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Journal

AIDS and Behavior, 24(7)

ISSN

1090-7165

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Publication Date

2020-07-01

DOI

10.1007/s10461-020-02783-8

Peer reviewed

HHS Public Access

Author manuscript

AIDS Behav. Author manuscript; available in PMC 2021 July 01.

Published in final edited form as:

AIDS Behav. 2020 July ; 24(7): 2178–2187. doi:10.1007/s10461-020-02783-8.

The effect of depression on adherence to HIV pre-exposure prophylaxis among high-risk South African women in HPTN 067/ ADAPT

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Abstract

Background: Oral pre-exposure prophylaxis (PrEP) is highly efficacious but low adherence undermines effectiveness. Depression, common in African women, may be a barrier to consistent PrEP use. We aimed to assess the relationship between depression, psychosocial mediators, and PrEP adherence among South African women.

Methods: We analyzed data from 174 South African women in HPTN 067, an open-label oral PrEP trial conducted from 2011–2013. Participants were followed for 24 weeks. PrEP adherence was measured via Wisepill™ and weekly self-report interview data. We considered participants "adherent" at week 24 if Wisepill™ and interviews indicated that ≥80% of expected doses were taken in the prior month. Elevated depressive symptoms were assessed using the 20-item Center for Epidemiological Studies-Depression (CES-D) scale. We used marginal structural models to

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COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of potential conflicts of interest: All authors declare no conflicts of interest.

Conflicts of Interest
All other authors report no potential conflicts of interest.

estimate the effect of elevated symptoms at baseline on PrEP adherence at week 24 and to assess whether the direct effect changed meaningfully after accounting for mediating effects of stigma, social support, and PrEP optimism.

Results: High PrEP adherence occurred less often among women with elevated depressive symptoms (N=35; 44.3%) compared with those without (N=52; 54.7%; adjusted relative risk [aRR]: 0.79; 95% confidence interval [CI]: 0.63–0.99). The effect of elevated depressive symptoms on PrEP adherence persisted in models accounting for the mediating influence of stigma (aRR: 0.74; 95% CI: 0.51–0.97) and PrEP optimism (aRR: 0.75; 95% CI: 0.55–0.99). We also found a direct effect of similar magnitude and direction when accounting for social support as the mediating variable, although this adjusted relative risk estimate was not statistically significant (aRR: 0.77; 95% CI: 0.57–1.03).

Conclusions: Depressive symptoms were common and associated with lower PrEP adherence among South African women. Future work is needed to determine whether depression services integrated with PrEP delivery could improve PrEP effectiveness among African women.

Keywords

Depression; HIV; Pre-exposure prophylaxis; Africa; Women

INTRODUCTION

Daily oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) pre-exposure prophylaxis (PrEP) is >90% effective in preventing HIV transmission when adherence is high [1–4]. While open-label and demonstration projects have shown that women at high risk for HIV are generally able to adhere to daily oral PrEP regimens, these studies also reported waning PrEP adherence over time [5,6]. Qualitative studies have identified important psychosocial barriers to regular pill-taking for women in the context of placebo-controlled and early open-label PrEP trials including anticipated and experienced stigma, lack of social support, concerns about safety, and low perceptions of HIV risk and PrEP effectiveness [7,8]. Mental health conditions, including depression, are also known barriers to healthcare engagement and medication adherence, and recent analyses have documented an influence of depressive symptoms on PrEP non-adherence [9,10].

Depression is highly prevalent worldwide, particularly among women, who are 1.5–3 times more likely to experience lifetime depression than men [11]. In addition, studies in the United States and sub-Saharan Africa have found that depressive symptoms are related to sexual behaviors, HIV-related stigma, and poor instrumental and emotional social support [12,13]. The relationship between depression, stigma, and social support is quite complex and likely bidirectional, with studies often describing elevated depressive symptoms as an outcome of high levels of stigma and low social support [12–14,16]. However, the relationship between depression, stigma, and social support depends on the specific constructs being measured (e.g., anticipated versus enacted stigma). Recent longitudinal research found that depressive symptoms can act as a predictor of anticipated HIV-related stigma [17,18]. In addition, depression can lead to low perceived social support as individuals with elevated depressive symptoms often isolate themselves from peer and

healthcare worker support [19,20]. Depression, anticipated stigma, and instrumental social support have each been shown to strongly directly influence HIV treatment adherence and healthcare engagement [12–16], and these variables may also modify one another and indirectly influence HIV outcomes including PrEP adherence [15].

Optimism about PrEP effectiveness, alternatively described as “perceived impact of PrEP on one’s sex life”, “perceived benefit of PrEP”, and “attitudes about PrEP”, has also been hypothesized to have a direct impact on PrEP initial and adherence [21]. In several recent empirical studies, PrEP optimism has been associated with higher likelihood of contemplating PrEP use and discussing PrEP with a provider, greater self-efficacy to use PrEP, and increased PrEP adherence, and has also been associated with increased condomless sex in a cohort of individuals using PrEP [22–25]. Moreover, studies in populations living with chronic medical conditions have consistently documented the negative influence of depressive symptoms on beliefs about the effectiveness of medical treatment and satisfaction with medical treatment and have found that treatment optimism is a mediator of the relationship between depression and diet and exercise regimens, medication adherence for heart conditions, cystic fibrosis and diabetes, and smoking cessation [26,27]. Overall, this body of research provides strong evidence of the high prevalence of depression among people living with HIV, the influence of depression on anticipated stigma, perceived and instrumental social support, and treatment optimism, and the potential for these factors to influence HIV acquisition and treatment adherence.

While the role of depression on PrEP adherence is gaining recognition [9,10,28], less is understood about whether the impact of depressive symptoms on PrEP use persist after accounting for any mediating influence on stigma, social support, and optimism about PrEP effectiveness. The relationship between depressive symptoms, psychosocial mediators, and PrEP adherence is quite complex and likely confounded by other factors like sexual behavior and risk perceptions about HIV [29]. To contribute information to this gap, we: 1) evaluate the total effect of depression on PrEP adherence and 2) explore whether the relationship between depression and adherence remained after accounting for potential psychosocial mediators and confounding variables among a cohort of 174 HIV-uninfected women participating in an open-label randomized trial in South Africa. We hypothesized that depression would be associated with low PrEP adherence and that the strength of this direct association would be meaningfully altered after controlling for anticipated HIV-related stigma, instrumental social support, and optimism about PrEP efficacy.

METHODS

Study design and participants

The HIV Prevention Trials Network (HPTN) 067/Alternative Dosing to Augment PrEP Pill Taking (ADAPT) study was a randomized, open-label trial of daily versus intermittent oral FTC/TDF-based PrEP conducted from 2011–2014. The study enrolled high-risk women in Cape Town, South Africa and transgender women and men who have sex with men (MSM) in Bangkok and Harlem [5,30]. This analysis is limited to cisgender female participants because of the higher depression prevalence among women [11], links between depression and PrEP adherence in African women [9], and pharmacokinetic data indicating that PrEP

may be less forgiving of missed doses with respect to vaginal compared to rectal HIV exposure [31]. Eligible women were HIV-antibody negative, ≥18 years, literate in English or Xhosa, and had at least one risk factor for HIV in the six months prior to enrollment (e.g., sex with more than one partner, history of sexually transmitted infection).

Enrolled participants completed a five-week period of once a week directly-observed-dosing and were then randomly assigned to one of three FTC/TDF PrEP dosing regimens: daily (one tablet every day); time-driven (one tablet twice a week, plus a post-sex dose); and event-driven (one tablet before and after sex; we based the time- and event-driven regimens on available animal model data at the time when HPTN 067/ADAPT was designed, but models now suggest that more regular PrEP dosing is likely needed to achieve protective drug concentrations in vaginal tissue) [5,31]. Regimens were assigned in a 1:1:1 ratio for each site. After randomization and counseling about their dosing regimen, participants received a one-month supply of PrEP in an electronic dose monitoring device (Wisepill™). Follow-up visits occurred at 4, 12, and 24 weeks post-randomization and participants received HIV testing, counseling, and PrEP refills.

Data collection

Participants completed computer-assisted self-interviewing (CASI) surveys (in English or Xhosa) to provide data on depression, drug and alcohol use, HIV risk perception, sexual behavior, social support, stigma related to HIV and PrEP, and optimism about PrEP effectiveness. Data on demographics, depression, and drug and alcohol use were assessed at baseline. Data on social support, stigma related to HIV and PrEP, and optimism about PrEP effectiveness were collected at the 12-week visit and PrEP adherence data were collected at the 24-week visit. Sexual behavior and HIV risk perceptions were measured at baseline and the 4-week and 12-week study visits.

PrEP use was assessed with Wisepill™ electronic monitoring devices that record a date-time stamp with every closure and transmit the data to a cloud-based database. Trained staff also conducted weekly in-person or phone interviews to collect dates, times, and types of sex ‘events’ in the prior week. These data were used to calculate the expected number of PrEP doses for participants in the event-driven and time-driven arms. Weekly interviews were also used to adjust Wisepill™ recorded times for doses removed and taken later or for openings not associated with pill-taking.

Measures

PrEP adherence was defined as the percentage of PrEP doses taken out of expected doses during the period between 20 and 24 weeks. The number of expected doses excluded days for which PrEP was not dispensed due to missed visits, protocol-defined stops, or refill refusals. Participants were considered to have high adherence at the 24-week visit if ≥80% of expected doses were taken in the prior month. We excluded visits when event-driven arm participants were not expected to have taken PrEP doses (N=13).

Depression was measured at the baseline and 24-week visits with the 20-item version of the Center for Epidemiologic Studies-Depression scale (CES-D) [32]. A sum score ≥16 was indicative of elevated depressive symptoms (range 0–60). This cutoff value has been

previously validated with women in sub-Saharan Africa and corresponds well with clinical depression diagnosis [23].

Anticipated HIV-related stigma was measured at the 12-week visit with two items asking participants whether they are worried that someone will see them taking a pill and think they have HIV ("Many people have a hard time taking the study pills exactly when they are recommended. In the past three months, did you find it hard to take your pills as recommended because: 1) I was worried about others thinking I have HIV because they saw me taking the pill; 2) I was worried about how people would react if they saw me taking the study pill"). Those who endorsed either item (by responding "yes") were considered to anticipate stigma. Instrumental social support was measured at the 12-week visit with two items asking whether participants receive help taking PrEP from 1) family or friends or 2) from study staff ("Rate how much you agree or disagree with each statement: 1) People who are important to me support me in taking the study pills; 2) The staff at the clinic support me in taking the study pills"). Those who endorsed either item (by either responding "agree" or "somewhat agree") were considered to have instrumental social support related to PrEP. PrEP optimism was measured at the 12-week visit with five items asking about the degree to which participants feel that PrEP protects them from HIV and may influence their sexual behavior (e.g., "If I am taking the study pills I would worry less about HIV"; "Taking the study pills means I can worry less about safer sex"; "If I am taking the study pills I could have more sex partners"). Scores from the Likert responses across the five items were summed for each participant (2= "agree"; 1= "somewhat agree"; 0= "neither agree nor disagree"; −1= "somewhat disagree"; −2= "disagree") and classified into a binary variable around a sum score of zero (1= high levels of PrEP optimism or responding mostly "agree" or "somewhat agree"; 0= low levels of PrEP optimism or responding mostly "disagree" or "somewhat disagree").

Alcohol use was measured using the validated Alcohol Use Disorders Identification Test (AUDIT) scale (range 0–40; score ≥8 indicates heavy alcohol use) [33]. Illicit drug use was measured using the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) scale and was coded as a binary variable (any or none) [34]. HIV risk perception was measured with a visual analogue scale item asking participants about the chance that they will acquire HIV at some point in their life. Responses ranged from 0 (no chance) to 8 (very high chance). A score ≥6 indicated high risk perception. Sexual behavior over the past three months was measured with six individual items assessing the number of sex partners, number of sex partners with whom condoms were used, number of HIV-positive sex partners, number of sex acts, number of sex acts when a condom was used, and frequency of transactional sex. Condomless sex was coded as a binary variable based on reported number of sex acts and number of sex acts when a condom was used (1=any condomless sex in the prior three months; 0=no condomless sex in the prior three months).

Causal model

Our primary exposure of interest was depression measured at the baseline study visit and our primary outcome was PrEP adherence assessed at the week 24 visit (Figure I). Potential mediators of the relationship included anticipated stigma, instrumental social support, and

optimism about PrEP effectiveness. All three variables were measured at the week 12 visit with items that assessed feelings at the time of data collection, ensuring temporality between the exposure, mediator, and outcome measurement. We hypothesized that elevated depressive symptoms would cause anticipated HIV-related stigma, lower instrumental social support to take PrEP, and lower PrEP optimism at week 12, which in turn would cause reduced PrEP adherence at week 24. Age, marital status, education, alcohol use, and drug use were all measured at baseline and were considered confounders of the exposure and mediator relationship, mediator and outcome relationship, and exposure and outcome relationship [24]. Sexual behavior (e.g., condomless sex) and HIV risk perceptions were measured longitudinally at baseline, week 4, and week 12 study visits with questions referring to behavior and risk perceptions over the prior three months. These variables were considered to be confounders of the relationship between depression and PrEP adherence and the relationship between the mediators and PrEP adherence, as they could impact these psychosocial variables and participant's PrEP use [29,35,36]. Moreover, depression at baseline could influence condomless sex and HIV risk perceptions at the week 4 and week 12 visits. For example, prior studies have found associations between depressive symptoms, increased HIV risk perceptions, and changes in sexual behavior (increased condomless sex and number of sex partners among individuals with mild to moderate depression and reduced frequency of sexual intercourse for individuals with severe depression) and these dynamic changes in risk perceptions and sexual behavior could then affect a woman's need and desires for PrEP [22,35,36]. Therefore, in addition to their role as confounding variables, sexual behavior and HIV risk perceptions are also affected by the depression exposure at the prior study visit and must be adjusted for using marginal structural models rather than traditional regression approaches.

Statistical analyses

We estimated the population-level total effect of depression on PrEP adherence using marginal structural models to adjust for confounding variables. We first computed stabilized inverse probability weights using logistic regression to predict the probability of having elevated depressive symptoms. These exposure weights were calculated with age, marital status, education, alcohol and drug use, and HIV risk perception, and sexual behavior (condomless sex), identified as confounding variables *a priori* because of their known associations with depression and adherence [29]. Our exposure weights were included in regression models with a log link, binomial distribution, and robust standard errors to estimate relative risks.

We similarly used marginal structural models to estimate controlled direct effects of depression on PrEP adherence after accounting separately for each mediator. This modeling approach allowed us to quantify the magnitude of the association between elevated depressive symptoms and PrEP adherence that remained after removing any downstream influence of anticipated stigma, instrumental social support, and PrEP optimism on adherence, while also accounting for mediator-outcome confounders that were affected by elevated depressive symptoms (HIV risk perception and condomless sex). The controlled direct effect estimates the amount that PrEP adherence would change, on average, if everyone in the population changed from not depressed to depressed and the mediators were

held at a fixed level. We calculated stabilized inverse probability weights for each mediator using the depression exposure and the same confounding variables from the exposure weight models (age, marital status, education, alcohol and drug use, HIV risk perception, and condomless sex). We then multiplied the mediator weights by the exposure weights to calculate total weights for each mediator. The total weights were included in regression models and we ran separate regression models for each mediator.

Before conducting our analyses, we used Monte Carlo Markov Chain (MCMC) models to impute missing confounder and mediator variable data over six datasets. For binary variables, imputed data were rounded to the nearest whole number. We ran our models on the full sample in each imputed dataset and combined the resulting estimates using Rubin's method.

We conducted several additional analyses to explore whether our findings were robust to changes in variable measurement and imputation procedures. First, we repeated our marginal structural model analyses using a binomial distribution and identity link to estimate risk differences for the total and direct effects. Second, we tested for the presence of moderated-mediation between the exposure and each of the mediators by calculating controlled direct effects with interaction terms in the models. Third, we examined the dose-response relationship for the total effect by varying the definition of PrEP adherence to ≥70% and ≥95% of expected PrEP doses. Fourth, we restricted our total and direct effect models to participants in the daily arm only (N=57) and those who had complete mediator and confounder data available (N=158). Finally, we conducted quantitative bias analysis to estimate the potential influence of a binary unmeasured confounder of the relationship between mediators and PrEP adherence. We specified a range of bias parameter values (e.g., the prevalence of intimate partner violence in the population and its influence on PrEP) and examined the bounds within which our findings remained significant.

All analyses were conducted using SAS 9.4 (Cary, North Carolina, USA).

Ethical statement

Ethical approval was obtained by the Human Research Ethics Committee (HREC) in South Africa and the protocol was reviewed by the National Institutes of Health (NIH) Division of AIDS (DAIDS) prior to implementation. Participants provided written informed consent in their preferred language. The protocol was registered at ClinicalTrials.gov (identifier NCT01327651).

RESULTS

Participant characteristics

A total of 178 HIV-uninfected South African women were enrolled and randomized in the HPTN 067 study. Among the 174 women (97.8%) with CES-D scores at baseline, 57 (32.8%) were randomized to daily PrEP, 58 (33.3%) were in the time-driven arm, and 59 (33.9%) were in the event-driven dosing arm (Table 1). Almost half of the participants (N=79; 45.4%) had CES-D scores ≥16. The median age at enrollment was 26 years (interquartile range [IQR] 21, 37 years). CES-D scores remained consistent throughout study

follow-up and 46.7% of participants had scores ≥16 at their final study visit (N=77 of 164 participants retained). Among four women who seroconverted during follow-up, none had elevated depressive symptoms at baseline and only one had high PrEP adherence at the 12-week visit.

Retention rates were high throughout follow-up (>90% attended all visits) and did not differ by arm or CES-D scores. Prior to imputation, we had complete exposure, mediator, and outcome data for 159 (91.4%) participants. Week 12 visit data on all mediators were available for 162 of 174 participants (93.1%). Approximately 16.0% of participants (N=26) reported high levels of PrEP optimism, 14.2% (N=23) reported anticipated HIV-related stigma, and 31.5% (N=51) reported instrumental social support related to PrEP use at week 12. Missing mediator and confounder data were not associated with depression or PrEP adherence. We had PrEP adherence data at week 24 for 164 participants (94.3%).

Total effect of depression on PrEP adherence

High PrEP adherence (≥80%) was detected among 53.0% of 164 participants with week 24 adherence data (N=87) and occurred less often among women with depression than among women without depression (44.3% versus 54.7%, chi-squared test statistic: 2.78, p-value: 0.09). After adjusting for confounders, women with depression were less likely to have high PrEP adherence than women without depression (adjusted risk ratio [aRR]: 0.79, 95% confidence interval [CI]: 0.63, 0.99, Table 2). In our model estimating the risk difference of high PrEP adherence by depression groups, we found there were 15 fewer participants with high PrEP adherence per 100 participants with depression compared to participants without depression (adjusted risk difference [aRD]: −0.15, 95% CI: −0.31, 0.01; Table 2). Our findings were robust to changes in the sample: the total effect remained statistically significant for participants who had complete data available prior to imputation (aRR: 0.77, 95% CI: 0.56, 1.00) and was a similar magnitude for participants in the daily dosing arm (aRR: 0.71, 95% CI: 0.41, 1.24). The strength of the association decreased with PrEP adherence cutoffs of 70% (aRR: 0.89, 95% CI: 0.76, 1.03) and 95% (aRR: 0.91, 95% CI: 0.77, 1.09) of expected doses.

Controlled direct effect of depression on PrEP adherence

In our model accounting for anticipated stigma as a mediator of the association between depression and PrEP adherence, we estimated a statistically significant controlled direct effect of 0.74 (95% CI: 0.51, 0.97; Table 3), which was quite similar to the total effect estimate. The point estimates for the direct effect did not change considerably in models with an interaction term between depression and HIV-related stigma (aRR among those without stigma: 0.74, 95% CI: 0.52–1.05; aRR among those with stigma: 0.75, 95% CI: 0.29–1.98).There were 18 fewer participants with high PrEP adherence per 100 participants with depression compared to participants without depression, while holding stigma values fixed (aRD: −0.18, 95% CI: −0.35, −0.01, p-value: 0.04).

Considering instrumental social support as a mediator, we estimated controlled direct effect point estimates that were similar to the total effect on both the relative (aRR: 0.77, 95% CI: 0.57, 1.03) and absolute scales (aRD: −0.15, 95% CI: −0.32, 0.02), although without

statistical significance (Table 3). We did not detect a meaningful interaction effect between depression and social support (aRR among those without social support: 0.79, 95% CI: 0.55–1.13; aRR among those with social support: 0.72, 95% CI: 0.27–1.92). The controlled direct effect was also not substantially changed when PrEP optimism was included as the mediating factor: we found a statistically significant direct effect on the relative scale (aRR: 0.75, 95% CI: 0.55, 0.99) but not on the absolute scale (aRD: −0.15, 95% CI: −0.32, 0.01). However, the controlled direct effect point estimates changed when including an interaction term between depression and PrEP optimism (aRR among those without optimism: 0.69, 95% CI: 0.50–0.98; aRR among those with optimism: 1.19, 95% CI: 0.37–2.03), meaning that elevated depressive symptoms only have a statistically significant negative direct effect on PrEP adherence among participants who do not believe that PrEP will protect them from HIV. For participants who feel optimistic that PrEP will protect with them from HIV, their elevated depressive symptoms do not have a direct negative effect on PrEP adherence.

Our controlled direct effect coefficients were robust to changes in the definition of PrEP adherence, although they were no longer statistically significant when PrEP adherence was defined as ≥95% of expected doses or in the sample of daily arm participants. They were similar in magnitude and statistical significance among those with complete data before imputation. Our bias analysis indicated that an unmeasured confounder of the mediator and outcome relationship would need to have a 35% prevalence difference between depressed and non-depressed individuals and a strong effect on PrEP adherence (RR ≥2.00) to alter our findings of a statistically significant controlled direct effect.

DISCUSSION

In this open-label randomized evaluation of PrEP dosing regimens in South Africa, women with depression were less adherent to PrEP. The association between depressive symptoms and PrEP adherence remained even after controlling for the mediating influence of anticipated stigma, instrumental social support, and optimism about PrEP effectiveness. This finding is particularly important given that in this cohort and other sub-Saharan African settings the burden of depression is quite high among women, and women have been found to experience difficulty adhering to daily oral PrEP over time [5,11].

Consistent with these findings, another recent analysis found that depressive symptoms had a strong negative influence on PrEP adherence among women in Kenya and Uganda [9]. A study in the United States reported that depression was associated with low PrEP adherence among MSM [28]. Work from the iPrEX OLE team found that depression may have a stronger effect on adherence for women than men, pointing to possible gender differences in depression severity or the mechanism by which depression influences adherence [10]. Links between depression and antiretroviral therapy and oral contraceptive adherence have also been established, indicating that there may be a negative relationship between depressive symptoms and daily medication use for other medications and populations [37,38]. In this analysis, we found that the negative relationship between depression and PrEP adherence persisted even after accounting for mediation by stigma, social support, or optimism about PrEP effectiveness. There are two potential explanations for our results: 1) stigma, social support, and/or optimism about PrEP effectiveness do not truly mediate the relationship

between depression and PrEP adherence or the direct association between depression and adherence is stronger than any indirect association through these factors; or 2) these variables do mediate the relationship but were measured incorrectly or too infrequently to detect a change in the controlled direct effect. Infrequently measured mediators prevented us from exploring questions of serial mediator or examining the potentially lagged impact of these variables at different time points in relation to depressive symptoms and PrEP adherence measurement. The relationships between depression, stigma, and social support are likely complex and bidirectional, and it is possible that depressive symptoms mediate relationships between these other psychosocial constructs and PrEP use [12–14,16]. We did not observe strong effects of stigma and social support on PrEP use but our dataset has limitations related to construct measurement and infrequent data collection and additional research is needed to explore changes in depression, stigma, social support, and PrEP use over time.

While our results have interestingly pointed to a robust association between depression and PrEP adherence, the mechanisms for the association between depression and daily medication use are not well-understood. Depression could lead to lower healthcare engagement and is a predictor of feelings of social isolation and lower trust in sexual partners and medical personnel 39]. Among individuals at risk of HIV, these feelings could lead to changes in perceived HIV risk, self-care, anticipated stigma related to HIV or PrEP, and instrumental and emotional social support to continue using daily PrEP [7,16,39]. Depression has also been linked with changes in sexual behavior. In Eastern Africa, depressive symptoms were associated with increased condomless sex and partners, but other analyses found that depression was related to reduced frequency of sexual intercourse [35,36]. Within the context of PrEP delivery, these dynamic changes in sexual behavior related to depression could affect a woman's need and desires for PrEP. We hypothesized that the strength of the association between depressive symptoms and PrEP adherence would exhibit a dose-response relationship, whereby the analysis with a PrEP adherence cutoff of 95% would result in a stronger association than the primary analysis with a cutoff of 80% of expected doses. However, only a small group of individuals met the cutoff for high adherence using the 95% cutoff (N=55; 33.5% of visits) and this cutoff likely resulted in non-differential misclassification of our outcome measure (by classifying participants who took approximately five PrEP doses per week as having low PrEP adherence) which could have attenuated our effect estimate. It is also possible that individuals who had formed daily PrEP taking habits were able to take PrEP seven days a week (95% cutoff), regardless of their depressive symptoms, while those with moderately high but not perfect adherence (80% cutoff) were more affected by depressive symptoms.

The strengths of this study include the prospective cohort which allowed us to establish temporality of the association between depression, PrEP adherence, and potential mediators. Data on depressive symptoms were collected using a validated screening tool, and data on PrEP use were rigorously collected with electronic monitoring devices and adjusted using weekly interview data. Overall retention rates were high in the sample and bias due to differential attrition by depressive symptoms was likely minimal.

Limitations of this study included a small sample size and infrequent measurement of depression and mediators, which reduced our ability to assess change over time. However, CES-D scores were stable between baseline and Week 24, indicating that depression may have remained consistent. We were unable to examine serial mediation because the mediators were all measured at the same visit. Scales for stigma, social support, and PrEP-related optimism were adapted from instruments for ART use but had not been previously validated, and the binary classification of these mediators may have resulted in measurement error. However, it was necessary to classify the exposure and mediator variables into binary categories in order to estimate weights and fit our marginal structural models (weights for continuous variables could be derived using density estimates from linear regression models but this often results in unstable weights). In addition, there may be non-differential misclassification of binary depression status with respect to adherence, which would have attenuated our estimates. The HPTN 067 protocol was not designed with this analysis in mind, and there are limitations of unmeasured (e.g., intimate partner violence), infrequently measured (e.g., drug and alcohol use), and potentially incorrectly measured confounders. In estimating the controlled direct effect, we were particularly concerned about unmeasured confounding of the exposure and mediator and mediator and outcome relationships. However, sensitivity analyses indicated that a confounder would need to have a strong association with the outcome and be relatively common in our population to alter conclusions. PrEP adherence was measured via electronic device and self-report, both of which may be biased. We could not examine effects on continuous PrEP dosing or drug concentrations because participants in the event-driven and time-driven arms had less consistent PrEP use by design. Finally, our findings may not be generalizable to populations accessing PrEP through public programs.

The controlled direct effect estimate allows us to understand whether intervening on stigma, social support, and PrEP optimism would have a meaningful public health impact among a population of high-risk women taking PrEP. Our results showing the robust effect of depression on lower PrEP adherence point to a potential need for future interventions to incorporate mental health services with PrEP delivery for women. Moreover, interventions targeting stigma, social support, and optimism about PrEP effectiveness may not have a substantial impact at improving PrEP adherence in this population. Interventions integrating depression care into existing ART and prenatal care programs are being implemented with success in sub-Saharan Africa, which suggests that depression services can be implemented in busy healthcare settings [40]. While additional research is necessary to understand the mechanisms by which depression influences PrEP adherence, our results support the integration of regular depression screening, referral, and treatment into PrEP delivery programs, which may reduce the burden of depression, improve PrEP effectiveness, and prevent PrEP from becoming a missed public health opportunity among African women.

ACKNOWLEDGMENTS

The authors thank the individuals who participated in the study, the team at the Emavundleni Clinical Research Site in Cape Town, South Africa, and the HIV Prevention Trials Network that supported data collection and management for this work.

Research involving human participants and/or animals: All procedures performed were in accordance with the ethical standards of the Human Research Ethics Committee (HREC) in South Africa, the National Institutes of Health (NIH) Division of AIDS (DAIDS), and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Sources of Funding: RMG has been a site investigator for clinical trials funded by GlaxoSmithKline (GSK; managed by ViiV Healthcare) and Gilead Sciences to the Gladstone Institutes and the San Francisco AIDS Foundation. KRA received an unrestricted educational grant to the University of Michigan from Gilead Sciences (2015–2017).

This work was supported by award numbers UM1-AI068619, UM1-AI068617, UM1-AI068613, and R01 AI118575, from the NIH (National Institute of Allergy and Infectious Diseases [NIAID], National Institute of Mental Health [NIMH], and National Institute on Drug Abuse [NIDA]) to HPTN. This work was also supported in part by the Emory-CDC HIV/AIDS Clinical Trials Unit award number UM1AI069418 from the NIH (NIAID). JV was supported by the NIMH of the NIH (grant F31 MH113420). Gilead Sciences donated study medication to the NIH to support this study. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIAID, the National Institutes of Health, or the U.S. Centers for Disease Control and Prevention. The use of a trademark name herein does not indicate government endorsement.

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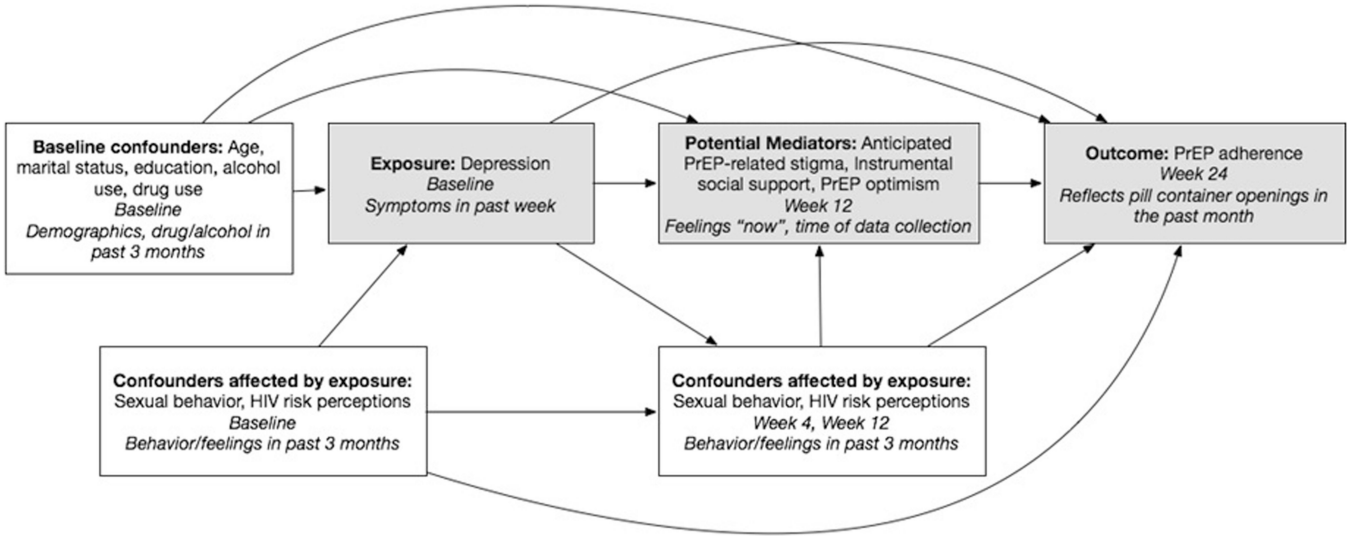

Figure I.

Causal model of the relationships between depressive symptoms, mediators, and PrEP adherence over follow-up[1]

[1]Italicized text refers to the visit when data were collected and the reference time period for the variables assessed. For example, data on sexual behavior and HIV risk perceptions were collected at baseline, week 4, and week 12 and all questions asked about behaviors or feelings in the three months prior to data collection.

Table I.

Characteristics of the study sample, by study arm (N= 174 unless otherwise indicated)

Characteristic	CES-D Score	
	CES-D <16 (N=95; 54.6%)	CES-D ≥16 (N=79; 45.4%)
Randomized arm		
Daily	30 (31.6%)	27 (34.2%)
Time-driven	35 (36.8%)	23 (29.1%)
Event-driven	30 (31.6%)	29 (36.7%)
≤25 years old	56 (59.0%)	31 (39.2%)
Never married	75 (79.0%)	66 (83.5%)
Secondary education completed	42 (44.2%)	18 (22.8%)
Black ethnic origin	94 (99.0%)	79 (100.0%)
Number of sex partners, 3 months prior to enrollment	1 (1–1)	1 (1–1)
Number of vaginal or anal sex acts, 3 months prior to enrollment	5 (2–11)	4 (1–6)
Any sex without a condom, 3 months prior to enrollment (N=167)	58 (62.4%)	43 (58.1%)
Transactional sex (N=172)	5 (5.3%)	11 (14.1%)
Drug use	8 (8.4%)	14 (17.7%)
AUDIT score ≥8	24 (25.3%)	28 (35.4%)
HIV risk perceptions		
Low chance of becoming HIV infected	57 (60.0%)	41 (51.9%)
High chance of becoming HIV infected	5 (5.3%)	13 (16.5%)
Unknown chance of becoming HIV infected	33 (34.7%)	25 (31.7%)
Anticipated stigma at Week 12 (N=162)	9 (10.2%)	14 (18.9%)
Instrumental social support at Week 12 (N=162)	27 (30.7%)	24 (32.4%)
PrEP optimism at Week 12 (N=162)	12 (13.6%)	14 (18.9%)

Data are presented as number (%) for categorical variables and median (interquartile range [IQR]) for continuous variables.

CES-D= Center for Epidemiologic Studies Depression scale; AUDIT= Alcohol Use Disorders Identification Test

Table II.

Total effect estimates for the association between depression and PrEP adherence (N=164 participants with PrEP adherence data available at Week 24)[1]

	Visits with high PrEP adherence[1] (N=87; 53.0%)	Relative scale[2]		Absolute scale[2]	
		RR (95% CI)	p-value	aRD (95% CI)	p-value
Depression	35 (44.3%)	0.79 (0.63, 0.99)	0.05	−0.15 (−0.31, 0.01)	0.07
No depression	52 (54.7%)	REF	REF	REF	REF

aRR= adjusted relative risk; aRD= adjusted risk difference; 95% CI= 95% confidence interval

[1]Participants were considered adherent to PrEP if their adjusted Wisepill data indicated that they had taken ≥80% of expected pills at the Week 24 study visit

[2]Stabilized inverse probability weights account for confounding by the sets of baseline confounders (age, marital status, education, alcohol use, drug use) and longitudinal confounders (any unprotected sex, HIV risk perceptions; weight mean=0.99; range=0.47–2.38)

Table III.

Controlled direct effect estimates for the association between depression and PrEP adherence[1] for each mediator (N=164 participants with PrEP adherence data available at Week 24)

Exposure	Mediator	Outcome	Relative scale[2]		Absolute scale[2]	
			aRR (95% CI)	p-value	aRD (95% CI)	p-value
Depression	Stigma	PrEP adherence	0.74 (0.51, 0.97)	0.02	−0.18 (−0.35, −0.01)	0.04
Depression	Social support	PrEP adherence	0.77 (0.57, 1.03)	0.07	−0.15 (−0.32, 0.02)	0.09
Depression	PrEP optimism	PrEP adherence	0.75 (0.55, 0.99)	0.05	−0.15 (−0.32, 0.01)	0.08

aRR= adjusted relative risk; RD= adjusted risk difference; 95% CI= 95% confidence interval

[1]Participants were considered adherent to PrEP if their adjusted Wisepill data indicated that they had taken ≥80% of expected pills at the Week 24 study visit

[2]Stabilized inverse probability weights account for confounding by the sets of confounders (age, marital status, education, alcohol and drug use, HIV risk perception, and condomless sex) and a given mediator (depression weight: mean=0.99; range=0.47–2.38; stigma weight: mean=0.98; range=0.41–3.12; social support weight: mean=0.99; range=0.38–3.12; optimism weight: mean=0.98; range=0.38–2.50)