Incidence and Correlates of STIs among Black Men who have Sex with Men Participating in a US PrEP Study

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Word Count: 3343

Abstract:
Body (text only):
Figures: 1
Tables: 4

MeSH Headings:

Running Head:

Abstract: Will write once decide on Journal.

Background.

HIV incidence in the United States (US) is slowly declining over time, but an estimated 40,000 new infections still occur each year.[1] Since persons living with HIV (PLwHIV) who achieve virologic suppression have effectively no risk of transmitting the virus to others,[2-4] linkage to care and initiation of antiretroviral therapy have likely contributed greatly to this declining trend. However, the benefits of "treatment as prevention" and other new biomedical prevention technologies[5,6] are not distributed equally across subpopulations affected by HIV. Black communities continue to experience the most severe burden of HIV rates of all racial/ethnic groups in the US, with Black men who have sex with men (MSM) most disproportionately impacted.[7] In 2016, Black MSM accounted for 26% of the 39,782 new HIV diagnoses in the US. Furthermore, while the overall rate among Black MSM has not changed, there was a 30% increase in HIV infection rates among those ages 25-34 between 2011 and 2015.[7] Modeling studies have estimated that if the current trends do not change, one in two Black MSM will be diagnosed with HIV in his lifetime[8], and that if current incidence rates persist, 40% of Black MSM will be HIV-infected by age 30.[9]

The low uptake of pre-exposure prophylaxis (PrEP) among Black MSM to date is likely an important contributor to this persistent disparity in HIV incidence.[10,11] Since FDA approval of oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) as PrEP in 2012, the number of PrEP users has steadily increased – but utilization is concentrated among White MSM.[12,13] While Black MSM in the US have the highest rate of HIV infections, it is estimated that only about 10% of PrEP users are Black.[12] In 2015, of 813,970 MSM with indications for PrEP, 38% were Black, 29% were White, and 27% were Latino.[14] An evaluation of the PrEP care continuum on an Atlanta cohort of MSM (n=562) found that while Black MSM were equally likely to report awareness of and willingness to use PrEP compared to White MSM, Black MSM were less likely to receive a PrEP prescription (24.2 vs. 34.8%) and achieve protective levels (12.3% vs. 17.8%).[15]

Further complicating the reduction of HIV among the highest risk groups is the relationship between HIV and other sexually transmitted infections (STIs). Individuals with active STIs are at greater susceptibility for HIV

infections and vice versa.[16-18] Among MSM, STIs have dramatically increased in the last decade.[19,20] There is general concern that expanded use of PrEP may lead to increased incidence of bacterial STIs, but available data thus far have been mixed.[21]. The mechanism by which PrEP use could lead to higher STI incidence may be explained by the sexual behavior of those who initiate PrEP (men who already engage in condomless anal sex (CAI) and/or have multiple sexual partners) who seek HIV prevention due to their established patterns of sexual behavior [20]. Other non-causal, potentially confounding, reasons include the increased frequency of screening and diagnosis of asymptomatic infections as part of the clinical standards of PrEP use.[22] However, limited data exist regarding STI risk in Black MSM PrEP users, despite the fact that Black MSM have been identified as one of the highest risk groups for HIV and other STI acquisition.[7,8,23,24]

We sought to examine STI incidence among PrEP users by studying a unique cohort of Black MSM recruited for HIV Prevention Trials Network (HPTN) Study 073 (clinicaltrials.gov: NCT01808352). This multi-site, open-label demonstration study explored whether provision of a structural intervention (client-centered care coordination, or C4) could improve acceptance of and adherence to oral FTC/TDF among Black MSM. The C4 model integrates an evidence-based, public health strategy with a self-determination theory-based approach to counseling and client engagement.[25,26] Objectives of the parent study included description of the initiation, acceptability, safety, and feasibility of PrEP for Black MSM. The purpose of this secondary analysis was to characterize the relationship between PrEP uptake and use and incident STIs among participants enrolled in HPTN 073.

Methods

Parent Study

HPTN 073 enrolled 226 HIV-uninfected Black MSM between August 2013 and September 2014 in three US cities: Los Angeles, CA; Washington, DC; and Chapel Hill, NC. To be eligible, participants had to provide informed consent, be over age 18, self-identify as male at birth and Black (multiracial/multiethnic men were also eligible), and self-report at least one of the following HIV risk behaviors or characteristics: CAI with a male partner, anal intercourse with more than three male partners, exchanging any anal sex with a male partner for money, gifts, shelter or drugs, anal intercourse with a male partner while using drugs or alcohol, or having a male

sex partner and an STI diagnosis in past six months. In addition, all participants had to be clinically eligible to receive FTC/TDF based on laboratory testing.[27]

At screening, all participants were offered HIV and STI testing along with C4 (which included referrals for healthcare and prevention services and harm reduction counseling). In addition, participants were offered FTC/TDF and all related clinical testing free of charge. Participants could choose to initiate oral PrEP at any study visit until week 48, per their request and upon confirmation of a non-reactive antigen/antibody combination HIV test. Participants could also choose to discontinue PrEP at any point during the course of the study. Following informed consent and enrollment, participants had study visits at weeks 4, 8, and 13; visits occurred quarterly thereafter, up to 12 months. At weeks 26 and 52, men were tested for syphilis, and rectal and urethral gonorrhea and chlamydia. Rapid plasma reagin (RPR) testing for syphilis was obtained from plasma specimens; reactive titers were confirmed using a treponemal-specific assay per local testing protocols. Testing for *Chlamydia Trachomatis* (CT) and *Neisseria Gonorrhoeae* (NG) were performed for urine and rectal swab samples using the Aptima Combo 2 Assay for CT/NG assay (Hologic, San Diego, CA) by the HPTN Laboratory Center. Pharyngeal STIs were not specifically tested for per protocol but were reported as adverse events (AEs), if detected. At each visit, participants completed an audio-computer assisted self-interview (ACASI).

Safety Monitoring

The HPTN 073 study protocol was approved by the institutional review boards of University of California at Los Angeles, University of North Carolina at Chapel Hill, and George Washington University. All study participants provided written, informed consent and completed an informed consent assessment to ensure a thorough understanding of the study prior to enrollment.

Measures

Sexual risk behaviors: At baseline and each follow-up ACASI, participants were asked about engagement in insertive and receptive condomless anal intercourse (CAI) with primary (main) and casual male partners.

Engagement in CAI (any, insertive and receptive) was dichotomized; participants reporting ≥ 1 instance in CAI in the past 3 months vs. participants reporting no instances of CAI.

PrEP adherence was examined in two ways: self-report data were collected by interview instrument and blood levels indicating short term (Plasma or PBMC) adherence ≥4 pills per week. The Visual Analogue Scale (VAS) was used to measure self-reported adherence to PrEP in the past 30-days.[28] Patients were presented with a line anchored at 0% and 100%; provided with examples of what 0, 50%, and 100% adherence would represent; and asked to assess their own PrEP medication adherence. The biological measure of short-term PrEP adherence was defined as those who met the 90% sensitivity threshold for ≥4 doses of FTC/TDF per week from any of the two samples types (Plasma and PBMC) related to tenofovir (TFV) and emtricitabine (FTC) measurements: ≥4.2 ng/mL for TFV and ≥4.6 ng/mL for FTC in plasma; 9.9 fmol/10^6 for TFV diphosphate (TFV-DP) and 0.4 fmol/10^6 for FTC triphosphate in PBMCs. These measures of adherence for plasma and PBMC samples were established by the directly observed dosing study, HPTN 066.[29]

Statistical Analysis

Following univariate description of the participants' demographic, behavioral, and clinical characteristics at baseline, logistic regression was used to examine the unadjusted and adjusted associations between STI incidence and PrEP uptake adjusting for site differences. Incidence rates and confidence intervals were calculated based on a Poisson distribution. Person-years (PY) of follow-up time were calculated to the first STI diagnosis or last STI date from either the PrEP acceptance date or study enrollment date, depending if the participant accepted PrEP or not. Associations between age, PrEP acceptance, sexual behaviors, and new STI cases were evaluated using generalized estimating equations (GEE) to account for the repeated observations at weeks 26 and 52 with adjusting for site differences. Among participants who acquired HIV during study follow-up, STI diagnoses are not counted after HIV seroconversion, as different psychosocial and physiologic states may obscure the relationship between PrEP and STIs. All analyses were conducted in using SAS version 9.4 (SAS Institute, Cary, NC).

Results.

Characteristics of Participants.

Detailed characteristics of participants in HPTN 073 are described elsewhere.[30] Briefly, of 226 enrolled participants, 86% self-identified as Black or African American only, 25% had a high school diploma or less, 48% reported an annual income of less than $20,000, 73% and 20% identified as gay or bisexual, respectively. The median age was 26 years (interquartile range [IQR] 23 to 32), and 91 men (40.3%) were age 25 or younger.

Baseline and Incident STIs

STI prevalence was 14.2% at the baseline visit. The most common STI at baseline was chlamydia (10.2%; 1.8% urethral and 9.1% rectal) followed by gonorrhea (5.3%; 0.9% urethral and 4.6% rectal) and syphilis (1.3%). These proportions did not change substantially at week 26 (16.2%) or week 52 (18.2%) (P = 0.85) (Figure 1). Rectal STIs accounted for the largest proportion of infections at all three visits (11.5%, 11.8%, and 9.6%). At the baseline visit, men younger than 25 years old had a higher STI prevalence than older men (25.3% versus 6.7%), and those rates translated into a 4 times higher odds of an STI in younger men (odds ratio [OR] 4.39, 95% confidence interval [CI]: 1.91, 10.11).

Sixty men (26.5%) acquired an STI during follow-up, and 9 men (4%) had an STI at both follow-up visits. Incident STIs by visit and short term PrEP adherence demonstrated by blood levels at each visit are described in Table 1. Regardless of PrEP acceptance, compared to men who were 25 years and older, those men younger than 25 were more likely to have STIs at both 26 (9.2% (11/120) versus 26.5% (22/83)) and 52 weeks (16.0% (19/119) versus 22.0% (18/82)). At week 26, those who accepted PrEP had similar rates of STIs whether or not they reported any CAI in the prior 3 months (19.3% any CAI; 15.5% no CAI). Among the 4 participants at week 26 who were diagnosed with an STI (3 of whom had rectal infections) and had not opted to take PrEP, none reported CAI in the past 3 months – suggesting the potential for reporting bias. At week 52, 18 participants who denied CAI in the past 3 months were diagnosed with a new STI (9 of which were rectal infections), including 15 men who accepted PrEP and 3 who did not.

Over the entire study follow-up period, there was an STI incidence rate of 34.2 cases per 100 person-years (95% CI: 27.4, 42.9; Table 2). No statistically significant differences in STI incidence were found by study visit week or by PrEP acceptance. Among those men with at least 1 incident STI, adherence (both self-report and as measured by PK) was low at both 26 and 52 weeks (26.7% self reported adherence >=60%; 28.4% had PK short term adherence >= 4 days/week).

Correlates of Incident STIs

Several characteristics were associated with having an incident STI prior to adjustment for confounders as shown in Table 3, including being less than 25 years old, having a prevalent STI at baseline, and having greater than the mean number of minutes of C4 contact time. In the adjusted analysis, only the presence of a baseline STI diagnosis (OR 4.23, 95% CI: 1.82, 9.87; $p<0.001$) and additional minutes of C4 (OR 1.03, 95% CI: 1.00, 1.06; $p=0.027$) remained associated with having an incident STI. We saw no statistically significant association between PrEP uptake, self-reported PrEP adherence, or PrEP adherence measured by PK levels (Table 3).

Changes in Condomless Anal Intercourse

There was no statistically significant change in self-reported insertive or receptive CAI over time. Nearly half of participants (45.8%) reported insertive CAI at baseline, which remained stable during follow-up (p=0.096). Slightly fewer men (44.9%) reported receptive CAI at baseline, which also remained stable during follow-up (p=0.180). Overall, the proportion of participants report CAI was lower for those not accepting PrEP compared to those aceepting PrEP at all time points (Table 4). Decreased rates of CAI (both receptive and insertive were observed from baseline through week 52) among both men accepting and not accepting PrEP.

Relationship between incident HIV infections and STIs

Overall there were 8 incident HIV infections diagnosed during the study. Two of these men were diagnosed with incident STIs at the time of seroconversion (one man who accepted PrEP diagnosed with syphilis and one man who did not accept PrEP was diagnosed with urethral gonorrhea). Two participants who seroconverted were diagnosed with chlamydia at basline (one rectal and one urethral infection).

Discussion

To our knowledge, this is the first study to evaluate longitudinal acquisition of STIs in a sample of US Black MSM being offered PrEP. Overall, 26.5% of participants in HPTN 073 were diagnosed with an STI over the course of the study, a rate lower than what was seen in other recent PrEP clinical trials and demonstration projects.[31,32] While direct comparisons cannot be made – particularly given that the majority of previous studies enrolled few Black MSM [31,32] – these results provide valuable insight into ongoing risk behaviors among the population most impacted by HIV infection in the US.

In registrational trials of FTC/TDF for PrEP, a high incidence of STIs was observed but there was no conclusive evidence for risk compensation among PrEP users. Indeed, some studies reported a decline in key metrics of STI risk (e.g. decreased number of sex partners or frequency of condomless sex).[32-35] In IPERGAY, a double blind, placebo controlled trial of coital event-based PrEP for MSM, the proportions of participants with a new STI during follow-up were not significantly different (41% in the FTC/TDF group and 33% in the placebo group).[36] Similarly, even though there was a high incidence of STIs among participants in the US PrEP Demonstration Project, the rate did not increase over time while people were on PrEP.[31] However, other studies suggest higher rates of STIs among MSM who use PrEP compared to non-PrEP users.[37-39] This may simply be a function of the risk profile of early adopters of PrEP – a population of MSM who might already engage more often in CAI and/or have multiple sex partners.[20] An apparent increased STI incidence among PrEP users could also be an artifact of more frequent and consistent screening in this population.[22]

The low overall rate of STI acquisition we observed is encouraging as efforts to increase uptake of PrEP in this population expands. Nationwide, rates of STIs are 4.6, 6.6 and 8.9 time higher in Black men compared to White men for syphilis, chlamydia and gonorrhea, respectively.[23] A recent cohort study found that among MSM accessing medical care at a Boston community health center between 2005-2015, STI diagnoses increased more than 8-fold. Though Black MSM made up only 6% of the participants, multivariable analyses demonstrated that being an MSM of color was independently associated with being diagnosed with a new STI.[40] Thus, when

situated within the context of disparate rates of STIs reported among Black MSM compared with MSM of other races[41], the low overall rates of STIs are encouraging as efforts to increase uptake of PrEP in this population expands. Of note, the men in this study were offered a culturally tailored behavioral intervention, C4, which may have attenuated their sexual risk behavior.

Being younger than 25 quadrupled the odds of having an STI at screening, and those with STIs at baseline were more likely to have an incident STI at any follow-up visit. Black MSM with STIs at PrEP initiation may require additional counseling regarding sexual risk behaviors during follow-up. While a recent study showed that on demand post-exposure prophylaxis (PEP) with doxycycline reduced the incidence of chlamydia infection and syphilis in high risk MSM enrolled in a PrEP study[42], the utility of this strategy for Black MSM, particularly its durability and impact on antibiotic resistance, requires further investigation.

The overall low adherence to PrEP among those Black MSM in this study with incident STIs is concerning. Given that MSM with a history of syphilis or anorectal STIs have a greater risk of subsequent HIV acquisition[43-45], additional efforts to develop effective adherence interventions for Black MSM on PrEP is critical. This finding is echoed by a recent 24-week demonstration project PrEP among young MSM (aged 18-22 years), which found that at all times, median TFV-DP levels for Black MSM participants were below the protective threshold of greater than or equal to four pills per week.[46]

Rates of STIs were similar among those who chose to start PrEP in this study compared to those who declined PrEP, with no increase in incidence over time. While this aligns with the lack of increase in participant self-reported CAI over time, self-report of sexual risk behaviors may not always be an accurate reflection of risk. Indeed, we found that nearly 50% of participants at both week 26 and 52 who reported no CAI in the past 3 months, were diagnosed with a new STI. This echoes previous findings from a cohort of 485 young Black MSM recruited in Jackson, Mississippi, among whom 19.4% of rectal STI infections would have been missed if screening had not occurred on those denying any receptive anal sex.[47]

Men who had more minutes of C4 were more likely to have an incident STI during study follow-up. This may indicate that those men had more complex social situations and higher needs, including ongoing risk behaviors for STI acquisition that required more counseling time and referalls. Among Black MSM, factors such as social isolation and experiences of racism and homophobia have been shown to drive sexual risk taking.[48-50] Further, structural factors, including financial hardship, incarceration and unstable housing have been associated with increased STIs among Black MSM.[48,51] Additional analyses unpacking the time spent on care coordination activites to address participants' sexual health needs will be informative to understand how to tailor future interventions to address both ongoing risk and additional psychosocial stressors experienced by this population.

There were some limitations in this study that must be mentioned. Screening for STIs only occurred at baseline and weeks 26 and 52 study visits, thus potentially underestimating the number of STIs among participants. Participants were queried at each study visit (weeks 4, 8, and quarterly thereafter, up to 12 months) regarding any interim testing they had done, resulting in our awareness of 5 additional diagnoses and 3 cases of presumptive treatment at other clinic sites. Recent data and CDC guidelines suggest more frequent testing (every 3 months) than was provided in this study, is warranted for those on PrEP.[27] In addition, STI screening in this study did not include sampling for pharyngeal gonorrhea, which should be encouraged moving forward, given concerns regarding the possible role of pharyngeal gonococcal infection, as a reservoir of antimicrobial-resistant infection which could have future implications for the prevention and control of gonorrhea in MSM on PrEP.[52-54] Further, as mentioned above, sexual risk behavior data collected by self-report. While ACASIs have been shown to minimize social desirability bias when reporting sexual risk behaviors[55-57], the fact that many men who reported no CAI were diagnosed with new STIs is concerning.

Conclusions

The expansion of effective models of combination HIV and STI prevention, including PrEP, provides a unique and timely opportunity to address the lack of progress to date in reducing HIV incidence among Black MSM.[58] However, PrEP for Black MSM should not be delivered "in isolation" but as part of a combination prevention package that incorporates frequent STI screening and treatment and addresses Black MSM's pervasive ongoing

exposure to adverse social and structural conditions, as well as a confluence of individual factors that continue to impact their overall health.

Figure 1: STIs at Screening and Follow-up

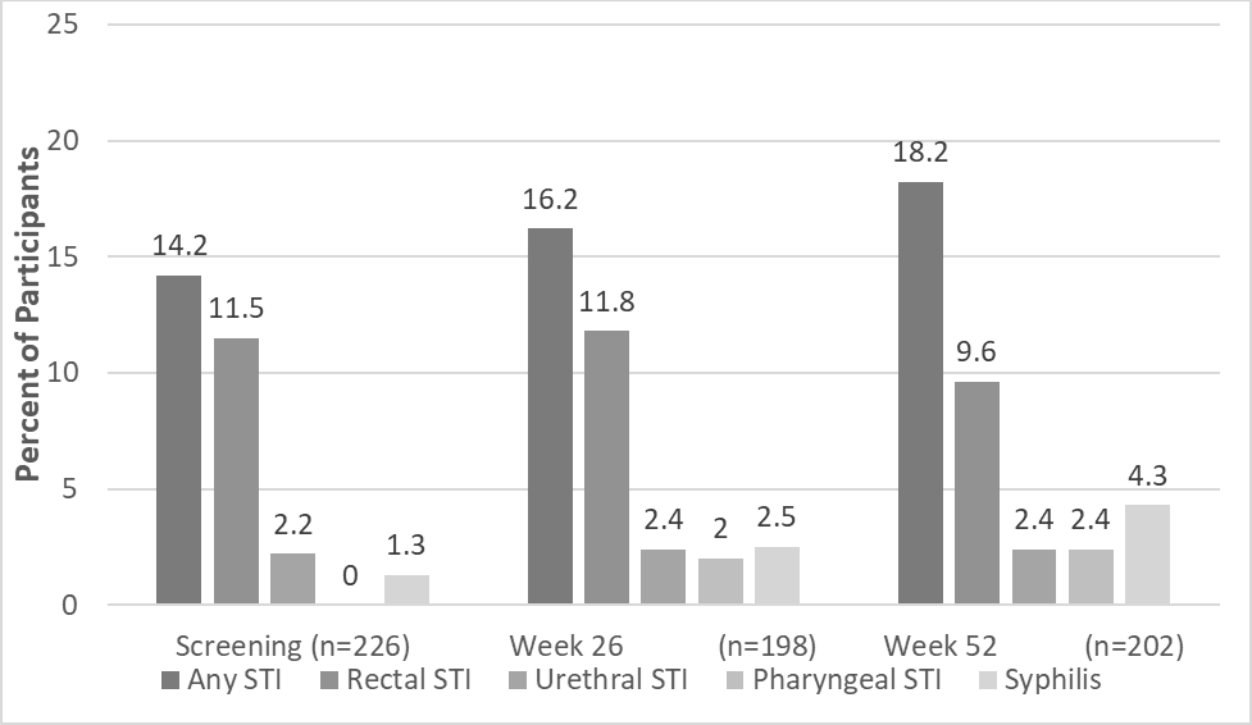

Table 1: Characteristics of Incident STIs by PrEP Acceptance and Visit

	Week 26 PrEP Accept % (n/N)	Week 26 PrEP Not Accept % (n/N)	Week 52 PrEP Accept % (n/N)	Week 52 PrEP Not Accept % (n/N)
Any STI	17% (29/167)	11% (4/36)	19% (31/166)	17% (6/35)
Age				
≥25	10.6% (10/94)	3.8% (1/26)	15.6% (15/96)	17.4% (4/23)
<25	26.0% (19/73)	30.0% (3/10)	22.9% (16/70)	16.7% (2/12)
Baseline Any STI Diagnosis				
No	12.9% (18/139)	12.1% (4/33)	15.7% (22/140)	18.8% (6/32)
Yes	39.3% (11/28)	0.0% (0/3)	34.6% (9/26)	0.0% (0/3)
Any CAI (past 3 months)				
No	15.5% (11/71)	17.4% (4/23)	18.1% (15/83)	12.0% (3/25)
Yes	19.3% (16/83)	0.0% (0/11)	17.8% (13/73)	37.5% (3/8)
Any receptive CAI (past 3 months)				
No	17.2% (15/87)	14.8% (4/27)	15.7% (16/102)	11.5% (3/26)
Yes	17.9% (12/67)	0.0% (0/7)	22.2% (12/54)	42.9% (3/7)
Any insertive CAI (past 3 months)				
No	20.2% (18/89)	15.4% (4/26)	15.6% (15/96)	11.1% (3/27)
Yes	13.8% (9/65)	0.0% (0/8)	21.7% (13/60)	50.0% (3/6)
Any Alcohol/Drug use 2 hrs. before or during Sex (past 3 months)				
No	16.3% (16/98)	8.3% (2/24)	15.8% (16/101)	18.5% (5/27)
Yes	19.6% (11/56)	20.0% (2/10)	21.8% (12/55)	16.7% (1/6)
Self-Report adherence ≥60%				
No	22.6% (7/31)	n/a	26.3% (5/19)	n/a
Yes	16.8% (18/107)	n/a	15.7% (13/83)	n/a
PK short term adherence ≥4 days/week				
No	19.0% (11/58)	n/a	17.1% (13/76)	n/a
Yes	16.7% (17/102)	n/a	20.9% (18/86)	n/a
Average C4 minutes				
Mean (SD)	30 (7.8)	30 (7.8)	29 (6.3)	36 (15.2)
Min, Max	20, 50	23, 41	16, 41	18, 60
Median	29	28	28	31
25th, 75th %tile	24, 34	25, 36	24, 34	30, 48

Table 2. STI Incidence Rate by PrEP Acceptance

	STI (n)	Person - years	Incidence Rate (95% CI) per 100 person years	P-Value
Overall (all participants)	70	204.6	34.2 (27.4, 42.9)	
All Weeks				0.4658
Not on PrEP	11	39.2	28.1 (15.5, 50.7)	
On PrEP	59	165.4	35.7 (27.6, 46.0)	
Week 26				
Not on PrEP	5	20.2	24.8 (10.3, 59.6)	0.4363
On PrEP	28	77.3	36.2 (25.0, 52.4)	
Week 52				
Not on PrEP	6	19.0	31.5 (14.2, 70.2)	0.8048
On PrEP	31	88.1	35.2 (24.8, 50.0)	

Table 3. Correlates of Incident STIs

	At least one incident STI % (n/N)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age			
>=25	21.4% (27/126)	Ref	
<25	38.6% (34/88)	**2.39 (1.36, 4.20)**	1.41 (0.60, 3.31)
PrEP Acceptance			
Not on Prep	25.0% (10/40)	1.47 (0.73, 2.96)	
On Prep	29.3% (51/174)	Ref	
Baseline Any STI Diagnosis			
No	24.0% (44/183)	Ref	
Yes	54.8% (17/31)	**3.20 (1.67, 6.11)**	**4.23 (1.82, 9.87)**
Any CAI (past 3 months)			
No	26.5% (27/102)	Ref	
Yes	30.5% (29/95)	1.20 (0.69, 2.07)	
Any Receptive CAI (past 3 months)			
No	27.4% (32/117)	Ref	
Yes	30.0% (24/80)	1.39 (0.79, 2.45)	
Any Insertive CAI (past 3 months)			
No	28.1% (34/121)	Ref	
Yes	28.9% (22/76)	1.14 (0.67, 1.94)	
Any Alcohol/Drug 2 hrs. before or during Sex (past 3 months)			
No	27.3% (35/128)	Ref	
Yes	30.4% (21/69)	1.34 (0.75, 2.40)	
Self-Report adherence >=60pct			
No	35.5% (11/31)	Ref	
Yes	26.7% (28/105)	0.60 (0.27, 1.31)	
PK short term adherence >= 4 days/wk			
No	33.3% (21/63)	Ref	
Yes	28.4% (29/102)	1.16 (0.65, 2.08)	
Average C4 minutes			
Mean (SD)	30 (9.5)	1.02 (1.00, 1.05)	**1.03 (1.00, 1.06)**
Median(Q1,Q3)	28 (23,34)		

Table 4: Proportion of participants reporting condomless insertive anal sex (CAI) by PrEP acceptance and week on study.

PrEP Acceptance		Baseline Visit	Week 26	Week 52
Yes	Overall CAI	105/177 (59.3%)	84/156 (53.9%)	73/161 (45.3%)
	Insertive CAI	90/177 (50.9%)	65/156 (41.7%)	60/161 (37.3%)
	Receptive CAI	83/177 (46.9%)	68/156 (43.6%)	54/161 (33.5%)
No	Overall CAI	19/48 (39.6%)	11/34 (32.4%)	10/38 (26.3%)
	Insertive CAI	13/48 (27.1%)	8/34 (23.5%)	8/38 (21.0%)
	Receptive CAI	18/48 (37.5%)	7/34 (20.6%)	8/38 (21.0%)

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