A Primary Care Intervention to Increase HIV Pre-Exposure Prophylaxis (PrEP) Uptake in Patients with Syphilis

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Abstract

Identifying candidates for HIV pre-exposure prophylaxis (PrEP) is a barrier to improving PrEP uptake in priority populations. Syphilis infection is an indication for PrEP in all individuals and can be easily assessed by primary care providers (PCP) and health systems. This retrospective study evaluated the impact of a multidisciplinary provider outreach intervention on PrEP uptake in patients with a positive syphilis test result in a safety-net hospital-based primary care practice. The PCPs of PrEP-eligible patients with a positive syphilis result were notified via the electronic medical record (EMR) about potential PrEP eligibility and institutional HIV PrEP resources. Rates of PrEP offers and prescriptions were compared in the pre (8/1/2018-12/31/2018, $n = 60$) and post (1/1/2019-5/31/2019, $n = 86$) intervention periods. Secondary analyzes evaluated receipt of appropriate syphilis treatment and contemporaneous screening for HIV, gonorrhea, and chlamydia. No significant differences in the overall proportion of patients offered (15% vs 19%) and prescribed (7% vs 5%) PrEP were observed between the pre- and post-periods. Overall, 7% of positive tests represented infectious syphilis. The rate of appropriate syphilis treatment was equivalent (57% vs 56%) and contemporaneous screening for other sexually transmitted infections was suboptimal across the entire study period. Although any positive syphilis test may be an easily abstracted metric from the EMR, this approach was inclusive of many patients without current HIV risk and did not increase PrEP uptake significantly. Future research into population health approaches to increase HIV prevention should focus on patients with infectious syphilis and other current risk factors for incident HIV infection.

Keywords

HIV, HIV pre-exposure prophylaxis (PrEP), sexually transmitted infection, syphilis

Introduction

HIV pre-exposure prophylaxis (PrEP) reduces HIV acquisition in diverse populations with sexual[1-4] and/or injection-related HIV risk behaviors.[5] Daily tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for PrEP was approved by the Food and Drug Administration (FDA) in 2012, has been endorsed by the Centers for Disease Control and Prevention (CDC) in 2014,[6] and received a grade A recommendation the United States Preventive Services Task Force (USPSTF) in 2019.[7]

Despite PrEP's efficacy and guideline support, the CDC estimated in 2018 that just 90 000 of 1.1 million eligible Americans had received a PrEP prescription in the prior year, and studies consistently demonstrate racial and ethnic disparities in PrEP use.[8] Massachusetts has one of the highest PrEP-to-need ratios in the United States, with approximately 12 people prescribed PrEP for every one new diagnosis of HIV.[9] However, because of access barriers to preventive health services, fractured sexual health care systems, and stigma surrounding disclosure of HIV risk behaviors, identifying PrEP candidates still presents a challenge for providers and health systems.

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Machine learning strategies have made it possible for electronic medical records (EMR) to identify patients at high risk of HIV infection using a variety of risk factors in order to improve PrEP delivery;[10–16] however, this strategy is not yet available in health systems that lack robust information systems infrastructure. Several non-automated approaches have shown promise in increasing PrEP uptake in populations at risk, including direct patient outreach,[17] peer outreach,[18,19] home-based services,[20] leveraging of local health department services,[21] and the use of a PrEP coordinator.[22,23]

Syphilis infection is one objective, easily measured, and potent risk factor for incident HIV infection[24–27] and it is an indication for PrEP in all populations.[6,7] In fact, one in five men diagnosed with infectious syphilis or potentially infectious syphilis (ie late latent syphilis with RPR titer ≥1:32, suggesting recent infection) will acquire HIV in the next ten years,[28] yet many patients with syphilis infection are not linked to HIV prevention services. Identifying patients with syphilis represents an opportunity to lower the risk of HIV infection by offering PrEP. The purpose of this study is to assess the impact of provider outreach on PrEP uptake among patients with syphilis in a hospital-based general internal medicine primary care practice.

Materials and Methods

Site

This study took place within the General Internal Medicine (GIM) practice at Boston Medical Center (BMC), a large, urban, safety-net hospital affiliated with Boston University School of Medicine. BMC supports a hospital-wide HIV PrEP team, including a full time Quality Manager, a part-time Infectious Diseases attending physician, and a part-time GIM attending physician with funding from the Massachusetts Department of Public Health. During the study period, the standard approach to syphilis screening at BMC employed a "reverse algorithm" starting with pooled syphilis IgG/IgM antibodies (current procedural terminology 86780, Abbott Laboratories, Chicago, IL). A positive result reflexes to rapid plasma reagin (RPR) testing, and titers are performed if positive. When antibody testing is reactive and RPR non-reactive, the sample reflexes to a *Treponema pallidum* particle agglutination assay (TPPA) to resolve the discrepancy.

Intervention

Prior to January 2019, GIM patients with positive syphilis test results were offered PrEP at the discretion of their provider, without specific outreach from the PrEP team or decision support. In January 2019, the BMC HIV PrEP team instituted a new protocol to increase PrEP uptake among patients with bacterial sexually transmitted infections (STI). A report of patients with positive laboratory test results for chlamydia (CT), gonorrhea (GC), syphilis IgG/IgM antibody, RPR, or TPPA is generated and reviewed by the PrEP program manager each day. When a patient with a positive syphilis or gonorrhea result is identified who is potentially PrEP eligible by CDC criteria,[6] the BMC PrEP team contacts the patient's primary care provider (PCP) using a form letter sent via the EMR that alerts PCPs to the patient's potential PrEP eligibility and offers institutional PrEP resources (Supplement 1). PCPs can recommend against PrEP, can prescribe PrEP on their own (with or without navigation support from the PrEP team), or they can request that the PrEP team arrange a PrEP consult visit in the primary care or STI clinics. If PCPs do not respond to the EMR form letter within 5 business days, the PrEP team reaches out to the patient directly via phone. Outreach is not provided for all positive chlamydia tests due to high volume exceeding team capacity and relatively lower association with HIV acquisition.

Study Design

In order to evaluate the impact of this intervention on PrEP uptake among GIM patients with syphilis, a retrospective chart review was performed of GIM patients with any positive syphilis test from 8/1/2018 to 12/31/2018 (pre-intervention) and 1/1/2019 to 5/31/2019 (post-intervention). Patients were included if they were age 18 years or older, followed by a GIM PCP (defined as GIM provider listed in EMR PCP field and at least one office visit in the past three years), and potentially eligible for PrEP. Patients already taking TDF/FTC for HIV PrEP and those medically ineligible for PrEP due to known HIV infection or an estimated glomerular filtration rate < 60 mL/min were excluded. Chart review was performed to determine syphilis stage according to CDC criteria.[29] Infectious syphilis was defined as primary, secondary, or early latent syphilis. Potentially infectious syphilis was defined as late latent syphilis with elevated RPR titer (≥1:32, suggesting recent infection).

Additional demographic and clinical variables, including STI history, syphilis treatment, TDF/FTC offers (defined below), and TDF/FTC prescriptions were abstracted from the EMR and BMC PrEP program clinical registries by authors RB and JS and cross-checked for accuracy by JT. Several variables relevant to HIV risk, including history of injection drug use, sex and gender of partners, and gender identity were not captured consistently in the EMR and therefore were not abstracted. Deidentified data were entered into, cleaned, and analyzed in Microsoft Excel (Microsoft, Inc).

In order to assess for an intervention effect, we compared the proportion of GIM patients with a positive syphilis test result who were 1) offered PrEP (defined as EMR documentation that PrEP was offered to the patient by any team member) and 2) prescribed PrEP (defined as presence of a prescription for TDF/FTC from any provider within the EMR) within one month of syphilis test result in the pre- and post-intervention periods. Secondary outcomes included receipt of guideline-recommended syphilis treatment within 30 days, time from syphilis diagnosis to PrEP prescription, and rates of contemporaneous HIV, gonorrhea, and chlamydia screening (ie, testing completed within 1 week of initial syphilis testing). Finally, in order to consider results in the context of overall

PrEP trends in this GIM practice, the total number of PrEP prescriptions to GIM patients per month were abstracted from an existing PrEP quality improvement registry.

Statistical Analyzes

Descriptive statistics were used to characterize the study population. In order to compare the pre- and post-intervention periods, chi-square tests were used for categorical variables and t-test for continuous variables (*Social Science Statistics*, Jeremy Stangroom).[30] For results with any cell with a very small sample size < 5, Fisher exact tests were run to confirm chi-square results and results of the Fisher exact test are presented in tables.[30]

Ethical Approval and Informed Consent

The study was approved as exempt by the BMC Institutional Review Board on May 23, 2019 (IRB H-38401) on the basis that data initially obtained for non-research purposes were retroactively collected, anonymized, and stored in a Health Insurance Portability and Accountability Act (HIPAA) compliant manner.

Results

Participant Characteristics

During the study period, 10 598 syphilis tests were ordered institution-wide for 10 475 individual patients, including 3508 patients with a GIM PCP. Among the 186 unique GIM patients with a positive syphilis test, 40 (22%) were clinically ineligible for PrEP initiation due to impaired renal function (21/40), existing PrEP use (14/40), or HIV infection (5/40). A total of 60 patients in the pre-intervention period and 86 in the post-intervention period were included in final analyzes. Baseline characteristics with regards to age, sex, race, and prior syphilis infection were similar between each group, although there was a significantly higher proportion of late latent syphilis in the post-intervention period (Table 1).

PCP Outreach

Overall, 68% (59/86) of PCPs of patients with a positive test were engaged by the PrEP team in the post-intervention period. The majority (38/59) received the EMR form letter and 37/38 PCPs responded. In an additional 21/59 cases, the PrEP team engaged PCPs via other routes, including phone, email, and proactive outreach from the PCP before an EMR letter was sent. Of those patients whose PCPs were sent a form letter, 66% (25/38) received outreach from the institutional PrEP Team rather than from the PCP due to PCP request for support.

PrEP Offers and Prescribing

Overall, 15% (9/60) of patients were offered PrEP in the pre-intervention period compared to 19% (16/86) in the post-intervention period ($P = .56$). No significant difference in rates of PrEP prescriptions (7% vs 5%, $P = .72$) were observed. Rates of overall PrEP offers/prescriptions did not vary by sex, age, race, proportion of infectious syphilis, or proportion of all infectious and potentially infectious syphilis (primary, secondary, or early latent disease or late latent with RPR ≥1:32) in either group (Table 2).[28]

Among the 38 patients who received the provider EMR letter intervention, 37% (14/38) were offered PrEP and 10% (4/38) received a prescription. Among the 21 patients whose PCPs engaged with the PrEP team via other routes, 10% (2/21) were offered PrEP and 0% (0/21) received a prescription. No PrEP offers or prescriptions were observed among the patients whose PCPs received no form of PrEP team engagement.

The mean duration of time between positive test result and PrEP offer did not change significantly between the pre- and post-intervention periods (8.0 vs 15.6 days, $P = .08$).

Table 1. Participant Characteristics.

	Overall n = 146	Pre-Period n = 60	Post-Period n = 86	P-value
Age, years (mean)	55.4	54.1	56.2	.38
Sex, male, n (%)	86 (59)	36 (60)	50 (58)	.82
Race				
Black, n (%)	97 (66)	44 (73)	53 (62)	.14
White, n (%)	5 (3)	2 (3)	3 (3)	1
Other Race Indicated, n (%)	9 (6)	5 (8)	4 (5)	.45
Declined, n (%)	35 (24)	9 (15)	26 (30)	.05
Ethnicity				
Hispanic, n (%)	30 (21)	9 (15)	21 (24)	.24
Primary Care Provider				
GIM faculty, n (%)	97 (66)	43 (72)	54 (63)	.26
GIM nurse practitioner, n (%)	17 (12)	6 (10)	11 (13)	.80
GIM resident, n (%)	32 (22)	11 (18)	21 (24)	.38
Syphilis Stage				
Primary,[a] n (%)	2 (1)	2 (3)	0 (0)	.17
Secondary,[a] n(%)	3 (2)	2 (3)	1 (1)	.57
Tertiary, n (%)	8 (5)	5 (8)	3 (3)	.27
Presumed neurosyphilis, n (%)	7 (5)	5 (8)	2 (2)	.12
Confirmed neurosyphilis, n (%)	1 (1)	0 (0)	1 (1)	1
Early latent,[a] n (%)	5 (3)	3 (5)	2 (2)	.40
Late latent,[b] n (%)	69 (47)	23 (38)	46 (53)	.07
False Positives, n (%)	5 (3)	2 (3)	3 (3)	1
Requiring Treatment, n (%)	87 (60)	35 (58)	52 (60)	.80
Unknown, n (%)	2 (1)	0 (0)	2 (2)	.51
Prior Treated, n (%)	52 (36)	23 (38)	29 (34)	.57

[a]Denotes infectious syphilis.
[b]Includes latent infections of unknown duration.
$^\gamma P < .05$.

Table 2. PrEP Offers and Prescriptions by Subgroup.

	Offered PrEP			Prescribed PrEP		
	Pre (n = 60)	Post (n = 86)	P	Pre (n = 60)	Post (n = 86)	P
Overall, n (%)	9 (15)	16 (19)	.56	4 (7)	4 (5)	.72
Days to event, mean	15.6	8.0	.08	2.8	16.3	.18
Days to event, median	8	18		2.5	17	
Days to event, range	0 to 19	1 to 30		0 to 6	1 to 30	
Age, mean	45.0	46.4	.82	39.8	38.3	.87
Sex						
Male, n (%)	6 (10)	9 (10)	.88	4 (7)	2 (2)	.23
Female, n (%)	3 (5)	7 (8)	.46	0 (0)	2 (2)	.51
Race/Ethnicity						
Black	6 (10)	8 (9)	.64	2 (3)	2 (2)	1
Hispanic Ethnicity	1 (2)	3 (3)	.65	1 (2)	1 (1)	1
Syphilis Stage						
Infectious, n (%)	4 (7)	3 (3)	.45	2 (3)	1 (1)	.57
Infectious + Potentially Infectious,[a] n (%)	4 (7)	3 (3)	.45	2 (3)	1 (1)	.57
Late Latent, n (%)	4 (7)	10 (12)	.40	2 (3)	3 (5)	1

[a]Includes infectious (ie primary, secondary, and early latent) plus potentially infectious (ie late latent with RPR ≥1:32) cases.

Similarly, there was no significant difference in time from test result to PrEP prescription (2.8 vs 16.3 days, $P = .18$). The majority of PrEP offers overall (64%, 16/25) and prescriptions (50%, 4/8) came from the GIM PrEP team or infectious disease providers. The proportion of offers and prescriptions by provider type did not differ significantly pre- and post-intervention.

Among the 10 patients with infectious syphilis (7 pre- and 3 post-intervention), 70% (7/10) received an offer for PrEP during the study period and 30% (3/10) received a PrEP prescription. The proportion of patients with infectious syphilis who were offered and prescribed PrEP was not statistically different between the pre- and post-intervention arms. None of the patients with latent syphilis and RPR titer ≥ 1:32 received a PrEP offer or a prescription.

Syphilis Treatment Outcomes

There was no statistical difference between treatment for syphilis between the two groups; 57% (20/35) of patients pre-intervention requiring treatment were correctly treated within 30 days of syphilis diagnosis compared with 56% (29/52) post-intervention ($P = .90$). Ultimately, 77% (67/87) of patients requiring treatment across both groups had documentation of guideline-concordant treatment, with no significant difference between the pre- and post-intervention groups (71% vs 81%, $P = .31$). There was no statistically significant difference in the mean duration of time between diagnosis and correct treatment in those treated within 30 days (8.9 days pre-intervention vs 12.3 days post-intervention, $P = .15$, median 7 days vs 10 days), nor in the subgroup of patients with infectious syphilis (7 days vs 11 days, $P = .55$). Overall, 100% (10/10) of patients diagnosed with infectious syphilis during the study period were appropriately treated.

Syphilis

Overall, the majority of positive syphilis tests (87/146, 60%) represented untreated syphilis, including 69/146 (47%) cases of late latent syphilis or latent syphilis of unknown duration and 13/146 (8.9%) cases of infectious or potentially infectious syphilis (Table 1). One third of positive syphilis tests (52/146, 36%) represented previously treated syphilis without evidence of reinfection.

STI Screening Practices

Just 62% (91/146) of patients overall received contemporaneous HIV screening and 41% (60/146) received contemporaneous GC/CT screening across the entire study period; screening rates did not differ between the pre- and post-intervention periods. Among those not concurrently screened for HIV, 47% (26/55) had no lifetime test on file. The proportion of patients screened for HIV, gonorrhea, and chlamydia did not vary significantly between the pre- and post-intervention periods. The majority of patients across the entire sample who underwent GC/CT screening were screened at a single site (92%, 55/60), most commonly urine (67%, 40/60). Approximately 24% (5/24) of women screened for GC/CT were screened using urine testing only.

Overall GIM PrEP Trends

Across our entire GIM population in patients with and without syphilis, the mean number of patients prescribed PrEP (inclusive of new and continued prescriptions) was 28 per month in the pre-intervention period, increasing to 37 per month post-intervention ($P = .02$).

Discussion

PrEP is an effective HIV prevention tool, but it continues to be inadequately prescribed to priority populations. Given the challenges in eliminating individual patient- and provider-level barriers to PrEP uptake, systems interventions offer promise in increasing PrEP utilization.[17–23] We evaluated the efficacy of outreach to the PCPs of all patients with positive syphilis test results using a protocol that could be scaled to health systems without advanced information technology infrastructure. Results demonstrate that this intervention resulted in no significant changes in PrEP offer and prescription rates.

The lack of demonstrated intervention effect may be due to several factors. First, we captured a high proportion of patients with late latent syphilis, latent syphilis of unknown duration, and previously treated syphilis, most likely due to the use a reverse syphilis screening algorithm.[31] Therefore, our inclusion criteria - all patients with a positive syphilis test – likely captured many patients not meeting CDC criteria for PrEP due to remote sexual risk. While this protocol relied on easily abstracted data that did not need to be interpreted by a clinical team member (ie, to determine syphilis stage) before outreach, future systems interventions to increase PrEP uptake should be more specific in targeting patients with infectious or potentially infectious syphilis who are more likely to have recent and/or ongoing HIV risk behaviors conferring PrEP eligibility.

Additionally, incomplete intervention fidelity during the post-intervention period may have limited observed effect, with just 44% of PCPs receiving the planned EMR letter and 69% engaging with the PrEP team via any route. Anecdotally, incomplete intervention coverage was due to staffing capacity. There was a trend towards higher rates of PrEP offers and prescriptions in patients whose PCPs received the EMR letter compared to other types of engagement or no engagement, though this must be interpreted with caution as the PrEP team prioritized patients tested due to current sexual risk when capacity was limited, and numbers are small.

Although the majority of study participants did not have evidence of recent syphilis infection, observed rates of infectious (7%) and infectious or potentially infectious syphilis (9%) among PrEP eligible GIM patients suggested an important role for increased screening and PrEP outreach to this subgroup as well as additional STI screening. However, low absolute numbers limited our ability to draw conclusions about PrEP offers and uptake in this population.

Additionally, baseline rates of PrEP prescribing among the overall population of GIM patients with a positive syphilis test (7.5%) suggested that patients with syphilis who are eligible for PrEP in this practice were already being identified and prescribed PrEP through other mechanisms. It is possible that a similar protocol would be more effective in systems with lower baseline PrEP prescribing rates. Furthermore, it is also possible that the provider outreach protocol (Supplement 1) did not provide enough decision support for PCPs, limiting the efficacy of this intervention. Although this study was not designed to evaluate the impact of the protocol on overall

GIM PrEP prescriptions in patients without syphilis, it is also possible that significant overall increase in PrEP prescriptions per month regardless of syphilis status represented an unmeasured impact of this intervention with regards to increasing PrEP visibility.

Our results add to the literature demonstrating insufficient STI screening rates in a high risk environment.[32,33] We found that rates of contemporaneous screening for HIV, gonorrhea, and chlamydia among patients with positive syphilis test results were low, and the lack of testing at multiple sites suggests insufficient screening practices even in those who underwent screening. Concurrent HIV screening was insufficient especially in those without prior HIV testing, which concords with national data suggesting inadequate HIV screening in adults.[34] Importantly, a significant proportion of women with positive syphilis tests who received screening for gonorrhea and chlamydia were screened via urine testing only, which has a lower sensitivity than vaginal swab, the recommended method, for detection of GC/CT in women.[35] These data identify key areas for improvement, as those at risk for sexually transmitted syphilis are additionally at risk for other bacterial STIs and HIV, and vice versa. Inadequate bacterial STI screening can also present a barrier to identifying PrEP eligible patients, as PrEP is indicated for all patients with syphilis or gonorrheal infections within the past 6 months, as well as for men who have sex with men with recent chlamydia.[7]

This study has several limitations with regards to study design and implementation. First, we studied a post-intervention period that immediately followed implementation; it is possible that the impact of the intervention on PrEP uptake will increase over time as it becomes more effectively integrated into PrEP team and clinician workflow. As noted above, although the goal of the intervention was to implement an EMR letter-based intervention, we observed diverse pathways of engagement between the PrEP team and PCPs. Given that 68% of PCPs were engaged by the PrEP team, we believe the overarching study conclusion, that PCP outreach for all patients with positive syphilis tests may be too broad an approach to meaningfully increase PrEP uptake, remains valid.

The short study period also contributed to fewer total observations, and thus our current study may be underpowered to detect significant differences between the pre- and post-intervention periods. Future analyzes will evaluate the impact of the intervention on PrEP offers among patients with gonorrhea, chlamydia, and syphilis, which may mitigate power limitations. Although chlamydia was not included as an indication for PrEP in the 2017 CDC update for heterosexual people, this type of intervention offers the opportunity to identify people with frequent chlamydial infections who may be at higher risk for HIV and intervene.[6]

We were additionally unable to abstract data on current sexual and injection-related HIV risk behaviors due to inconsistent clinical documentation to determine the total proportion of the population meeting clinical criteria for PrEP and fully evaluate the adequacy of STI screening (including indications for

extra-genital testing). Lastly, our study focused on the prescription of daily TDF/FTC rather than alternative dosing regimens[36] or the use of tenofovir alafenamide (TAF)/FTC,[37] neither of which were FDA-approved for HIV PrEP during our study period.

Conclusion

In summary, an EMR-based outreach to the providers of patients with positive syphilis test results was not associated with increased PrEP uptake or improvements in syphilis treatment in our GIM sample. Future work should more specifically target those with recent syphilis infection and other evidence of recent HIV risk behaviors.

Author Contribution

Conceptualization (RWB, JS, JT), data curation (RWB, JS, JT), data analyzes (RWB, RDB, JT), interpretation (RWB, JS, AU, RDB, JT), writing – original draft (RWB, JT), and writing – review and editing (RWB, JS, AU, RDB, JT). All authors approved the final version of this manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Statement

This study was approved as exempt by the BMC Institutional Review Board on May 21, 2019 [H-38401] on the basis that data initially obtained for non-research purposes were retroactively collected, anonymized, and stored in a HIPAA compliant manner. Written informed consent was waived.

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Supplemental material

Supplemental material for this article is available online.

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