within maternal and child health clinics in Kenya: results from an implementation programme. Lancet HIV **2020**; 7:e38–48.

12. Joseph Davey DL, Mvududu R, Mashele N, et al. Early pre-exposure prophylaxis (PrEP) discontinuation among pregnant and postpartum women: implications for maternal PrEP roll out in South Africa [preprint]. medRxiv **2021**.
13. Joseph Davey DL, Bekker LG, Gorbach PM, et al. Delivering preexposure prophylaxis to pregnant and breastfeeding women in sub-Saharan Africa: the implementation science frontier. AIDS **2017**; 31:2193–7.
14. Pintye J, Davey DLJ, Wagner AD, et al. Defining gaps in pre-exposure prophylaxis delivery for pregnant and post-partum women in high-burden settings using an implementation science framework. Lancet HIV **2020**; 7:e582–92.
15. Joseph Davey DL, Pintye J, Baeten JM, et al. Emerging evidence from a systematic review of safety of pre-exposure prophylaxis for pregnant and postpartum women: where are we now and where are we heading? J Int AIDS Soc **2020**; 23:e25426.
16. Joseph Davey DL, Knight L, Markt-Maloney J, et al. "I had made the decision, and no one was going to stop me"—facilitators of PrEP adherence during pregnancy and postpartum in Cape Town, South Africa. AIDS Behav **2021**; 25:3978–86.
17. Agot K, Taylor D, Corneli AL, et al. Accuracy of self-report and pill-count measures of adherence in the FEM-PrEP clinical trial: implications for future HIV-prevention trials. AIDS Behav **2015**; 19:743–51.
18. Montgomery ET, Mensch B, Musara P, et al. Misreporting of product adherence in the MTN-003/VOICE trial for HIV prevention in Africa: participants' explanations for dishonesty. AIDS Behav **2017**; 21:481–91.
19. van der Straten A, Stadler J, Luecke E, et al. Perspectives on use of oral and vaginal antiretrovirals for HIV prevention: the VOICE-C qualitative study in Johannesburg, South Africa. J Int AIDS Soc **2014**; 17(3 Suppl 2):19146.
20. Amico KR, Wallace M, Bekker LG, et al. Experiences with HPTN 067/ADAPT study-provided open-label PrEP among women in Cape Town: facilitators and barriers within a mutuality framework. AIDS Behav **2017**; 21:1361–75.
21. Hebel S, Kahn-Woods E, Malone-Thomas S, et al. Discrepancies between self-reported adherence and a biomarker of adherence in real-world settings. J Acquir Immune Defic Syndr **2020**; 85:454–7.
22. Drain P, Ngure K, Mugo N, et al. Testing a real-time tenofovir urine adherence assay for monitoring and providing feedback to preexposure prophylaxis in Kenya (PUMA): protocol for a pilot randomized controlled trial. JMIR Res Protoc **2020**; 9:e15029.
23. Landovitz RJ, Beymer M, Kofron R, et al. Plasma tenofovir levels to support adherence to TDF/FTC preexposure prophylaxis for HIV prevention in MSM in Los Angeles, California. J Acquir Immune Defic Syndr **2017**; 76:501–11.
24. Koester KA, Liu A, Eden C, et al. Acceptability of drug detection monitoring among participants in an open-label pre-exposure prophylaxis study. AIDS Care **2015**; 27:1199–204.
25. van der Straten A, Montgomery ET, Musara P, et al. Disclosure of pharmacokinetic drug results to understand nonadherence. AIDS **2015**; 29:2161–71.
26. Corneli A, Perry B, Agot K, et al. Facilitators of adherence to the study pill in the FEM-PrEP clinical trial. PLoS One **2015**; 10:e0125458.
27. Spinelli MA, Rodrigues WC, Wang G, et al. Brief report: high accuracy of a real-time urine antibody-based tenofovir point-of-care test compared with laboratory-based ELISA in diverse populations. J Acquir Immune Defic Syndr **2020**; 84:149–52.
28. Gandhi M, Wang G, King R, et al. Development and validation of the first point-of-care assay to objectively monitor adherence to HIV treatment and prevention in real-time in routine settings. AIDS **2020**; 34:255–60.
29. Daughtridge G. Development and validation of a point-of-care, urine assay to measure adherence to PrEP and ART. IAS Conference on HIV Science (Mexico City, Mexico). July 14–21, 2019.
30. Department of Health South Africa. National HIV counselling and testing policy guidelines. Available at: https://www.health-e.org.za/wp-content/uploads/2015/07/HCT-Guidelines-2015.pdf. Accessed 9 June 2017.
31. Ickovics JR, Meisler AW. Adherence in AIDS clinical trials: a framework for clinical research and clinical care. J Clin Epidemiol **1997**; 50:385–91.
32. Bernstein M, Phillips T, Zerbe A, et al. Intimate partner violence experienced by HIV-infected pregnant women in South Africa: a cross-sectional study. BMJ Open **2016**; 6:e011999.
33. Moran A, Mashele N, Mvududu R, et al. Maternal PrEP Use in HIV-uninfected pregnant women in South Africa: role of stigma in PrEP initiation, retention and adherence. AIDS Behav **2021**:1–13.
34. Oyaro P, Kwena Z, Bukusi EA, Baeten JM. Is HIV self-testing a strategy to increase repeat testing among pregnant and postpartum women? A pilot mixed methods study. J Acquir Immune Defic Syndr **2020**; 84:365–71.
35. Balán IC, Giguere R, Lentz C, et al. Client-centered adherence counseling with adherence measurement feedback to support use of the dapivirine ring in MTN-025 (The HOPE Study). AIDS Behav **2021**; 25:447–58.
36. Celum CL, Gill K, Morton JF, et al. Incentives conditioned on tenofovir levels to support PrEP adherence among young South African women: a randomized trial. J Int AIDS Soc **2020**; 23:e25636.
37. Alexander Moran LM, Mashele N, Coates T, et al. Maternal PrEP use in HIV-uninfected pregnant women in South Africa: role of Stigma in PrEP initiation and persistence. International Workshop on HIV Pediatrics (Virtual). August 2020.
38. Joseph Davey D. Partners support, disclosure and side effects: facilitators of high maternal PrEP adherence in Cape Town, South Africa. HIVR4P (Virtual). January 2021.
39. Thirumurthy H, Masters SH, Mavedzenge SN, et al. Promoting male partner HIV testing and safer sexual decision making through secondary distribution of self-tests by HIV-negative female sex workers and women receiving antenatal and post-partum care in Kenya: a cohort study. Lancet HIV **2016**; 3:e266–74.
40. Masters SH, Agot K, Obonyo B, et al. Promoting partner testing and couples testing through secondary distribution of HIV self-tests: a randomized clinical trial. PLoS Med **2016**; 13:e1002166.
41. Choko AT, Corbett EL, Stallard N, et al. HIV self-testing alone or with additional interventions, including financial incentives, and linkage to care or prevention among male partners of antenatal care clinic attendees in Malawi: an adaptive multi-arm, multi-stage cluster randomised trial. PLoS Med **2019**; 16:e1002719.
42. Gichangi A, Wambua J, Mutwiwa S, et al. Impact of HIV self-test distribution to male partners of ANC clients: results of a randomized controlled trial in Kenya. J Acquir Immune Defic Syndr **2018**; 79:467–73.