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BRIEF REPORT

Provider Adherence to Pre-exposure Prophylaxis Monitoring Guidelines in a Large Primary Care Network

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Insufficient pre-exposure prophylaxis (PrEP) laboratory monitoring could increase HIV resistance and sexually transmitted infections. We examined test-ordering in a primary care network. Providers did not order HIV testing before almost one-quarter of PrEP initiations; panel management was associated with higher testing. Effective monitoring is needed to maximize PrEP's preventive impact.

Keywords. behavioral disinhibition; HIV; pre-exposure prophylaxis; renal insufficiency; sexually transmitted infections.

Pre-exposure prophylaxis (PrEP) is effective to prevent HIV infection, but its impact on HIV drug resistance, sexually transmitted infections (STIs), and renal toxicity is debated [1–4]. HIV drug resistance was found in <0.5% of participants on PrEP who HIV-seroconverted in studies, developing primarily during unrecognized acute HIV [3, 5]. HIV testing before initiating PrEP is therefore critical to avoid resistance, as well as to prevent forward HIV transmission with a potentially resistant, unrecognized virus. Furthermore, if PrEP adherence is poor and breakthrough HIV infection occurs, PrEP continuation without monitoring could also lead to resistance. Some have expressed concern that PrEP use may lead to increased risk behavior, that is, risk compensation, which in turn could lead to increased STIs [6]. Jenness et al. modeled a scenario among men who have sex with men (MSM) on PrEP in the United States in which STI incidence could decrease even with risk compensation as long as regular STI screening occurred [7]. Although PrEP-related renal toxicity is rare, and usually reversible, early identification is important [8]. For PrEP to be implemented effectively, PrEP providers will need to perform laboratory monitoring [9–11].

The only prior analysis of PrEP laboratory testing in a clinical setting occurred within an integrated health system's specialized PrEP clinic in a population that was 99% MSM and 70% white [10, 12]. Little is known about implementation of monitoring in primary care settings and diverse patient populations.

We examined factors associated with adherence to recommended monitoring in a network of 15 safety net, primary care clinics in the San Francisco Health Network. These 15 San Francisco Public Health Primary Care Clinics (SFPCCs) serve a diverse, predominantly publically insured or uninsured population of San Francisco residents.

METHODS

We analyzed data for all patients receiving PrEP prescriptions in the SFPCC from January 1, 2013, until July 31, 2017. We extracted demographic, laboratory, and prescription data, including test-ordering and completion dates. Outcomes included test-ordering and completion for HIV, gonorrhea, chlamydia, syphilis, and creatinine, as well as positive HIV/STI results.

We examined ordering and completion of HIV testing in the 30 days before an initial PrEP prescription, a generous window given Centers for Disease Control and Prevention (CDC) recommendations for HIV testing within 1 week before initiating PrEP. For STIs (any gonorrhea, chlamydia, or syphilis testing) and creatinine, we loosened the definition of completion of baseline testing by using the interval from 90 days before to seven days after the first prescription.

We assessed follow-up monitoring during periods covered by a PrEP prescription plus refills, defined as no more than 90 days without an active prescription. Given CDC recommendations for quarterly HIV testing, we assessed testing for HIV within complete 4-month active follow-up intervals to allow for scheduling delays. For STIs and creatinine, we examined testing within complete 6-month active follow-up intervals based on CDC guidelines, although local recommendations are for STI testing quarterly.

We used logistic regression to assess associations of HIV/STI test-ordering with factors including age, gender, race/ethnicity, PrEP indication, provider panel size, prescription duration, year, and receipt of a panel management program [9, 10, 12, 13]. Panel management is a population-based care approach that proactively focuses on the health of an entire population of patients assigned to a clinic, rather than only during care visits. Panel management used at 2 clinics for part of the study period

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included an active PrEP patient registry, follow-up reminders, and availability of pharmacists for follow-up visits. Primary PrEP indication as documented by the medical provider was classified as MSM, sero-different relationship, transgender women who have sex with men (TGWSM), high-risk heterosexual sex, and people who inject drugs (PWID). In assessing follow-up testing, robust standard errors were used to account for within-participant correlation of responses over multiple active intervals.

Finally, we assessed HIV/STI incidence during follow-up using person-time methods, with Poisson confidence intervals, and contrasted incidence in periods of active and inactive PrEP prescriptions using Poisson models.

RESULTS

During the study period, 405 patients received PrEP; the median PrEP prescription duration was 11.3 months. Most (85%) were male sex at birth, with a median age of 34 years. The cohort was racially/ethnically diverse, with 13% African American, 8% Asian, 26% Latino, 17% other, and 36% white. Approximately two-thirds had a PrEP indication as MSM, 13% TGWSM, 15% sero-different relationship, 5% high-risk heterosexual sex, and 1% PWID.

Provider Test-Ordering and Patient Completion

Provider adherence to ordering recommended testing was suboptimal: providers ordered initial HIV testing only 77% of the time, and gonorrhea, chlamydia, or syphilis STI testing 81% of the time. Extending the initial HIV testing window to 1 week after the initial prescription only increased HIV testing to 79%. Patient completion of tests was only marginally lower: 74% and 79%, respectively. Providers ordered initial creatinine testing in 85% of patients (84% patient completion). For follow-up testing, providers ordered HIV testing in 68% of 4-month intervals and STI testing in 67% of 6-month intervals (63% and 64% completion, respectively). When excluding the 66 individuals who were PWID or in sero-different relationships, for whom perceived STI risk may be lower, providers ordered STI testing in 83% of PrEP starts and 72% of follow-up intervals. In MSM, providers ordered extragenital screening (pharyngeal or rectal) 70% of the time a urine test was ordered (Supplementary Table 1).

Factors Associated With Provider Test-Ordering

In adjusted analysis, we found that providers were less likely to order initial testing for older patients. Panel management was associated with higher odds of ordering initial STI but not HIV testing. Initial STI testing was higher in later years ($P < .001$ for trend), with a trend toward higher HIV testing in later years ($P = .06$).

Patterns were somewhat different for follow-up testing. Specifically, we found that providers were less likely to order HIV testing for older patients, male patients, when prescriptions were written for >90-day duration, and in later intervals. Providers caring for ≥2 PrEP patients and those at clinics with panel management were more likely to order follow-up HIV testing. Predictors of ordering timely follow-up STI testing differed from HIV testing: although providers were less likely to order testing in older patients, they were less likely to order testing in those in sero-different relationships, and for African Americans vs White patients. STI follow-up testing was higher in later years ($P = .03$ for trend) (Table 1).

Breakthrough HIV Infections and STI Incidence

After starting PrEP, 19% of patients were diagnosed with an STI. While maintaining an active PrEP prescription, gonorrhea incidence was 10.9 per 100 person-years, 12.0 for chlamydia, 2.4 for syphilis, 23.9 for any STI, and 0.3 for HIV (2 individuals: 1 after self-discontinuing, 1 using PrEP intermittently). Genotypes of these 2 individuals were both wild-type. STI incidence per 100 person-years was higher during PrEP use than during PrEP gaps of ≥90 days (23.9 vs 10.4, $P < .001$) (Supplementary Table 1).

DISCUSSION

In a diverse sample of 405 PrEP patients, we observed suboptimal lab monitoring and STI testing by providers. In particular, providers did not order HIV testing before almost one-fourth of PrEP initiations and one-third of follow-up intervals, which could increase risk of HIV drug resistance and forward HIV transmission after unrecognized HIV infection. Our findings occurred in the context of 2 HIV seroconversions and almost one-fifth developing an STI. Our data raise concerns about disparities in test-ordering for older and male patients, and with follow-up STI testing for African Americans.

The association with older patient age and lower HIV and STI test-ordering could be related to the perception that older PrEP patients may be at lower risk. However, the upper half of our sample's interquartile age range, 34–46, falls within the age deciles with the greatest proportion of new HIV diagnoses in San Francisco from 2012–2016; we are unable to compare STI incidence rates in older vs younger participants as testing was not equivalent in these 2 populations [14]. Furthermore, African Americans are the population with the highest STI incidence in San Francisco [14].

Later years were associated with higher HIV/STI test-ordering, potentially related to SFPCC PrEP educational efforts that began in 2016. The association of panel management with higher testing indicates that panel management could be effective, particularly given well-defined testing intervals and the success of panel management in other preventive measures [9].

The 2 HIV seroconversions after PrEP discontinuation emphasize the importance of PrEP persistence and adherence [9]. The number of STIs in our sample is high compared with the general primary care population; it is, however, low compared with a specialty PrEP program in San Francisco, in which 42% developed an STI over 12 months [10]. The lower amount of STIs in our

Table 1. Factors Associated With Ordering Initial and Follow-up HIV Testing[a] and Gonorrhea, Chlamydia, or Syphilis Testing[b] During Active PrEP Intervals

	Initial HIV AOR (95% CI)	Initial Gonorrhea, Chlamydia, or Syphilis AOR (95% CI)	Follow-up HIV AOR (95% CI)	Follow-up Gonorrhea, Chlamydia, or Syphilis AOR (95% CI)
Patient age per 10 y	**0.71 (0.57–0.88)**	**0.57 (0.44–0.74)**	**0.84 (0.72–0.97)**	**0.70 (0.56–0.87)**
Female vs male at birth	0.71 (0.30–1.64)	2.05 (0.64–6.57)	**2.05 (1.10–3.81)**	1.13 (0.44–2.88)
Race/ethnicity vs white				
African American	1.48 (0.58–3.79)	2.63 (0.77–9.06)	0.57 (0.30–1.09)	**0.45 (0.22–0.92)**
Asian	0.90 (0.35–2.37)	1.07 (0.50–2.28)	0.56 (0.30–1.04)	0.81 (0.37–1.77)
Latino	0.77 (0.41–1.43)	1.49 (0.44–5.02)	0.83 (0.51–1.32)	1.03 (0.56–1.90)
Other	1.01 (0.48–2.11)	0.86 (0.38–1.95)	0.60 (0.34–1.03)	0.72 (0.31–1.65)
PrEP indication vs MSM				
TGWSM	0.77 (0.32–1.86)	1.61 (0.44–5.92)	1.27 (0.68–2.40)	2.86 (0.79–10.30)
Sero-different relationship	0.90 (0.42–1.90)	0.62 (0.26–1.45)	0.78 (0.50–1.23)	**0.39 (0.19–0.78)**
Other[c]	2.23 (0.48–2.11)	0.69 (0.14–3.26)	0.66 (0.23–1.91)	0.60 (0.16–2.24)
≥2 PrEP patients per provider	0.66 (0.34–1.30)	0.62 (0.29–1.31)	**1.64 (1.05–2.57)**	1.68 (0.92–3.09)
Duration of PrEP prescription vs 30 d				
31–90 d	—	—	0.62 (0.27–1.42)	0.72 (0.25–2.11)
>90 d	—	—	**0.37 (0.17–0.81)**	0.61 (0.21–1.79)
Active PrEP interval index number[d] vs first interval				
2nd	—	—	**0.66 (0.44–0.98)**	1.33 (0.81–2.17)
≥3rd	—	—	**0.57 (0.38–0.84)**	1.22 (0.63–2.38)
Active panel management program	1.51 (0.69–3.28)	**4.19 (1.10–15.86)**	**2.22 (1.31–3.74)**	1.95 (0.99–3.85)
Year vs 2013/14				
2015	1.35 (0.69–2.66)	1.55 (0.78–3.10)	1.28 (0.69–2.40)	1.21 (0.64–2.29)
2016	**2.45 (2.26–5.15)**	**6.65 (2.69–16.47)**	1.70 (0.90–3.19)	**2.38 (1.18–4.80)**
2017	2.62 (0.97–7.08)	**5.68 (1.61–19.98)**	1.36 (0.64–2.87)	2.22 (0.56–8.82)

Bolded values indicate statistically significant values at 95% CI.

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; TGWSM, transgender women who have sex with men.

[a]For initial testing, measured 30 days before the initial PrEP prescription. For follow-up, examined over 6-month active PrEP prescription intervals, with a gap in PrEP defined as >90 days; both using logistic regression.

[b]For initial testing, measured 90 days before and 7 days after the initial prescription. For follow-up, examined over 4-month active PrEP prescription intervals, with a gap in PrEP defined as >90 days; both using logistic regression.

[c]Other indication includes people who inject drugs and high-risk heterosexual sex.

[d]PrEP interval index number captures temporal order of active PrEP prescription intervals, that is, the first 4-month interval for a patient would have an index number of 1.

cohort could be related to suboptimal STI test-ordering or provision of PrEP to patients in general primary care with diverse PrEP indications, potentially a population at lower risk of STIs.

Limitations of this study include the assessment of active PrEP status by prescription data only, incomplete data in providers' charting, inability to account for testing outside the network, and limited generalizability to populations not within a primary care, safety net setting.

Although we discovered suboptimal HIV and STI testing in a primary care population, our data suggest the promise of panel management, which could address disparities in PrEP testing. Future research into innovative population management strategies could help minimize PrEP's potential risks and maximize its preventive impact.

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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Human subjects. The procedures followed were in accordance with the ethical standards of the Helsinki Declaration of the World Medical Association. All patient information was anonymized as far as possible. The study was approved by the University of California, San Francisco, Institutional Review Board (IRB) and the San Francisco Department of Public Health. The study was deemed exempt from the requirement to obtain individual informed consent from all participants by the IRB and Department of Public Health.

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