Title

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Journal

AIDS and behavior, 20(7)

ISSN

1090-7165

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Publication Date

2016-07-01

DOI

10.1007/s10461-016-1415-9

Peer reviewed

HHS Public Access

Author manuscript

AIDS Behav. Author manuscript; available in PMC 2017 July 01.

Published in final edited form as:

AIDS Behav. 2016 July ; 20(7): 1527–1534. doi:10.1007/s10461-016-1415-9.

The effect of depressive symptoms on adherence to daily oral PrEP in men who have sex with men and transgender women: A marginal structural model analysis of the iPrEx OLE study

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Introduction

Pre-exposure prophylaxis (PrEP) with oral emtricitabine and tenofovir disoproxil fumarate (FTC/TDF) has proven to be one of the most promising new HIV prevention tools. Over the past 5 years, results from numerous studies have supported its efficacy and safety.(1–6) These studies had a wide range of efficacy estimates from intention-to-treat analyses, but when adherence was consistently high, estimated efficacy was found to be greater than 90%. (1,3,7) As a result, in 2012, the US Food and Drug Administration approved the use of daily, oral FTC/TDF for the prevention of HIV.(8)

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Conflict of Interest: DVG has received fees from ViiV, a manufacturer of an investigational compound being investigated for use as PrEP. RA has an educational grant from Gilead Sciences through the University of Michigan. KM has received unrestricted research and education grants from Gilead Sciences. RMG has received honoraria from Clinical Care Options. RMG served as a consultant for Siemens Healthcare on their guidelines panel. The remaining authors have no conflicts of interest to disclose.

Ethical Statement:

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Adherence

As with any medication, PrEP efficacy is highly dependent on adherence. Currently, FTC/TDF for PrEP is indicated for daily oral dosing. However, modeling studies estimate that 4 pills/week are likely sufficient to achieve complete protection from HIV infection.(7) While this makes the regimen forgiving of occasional missed doses, achieving and sustaining high enough levels of adherence to secure protection from HIV remains challenging for some.(6,9) For example, in the iPrEx blinded trial and its open-label extension (OLE), transgender women (TGW) had consistently lower concentrations of drug than men who have sex with men (MSM) and, therefore, less protection from PrEP.(1,10,11)

iPrEx OLE offered PrEP to HIV-negative participants who had been enrolled in three prior randomized placebo-controlled PrEP trials. Those who reported having condomless receptive anal intercourse (ncRAI) or had serological evidence of herpes were more likely to elect to receive PrEP in OLE.(10) Higher education, older age, baseline ncRAI, greater number of sexual partners and a history of syphilis or herpes were associated with higher drug concentrations throughout the study. This suggests that some study participants successfully identify and appropriately react to times during which PrEP is most needed for protection from HIV (e.g., prevention-effective adherence(12)). However, given that many iPrEx OLE participants who had their blood levels tested were below the limit of quantitation, the need to better understand the factors that may influence PrEP adherence remains important.

Depression in MSM/TGW

An area that has been well-represented in the antiretroviral (ART) for HIV treatment literature and less so in the PrEP literature is the interplay between depression and adherence. Gaining a better understanding of the influence of depression on adherence to PrEP is particularly relevant given the high prevalence of depression and anxiety in MSM and TGW globally (31% and 62%, respectively).(13–17) Social isolation, stigma, and childhood trauma are all potential risk factors for depression and are more commonly experienced by MSM and TGW.(18) Prior studies have found that depressive symptoms may contribute to decreased agency, lower ability for self-care, and subsequently lower adherence to medication regimens.(18,19) Taken together, we hypothesize that depression in MSM and TGW may play an important role in adherence to PrEP. Additionally, given the higher prevalence of depression in TGW than MSM, we anticipate that the role of depression in adherence to PrEP may differ between TGW and MSM.

Given that depression has been shown to influence sexual behavior (16,20,21) and baseline sexual behavior is associated with subsequent higher adherence (10), we anticipate that sexual exposure is both a confounder and mediator of the effect of depression on adherence to PrEP.

Methods

Study design

iPrEx OLE was a cohort study that enrolled 1603 HIV-negative MSM/TGW at 11 study sites in 6 countries (Peru, Brazil, the United States, Ecuador, Thailand, and South Africa). The majority of study participants were from the Andean region (62%).(10) 1225 participants elected to take daily, oral FTC/TDF PrEP. All participants were followed for up to 72 weeks. Participants could elect to begin taking PrEP at any point during the first 48 weeks of the study.(10) Adherence was quantified by measuring drug levels in dried blood spots (DBS) in a nested case-cohort sample of the overall study (N=349)(22). Cases were all participants who became HIV infected during study follow-up, and controls were a sitestratified random sample of seronegative on-PrEP participants at baseline(10). All timepoints after drug dispensation were tested for drug concentrations. This analysis included all members of the original case-cohort sample for whom we had at least one assessment of depressive symptoms (N=334). Sampling weights were incorporated into the final model to reflect the case-cohort design.

Exposure, Outcome, and Other Covariates

Drug Concentration—Drug concentration measured in DBS at all time-points after PrEP dispensation (week 4, week 8, week 12, and every 12 weeks thereafter) reflects drug exposure over the prior month.(7) Using methods described previously,(23) drug concentrations were categorized according to dosing corresponding to the number of pills taken per week. The primary outcome for these analyses was a binary indicator of having DBS levels corresponding to taking ≥4 pills/week—a level that has been shown to be sufficient for maximum protection by PrEP.(7,10)

CES-D—Depressive symptoms were assessed at enrollment and every 24 weeks during follow-up using the 20-item Center for Epidemiologic Studies Depression Scale (CES-D). The CES-D is a valid and reliable screening tool for depression and anxiety symptoms. It has been validated in all 4 languages used in the iPrEx OLE study: Spanish, Portuguese, English and Thai.(24–29) The CES-D reflects depressive symptoms occurring in the prior 7 days,(30) and was categorized according to standard clinical cutoffs as follows: none-mild depression (CES-D 0-15); mild-moderate depression (CES-D 16-26); severe depression (CES-D 27+).(20) Pre-existing conditions of depression and anxiety were also recorded via interview at enrollment in the study.

Sexual Behavior—Sexual behavior was recorded at baseline and every 12 weeks thereafter via an interviewer-administered questionnaire. Questionnaires asked about behaviors occurring in the prior 12 weeks. Reported ncRAI and total number of male partners were the measures chosen to reflect sexual exposure in this analysis.

Baseline Confounders—Baseline confounders include study site, age at enrollment, highest level of education, gender identity (MSM or TGW), history of having a sexually transmitted infection (STI), pre-existing conditions of anxiety, and baseline sexual exposure measures (number of partners, history of having an HIV positive partner, and ncRAI).

Causal Model—Directed acyclic graphs (DAGs)(31) are non-parametric causal diagrams used to aid causal analysis. We hypothesized that sexual exposure functions as a time-varying confounder-mediator in the association between depressive symptoms and adherence to PrEP as described in DAG shown in Figure 1. The outcome is a binary indicator of DBS levels corresponding to ≥4 pills/week (DBS in the DAG). Time-fixed confounders (not shown in the DAG) include baseline sexual exposures, study site, age, highest level of education, and STI diagnosis s at baseline. To attempt to disentangle depressive symptoms from anxiety symptoms as measured by the CES-D, preexisting conditions of anxiety were also included in the model.

Statistical Analyses—A marginal structural logistic regression model (32) was used to estimate the association between depressive symptoms and protective adherence to daily, oral FTC/TDF PrEP in iPrEx OLE. In order to control for bias from time-varying confounding variables that may also be affected by prior depression status, we used inverse probability weights for the ordinal exposure categories (no depressive symptoms, mild depressive symptoms, and severe depressive symptoms) and censoring.(32,33) Stabilization with baseline variables provided a reasonable distribution of exposure weights (Mean: 1.0; Standard Deviation: 0.083; Range [0.21–3.12]).(34) The final weights were not truncated and included sampling weights, the exposure weights, and censoring weights. The structural model was estimated using logistic regression, robust standard errors, and included adjustment for all baseline covariates.(33) Multiplicative and additive interaction between CES-D scores and gender identity was also assessed using the final structural model.(35) Population attributable fraction (PAF) was calculated to estimate the absolute impact of treating depression on adherence to PrEP in both MSM and TGW. All analyses were conducted in STATA 13.1.(36)

Results

Study population

The final analysis included 334 participants. At baseline, most participants had a CES-D score less than 16 (72%), were from the Andean region (53%), were 25 years old or younger (32%), and had a maximum of a high school education (50%). 11% identified as a transgender woman, and 14% and 7% had reported pre-existing conditions of depression and anxiety respectively (Table I).

Depressive Symptoms and Adherence

The final structural model found a non-linear relationship between CES-D scores and odds of not having drug levels that conferred >90% protection from HIV infection based on the Wald test of linearity (chi^2=16.71, p<0.001) in MSM. MSM with CES-D scores between 16 and 26 were more likely to have protective drug levels (OR 1.66 95%CI [1.05, 2.60]) compared to those in the reference lowest CES-D category. MSM with CES-D scores >26 were less likely to have protective drug levels compared to those in the lowest CES-D category (OR 0.41 95%CI [0.22, 0.77]). Older age, higher education, and pre-existing conditions of anxiety were all associated with greater odds of protective levels of drug detection (Table II).

The model shows modest evidence in support of effect heterogeneity of CES-D on adherence between MSM and TGW, particularly in the middle category of CES-D scores (OR: 0.24 95%CI [0.05, 1.11]). Among TGW, participants with CES-D scores between 16 and 26 or CES-D scores >26 were less likely to have protective drug levels (OR 0.39 95%CI [0.09, 1.63]) and OR 0.55 95%CI [0.04, 8.04] respectively) than MSM. The marginal probability of protective adherence between transgender women and MSM by CES-D category shows the greatest discrepancy in adherence among those with CES-D scores between 16 and 26. (Table II)

Population Attributable Fraction

Given the baseline prevalence of mild-moderate depressive symptoms and severe depressive symptoms in MSM and TGW, the percent of inadequate adherence to PrEP that can be attributed to elevated CES-D is up to 1% and 6% respectively. (Table III)

Discussion

Overall, depressive symptoms played a modest role in adherence to PrEP, and the effect of depressive symptoms on adherence likely differs between MSM and TGW. In MSM, the relationship between depressive symptoms (as measured by the CES-D) and adherence is non-monotonic. Compared to CES-D scores below 16, we found that scores between 16 and 26 were associated with enhanced adherence, while CES-D scores of 27 or higher impaired adherence to PrEP regimens. In TGW, we find that any elevated CES-D scores above 16 are associated with decreased adherence to PrEP.

Severe depressive symptoms were substantially less common than mild-moderate depressive symptoms. It is possible that in cases of severe depression, because of psychomotor retardation, capacity for self-care and agency may be impaired such that adherence to medication becomes more challenging, as has been cited in other areas of depression research.(15,18,19) However, the absolute population impact of severe depressive symptoms on adherence to PrEP is relatively low. Based on the PAF, intervening on severe depressive symptoms would resolve at most 1% of the non-adherence in MSM and 3% in TGW. Thus, it is clear that severe depressive symptoms, as measured by the CES-D, do not play a major direct role in non-adherence to PrEP and should not preclude prescription of PrEP to those who need it.

In understanding the effect of moderate depressive symptoms (CES-D scores between 16 and 26) on adherence in MSM, it is important to consider the potential role of anxiety. The CES-D has been shown to be sensitive to both depressive and anxiety symptoms, but specific to neither.(30,37) Thus, it is possible that anxiety and depression may have opposite effects on adherence to PrEP. Controlling for baseline pre-existing conditions of anxiety was intended to help separate depression from anxiety in the CES-D measures, however misclassification of anxiety, frequent co-morbidity of the two conditions, and differential reporting of anxiety between sites may allow for there to be residual confounding by anxiety (Figure 2). The fact that pre-existing anxiety is such a strong predictor of increased adherence in MSM suggests that this hypothesis may be reasonable (Table II), but the overall findings regarding depressive symptoms and adherence were not significantly

changed when removing preexisting anxiety from the model (data not shown) suggesting that anxiety likely does not fully explain the observed pattern.

While severe anxiety has been shown to decrease adherence to HIV treatment,(38,39) mild to moderate anxiety may make some PrEP users more worried about potential HIV infections and more likely to adhere than those without any anxiety symptoms. Further work designed to disentangle the two constructs should be conducted to elucidate the individual effect of each on adherence. For example, the Beck depression inventory is a screening tool that is more specific to depressive symptoms alone and may be better suited for future studies to isolate the effect of depression.(40)

These analyses, while limited by a small sample of TGW, show a striking difference in the effect of depressive symptoms on adherence between MSM and TGW. Based on the marginal probabilities of protective adherence by CES-D category, it is evident that the discrepancy in adherence to PrEP between MSM and TGW that has been reported in prior studies(1,10,11) is concentrated among those with CES-D scores between 16 and 26 (Figure 3). Importantly, 24% of TGW in the current sample had CES-D scores that fell within this range, and thus the PAF for non-adherence is highest in this group (7%) (Table III).

Gender is known to play a role in the optimal CES-D cut-off to reflect clinical symptoms of depression, and studies have indicated that the cutoff should be higher for women than men (29). Post-hoc sensitivity analyses using higher CES-D cutoffs for categorizing TGW depressive symptoms did not impact the findings in the primary analyses (data not shown).

TGW in the iPrEx OLE study were concentrated in only a few study sites of the overall cohort, and differed from MSM in a number of important demographic characteristics (11). Thus, the standard regression adjustment methods employed here cannot fully disentangle the precise reasons for the observed differences in adherence between TGW and MSM. Future analyses designed specifically for addressing this question are required.

While the findings in TGW did not reach statistical significance, the difference in effect estimates of CES-D and in marginal probability of adherence between MSM and TGW is substantial and merits closer review. These results highlight the fact that MSM and TGW are two distinct populations with different cultural contexts and structural barriers to PrEP access and adherence. Studies that treat these populations as one homogenous group may inadvertently obfuscate important predictors of PrEP uptake and adherence that vary between the two populations. Additional studies with larger transgender populations need to be conducted in order to fully understand the barriers and facilitators of effective PrEP adherence.

Haberer and colleagues recently outlined a new paradigm for defining successful PrEP adherence, coined “prevention-effective adherence.”(12) This strategy defines successful adherence not just in terms of absolute drug-detection, but rather as drug-detection in the context of changing HIV-acquisition risk. Our study aimed to move closer to this outcome of interest by focusing on drug detection commensurate with full protection from HIV rather than absolute drug levels and by controlling for time-dependent confounding by sexual

behavior. While a helpful step in the right direction, further work needs to be done to better define a more specific outcome that reflects true prevention-effective adherence.

In conclusion, it is unlikely that depressive symptoms alone contribute greatly to decreased adherence to PrEP in either MSM or TGW on a population level. Given this, and the fact that PrEP has not been shown to increase depression in MSM/TGW(41), depressive symptoms should not contraindicate the prescription of PrEP. Instead, PrEP clinics should be used as another avenue for screening and treating mental health issues in this often vulnerable population. Further efforts should be made in both the research and clinical setting to explore and address the differences between TGW and MSM that may contribute to successful prevention-effective PrEP adherence.

Acknowledgments

Funding Source: We would like to thank and acknowledge the iPrEx and iPrEx OLE study participants. The iPrEx OLE study was funded by the US National Institutes of Health (5U01AI064002); study medication was donated by Gilead Sciences, which also supported travel expenses for non-US investigators to attend study meetings.

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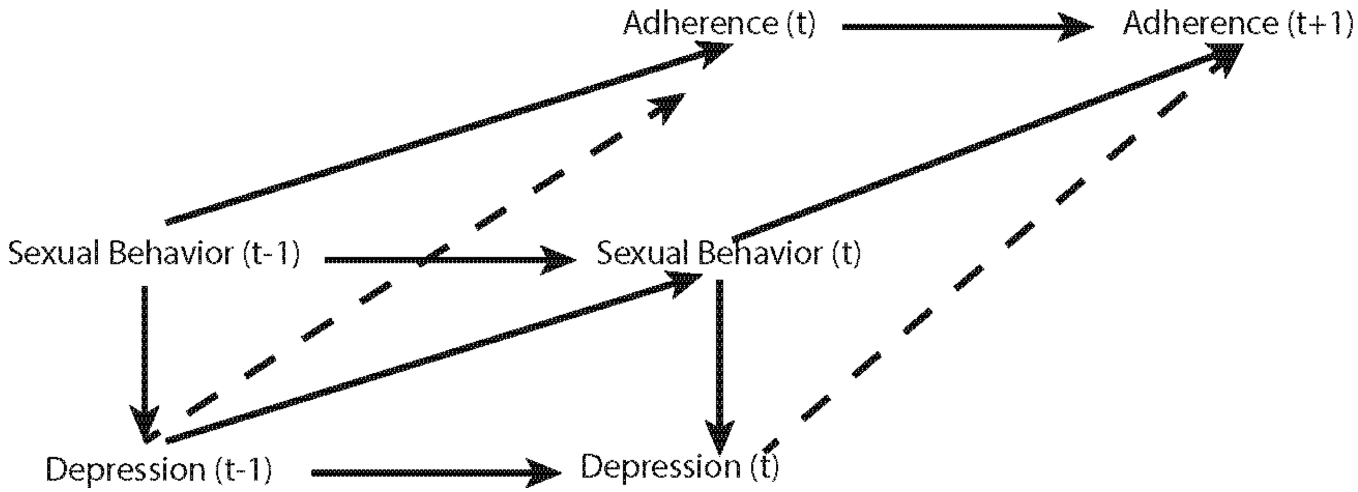

Figure 1.

Directed acyclic graph (DAG) illustrating the proposed causal model between depression, sexual behavior, and adherence to PrEP (as measured by drug concentrations in DBS) over time. Measures of sexual behavior reflect the prior 3 month interval, adherence measures (in DBS) reflect the prior 1 month, and CES-D captures depressive symptoms in the prior 7 days. Sexual behavior has been previously shown to predict subsequent adherence to PrEP in this cohort; depressive symptoms have been shown to influence subsequent sexual behavior in MSM; and sexual behavior may also influence subsequent depression. The model illustrates the need for a marginal structural model to control for timevarying confounding in which the confounder is also affected by prior exposure.

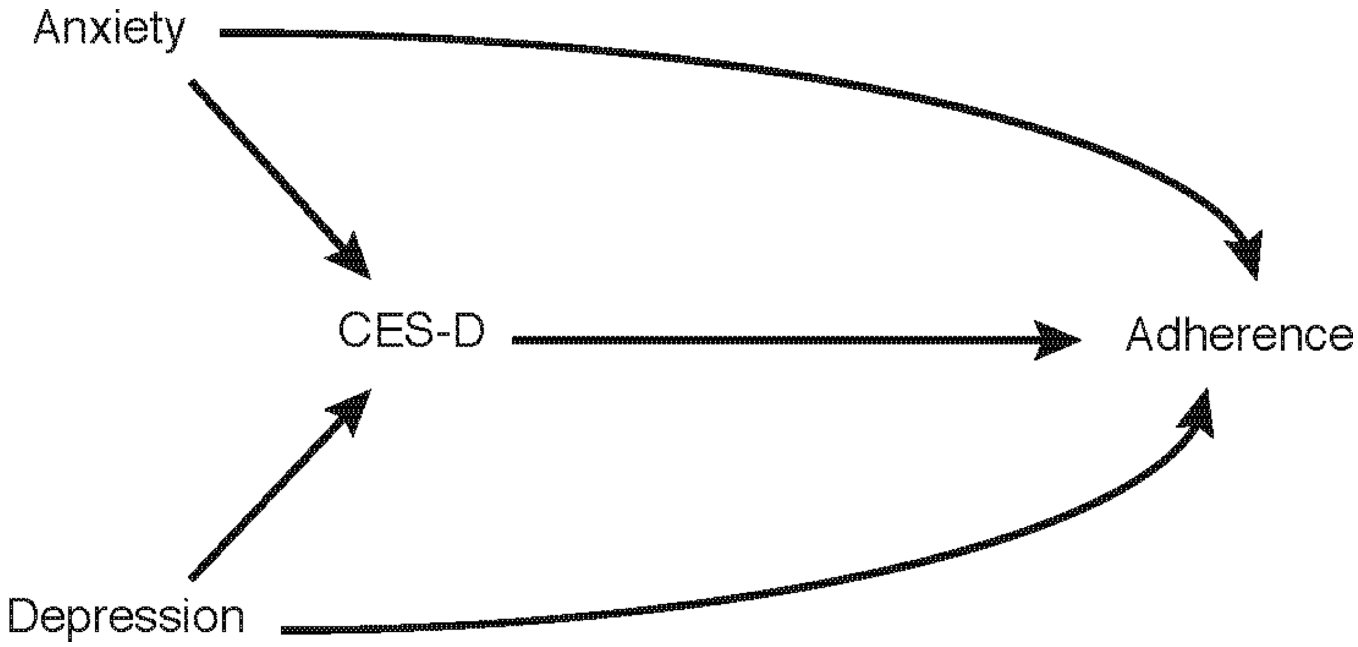

Figure 2.

A directed acyclic graph (DAG) illustrating the potential role of anxiety in confounding the relationship between CES-D and adherence to PrEP. This analysis adjusted for reported anxiety at baseline to block this confounding pathway. However, given the potential misclassification of anxiety in the study population, it is possible that residual confounding by anxiety may contribute to the observed non-monotonic relationship between CES-D and adherence.

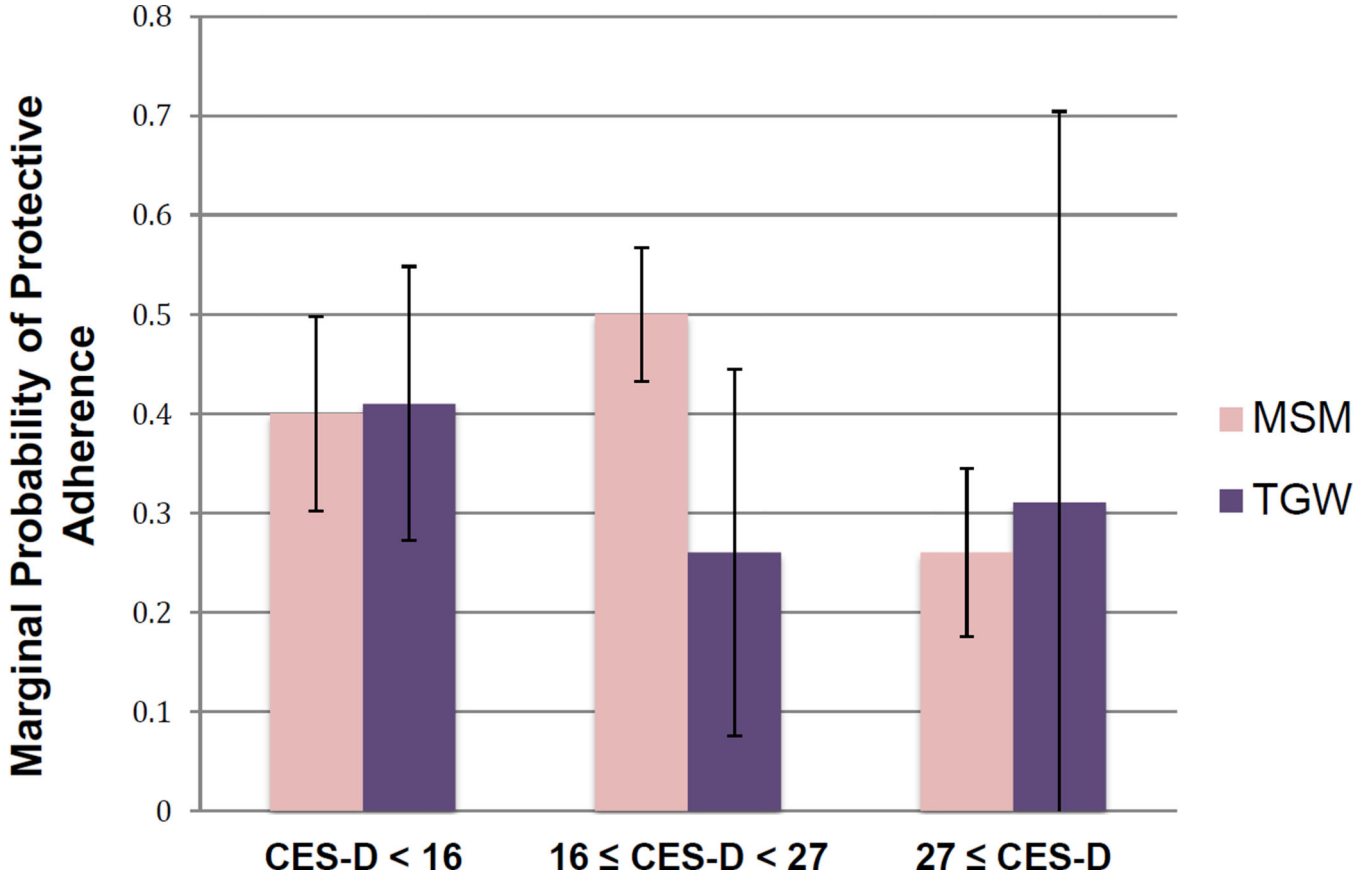

Figure 3.

The marginal probability of protective adherence by CES-D category and by MSM/TGW

Table III: Population level impact of severe depression on adherence to PrEP.

Table 1

Baseline Characteristics

	Frequency	Percent
Baseline CESD Score		
CESD less than 16	239	72
CESD 16–26	67	20
CESD greater than 26	28	8
Study region		
Andes	176	53
Brazil	70	21
United States	55	16
Thailand	18	5
South Africa	15	4
Age		
<= 25	106	32
> 25 – 30	77	23
> 30 – 39	80	24
> 40	71	21
Gender Identity		
MSM	296	89
TGW	38	11
Education		
Less than HS	69	21
High School	167	50
College	98	29
Pre-Existing Conditions		
Pre-Existing Depression	46	14
Pre-Existing Anxiety	24	7
Total Number of Participants:	334	

Table II

Odds of Protective Drug Levels

	Odds ratio	**95% Cl**
CESD scores		
CESD less than 16	Ref	–
CESD 16–26	1.66	[1.05, 2.60]
CESD greater than 26	0.41	[0.22, 2.39]
Trans identity	1.02	[0.44, 2.39]
CESD Trans interaction		
CESD 16–26* Trans	0.24	[0.05, 1.11]
CESD greater than 26* Trans	1.34	[0.09, 20.96]
Anxiety Pre-existing condition	3.88	[1.62, 9.27]
Clusters (Number of Participants)	334	

Exponentiated coefficients; 95% confidence intervals in brackets

Model also controlled for study site; age; education; and sexual behavior

Table III

Population Attributable Fraction (PAF) of Depressive Symptoms in MSM and Transgender Women. Population level impact of severe depression on adherence to PrEP.

		Baseline Prevalence	Marginal Probability of Insufficient Adherence[%]	Odds Ratio[*]	Population Attributable Fraction[#]
MSM	CES-D < 16	0.73	0.6	--	--
	16 ≤ CES-D < 27	0.2	0.5	0.6	−0.03[+]
	27 ≤ CES-D	0.07	0.74	2.44	0.01
TGW	CES-D < 16	0.61	0.59	--	--
	16 ≤ CES-D < 27	0.24	0.74	2.56	0.07
	27 ≤ CES-D	0.16	0.69	1.82	0.03

[%] Marginal probability of insufficient adherence

[*] Odds of not having sufficient drug levels for full protection

[#] Population attributable fraction represents the proportion of non-adherence that would be resolved if an intervention were to move all CES-D scores to the lowest category while holding all else constant.

[+] Negative value reflects the fact that adherence was highest among those with CES-D scores corresponding to mild-moderate depressive symptoms