Published in final edited form as:

AIDS Behav. 2020 November ; 24(11): 3192–3204. doi:10.1007/s10461-020-02881-7.

Greater Levels of Self-Reported Adherence to Pre-Exposure Prophylaxis (PrEP) are Associated with Increased Condomless Sex Among Men Who Have Sex with Men

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Abstract

The effectiveness of pre-exposure prophylaxis (PrEP) against HIV acquisition depends on treatment adherence; however, within-person associations between levels of PrEP adherence and engagement in condomless sex have not been well studied. In the context of a demonstration project, 372 men who have sex with men received once-daily PrEP and completed six study visits over 48 weeks. Two-part growth mixture modeling was used to examine the longitudinal trajectory of condomless anal intercourse (CAI) and self-reports of PrEP adherence, controlling for relevant covariates. Over time, greater PrEP adherence was contemporaneously associated with both a higher likelihood of engaging in any CAI and with a greater number of CAI acts. Substance use was also associated with a higher likelihood of engaging in CAI. Contemporaneous associations between self-reported PrEP adherence and CAI suggest that adherence behaviors may be motivated by the desire to mitigate risk of HIV infection; however, exact directionality is unknown.

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

Keywords

HIV; PrEP; Adherence; Risk compensation; Condomless sex

Introduction

Several randomized controlled and modeling studies have demonstrated that, with good adherence, oral pre-exposure prophylaxis (PrEP) using tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) results in significant declines in the risk of acquiring HIV. For example, analyses of individuals with detectable PrEP metabolites in the iPrEx trial estimated the risk of HIV infection to be reduced by 92% and pharmacologic modeling studies have similarly estimated rates of protection upwards of 90% [1, 2]. Given the high rates of efficacy against HIV, PrEP is a viable tool in the HIV prevention arsenal that can be used in conjunction with other evidence-based measures and practices, such as consistent use of condoms, routine HIV and other sexually transmitted infection (STI) testing, knowledge of sexual partners' HIV status, needle exchanges, and achieving undetectable viral load among those living with HIV [3–7].

Despite the utility of PrEP in preventing new HIV infections, concerns have been raised about the potential for increased rates of HIV-transmission risk behaviors, including increased condomless sex, termed “risk compensation.” As a cognitive-behavioral process, risk compensation arises when individuals upwardly-adjust their behavior to engage in greater risks because of the belief that they are protected from adverse consequences by virtue of using a risk-reduction measure [8, 9]. Outside of HIV prevention, risk compensation has been observed in other public health contexts (for instance, following the use of safety features such as seat-belts, bicycle helmets, and insurance) and has been variously termed “off-setting behavior,” “moral hazard,” and “behavioral disinhibition” [8, 10–14]. With regards to PrEP, concerns have been raised that risk compensation via increased condomless sex has the potential to lead to new HIV infections, if risk compensation occurs without adequate levels of PrEP adherence (typically defined as ~4 doses per week that result in concentrations of the PrEP metabolite tenofovir diphosphate (TFV-DP) of approximately 700 fmol/punch) and may contribute to the rising incidence rates of other STIs [8, 15–18].

The evidence for risk compensation in the context of PrEP use is mixed. Early efficacy trials and systematic reviews of randomized placebo-controlled trials suggested stable rates of condomless anal intercourse (CAI) among men who have sex with men (MSM) [1, 19–21]. In contrast, contemporary research using open-label studies has suggested that CAI may increase when individuals are on PrEP [22, 23]. Furthermore, there is evidence to suggest that, in addition to individual-level increases in CAI, risk compensation may operate at a community-level, with HIV-negative individuals who are not on PrEP increasing their CAI because of assumptions that their sex-partners are HIV-negative and on PrEP [24].

To date, evidence linking PrEP use with increases in CAI has been largely derived from cross-sectional analyses that are unable to capture the intra-individual variability that exists in levels of PrEP use and in CAI when both are examined over time [22, 23]. Separating

between-person and within-person effects is conceptually important as relations between mean levels, or between individuals, do not necessarily generalize to the relations found in the withinperson fluctuations that unfold over time [25]. Furthermore, assumptions of equivalence of between and within-person effects risk committing an ecological fallacy, where associations between variables at a group level may mistakenly be assumed to be the same at the individual level [26]. As a consequence, the current study was motivated to examine the intra-individual associations between CAI and PrEP adherence among MSM over a 48-week period.

Substance use, especially that of “club drugs” (e.g., methamphetamine, GHB, nitrites), is of relevance to risk compensation among MSM who are taking PrEP as it has been robustly associated with CAI and other sexual behaviors that place individuals at greater risk of HIV acquisition [27–29]. Substance use also has known impact on adherence behaviors and accumulating evidence suggests that it may lower PrEP adherence. In particular, recent work has found impaired PrEP adherence and lowered odds of optimal PrEP adherence in the context of alcohol, stimulants, and other drug use [30–32]. Hence, substance use among individuals on PrEP may facilitate greater risk of HIV acquisition through increased risk compensation and poorer adherence behaviors. Consequently, this study was also motivated to account for the influence of substance use on CAI and the potential interaction of substance use with PrEP adherence.

It was hypothesized that greater levels of PrEP adherence would be associated with within-person increases in engagement of risk compensation behaviors. Specifically, it was hypothesized that on visits where individuals retrospectively reported greater adherence to PrEP, they would also report contemporaneously engaging in increased CAI. These within-person effects were hypothesized to exist even after controlling for relevant sociodemographic covariates explaining differences between individuals in the rate and level of change of CAI. Given known associations between substance use and CAI, it was hypothesized that on visits where individuals reported increases in substance use, they would also report increased CAI. The interactive effect of substance use and PrEP adherence was also explored.

Methods

Participants and Procedure

Three hundred and ninety-eight individuals (395 MSM and 3 transgender women), aged 18 years or older, were recruited San Diego [UC San Diego], Harbor-UCLA Medical Center, Long Beach Department of Health and Human Services, and University of Southern California [USC]) between February 2013 and February 2015 and followed longitudinally until February 2016. Participants were randomly assigned to one of two arms (control or intervention) in an open-label, clinical demonstration project for PrEP use [33]. Individuals in both study arms had up to six in-person study visits at baseline (week 0), weeks 4, 12, 24, 36, and 48. Given the very small number of transgender women recruited in the parent study and the presence of research to suggest significant differences in vulnerability to HIV among MSM and transgender women, data from the 3 transgender women were not included in this study [34]. Furthermore, as guidelines on the number of assessments for growth models

recommend at least 3 time points, participants contributing data in these analyses were 372 cisgender MSM with at least three study visits. Thus, the outcome (CAI) was assessed on at least three study visits and PrEP use was recorded on at least two interim visits [35]. Of the 22 cisgender MSM who were excluded from analyses, 10 were in the control group and 11 in the intervention group and there were no differences in numbers among excluded participants in either arm due to early attrition ($t(19) = 0.606$, $p = 0.55$). On average, participants in this sample had 5.63 visits over the 48-week study period; there were no differences in the number of attended study visits by arm ($\text{Mean}_{\text{control}} = 5.63$ (SD = 0.85) vs. $\text{Mean}_{\text{intervention}} = 5.62$ (SD = 0.83), $t(370) = 0.11$, $p = 0.91$).

The main eligibility criteria for the parent study was substantial ongoing risk of HIV acquisition, defined as any of the following: (i) having at least one HIV-infected male sexual partner for 4 weeks, (ii) CAI with 3 male partners who were HIV-positive/of unknown HIV status over the last 3 months, or (iii) CAI during anal sex with 1 male partner and an STI diagnosis in the last 3 months. The aim of the primary study was to determine the efficacy of a text-messaging intervention (individualized Texting for Adherence Building—iTAB), compared to standard of care, in enhancing adherence to ART treatment [33]. Over a 48-week study period, all participants were prescribed and provided oncedaily PrEP with TDF/FTC, risk reduction and adherence counseling, and safety monitoring. Participants in the iTAB arm also received daily text messages, coinciding with their intended dosing-times, as adherence supports. Prior secondary analyses of data from this cohort indicated increased CAI over time [23]. In particular, previous work found evidence of significant increases in receptive CAI among MSM on PrEP and no evidence of change in CAI in a lagged comparison sample of MSM who did not receive PrEP. This current study differs from previous work in its examination of within-person, rather than between-person, change in CAI and in its examination of PrEP adherence and substance use as predictors of CAI.

The study protocol was approved by the relevant institutional review boards and all participants provided written informed consent.

Measures

The following variables were assessed longitudinally during study visits:

Condomless Sex.—The number of CAI acts in the previous 30 days was assessed by self-report using computer assisted self-interview (CASI) at each of the study visits. Participants were asked to report the number of unprotected anal receptive acts and unprotected anal insertive acts. In particular, participants were asked to report on the “number of unprotected anal receptive (their penis in you) acts” and the “number of unprotected anal insertive (your penis in them) acts”. Reports of unprotected (i.e., condomless) receptive and insertive acts were summed to obtain a measure of the total number of CAI acts within the last 30 days of each participant’s study visit.

Frequency of Condom.—Use At each study visit, participants were also asked to report how frequently they used condoms during anal receptive and insertive sex with their male partners using two questions on a 5-point Likert scale. Responses ranged from 0- “Never” to

4- “Always” and these two items were averaged (reports of abstinence were combined with “Always” responses).

PrEP Adherence.—Adherence to PrEP was also assessed via CASI using two items from a commonly used adherence questionnaire [36]. At visits subsequent to the baseline visit, participants provided responses to two questions: “In the last 30 days, how good of a job did you do at taking your PrEP medication in the way you were supposed to?” and “In the last 30 days, how often did you take PrEP medication in the way you were supposed to?” Responses were on a 6-point Likert scale, with anchors ranging from 0- “Very Poor”/ “Never” to 5- “Excellent”/ “Always” and were averaged to obtain a single measure of self-reported adherence. Our previous work has indicated good concordance between participant self-report of PrEP adherence and objective measures of adherence using the PrEP metabolites tenofovir diphosphate (TFV-DP) and emtricitabine triphosphate (FTC-TP) [37].

Substance Use.—Illicit polysubstance use over the last month was assessed at each of the study visits using a checklist via CASI; participants reported whether or not they recreationally used any of 10 substances typically associated with risky sex among MSM (i.e., (i) cocaine/crack, (ii) methamphetamine or other stimulants (e.g., amphetamine), (iii) heroin or other opioids (e.g., Vicodin), (iv) sedatives (e.g., Rohypnol), (v) antianxiety drugs (e.g., Valium), (vi) AIDS and Behavior 13 hallucinogens (e.g., LSD), (vii) dissociative drugs (e.g., PCP), (viii) inhalants (e.g., nitrous oxide), (ix) poppers (e.g. amyl nitrate), and (x) ecstasy [38].). Checklist items assessing extent of polysubstance use were obtained from the substance use disorder screening module of the Structured Clinical Interview for DSM-IV (SCID-IV) and endorsements on this measure were totaled [39, 40].

Biologic Measures of Adherence.—Pharmacologic estimates of PrEP adherence were also obtained at weeks 12 and 48 from dried blood spot (DBS) measurements. Following established procedures, DBS were created from 25 µl aliquots of whole blood samples spotted onto filter paper and analyzed using liquid chromatography/tandem mass spectrometry methods [33, 41]. Estimates of PrEP adherence were made from intracellular peripheral blood mononuclear cell (PBMC) measurements of tenofovir diphosphate (TFVDP) and emtricitabine triphosphate (FTC-TP). As TFV-DP has a half-life of approximately 17 days while FTC-TP has a half-life of about 1.5 days, TFV-DP is considered to be a measure of long-term adherence while FTC-TP is considered to be a measure of recent dosing [42]. Thus, TFV-DP was modeled as a continuous variable while FTC-TP was modeled dichotomously (i.e., as undetectable vs. detectable PrEP).

Potential Demographic and Contextual Covariates

A number of potential covariates, recorded at the baseline visit, were assessed for each participant:

Demographic Variables.—Sociodemographic descriptors, including participant age, income, years of education, race, and Hispanic ethnicity, were assessed at study entry. Income was assessed as a binary variable (above or below \$2000 per month) and years of

education was also assessed as a categorical variable with 5 levels ranging from “high school or less” to “advanced degree.”

Study Characteristics.—Several study-related variables, including assignment to intervention arm, site of enrollment, and study eligibility sexual risk criteria, were investigated as potential covariate controls. With regards to inclusionary risk criteria, sexual risk was included as a categorical variable with the following four groups: (i) 1 + HIV-infected partner for 4 weeks or more, (ii) CAI with 3 + sexual partners, (iii) CAI with 1 + partner and an STI diagnosis, and (iv) two or more of the previously-mentioned risk categories. Assignment of individuals to the various levels of the inclusionary risk criteria was mutually-exclusive, such that each participant was included in only one category and individuals endorsing more than one risk criteria were included only in the fourth group.

Data Analytic Strategy

To provide preliminary support for inferences drawn from the main analyses between self-reported measures of number of CAI acts and PrEP adherence, associations between CAI acts and biologic measures of adherence were first examined. In particular, regression models were used to examine the association between CAI and TFV-DP and FTC-TP for timepoints with available DBS data (i.e., weeks 12 and 48). As the count distribution of CAI was characterized by a preponderance of zeros and was significantly right-skewed, with a mean smaller than the variance, zero-inflated modeling with a negative binomial distribution for values greater than zero was used. Additionally, to corroborate analyses examining change over time in CAI acts, a multilevel regression with a random slope was carried out to examine change in the self-reported frequency of condom use over the study period.

To examine the main study hypotheses, two-part growth curve modeling was utilized to examine sexual risk and its relationship with covariates over time [43]. Growth curve models are multivariate applications of structural equation modeling that examine change among individuals over time [44]. Two-part growth models assume that non-normally distributed data are a product of two processes—one determining whether the outcome is zero (logistic) and the other determining the magnitude of the outcome if it is nonzero (count). Thus, CAI was modeled using two-part growth modeling, with a logistic component estimating the probability of engagement in CAI vs. no CAI and a truncated negative binomial model estimating the frequency of CAI when values greater than zero were observed. Two-part models have been previously utilized to examine longitudinal change in outcomes with infrequent occurrences, such as substance misuse, aggression, and other problematic behaviors [45–49].

Unconditional (without covariates) models were separately constructed in the logistic and count parts of the two-part growth model to identify the shape of change (i.e., intercept only, linear slope, etc.). As indices of relative fit are not available for two-part models with count distributions; goodness-of-fit for each part was compared across nested models using Satorra-Bentler χ^2 -difference tests [46, 50, 51]. Once the shape of change in CAI was separately identified, the binary and count parts were combined and a new two-part growth model estimated with separate, but correlated growth functions.

Baseline variables were individually examined as timeinvariant covariates potentially explaining between-person differences in the growth trajectories of either the probability of engaging in CAI or the frequency of CAI when it occurred. Covariates with some association to the growth trajectories were retained ($p < 0.10$). Subsequent to this, AIDS and Behavior 13 time-varying variables were added to the model. As the primary predictor, self-reported PrEP adherence was specified as a time-varying predictor of CAI with a random effect, capturing potential individual differences in the withinperson effect of adherence on CAI. Substance use and the interaction between substance use and PrEP adherence were included in the model as time-varying covariates with fixed effects. Because the median number of substances participants reported using was low (median = 2; Interquartile Range (IQR) = [1, 3]), substance use was modeled in analyses as a categorical predictor with four levels (i.e., 0, 1, 2, 3 or more substances). Thus, taken together, growth curve modeling was used to i) identify the overall trajectory of inter-individual change in CAI over time among MSM receiving PrEP, ii) account for the effects of baseline covariates on inter-individual change, and iii), examine the effect of adherence as a time-varying predictor of change in CAI, controlling for relevant covariates measured at the same time intervals.

All models were estimated in Mplus 7.4 using robust maximum likelihood estimation (MLR), with missing data modeled under standard missing data assumptions (i.e., as missing at random with inferences of probable missing values assumed by a full maximum likelihood algorithm based on the relationship between outcomes and predictors) [52, 53]. Regression models with CAI and DBS measures of PrEP adherence were estimated as single-level models with standard errors adjusted using a Huber-White sandwich estimator to account for the non-independence of observations [52, 54]. In longitudinal growth models, PrEP adherence was centered to disaggregate between-person influences from within-person effects [25]. Descriptive statistics were calculated in SPSS v.25 [55].

Results

Participants were on average 35.13 years old ($SD = 9.36$ years) and were predominantly White (78.8%) and non-Hispanic (71.5%). The majority of participants were highly-educated, reporting attaining a bachelor's level education or higher (55.9%), and with earnings of at least \$2000 a month (64.0%). Approximately half of participants were in the intervention arm (49.7%). Further study sample and variable descriptive statistics are provided in Tables 1 and 2.

Between-Person Associations Between CAI and Biologic Measures of Adherence

At weeks 12 and 48, higher levels of TFV-DP and FTC-TP were associated across individuals with decreases in the probability of reporting no CAI ($B = -0.001$, Odds Ratio (OR) = 0.999 [95% Confidence Interval (CI) = 0.997; 1.001], $p = 0.040$ and $B = -1.650$, OR 0.192 [0.087; 0.423], $p < 0.001$, respectively). Neither TFV-DP nor FTC-TP had significant inter-individual associations with the level of engagement in CAI at weeks 12 and 48. Thus, greater levels of pharmacologically-measured adherence were associated with higher odds of reporting engagement in CAI at weeks 12 and 48 but not with the degree to which individuals reported engaging in CAI.

Change in Frequency of Condom Use Over Time

Changes to the frequency of condom use over the 48-week study period was examined in a multilevel model with a random slope that captured the average within-person change of condom use over time. The random slope was significant and negative, indicating decreased condom use over the study period ($B = -0.010$, $p < 0.001$).

Initial Levels of CAI and Longitudinal Change Over Time

Using data from all assessment points over the 48-week study period, the longitudinal trajectory of CAI was first examined separately in logistic and count components of the two-part growth model. As there were no significant differences between models with linear and quadratic slopes for both logistic ($\chi^2(4) = 8.245$, $p = 0.083$) and count ($\chi^2(4) = 3.874$, $p = 0.423$) parts, the more parsimonious linear slope models were preliminarily selected [34]. Subsequently, a combined two-part model with linear slopes for the logistic (Part 1) and count (Part 2) models was estimated. Because the linear slope for Part 1 of the combined model was not significantly different from zero, χ^2 difference tests were carried out to determine the relative fit of a reduced model (i.e., Part 1: intercept only; Part 2: intercept and linear slope) compared to a full model (i.e., Part 1: intercept and linear slope; Part 2: intercept and linear slope). No significant differences were observed between the reduced and linear slope models for both Part 1 and Part 2 of the two-part model ($\chi^2(1) = 0.122$, $p = 0.727$). Given these findings, the reduced model was selected.

Regarding the probability of CAI (Part 1), the likelihood of participants engaging in CAI was 67% (intercept = 0.709, SE = 0.111, $p < 0.001$), which remained constant over time. In terms of the frequency of CAI (Part 2), the average number of CAI acts over the 30 days prior to baseline was 1.217 (SE 0.089, $p < 0.01$). Over the course of the study, the risk of CAI increased by 3.5% (Incidence Rate Ratio (IRR) = 1.035 [95% CI 1.02; 1.05], $p < 0.001$).

Predictors of CAI Growth Factors

Univariable regression analyses were used to identify demographic and baseline variables that could explain betweenperson variability in the growth trajectories of CAI; age, education, recruitment site, and sexual risk inclusion criteria were associated with CAI ($p < 0.10$). With regards to the probability of engaging in CAI at baseline (Part 1), compared to individuals reporting CAI with 3 + partners at baseline, those reporting CAI with at least one partner living with HIV and those endorsing multiple sexual risk behaviors were nearly twice as likely to report engaging in CAI in the 30 days prior to baseline (OR 1.881 [95% CI 1.103; 3.206], $p = 0.020$ and OR 1.853 [95% CI 1.151; 2.984], $p = 0.011$, respectively). Additionally, compared to individuals with a high school education or less, those with some post-graduate education (OR 0.314 [95% CI 0.100; 0.983], $p = 0.043$) and those with advanced degrees (OR 0.384 [95% CI 0.180; 0.820], $p = 0.013$) were less likely to report engaging in CAI at the beginning of the study. Site of recruitment was marginally associated with the probability of CAI; relative to individuals recruited at UC San Diego, those recruited at Harbor-UCLA had marginally lower likelihood of engaging in CAI at baseline (OR 0.523 [95% CI 0.256; 1.070], $p = 0.076$). With regards to the frequency of CAI (Part 2), older individuals had lower baseline levels of CAI (IRR 0.977 [95% CI 0.960; 0.994], $p =$

0.007). Furthermore, participants reporting condomless sex with an HIV + partner in the month before study entry also had marginally greater rates of engaging in CAI at baseline (IRR 1.406 [95% CI 0.941; 2.101], $p = 0.097$).

Neither race nor income was associated with the likelihood of engaging in CAI nor the extent of sexual risk behavior over time. Although assignment to study arm was not associated with between-person differences in CAI, interventional status was maintained as a time-invariant predictor in order to control for potential effects of group assignment once adherence to PrEP was included in the model.

Time-Varying Predictors of CAI

Figure 1 depicts the full model tested with both timeinvariant and time-varying predictors. Consistent with the convention in multilevel modeling, the time-varying effects of substance use, PrEP adherence, and the interaction between PrEP adherence and substance use were modeled as equivalent at each time point and captured by constrained estimates [46]. As interaction between PrEP adherence and substance use was not significant, the interaction was removed from the model and only the main effects of PrEP adherence and substance use are reported.

Above and beyond substance use, the random slope of PrEP adherence on CAI was significant. In particular, individuals who reported greater adherence to PrEP were also more likely to report having engaged in CAI (OR 1.408 [95% CI 1.119; 1.771], $p = 0.004$) and a greater number of CAI encounters (IRR 1.171 [95% CI 1.043; 1.315], $p = 0.002$) that same visit. Substance use was associated with a higher likelihood of engaging in CAI over the same period, but not with individual-level changes in CAI frequency. Specifically, compared to visits where participants reported no substance, on visits where a participant reported using one substance, their odds of engaging in CAI increased by 1.87 times (95% CI 1.257; 2.776). When they reported using two substances, their odds increased 1.61 times (95% CI 1.060; 2.444) and, when they reported using three or more substances, their odds of engaging in CAI increased 3.11 times (95% CI 1.900; 5.084). Table 3 presents results of these within-person regression analyses, controlling for the between-person effect of baseline covariates on growth factors.

Discussion

Recent open-label PrEP demonstration studies suggest that, across individuals, PrEP use may be associated with increases in CAI; however, little is known about the extent to which intra-individual variability in PrEP adherence is associated with fluctuations in engagement in CAI. Thus, the objective of the present study was to examine the longitudinal association between PrEP adherence and CAI among MSM receiving PrEP. Two-part growth modeling was used to examine the concurrent associations between PrEP adherence and CAI among MSM across six visits spanning a period of 48 weeks.

Prior to examining associations between self-reported adherence and CAI, we examined the association of biologic measures of adherence (TFV-DP and FTC-TP) with engagement in CAI. Detectable levels of FTC-TP were associated with higher odds of reporting

engagement in CAI at weeks 12 and 48 while TFV-DP was associated with small increases in the likelihood of engaging in CAI. To further bolster analyses of risk compensation defined as increases in CAI, we also examined intra-individual changes to participants' reported use of condoms over time. The effect of time on frequency of condom use was significant and negative, indicating that, as the study progressed, there were individual-level decreases in condom use. Similar declines in condom use following PrEP initiation among MSM have been noted in other research [24, 56].

Regarding the trajectory of CAI, across participants and longitudinally, the odds of participants engaging in any CAI remained constant and similar to those at baseline; however, the mean number of CAI acts increased over time. Baseline sociodemographic factors were also assessed as predictors of the between-person trajectories of CAI and, consistent with the findings of other studies, younger age and fewer years of education were associated with higher probabilities of engaging in CAI at study entry [57]. With regards to the within-person relationship between PrEP adherence and CAI over time, at visits on which participants reported greater adherence to PrEP, they had a higher likelihood of reporting CAI in the last 30 days and they reported a greater number of CAI acts. Specifically, a one-unit increase (on the 6-point measure of PrEP adherence) in an individual's levels of adherence was associated with a 1.41 times increase in that individual's odds of engaging in CAI. Additionally, a one unit increase in adherence was also associated with a 17.1% increase in the number of CAI acts. Thus, as adherence increased (or decreased) over time, participants reported corresponding increases (or decreases) in both the likelihood of having engaging in CAI and in the number of CAI acts.

Previous studies have found substance use to be associated with increased sexual disinhibition and engagement in risky sexual behaviors and, paralleling the findings of other studies, substance use was also a significant predictor of CAI; however, substance use did not moderate the effect of PrEP adherence on CAI [58]. We found substance use to be a significant individual-level predictor of the likelihood of engaging in CAI, with the odds of engaging in CAI being greater with any use of illicit/party substances and highest with the use of three or more substances. Our findings of larger increases in CAI with the use of three or more substances than with use of one or two suggest that, although there is risk of increased CAI with any substance use, risk compensation may not rise monotonically with substance use.

Altogether, this study's findings suggest nuance to the impact that PrEP use may have on sexual risk compensation. For instance, between-person increases in the number of CAI acts, without concomitant changes to the probability of engaging in CAI over time, suggest that PrEP use coincided with increase in CAI only among individuals with higher baseline probabilities of engaging in CAI. Furthermore, examining CAI in growth models with both timeinvariant and time-varying predictors revealed disparate patterns of associations within-person from those captured between-person. In particular, although the probability of engaging in CAI across individuals did not change over time and the median number of CAI acts across individuals was low, within-person fluctuations in adherence and changes in substance use were associated with contemporaneous intra-individual changes in the probability and extent of engagement in CAI.

Recent open-label and real-world clinical studies suggest that PrEP use reduces rates of HIV acquisition, even in the context of risk compensation. For instance, analyses from the Pre-exposure option for Reducing HIV in the UK (PROUD) study and of clinical practice data from a large US health network revealed decreases in HIV infections among individuals using PrEP, despite self-reported decreases in condom use [59, 60]. Mathematical models similarly suggest that individuals with no or inconsistent condom use may also benefit from PrEP, assuming either modest (about 50% of doses) or high (4 + doses a week) PrEP adherence [61–64]. Simulation studies further suggest that increased risk of HIV acquisition with PrEP use may only occur in scenarios characterized by extreme and highly unlikely behavioral changes that are not reflective of empirical findings (such individuals with consistent condom use for all anal sex acts becoming inconsistent in both condom and PrEP use or individuals drastically increasing CAI by both completely abandoning condom use and radically increasing their numbers of new partners) [59, 65, 66]. This suggests that, if the directionality of increased CAI with increased PrEP adherence holds true, risk compensation in the context of increased PrEP adherence may not be to the detriment of HIV prevention efforts. With regards to other STIs, there is good evidence to suggest that greater PrEP use may result in significant declines in STI incidence among at-risk individuals because of the implementation of the Centers for Disease Control's PrEP prescribing guidelines that recommend ongoing screening and treatment of STIs [63, 67]. However, as the highest level of protection from HIV and other STIs is seen among individuals who consistently use condoms and are adherent to PrEP, the strongest evidence is to include both PrEP and condom use as tools to use in a comprehensive strategy to reduce the incidence of HIV and other STIs.

A strength of this work is in its methodology, with PrEP adherence and CAI measured repeatedly across time, permitting the examination of within-person effects. Although biases in recall are a potential limitation to retrospective reporting of adherence, previous work with this participant sample has found good concordance between self-reports of adherence and biological measures of adherence (TFV-DP and FTC-TP) assessed via dried blood spot measurements (DBS) [37, 68]. Additionally, analyses using DBS data available at weeks 12 and 48 in this study also indicate betweenperson associations between biological measurements of adherence and CAI. Thus, although objective measures of adherence through DBS were not obtained at every visit to relate to CAI within a growth curve modeling framework, the self-reports of adherence obtained in this study are likely an acceptable proxy for actual PrEP adherence behaviors [37, 69]. Future work should consider incorporating frequent assessments of adherence via DBS measurements in order to bolster associations found utilizing self-reported measurements.

There is strong evidence to suggest that substance use and CAI have close temporal associations among MSM, with substances sometimes used to enhance pleasure during sexual encounters, facilitate disinhibition, and maintain stamina; thus, it is a limitation of this work that we were unable to examine the co-occurrence of these two variables [28, 70]. Future longitudinal work may benefit from assessing CAI and its correlates using ecological momentary assessment methods in order to capture observations closer to their real-time occurrences and in more naturalistic settings [71]. An added benefit of obtaining more frequent measures of adherence, substance use, and CAI, closer in time to their occurrences,

would be the ability to also examine causality and direction of effects using lagged models. Additionally, although PrEP adherence and substance use were found to influence CAI, their interaction was not significant, suggesting independent effects on risk compensation. Future work with larger samples is required to corroborate the potentially mutually-influential ways that substance use and PrEP adherence may influence risk compensation. Furthermore, as the absolute median levels of engaging in CAI were relatively low in this study; future studies should consider examining associations between CAI and PrEP adherence among individuals who may have higher baseline levels of engaging in CAI (e.g., individuals who engage in commercial sex work) and include examinations of the incidence of STIs.

It is worth noting that our findings differ from those of a recent study that examined PrEP adherence and risk compensation among young MSM, with findings of no significant intra-individual changes to CAI when individuals reported perfect versus imperfect PrEP dosing [72]. Our contrasting study findings suggest that individuals' graded reports of adherence, rather than their complete adherence, may be more strongly-related to risk compensation. Lastly, this study found evidence of between-person increases in CAI across individuals, as captured by the linear slope growth factor, but did not find covariates of change, suggesting unexamined predictors. Furthermore, the significant random slope, capturing between-person variability in the within-person association of CAI on adherence, suggested that the link between increased adherence and CAI is stronger in some individuals than in others. This suggests the possibility of moderators of the association between adherence and CAI. Future work should consider examining interindividual factors that may be associated with motivations to engage in CAI (for example pleasure, condom self-efficacy) that are malleable and amenable to intervention [73–75]. In particular, given the substantial proportion of individuals with serodiscordant partners (approximately 25% of participants at baseline in this sample), some of whom were likely primary partners, relationship-oriented variables (such as intimacy) and the inclusion of dyadic or partner data may be relevant constructs to understanding change in CAI in the context of PrEP use [73, 74, 76].

Other limitations of this work include the combination of insertive and receptive condomless anal sex, as CAI of any kind was relatively infrequent among participants in this sample. Given evidence to suggest a higher probability of HIV acquisition from receptive vs. insertive CAI, the implications of risk compensation in the context of PrEP may differ depending on the type of CAI individuals engage in [77].

Additionally, our sample was of predominantly White participants, potentially limiting generalizability of findings among more diverse individuals. Furthermore, participants in this sample were recruited at a time when PrEP availability and coverage by insurance was limited; thus, early adopters of PrEP may differ in their sexual risk profiles and in their adherence to PrEP, when compared to more recent cohorts of individuals initiating PrEP.

Conclusions

This study's findings of within-person changes in CAI in response to shifts in adherence and substance use suggests that risk compensation in the context of PrEP use is dynamic and changes with contextual factors. Furthermore, intra-individual associations between levels of

PrEP adherence and engagement in risk compensation suggest that individuals may make decisions about condom use based upon their perceived level of protection due to PrEP. In particular, individuals may engage in more CAI when they perceive greater protection against HIV because of good adherence to PrEP and correspondingly decrease CAI when they are less adherent; however, the direction of effects is yet to be determined. Future work should aim to determine the temporal associations between CAI and PrEP adherence.

Acknowledgements

This work was supported by the California HIV Research Program (CHRP: EI-11-SD-005). Study drug was provided by Gilead Sciences and DBS assays were paid for through a grant from Gilead Sciences. The authors would like to thank all the participants who volunteered for this study and all research coordinators and assistants who made data collection possible.

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Figure 1:
Diagrammatic Representation of the Full Model Tested (Two-part growth model of Condomless anal intercourse with time-varying and time-invariant predictors)

Notes:

Substance use = Subs. Use; Pre-exposure prophylaxis adherence = PrEP Adh.; Condomless anal intercourse = CAI; int. = intercept.

Small filled circles on arrows denote random slopes while small filled circles at the end of arrows denote random intercepts estimated in the model. Double-headed arrows denote correlations between growth factors.

Table 1:

Participant Demographics and Sample Characteristics (N= 372)

Characteristic	Control	Intervention	Difference test
Age, mean (SD)	35.20 (8.73)	35.06 (9.98)	$t(370) = 0.14, p = \text{ns}$
Education, n (%)			$\chi^2(4) = 6.40, p = \text{ns}$
High School or Less	9 (4.8%)	17 (9.2%)	
Some College	67 (35.8%)	71 (38.4%)	
Bachelors	68 (36.4%)	62 (33.5%)	
Some Post-Graduate	13 (7.0%)	5 (2.7%)	
Advanced Degree	30 (16.0%)	30 (16.2%)	
Race and Ethnicity, n (%)			
White	146 (78.1%)	147 (79.5%)	$\chi^2(1) = 0.11, p = \text{ns}$
Hispanic	53 (28.3%)	53 (28.6%)	$\chi^2(1) = 0.10, p = \text{ns}$
Income, n (%)			$\chi^2(1) = 0.495, p = \text{ns}$
< \$2000 per month	38 (20.3%)	38 (20.5%)	
>= \$2000 per month	130 (69.5%)	108 (58.4%)	
Did not state	19 (10.2%)	39 (21.1%)	
Recruitment Site			$\chi^2(3) = 0.15, p = \text{ns}$
Site 1	84 (44.9%)	82 (44.3%)	
Site 2	24 (12.8%)	23 (12.4%)	
Site 3	18 (9.6%)	20 (10.8%)	
Site 4	61 (32.6%)	60 (32.4%)	
Inclusionary Risk Criteria, n (%)			$\chi^2(3) = 7.19, p = .066$
No condom use with 1+ HIV-infected partner	45 (24.1%)	48 (25.9%)	
No condom use with 3+ sexual partners	68 (36.4%)	81 (43.8%)	
No condom use with 1+ partner and an STI diagnosis	2 (1.1%)	6 (3.2%)	
Two or more risk categories	72 (38.5%)	50 (27.0%)	

Notes:

SD = Standard Deviation; STI = Sexually transmitted infection.

Table 2:

Descriptive Statistics of Study Variables

Variable	N	Median [IQR]	Observed Range	Intraclass correlation (ICC)
CAI				0.294
Baseline	372	1 [0, 5]	0–105	
Week 4	367	1 [0, 5]	0–100	
Week 12	366	2 [0, 6]	0–89	
Week 24	349	2 [0, 5]	0–110	
Week 36	327	2 [0, 6]	0–167	
Week 48	312	2 [0, 7]	0–60	
PrEP Adherence				0.374
Week 4	366	5.00 [4.00, 5.00]	0.00–5.00	
Week 12	366	4.50 [4.00, 5.00]	0.00–5.00	
Week 24	349	4.50 [4.00, 5.00]	0.00–5.00	
Week 36	354	4.50 [4.00, 5.00]	0.00–5.00	
Week 48	311	4.50 [4.00, 5.00]	0.00–5.00	
Substance Use				0.726
Baseline	371	1 [0, 3]	0–9	
Week 4	371	2 [1, 2]	0–8	
Week 12	366	1 [0, 3]	0–10	
Week 24	349	1 [0, 2]	0–10	
Week 36	327	1 [0, 2]	0–9	
Week 48	312	1 [0, 3]	0–10	

Notes:

The intraclass correlation (ICC) represents the proportion of the total variance in each measure accounted for by clustering within individuals.

CAI = Condomless anal intercourse; PrEP = pre-exposure prophylaxis; IQR = Interquartile range.

Table 3:

Model Estimates for the Two-Part Growth Model of Condomless Anal Intercourse (CAI) with Time-Varying and Time-Invariant Predictors

	Estimate	SE	OR/IRR	95% CI	
				Lower	Upper
Part 1: Engaging in Any CAI vs. no CAI (logistic)					
<i>Time-varying (within-person)</i>					
^a PrEP adherence	0.342 **	0.117	1.408	1.119	1.771
^b One substance	0.625 **	0.202	1.868	1.257	2.776
^b Two substances	0.476 *	0.213	1.610	1.060	2.444
^b Three or more substances	1.134 ***	0.251	3.108	1.900	5.084
<i>Time-invariant: Predicting intercept (between-person)</i>					
Age	−0.004	0.013	0.996	0.971	1.022
^c Some college	−0.312	0.366	0.732	0.357	1.500
^c Bachelors	−1.090	0.620	0.336	0.100	1.133
^c Some postgraduate	−0.589 [†]	0.374	0.555	0.267	1.155
^c Advanced degree	−1.037 *	0.424	0.355	0.154	0.814
Intervention arm	0.072	0.229	1.075	0.686	1.683
^d Site 2	−0.625	0.397	0.535	0.246	1.165
^d Site 3	−0.234	0.553	0.791	0.268	2.340
^d Site 4	−0.318	0.258	0.728	0.439	1.206
^e CAI with HIV+ partner	0.910 **	0.310	2.484	1.353	4.561
^e CAI with STI	0.296	0.924	1.344	0.220	8.224
^e Two or more risk factors	0.921 **	0.277	2.512	1.459	4.323
Growth factor mean	0.000	0.000	1.000	1.000	1.000
Part 2: Frequency of CAI (count)					
<i>Time-varying (within-person)</i>					
^a PrEP adherence	0.158 **	0.059	1.171	1.043	1.315
^b One substance	−0.004	0.110	0.996	0.803	1.236
^b Two substances	−0.014	0.122	0.986	0.776	1.253
^b Three or more substances	0.145	0.126	1.156	0.903	1.480
<i>Time-invariant: Predicting intercept (between-person)</i>					
Age	−0.019 [†]	0.010	0.981	0.962	1.001
^c Some college	0.294	0.361	1.342	0.661	2.723
^c Bachelors	0.070	0.358	1.073	0.532	2.163
^c Some postgraduate	−0.409	0.535	0.664	0.233	1.896

	Estimate	SE	OR/IRR	95% CI	
				Lower	Upper
^c Advanced degree	−0.009	0.421	0.991	0.434	2.262
Intervention arm	−0.065	0.169	0.937	0.673	1.305
^d Site 2	0.014	0.301	1.014	0.562	1.829
^d Site 3	−0.188	0.404	0.829	0.375	1.829
^d Site 4	−0.315	0.199	0.730	0.494	1.078
^e CAI with HIV+ partner	0.296	0.234	1.344	0.850	2.127
^e CAI with STI	−0.408	0.760	0.665	0.150	2.949
^e Two or more risk factors	0.209	0.190	1.232	0.849	1.789
Growth factor mean	1.017 **	0.374	2.765	1.328	5.755
<i>Time-invariant: Predicting slope (between-person)</i>					
Age	−0.001	0.001	0.999	0.997	1.001
^c Some college	−0.015	0.040	0.985	0.911	1.065
^c Bachelors	0.008	0.040	1.008	0.932	1.090
^c Some postgraduate	−0.028	0.050	0.972	0.882	1.073
^c Advanced degree	0.009	0.044	1.009	0.926	1.100
Intervention arm	0.003	0.015	1.003	0.974	1.033
^d Site 2	−0.035	0.028	0.966	0.914	1.020
^d Site 3	0.022	0.040	1.022	0.945	1.106
^d Site 4	0.020	0.017	1.020	0.987	1.055
^e CAI with HIV+ partner	0.008	0.020	1.008	0.969	1.048
^e CAI with STI	−0.074 **	0.025	0.929	0.884	0.975
^e Two or more risk factors	0.010	0.018	1.010	0.975	1.046
Growth factor mean	0.036	0.040	1.037	0.958	1.121

Notes:

[†] 0.05 < p < 0.10,

* 0.01 < p < 0.05,

** 0.001 < p < 0.01,

*** p < 0.001.

^a The random slope of the within-person effect was estimated.

^b Estimates for educational level were relative to individuals with a high school education or less.

^c Estimates for site of recruitment were relative to individuals recruited from Site 1.

^d Estimates for inclusionary sexual risk criteria for study eligibility were relative to individuals with 3+ sexual partners.

The dispersion parameters for continuous CAI (modeled using a truncated negative binomial distribution) were significant at all time points (p < 0.05).

Standard Error = SE; Odds Ratio = OR; Incidence Risk Ratio = IRR; Confidence Interval = CI.

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