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Sexually transmitted infections among participants in an HIV PrEP adherence trial

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Abstract

Background: HIV PrEP effectiveness is highly dependent on adherence. High STI incidence has been reported among PrEP users. We assessed the relationship between STI incidence (CT, NG, and syphilis) and PrEP adherence.

Methods: We performed a subanalysis of a controlled, open-label, two-arm, randomized clinical demonstration project of a text-message based adherence intervention. Participants had 48 weeks of follow-up and had STI testing every 12 or 24 weeks. PrEP adherence was measured at week 48 using intracellular tenofovir-diphosphate drug concentrations. We calculated incidence rate ratios for STIs among those adherent as compared with those not adherent to PrEP.

Results: Of the 381 assessed for CT, NG and syphilis at one or more follow-up visits, there were 16 cases of syphilis or 5.0 per 100 person years (95% CI: 2.6, 7.5); 63 cases of NG or 26.3 per 100 person years (95% CI: 19.8, 32.8); and 81 cases of CT or 36.3 per 100 person years (95% CI: 28.4, 44.2). We found no association between adequate PrEP adherence and STI incidence (aIRR: 0.97 95% CI: 0.67, 1.40).

Conclusions: We found that the incidence of STIs was not significantly different between those adherent to PrEP and those non-adherent. Further research is needed to assess how PrEP use may impact STIs over time.

Keywords

Sexually transmitted infections, pre-exposure prophylaxis, men who have sex with men

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Introduction

HIV pre-exposure prophylaxis (PrEP) with oral tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) is an efficacious strategy for HIV prevention.[1-4] PrEP is indicated for those at high risk for HIV infection and those individuals are also at high risk for other sexually transmitted infections (STIs).[5] In the United States, CDC recommendations for PrEP management include at least bi-annual screening for STIs.[6] Therefore, an additional advantage of PrEP is that it may bring into care those who are at risk for an STI but who would not otherwise be seeking screening for STIs.

High STI incidence has been reported among HIV PrEP users.[7-9] This finding may be due to PrEP cohorts being made up of people at higher risk, due to increased STI screening and detection, as well as changes in STI incidence generally over time.[10] In addition, some have hypothesized that PrEP use leads to *risk compensation*, the idea that perceived decreased risk of HIV infection may result in riskier sexual practices.[11] While PrEP offers protection against HIV and thus risk compensation may not have an impact on HIV incidence, PrEP effectiveness is highly dependent on PrEP adherence.[12, 13] In addition, if risk compensation leads to increased condomless sex, then it may lead to increased incidence of STIs. A recent meta-analysis found that PrEP was associated with increased new diagnoses of STIs in MSM.[14] That relationship was strongest for rectal *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) infections (Odds ratio: 1.39

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(95% CI: 1.03, 1.87). Those results suggest on-going risk behavior that could put someone at risk for HIV if they are not adherent to PrEP. A recent analysis by Whitfield et al. among Black MSM found that PrEP adherence was associated with number of partners but was not associated with HIV risk perception.[15] In a longitudinal study of young MSM in Chicago, researchers found evidence for risk compensation among young MSM taking PrEP who reported higher rates of receptive condomless anal sex than those not taking PrEP.[16] The study also found that the highest rates of receptive condomless anal sex occurred among young MSM who were on PrEP but were not highly adherent to their medication. This finding is in contrast with the idea of risk compensation, as we would assume that those most protected from HIV (those highly adherent to PrEP), may engage in riskier sexual behavior because of the perceived protection afforded by PrEP against HIV. A limitation of that study is that adherence to PrEP was self-reported and therefore may not reflect true PrEP adherence or biological protection. Thus, the impact of PrEP adherence on risk compensation is unknown. In our prior work, we found that greater self-reported adherence to PrEP was associated with increased condomless sex and time on PrEP was associated with reductions in condom use.[17] In a longitudinal study of young MSM, it was found that higher rates of condomless anal sex occurred during times when participants were on PrEP compared to times when they were not on PrEP.[16] However, in contrast to our prior work, that study also found the rate of receptive condomless anal sex was more common among those not adherent to PrEP compared to those not using PrEP. Further research is needed to better understand the broader relationship between PrEP adherence and potential risk compensation.

We conducted an analysis from a PrEP adherence study[18] to assess if STI incidence (CT, NG, and syphilis) was associated with PrEP adherence measured using intracellular tenofovir-diphosphate (TFV-DP) drug concentrations.

Methods

California Collaborative Treatment Group (CCTG) 595 was a controlled, open-label, two-arm, randomized clinical demonstration project to determine if the use of a text-message based adherence intervention improved retention and adherence to PrEP compared to standard of care PrEP delivery (clinicaltrials.gov NCT01761643).[18] The CCTG, a multi-institutional HIV clinical research network, enrolled participants at four urban Southern California study sites: University of California, San Diego; Los Angeles County-University of Southern California; Harbor-University of California Los Angeles; and Long Beach Health Department. The study began enrolling participants in February 2013 for 48 weeks follow-up or longer. The study completed in February 2016. All participants provided written informed consent, and the study was approved by the institutional review boards at each of the four participating sites.

The study methods have been published elsewhere[18]. In brief, eligible participants were English or Spanish speaking HIV-uninfected men who have sex with men (MSM) and transgender women 18 years of age or older at increased risk for HIV. HIV status was confirmed by a negative fourth generation antigen–antibody assay or an antibody assay with an HIV nucleic acid amplification test (NAAT). Risk for HIV was determined by meeting one of the following criteria: 1) At least one HIV-positive sexual partner for ≥4 weeks; 2) No condom use during anal intercourse with ≥3 male sex partners who are living with HIV or of unknown HIV status during the last 3 months; or 3) No condom use during anal sex with ≥1 male partner plus an STI diagnosis during the last 3 months. In addition, other safety inclusion and exclusion criteria were used.[18]

The study visits included an interview and occurred at baseline and weeks 4, 12, 24, and 48. Syphilis testing was conducted every 12 weeks throughout the study period with rapid plasma reagin (RPR) (Arlington Scientific, Springville, UT, USA) testing and confirmed with a treponemal test (LIAISON®, DiaSorin, Italy). A new diagnosis of syphilis was made by the study clinician considering any previous RPR and treponemal results that were available from the health department. CT and NG screening using a NAAT was performed every 12–24 weeks throughout the study period using specimens from three anatomic sites (rectal swab, pharyngeal swab, and urine) (Aptima Combo 2, Hologic, San Diego). A change to every 24 weeks was initiated in July 2014 due to cost constraints.

We used a cross-sectional measure of PrEP adherence estimated by intracellular TFV-DP using dried blood spots collected at week 48. We created categories of adherence: "highly adherent" was considered ≥ 1246 fmol/punch, consistent with seven doses per week (near perfect dosing); "adequate or better adherence" was ≥719 fmol/punch, consistent with four or more doses of TDF in the past week; and "low adherence" was <719 fmol/punch, consistent with less than four doses of TDF in the past week.[19]

We used descriptive statistics to provide detail on the characteristics of the study population and stratified by incident STI. We used chi-squared (or fishers exact in instances of low cell sizes) and Wilcoxon rank sum tests to assess differences between groups. We calculated the frequency of first incident STIs per 100 person years (PYs) for CT, NG, and syphilis as well as overall rates of infection (all anatomic sites/STIs combined) excluding those with a baseline prevalent infection from that calculation. Adjusted and unadjusted incidence rate ratios (IRR) and 95% confidence intervals (CIs) for STIs among those perfectly or adequately adherent as compared with those not adherent to PrEP were examined using a generalized estimating equation (GEE) under a Poisson distribution with a log link and exchangeable correlation. To further examine if the

effect of levels of PrEP adherence on incident NG and CT was modified by number of sexual partners by HIV status, we conducted stratified GEE analysis under a binomial distribution with a logit link, exchangeable correlation, and robust estimates. We did not include syphilis due to collinearity and insufficient power. The GEE model allowed for longitudinal assessment with varying lengths of follow-up within participants under the assumption of missing data completely at random. The multivariable GEE analysis was adjusted for age and any use of either poppers, methamphetamines, hallucinogen, dissociative, and/or cocaine selected a priori. All GEE analysis was conducted using in STATA 15.1, College Station, TX: StataCorp LP.

Results

From the 398 participants enrolled in the study, 381 had some prospective follow-up with a median follow-up time of 597 days (range 3–757 days). At baseline, there was one (0.25%) case of new syphilis and 31 (7.8%) prevalent syphilis infections that had previously been treated, 49 (12.3%) participants with a CT infection, and 22 (5.5%) participants with a NG infection.

Table 1 shows characteristics of the study participants stratified by incident syphilis, CT, and/or NG infection status. We found that reported number of partners living with and without HIV tended to be higher among those with incident STIs. In addition, incident CT and NG infection was associated with popper use (inhaled nitrites). The incidence rates for syphilis, CT, and NG are shown in Table 2 and are stratified by anatomic site of infection for CT and NG. Of the 394 participants, there were 63 incident NG cases and 81 incident CT cases.

Table 3 shows the incidence rates of NG, CT, and syphilis among the study participants by TFV-DP adherence levels, using the non-adherent category as the reference. We found no statistically significant associations between NG or CT infection and PrEP adherence level. Syphilis incidence was 2.16 times as high (95% CI: 0.49, 9.43) among those with perfect PrEP adherence (TFV-DP $\geq$ 1246 fmol/punch) compared to those not adherent (TFV < 719 fmol/punch); however, this association was not statistically significant.

Table 4 shows that the number of sexual partners by HIV status modified the effect of PrEP adherence on incident NG. Among MSM and transgender women who reported two or more HIV positive sexual partners, odds of NG was reduced for those with adequate or better adherence (AOR: 0.31, 95% CI: 0.14–0.68) and perfect adherence (AOR: 0.30, 95% CI: 0.12–0.78) compared with not adequate adherence. There was no observed risk of NG or CT among those reporting HIV negative or HIV status unknown (not shown in table) sexual partners regardless of the number of partners.

Discussion

In this study of PrEP adherence among 398 MSM and transgender women, we observed high rates of STIs that were comparable to other PrEP studies.[20, 21] These high rates of STIs may be related to risk behavior or could be associated with the increased STI testing and overall STI incidence increases in the United States in general. STI incidence is increasing in the United States particularly among populations affected by and at risk for HIV.[22] These increases in STI incidence began prior to the approval and widespread use of PrEP; the role that PrEP use may have in the spread of STIs is unknown. A recent modeling study suggests that PrEP uptake and routine sexual health screening may lead to reductions in CT and NG incidences.[10] We hypothesized that STI rates may be higher in those who were most PrEP adherent. However, we found that PrEP adherence was not associated with incident STI. We found that the number of sexual partners living with HIV modified the effect of PrEP adherence on incident NG; among participants with two or more HIV positive partners, adequate and perfect adherence reduced the odds of incident NG.

In a previous analysis from this study, we found that self-reported adherence to PrEP was associated with increased condomless sex and a higher likelihood of engaging in any condomless anal intercourse (CAI) and with a greater number of CAI acts.[17] However, in the present analysis, we did not find that objective PrEP adherence was significantly associated with high rates of syphilis, CT, or NG infection. One possible explanation is that although the number of condomless sexual acts may increase with greater PrEP adherence, this may not largely change the probability of STI acquisition from exposure to potentially the same sexual network. Infectious disease spread is dependent on the structure of the contact network,[23] thus networks must be taken into account when assessing STI risk. In addition, the impact of HIV prevention strategies, such as PrEP, and prevention interventions for STIs depend on the structure and characteristics of the sexual networks. HIV risk behaviors have demonstrated to be associated with structural network features such as number of sexual partners and connectivity of network members.[24-26] Future research should assess the relationship of PrEP adherence and risk compensation in the context of social and sexual networks.

Similar to our prior work, a meta-analysis by Traeger et al. (2018) described that most of the 16 included studies found evidence of increased condomless sex among MSM using PrEP.[14] Similarly, a qualitative study described shifting sexual decision making and behavioral norms about condom use in the era of PrEP.[27] Men in that qualitative study displayed extensive knowledge regarding their protection from HIV while on PrEP, thus their sexual decision making was informed by that knowledge of decreased

Table 1. Characteristics of MSM and transgender women participating in an HIV PrEP trial ($N = 398$) by incident gonorrhea, chlamydia, and syphilis infections.

	≥1 Gonorrhea Case(s) between weeks 2–48			≥1 Chlamydia Case(s) between weeks 2–48			≥1 syphilis Case(s) between weeks 2–48		
	No	Yes	*p*-value	No	Yes	*p*-value	No	Yes	*p*-value
N	321	77		289	109		361	20	
Race			0.61			0.081			0.63
White	237 (76%)	58 (75%)		210 (75%)	85 (78%)		270 (76%)	18 (90%)	
Asian	9 (3%)	3 (4%)		7 (2%)	5 (5%)		12 (3%)	0 (0%)	
Black	44 (14%)	8 (10%)		44 (16%)	8 (7%)		43 (12%)	2 (10%)	
Multiple/Other	23 (7%)	8 (10%)		20 (7%)	11 (10%)		28 (8%)	0 (0%)	
Age, median (IQR)	34 (29, 42)	30 (27, 35)	<0.001	34 (29, 42)	31 (27, 37)	0.007	33 (28, 41)	32.5 (29, 42.5)	0.89
Education			0.21			0.72			0.17
High school or less	30 (9%)	5 (6%)		25 (9%)	10 (9%)		28 (8%)	1 (5%)	
Some college	117 (36%)	32 (42%)		106 (37%)	43 (39%)		132 (37%)	11 (55%)	
Bachelor	102 (32%)	30 (39%)		101 (35%)	31 (28%)		122 (34%)	7 (35%)	
Some post-graduate	15 (5%)	4 (5%)		12 (4%)	7 (6%)		18 (5%)	1 (5%)	
Advance degree	57 (18%)	6 (8%)		45 (16%)	18 (17%)		61 (17%)	0 (0%)	
Annual income			0.39			0.50			0.55
<$24,000	66 (24%)	19 (30%)		60 (24%)	25 (28%)		75 (25%)	5 (31%)	
≥$24,000	204 (76%)	45 (70%)		185 (76%)	64 (72%)		229 (75%)	11 (69%)	
PrEP adherence at week 48			0.94			0.88			0.14
Not adequate	47 (18%)	14 (19%)		43 (19%)	18 (18%)		58 (11%)	2 (11%)	
Adequate	102 (37%)	27 (37%)		92 (39%)	37 (37%)		125 (40%)	4 (22%)	
Perfect	111 (43%)	32 (44%)		98 (42%)	45 (45%)		131 (42%)	12 (67%)	
Cocaine use[a]			0.024			0.81			0.63
No	240 (77%)	50 (65%)		210 (75%)	80 (74%)		268 (75%)	14 (70%)	
Yes	70 (23%)	27 (35%)		69 (25%)	28 (26%)		90 (25%)	6 (30%)	
Methamphetamine use[a]			0.36			0.24			0.087
No	237 (76%)	55 (71%)		215 (77%)	77 (71%)		275 (77%)	12 (60%)	
Yes	73 (24%)	22 (29%)		64 (23%)	31 (29%)		83 (23%)	8 (40%)	
Hallucinogens use[a]			0.021			0.40			1.00
No	267 (86%)	58 (75%)		237 (85%)	88 (81%)		300 (84%)	17 (85%)	
Yes	43 (14%)	19 (25%)		42 (15%)	20 (19%)		58 (16%)	3 (15%)	
Dissociative use[a]			0.075			0.29			1.00
No	257 (83%)	57 (74%)		230 (82%)	84 (78%)		289 (81%)	16 (80%)	
Yes	53 (17%)	20 (26%)		49 (18%)	24 (22%)		69 (19%)	4 (20%)	
Poppers use[a]			0.001			<0.001			0.34
No	127 (41%)	16 (21%)		121 (43%)	22 (20%)		133 (37%)	5 (25%)	
Yes	183 (59%)	61 (79%)		158 (57%)	86 (80%)		225 (63%)	15 (75%)	
Number HIV neg partners wk2-48, median (IQR)	9 (3, 17)	12 (6, 33)	<0.001	8 (3, 17)	12 (6.5, 24.5)	<0.001	9.5 (4, 19)	11 (8, 20.5)	0.24
Number HIV pos partners wk2-48, median (IQR)	2 (0, 5)	4 (1, 8)	0.013	2 (0, 5)	4 (1, 8)	0.006	2 (0, 6)	4 (2, 8.5)	0.053
Number HIV unknown partners wk2-48, median (IQR)	1 (0, 5)	3 (0, 8)	0.004	1 (0, 5)	2 (0, 7.5)	0.059	1 (0, 5)	2 (0, 7)	0.70

[a]Use at least once between weeks 2–48.

p-value are for Chi-square or Fishers exact test. Percentages are column totals. Perfect adherence is TFV≥1246 fmol/punch; adequate adherence is TFV 719–1246 fmol/punch.

vulnerability to HIV. This finding that those on PrEP may have a high level of the knowledge around the protection afforded by PrEP was supported in a longitudinal study of young MSM which found higher rates of condomless anal sex during times when participants were on PrEP compared to times when they were not on PrEP.[16] However, knowledge around the risk of bacterial STIs may be more limited.[27] Further research is needed to understand what

Table 2. Incidence rates of *Neisseria gonorrhoeae* infection (NG), *Chlamydia trachomatis* infection (CT), and syphilis among men who have sex with men and transgender women in a 48 weeks longitudinal PrEP adherence trial.

Infection type and site	Number of incident cases	Incidence rate per 100 person years (95% CI)
NG urine	7	2.2 (0.6, 3.8)
NG rectal	34	11.8 (7.9, 15.8)
NG throat	42	14.9 (10.4, 19.4)
CT urine	24	7.9 (4.7, 11.0)
CT rectal	70	27.4 (21.0, 33.8)
CT throat	5	3.4 (0.4, 6.3)
NG (all sites)	63	26.3 (19.8, 32.8)
CT (all sites)	81	36.3 (28.4, 44.2)
Syphilis	16	5.0 (2.6, 7.5)
Any STI	111	55.7 (45.3, 66.0)

Table 3. Generalized estimating equation (GEE) analysis of incidence rate ratio (IRR) of *Neisseria gonorrhoeae* infection (NG), *Chlamydia trachomatis* infection (CT), and syphilis among men who have sex with men and transgender in a 48 weeks longitudinal PrEP adherence trial by PrEP adherence level.

PrEP adherence level	IRR	95% CI	*p*	aIRR	95% CI	*p*
	Incident Gonorrhea					
Not adequate	Ref	-	-	Ref	-	-
Adequate or better	0.90	0.52–1.55	0.703	0.95	0.56–1.60	0.850
Perfect	1.01	0.56–1.82	0.979	1.11	0.63–1.97	0.720
	Incident chlamydia					
Not adequate	Ref	-	-	Ref	-	-
Adequate or better	0.93	0.58–1.49	0.763	1.02	0.62–1.68	0.935
Perfect	0.96	0.58–1.60	0.888	1.05	0.61–1.80	0.855
	Syphilis					
Not adequate	Ref	-	-	Ref	-	-
Adequate or better	1.76	0.41–7.57	0.445	1.59	0.37–6.67	0.532
Perfect	2.50	0.57–11.03	0.225	2.16	0.49–9.43	0.306
	Gonorrhea and/or chlamydia and/or syphilis					
Not adequate	Ref	-	-	Ref	-	-
Adequate or better	0.91	0.63–1.32	0.618	0.97	0.67–1.40	0.858
Perfect	0.96	0.65–1.43	0.852	1.03	0.69–1.53	0.888

Notes: Adjusted for age and any use of either poppers, cocaine, methamphetamine, dissociative, and/or hallucinogens. Incident cases are any positive rectal, throat, or urethral result after baseline. PrEP adherence not adequate is TFV<719 fmol/punch; Adequate or better adherence is TFV ≥719 fmol/punch; Perfect adherence is TFV≥1246 fmol/punch in dried blood spots GEE specification: Log link with Poisson distribution and exchangeable working correlation for multiple infections from the same individual. IRR, Incidence rate ratio; aIRR, Adjusted incidence rate ratio; CI, Confidence interval.

prevention messaging and education would impact STI incidence.

We found that STI incidence in our study was associated with popper use (inhaled nitrites). Poppers are often used among MSM to enhance sex and for the smooth muscle relaxant effects.[28] Popper use has been found to be associated with sexual behaviors including condomless sex and multiple partners that may increase HIV and STI risk.[28] In addition, we found STI incidence was associated with the reported number of partners.

The limitations of this study were that it was a demonstration project for the introduction of PrEP since this study started at a time when PrEP was not being routinely prescribed in the community. Therefore, this study sample may have self-selected as particularly high risk and thus chose to be early PrEP adopters—this could have influenced the behavioral risk for HIV and STIs in the study and may mean that the study population is not generalizable to the general population of people at risk for HIV. In addition, trial participation may have impacted health and sexual behaviors among participants. There was also reduced screening for STIs mid-study due to the high cost of regular screening at all three anatomic sites. Thus, it is not possible to distinguish between a single incident infection or multiple repeated infections between tests. Another limitation was the study only enrolled English or Spanish speakers.

Table 4. Generalized estimating equation (GEE) analysis of PrEP adherence on incident gonorrhea and chlamydia by number and HIV status of sexual partners.

		Incident Gonorrhea			Incident Chlamydia		
Sexual partner # and HIV status	PrEP adherence	AOR	95% CI	*p*	AOR	95% CI	*p*
≥2 HIV positive partners	Not adequate	-	-	-	-	-	-
	Adequate or better	**0.31**	0.14–0.68	0.004	0.70	0.29–1.70	0.431
	Perfect	**0.30**	0.12–0.78	0.014	0.88	0.35–2.24	0.788
≤1 HIV positive partner	Not adequate	-	-	-	-	-	-
	Adequate or better	1.36	0.62–2.94	0.438	1.01	0.51–2.01	0.977
	Perfect	1.64	0.71–3.79	0.250	0.91	0.42–1.95	0.802
≥2 HIV negative partners	Not adequate	-	-	-	-	-	-
	Adequate or better	0.64	0.30–1.37	0.251	0.92	0.44–1.93	0.829
	Perfect	0.77	0.34–1.73	0.526	0.98	0.45–2.13	0.951
≤1 HIV negative partner	Not adequate	-	-	-	-	-	-
	Adequate or better	1.41	0.59–3.37	0.434	0.96	0.44–2.09	0.916
	Perfect	1.66	0.57–4.84	0.357	0.86	0.35–2.10	0.739

Notes: Adjusted for age and any use of either poppers, cocaine, methamphetamine, dissociative and/or hallucinogens. Incident cases are any positive rectal, throat, or urethral result after baseline. PrEP adherence not adequate is TFV<719 fmol/punch; Adequate or better adherence is TFV ≥719 fmol/punch; Perfect adherence is TFV≥1246 fmol/punch in dried blood spots. GEE specification: Logit link with binomial distribution and exchangeable working correlation for multiple infections from the same individual. AOR, Adjusted odds ratio; CI, Confidence interval.

We used a cross-sectional measure of PrEP adherence. While this was a biological measure and therefore not subject to reporting biases, it may not reflect adherence over time.

In conclusion, MSM and transgender women who initiated PrEP soon after the approval of TDF/FTC for HIV prevention had high rates of STIs. We found that those adherent and non-adherent to PrEP remained at risk for STIs, and PrEP adherence was not associated with STI incidence. Further research is needed to assess how the impact of PrEP use may impact STIs over time and how public health efforts may integrate STI prevention with HIV PrEP programs.

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