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Trajectories of Adherence to Oral Pre-exposure Prophylaxis and Risks of HIV and Sexually Transmitted Infections

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Background. Pre-exposure prophylaxis (PrEP) effectiveness is highly dependent on medication adherence, which is associated with differential HIV risks and possibly sexually transmitted infection (STI).

Methods. This retrospective cohort study of PrEP users (01/01/2012–12/31/2021) used the MarketScan database of commercially insured enrollees to examine PrEP adherence trajectory groups' associations with HIV and STI acquisition risks. Distinct PrEP adherence trajectories were identified by group-based trajectory modeling among individuals who used oral PrEP. The primary outcome was HIV acquisition incidence, and secondary was STI rate, compared among trajectory groups. Inverse probability treatment weighting time-varying Cox proportional hazards models assessed HIV acquisition, and Poisson regression models assessed STI.

Results. Among 23 258 oral PrEP users, 4 distinct PrEP adherence patterns were identified: minimal use (10.5% of the cohort), rapidly declining (25.4%), gradually declining (24.3%), and consistently high (39.8%). Compared with the minimal use group, the gradually declining (adjusted hazard ratio [AHR], 0.53; 95% CI, 0.31–0.90) and consistently high (AHR, 0.50; 95% CI, 0.30–0.84) PrEP adherence groups showed decreased HIV incidence risks. Compared with the minimal use group, the rapidly declining (adjusted incidence rate ratio [AIRR], 1.35; 95% CI, 1.07–1.72), gradually declining (AIRR, 1.73; 95% CI, 1.38–2.18), and consistently high (AIRR, 2.06; 95% CI, 1.64–2.58) groups were associated with increased STI risk.

Conclusions. These findings underscore the benefits of continuing and remaining adherent to PrEP and may also inform public health strategies, clinical guidelines, and interventions aimed at maximizing the effectiveness of PrEP in reducing new HIV infections while developing targeted strategies to prevent STIs with PrEP use.

Keywords. group-based trajectory models (GBTMs); HIV; MarketScan; pre-exposure prophylaxis (PrEP); sexually transmitted infections (STIs).

The US HIV epidemic continues to pose a considerable public health concern despite substantial advancements in prevention and treatment. The Centers for Disease Control and Prevention (CDC) estimates that ~1.2 million people in the United States have HIV, including 13% who are unaware of their infection status [1]. In 2021, 32 100 new HIV cases were reported, mostly among individuals assigned male at birth (81%), individuals aged 13–34 years (58%), and individuals geographically located in the southern United States (52%) [1].

Several randomized clinical trials (RCTs) [2–4] have demonstrated the efficacy of oral emtricitabine-tenofovir disoproxil fumarate (FTC-TDF) and emtricitabine-tenofovir alafenamide (FTC-TAF) in preventing HIV acquisition. The Pre-exposure Prophylaxis (PrEP) Initiative (iPrEx) [2] and DISCOVER [3] trials reported substantial HIV risk reduction with good adherence in men who have sex with men (MSM). These trials demonstrated that adherence was crucial for PrEP efficacy, with high adherence leading to greater protection. A pharmacokinetic analysis of iPrEX revealed 99% HIV risk reduction with daily PrEP use [5]. Conversely, the Vaginal and Oral Interventions to Control the Epidemic (VOICE) trial showed no difference in HIV incidence between PrEP and placebo among women, as only 29% of the FTC-TDF group had detectable tenofovir levels, highlighting

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the importance of adherence [6]. Several studies have used single measures, such as the proportion of days covered (PDC), to assess PrEP adherence, often applying arbitrary thresholds (eg, PDC ≥80%) [7, 8]. However, single measures may misinterpret diverse and evolving patterns of nonadherence that may provide insights for interventions. Some studies have sought to understand PrEP use patterns through group-based trajectory models (GBTMs) that identify distinct patient subgroups with similar medication use patterns and provide a trajectory of average medication adherence for each subgroup over time [9–11]. However, those studies did not evaluate HIV and STI outcomes associated with different PrEP use trajectories among commercially insured US PrEP users.

PrEP effectively reduces HIV transmission when used consistently, but concerns arise about potential increased STI risk due to behavior changes, known as PrEP-related risk compensation. With PrEP use, risk compensation may lead to increased condomless sex or number of sexual partners, resulting in STI acquisition [11], thereby diminishing the benefits of HIV prevention. Similar to many studies [12, 13], the PROUD (pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection) study [14], an open-label trial of MSM randomly assigned to receive PrEP immediately or after 1 year, reported no significant difference in STI rates between groups, suggesting an absence of risk compensation. PROUD study findings were inconsistent with data from the Pre-exposure Prophylaxis Expanded (PrEPX) trial, an open-label study reporting increased STI incidence during a 1.1-year follow-up [15]. On the other hand, evidence of risk compensation has been observed in other studies outside of clinical trials reporting increases in anal condomless sex partners, rectal chlamydia, and urethral gonorrhea after PrEP initiation [7, 16].

Building on our prior research that identified trajectories of PrEP adherence and patient characteristics associated with the least and most PrEP adherence trajectories [11], this investigation fills knowledge gaps in clinical practice outcomes of PrEP use. We used GBTM to identify unique trajectories of oral PrEP adherence and then examined associations between the trajectories and risks of HIV and STI diagnoses. Additionally, we compared rates of STI diagnosis before and after PrEP use within each trajectory group.

METHODS

Study Design and Data Sources

This retrospective cohort study of new PrEP users used the MarketScan Commercial Insurance Research Database from January 1, 2012, to December 31, 2021. This nationwide administrative claims database captures patient-level pharmacy and medical claims for health care services received by >273 million employees and their dependents covered by employer-sponsored insurance, with a greater representation in the South. This study was approved by the University of Florida Institutional Review Board, which waived the requirement for obtaining informed patient consent because the data were deidentified. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

Study Population

Using a previously developed algorithm [17], we identified individuals aged 12 to 64 years in the MarketScan database who were prescribed at least 30 days of oral FTC-TDF or FTC-TAF for PrEP (Supplementary Figures 1 and 2). We required individuals to have continuous enrollment in commercial health insurance for the 12 months preceding initiation of PrEP and 30 days following initiation. We excluded individuals with diagnosis codes (using *International Classification of Diseases*, Ninth [ICD-9] and Tenth [ICD-10] Revisions) or prescriptions for HIV, hepatitis B virus, or HIV postexposure prophylaxis (PEP) within the year before PrEP initiation and 30 days after initiation. At least 30 days of PrEP use was required to distinguish from PEP use, which entails TDF/FTC or TAF/FTC in conjunction with raltegravir or dolutegravir for 28 days [18]. The index date was defined as day 31 following the start of PrEP (ie, day 1). This approach is consistent with literature using a previously developed algorithm [17]. The baseline period was 1 year before PrEP initiation. To ensure a sufficient PrEP adherence trajectory evaluation period, individuals were further required to be HIV negative and continuously enrolled in commercial health insurance for 180 days from the index date to be added to the PrEP cohort.

Medication Adherence

Based on dispensing date and days' supply, we calculated an interval-based (15 days) PDC, derived by dividing the total number of days covered with PrEP by 15 days in a 2-year period starting from the index date (GBTM assessment period). We calculated PDC until the earliest occurrence of disenrollment from the health insurance plan, HIV incidence, end of the GBTM assessment period (ie, 2 years), or end of the study (December 31, 2021).

Outcomes

The primary outcome was time to first HIV diagnosis, defined using 1 inpatient or 2 outpatient claims with ICD-9 or ICD-10-CM codes (Supplementary Table 1) [19]. PrEP users were followed up from the index date plus 180 days (HIV outcome measurement period) until HIV outcome, end of continuous enrollment, end of follow-up (720 days from index date), or end of study (December 31, 2021), whichever occurred first (Supplementary Figure 1). HIV outcome analysis follow-up started on the index date plus 180 days because we required participants to be HIV negative in the first 180 days after the index date.

In a sensitivity analysis, the HIV outcome was accessed beyond the GBTM measurement period. Hence, individuals were censored at HIV outcome, loss of insurance enrollment, or end of study, whichever occurred first.

The secondary outcome was STI occurrence rate, defined using a composite outpatient diagnosis of gonorrhea, chlamydia, or syphilis (Supplementary Table 1). We calculated the cumulative number of STI episodes per 90 days (count outcome). Because an STI diagnosis can occur multiple times during follow-up, STI claims within 30 days after a prior STI diagnosis claim were considered the same STI episode [15]. PrEP users were followed up from the index date (STI outcome measurement period) until HIV outcome, end of continuous enrollment, end of follow-up (720 days from index date), or end of study, whichever occurred first (Supplementary Figure 1). We further conducted a pre–post analysis, comparing the crude incidence of STI between each individual trajectory group before PrEP initiation (baseline) with itself after the index date. Like the STI outcome, STI history only considered gonorrhea, chlamydia, and syphilis.

Potential Confounders

Based on prior studies evaluating risk factors for HIV occurrence [20], we included a priori a defined set of covariates (identified by ICD-9 and ICD-10 diagnoses codes, as applicable) measured during the baseline period, including demographic characteristics, geographic region, insurance type, history of STI, substance use disorders, alcohol use disorder, PrEP initiation year, and severe mental illness (ie, major depression, schizophrenia, bipolar disorder, panic disorder, obsessive-compulsive disorder, post-traumatic stress, and borderline personality disorder) [20]. Race and ethnicity were not captured by the database, and thus were not included.

Statistical Analysis

We used GBTM to identify changing patterns of PrEP adherence over time. We used a flexible polynomial function of time (up to the fifth polynomial order) and a censored normal probability distribution to determine the number of PrEP adherence trajectory groups [21]. We used a dropout function in the GBTM to accommodate missing PDC. We selected the final model using a combination of the following: Bayesian information criterion to compare different numbers of trajectory models, trajectory subgroup proportions of at least 10% to aid clinical interpretation and application, and Nagin criteria to evaluate the final model's adequacy [21].

After identifying the final trajectory groups, we used the inverse probability of treatment weighting (IPTW) method to balance the differences in baseline patient characteristics and disease risk factors among trajectory groups. The predicted probability of an individual being assigned to a specific trajectory group (ie, propensity score) was estimated using multivariable logistic regression with the aforementioned baseline covariates. Balance between groups before and after IPTW was assessed using standardized mean differences (SMDs), with values >0.10 considered statistically significant differences. Among adherence trajectory groups, we calculated crude incidence rates for HIV. We used IPTW-weighted Cox proportional hazards regression models to compare risk of HIV outcome across PrEP adherence trajectories. HIV testing measured every 90 days (in alignment with PrEP guidelines) [22] was used as a time-varying covariate to mitigate detection bias.

For the STI outcome, we calculated each trajectory group's crude STI incidence rate. We used IPTW-weighted Poisson regression models (for count data) to compare STI diagnosis rates between PrEP adherence trajectory groups. We reported incidence rate ratios (IRRs) adjusted for STI testing as a time-varying covariate. STI testing was measured every 90 days from the index date (consistent with PrEP use guidelines of every 3–6 months) [22] to mitigate detection bias. For the pre–post analysis, we calculated each trajectory group's crude STI incidence rate in the baseline period, then used Poisson regression models to compare with rates during follow-up.

We used R Statistical Computing software, version 4.1.2, for data visualizations and performing IPTW calculations using the xgboost package and SAS, version 9.4 (SAS Institute Inc, NC), for other data analyses. A 2-sided $P < .05$ or 95% CI excluding 1 was considered statistically significant.

RESULTS

Among 23 258 new oral PrEP users identified, 22 233 (95.6%) were male (assigned at birth), 32.8% were 25 to 34 years of age, 39.6% resided in the US Southern region, 3509 (15.1%) had a severe mental illness, and 1361 (5.9%) received an STI diagnosis during the 1-year baseline period (Table 1). After assessing adherence trajectories with 2 to 5 groups, the final GBTM model included 4 groups (Supplementary Tables 2 and 3, Supplementary Figure 3). The 4 trajectory groups were PrEP minimal use (10.5%), rapidly declining (25.4%), gradually declining (24.3%), and consistently high (39.8%) adherence groups (Figure 1). Characteristics of PrEP users by adherence group were comparable after IPTW (all maximum SMD <0.10) (Table 1).

HIV Incidence

We identified 172 HIV infections during a mean (SD) follow-up of 386 (185) days. Crude incidence values per 10 000 person-years were 71.41 in the consistently high, 59.90 in the gradually declining, 70.93 in the rapidly declining, and 87.88 in the minimal use adherence groups (Table 2). In weighted IPTW Cox regression models, compared with the PrEP minimal use group, the gradually declining (adjusted hazard ratio [AHR], 0.53; 95% CI, 0.31–0.90) and consistently high (AHR, 0.50;

Table 1. Baseline Demographic and Clinical Characteristics of 23 258 PrEP Users by Trajectory Group Based on PrEP Adherence

			PrEP Adherence Trajectory Group								
	Total (n = 23 258)		Consistently High (n = 9246)		Gradually Declining (n = 5658)		Rapidly Declining (n = 5918)		Minimal Use (n = 2436)		
Characteristic	No.	%	No.	%	No.	%	No.	%	No.	%	Max SMD[a] After IPTW
Sex[b]											
Female	1025	4.4	133	1.44	129	2.3	302	5.1	461	18.9	0.06
Male	22 233	95.6	9113	98.6	5529	97.7	5616	94.9	1975	81.1	0.06
Age group											
12–24 y	4701	20.2	866	9.4	1239	21.9	1762	29.8	834	34.2	0.05
25–34 y	7617	32.8	2869	31.0	2042	36.1	2007	33.9	699	28.7	0.04
35–44 y	5140	22.1	2443	26.4	1200	21.2	1072	18.1	425	17.4	0.06
≥45 y	5800	24.9	3068	33.2	1177	20.8	1077	18.2	478	19.6	0.04
US geographic region											
Northeast	4977	21.4	1957	21.2	1187	21.0	1272	21.5	561	23.0	0.05
North Central	3853	16.6	1495	16.2	931	16.5	1012	17.1	415	17.0	0.02
South	9213	39.6	3668	39.7	2236	39.5	2379	40.2	930	38.2	0.06
West	5177	22.3	2112	22.8	1300	23.0	1245	21.0	520	21.3	0.04
Insurance plan											
PPO	11 678	50.2	4738	51.2	2799	49.5	2925	49.4	1216	49.9	0.03
HMO	3303	14.2	1329	14.4	789	13.9	851	14.4	334	13.7	0.01
CDHP	2861	12.3	1109	12.0	750	13.3	731	12.4	271	11.1	0.02
HDHP	2411	10.4	899	9.7	615	10.9	645	10.9	252	10.3	0.03
POS	1887	8.1	728	7.9	441	7.8	488	8.3	230	9.4	0.03
SUD	1253	5.4	361	3.9	318	5.6	388	6.6	186	7.6	0.06
STI history	1361	5.9	549	5.9	372	6.6	338	5.7	102	4.2	0.04
STI test history	15 416	66.3	6375	68.9	3781	66.8	3896	65.8	1364	56.0	0.03
SMI	3509	15.1	1169	12.6	863	15.3	1045	17.7	432	17.7	0.04
AUD	509	2.2	161	1.7	128	2.3	159	2.7	61	2.5	0.03
Others	656	2.8	257	2.8	156	2.8	155	2.6	88	3.6	0.04
Missing	462	2.0	186	2.01	108	1.9	123	2.1	45	1.9	0.03

Abbreviations: AUD, alcohol use disorder; CDHP, consumer-directed health plan; HDHP, high-deductible health plan; HMO, health maintenance organization; max, maximum; POS, point of service; PPO, preferred provider organization; PrEP, pre-exposure prophylaxis; SMD, standardized mean difference; SMI, severe mental illness; SUD, substance use disorder; STI, sexually transmitted infection.

[a]SMD >0.10 was considered a non-negligible difference.

[b]Sex assigned at birth.

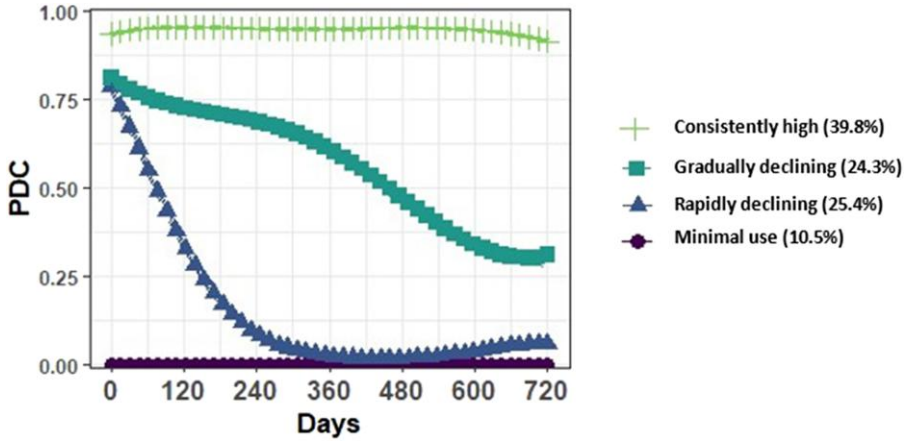

Figure 1. Adherence trajectories of PrEP use across 2 years from the index date. There was a total of 23 258 PrEP users. The minimal use group was the reference. Abbreviations: PDC, proportion of days covered; PrEP, pre-exposure prophylaxis.

Table 2. Incidence of HIV Among PrEP Adherence Trajectory Groups

	PrEP Adherence Trajectory Group			
Variable	Consistently High (n = 9246)	Gradually Declining (n = 5658)	Rapidly Declining (n = 5918)	Minimal Use (n = 2436)
No. of events	71	38	42	21
Follow-up duration, mean (SD), d[a]	392.51 (189.55)	409.27 (173.89)	365.23 (183.42)	358.04 (189.33)
Crude incidence, per 10 000 person-years	71.41	59.90	70.93	87.88
Unadjusted HR (95% CI)	0.65 (0.40–1.05)	0.63 (0.37–1.05)	0.72 (0.43–1.20)	Reference
Adjusted HR (95% CI)[b]	0.50 (0.30–0.84)	0.53 (0.31–0.90)	0.71 (0.43–1.18)	Reference
	0.70 (0.46–1.08)	0.75 (0.48–1.17)	Reference	…
	0.94 (0.62–1.42)	Reference	…	…

Abbreviations: HR, hazard ratio; PrEP, pre-exposure prophylaxis.

[a]Follow-up from index date plus 180 days.

[b]HIV testing was controlled as a time-varying covariate (adjusted HR, 1.22; 95% CI, 1.07–1.40).

95% CI, 0.30–0.84) adherence groups were associated with lower risk of HIV. HIV risk between the minimal use and rapidly declining adherence groups was not statistically significantly different (AHR, 0.71; 95% CI, 0.43–1.18).

In the sensitivity analysis that assessed HIV outcome beyond the 2-year GBTM measurement period, compared with the PrEP minimal use group, only the consistently high adherence group was associated with lower risk of HIV (AHR, 0.57; 95% CI, 0.37–0.89) (Supplementary Table 4).

STI Rate

For the secondary outcome, 4540 STIs were identified, with a mean (SD) follow-up of 566 (185) days. The consistently high and gradually declining groups had the highest crude incidence rates of STI (Table 3). In weighted IPTW Poisson regression models, compared with the PrEP minimal use group, the consistently high (adjusted incidence rate ratio [aIRR], 2.06; 95% CI, 1.64–2.58), gradually declining (aIRR, 1.73; 95% CI, 1.38–2.18), and rapidly declining (aIRR, 1.35; 95% CI, 1.07–1.72) adherence groups were associated with higher risk of STI (Table 3).

In pre–post analyses, the crude incidence of STI diagnosis was 72.1 per 1000 person-years during the baseline period and 125.87 per 1000 person-years during follow-up. Within the adherence trajectory groups, there was a statistically significant increase in STI crude incidence rates from baseline to after the index date for the gradually declining and consistently high PrEP adherence groups (Table 4).

DISCUSSION

This retrospective cohort study of a nationally representative sample of the general US population with oral PrEP use identified adherence trajectories based on longitudinal PrEP adherence patterns and assessed their associated risk of HIV and STI. We identified 4 PrEP adherence trajectories during 2 years of PrEP use. Distinct PrEP adherence trajectory groups were

Table 3. Incidence Rate of Sexually Transmitted Infection Among PrEP Adherence Trajectory Groups (Secondary Outcome)

Variable	PrEP Adherence Trajectory Group			
	Consistently High (n = 9246)	Gradually Declining (n = 5658)	Rapidly Declining (n = 5918)	Minimal Use (n = 2436)
No. of events	2467	1178	714	181
Follow-up duration, mean (SD), d[a]	572.51 (189.55)	589.27 (173.89)	545.23 (183.42)	538.04 (189.33)
Crude incidence per 1000 person-years	170.09 (68.26–177.03)	128.85 (121.91–136.51)	80.67 (75.19–86.87)	50.37 (43.43–58.40)
Unadjusted IRR (95% CI)	3.07 (2.45–3.84)	2.28 (1.81–2.88)	1.46 (1.14–1.86)	Reference
Adjusted IRR (95% CI)[b]	2.06 (1.64–2.58)	1.73 (1.38–2.18)	1.35 (1.07–1.72)	Reference
	1.52 (1.33–1.74)	1.28 (1.12–1.47)	Reference	…
	1.19 (1.07–1.31)	Reference	…	…

Abbreviations: IRR, incidence rate ratio; PrEP, pre-exposure prophylaxis.

[a]Follow-up from index date.

[b]STI testing was controlled as a time-varying covariate (adjusted incident rate ratio, 1.26; 95% CI, 1.24–1.28).

Table 4. Sexually Transmitted Infection Rates Before and After PrEP Initiation by Adherence Trajectory Group

Group	Before PrEP Initiation			After PrEP Index Date			*P* Value
	No. of Events	Follow-up Duration, Mean, d	Crude Incidence per 1000 Person-Years	No. of Events	Mean LOF, d	Crude Incidence per 1000 Person-Years	
Consistently high	681	365	73.65 (68.26–79.57)	2467	572.51	170.09 (68.26–177.03)	<.001
Gradually declining	460	365	81.30 (74.10–89.06)	1178	589.27	128.85 (121.91–136.51)	<.001
Rapidly declining	427	365	72.15 (65.70–79.21)	714	545.23	80.67 (75.19–86.87)	.07
Minimal use	123	365	50.49 (43.34–60.23)	181	538.04	50.37 (43.43–58.40)	.99

Abbreviations: LOF, length of follow-up; PrEP, pre-exposure prophylaxis.

associated with different clinical outcome risks. Compared with the minimal PrEP use group, consistently high PrEP adherence and gradually declining PrEP adherence were associated with significantly decreased risk of HIV acquisition. Those groups also had higher rates of STI.

Overall, our findings were consistent with those from previous studies, including iPrEX and Partners PrEP, which showed low HIV risk among patients with high adherence to PrEP [2, 4, 14]. A meta-analysis of RCTs also showed a strong association between PrEP adherence and PrEP efficacy, reporting 86% HIV risk reduction with at least 80% PrEP adherence, but only 45% HIV risk reduction with lower than 80% PrEP adherence [23]. Our results corroborate those of a prospective open-label GBTM study of PrEP users conducted in Australia that similarly identified 4 adherence trajectory groups and reported increasing HIV risk reduction with each higher PrEP adherence group than the least adherent group [9]. Similar to that study, we observed substantial nonadherence or a decrease in adherence over time, in line with previous concerns about high rates of PrEP discontinuation within 2 years of PrEP initiation [24, 25]. Individuals in this group face an elevated risk of contracting HIV. An observational study involving MSM with a 92% adherence rate to PrEP revealed no HIV seroconversions while using PrEP [7]. However, 2 participants in that study contracted HIV a few months after discontinuing PrEP. While the CDC recommends a daily PrEP regimen, we also found lower HIV risk in the trajectory group with gradually declining adherence, which can be explained by some protective effects of imperfect PrEP adherence, albeit not as much protection as a daily regimen [5, 26]. However, in our sensitivity analysis that followed up on patients for longer, there was a trend toward lower risk of HIV for the gradually declining PrEP adherence group, although it was not statistically significant. Our results thus support the importance of maintaining high adherence to PrEP through a daily PrEP regimen to ensure continuous protection from HIV.

By contrast, we found that groups with higher PrEP adherence were associated with increased risk of STI compared with the minimal use group. Additionally, our pre–post analysis showed that the more adherent PrEP groups had a statistically significant increase in incidence rates of STI after PrEP initiation. Our results contrast with those of some studies, including the PROUD trial, which found no evidence of risk compensation through increased STI acquisition and inconsistent reports on changes in condom use [12, 14, 27, 28]. One argument against risk compensation associates the influence of sexual networks with infectious disease dynamics [27, 29],

with variables such as concurrency and network size being recognized as significant HIV and STI risk factors [30, 31]. Thus, increasing condomless sexual acts with PrEP use may not significantly change the likelihood of acquiring STIs within the same sexual network [27]. While this argument is plausible, it is worth considering the possibility of shifting sexual norms, as a meta-analysis highlighted that more recent studies reported greater increases in STI diagnoses than older studies [32]. Our results align with those studies, including the PrEPX trial and 2 meta-analyses that reported increased STI rates with PrEP initiation [15, 32, 33]. A meta-analysis also reported evidence of increased condomless sex among MSM who use PrEP [32]. Higher STI rates and behavioral change have been postulated to be associated with a perception of reduced risk for HIV, leading to a higher willingness to engage in riskier sexual behavior [34, 35]. It may also plausibly be attributed to prioritization of risk communication on HIV over other STIs and condom use during counseling for PrEP use [36, 37]. Similar to the meta-analyses referenced above, our results corroborate the association of STI incidence with distinct patterns of PrEP adherence. Additional investigations are needed to comprehensively evaluate correlations between provider communication, risk compensation behavior, condom use, and PrEP adherence.

Our findings using GBTM support the importance of PrEP adherence for prevention of HIV, as groups with the highest adherence had the lowest HIV acquisition rates. However, they also suggest that users with consistently high PrEP adherence may have sexual behavior that increases the risk for STI acquisition compared with the PrEP minimal use group in clinical practice. The increase in STI rate appeared to be most substantial in the group with consistently high PrEP adherence, suggesting that this group was more likely to engage in sexual risk-taking behaviors and was most in need of PrEP to prevent HIV acquisition. While these individuals may be protected from HIV, the high incidence of STI presents a public health concern as the United States faces escalating rates of STI [38, 39]. Hence, a renewed focus on PrEP adherence, including the use of tools such as DoxyPEP [40] for preventing bacterial STIs, along with comprehensive STI counseling, is essential for this population. Our study highlights the importance of PrEP adherence and the need for frequent and consistent HIV and STI testing given previously published studies that reported suboptimal testing in this population [41, 42]. The use of PrEP is essential in the fight against the HIV epidemic, and efforts to further expand PrEP use among the individuals most at risk are necessary.

Limitations

This study has several limitations. First, our study relied on administrative data that lacked information on reasons for treatment discontinuation and on sexual and other social behaviors. To address the lack of behavior information, we controlled HIV and STI testing as time-varying covariates. Second, we used PDC based on pharmacy claims as a proxy measure of medication adherence, but we could not determine whether beneficiaries took the medications daily or on-demand (eg, 2-1-1 PrEP). Hence, we cannot infer a causal relationship between nondaily PrEP and outcomes, only an association. It is noteworthy that the Ipergay trial reported a relative risk reduction of 86% with on-demand PrEP use compared with placebo [26]. On the other hand, daily PrEP use has been associated with a 99%–100% HIV risk reduction with high adherence [5, 7]. Third, despite incorporating numerous covariates, we cannot exclude the possibility of unmeasured confounding related to race and ethnicity, which were not captured in our data. This is significant due to the observed racial disparities in PrEP use [43] and HIV incidence [1]. Fourth, although we used codes previously validated for such purposes, incomplete, missing, or miscoded claims may have affected our findings; however, coding errors are likely to be similarly distributed among the adherence trajectory groups. Fifth, our models did not incorporate the use of DoxyPEP, whose guidelines for use as an STI prevention strategy were released by the CDC after the study period (October 2023) [44]. Future studies assessing the relationship between PrEP adherence and STI occurrences should incorporate DoxyPEP as it is likely to impact outcomes. Finally, this study evaluated PrEP use only in individuals who were commercially insured, and thus our findings may not be applicable to other populations, such as uninsured individuals or those with public health insurance like Medicare or Medicaid.

CONCLUSIONS

This population-based retrospective cohort study provides evidence for the association of PrEP adherence with clinical outcomes among commercially insured PrEP users. Our findings indicated that groups with consistently high or gradually declining medication adherence trajectories were associated with lower risk of HIV compared with the PrEP minimal use group. However, groups with consistently high or gradually declining PrEP adherence were also associated with increased risk of STI. These findings may inform public health strategies, clinical guidelines, and interventions aimed at maximizing the effectiveness of PrEP use for reducing new HIV infections while developing targeted strategies to prevent STIs with PrEP use.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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