Immediate PrEP after PEP: Results from an Observational Nurse-Led PEP2PrEP Study

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Abstract
Patients who use post-exposure prophylaxis (PEP) are at ongoing risk for HIV acquisition after completing PEP. While the Centers for Disease Control and Prevention recommends pre-exposure prophylaxis (PrEP) use immediately after PEP, some practitioners are hesitant to offer PEP-to-PrEP (PEP2PrEP). We began offering PEP2PrEP in the sexually transmitted infection clinic in Ottawa, Canada on August 5, 2018. During the first 16 months of PEP2PrEP, 61 patients requested PEP and 46 were initiated; 30 of these patients agreed to PEP2PrEP and 26 followed through. None of our PEP patients had confirmed HIV exposures; all fulfilled the initiation criterion of condomless anal sex with a male partner of unknown HIV-status. During the study, the number of PEP requests and initiations was statistical unchanged, yet the seroconversion rate among patients who used PEP decreased from 1.7% pre-PEP2PrEP to 0% post-PEP2PrEP. Regarding follow-up, most discontinuations occurred between the PrEP intake and 1-month follow-up visit.

Keywords
HIV, PEP, PrEP, transition, nursing

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Introduction
Persons who use post-exposure prophylaxis (PEP), which is the use of antiretroviral medications after a potential HIV exposure to prevent seroconversion, are vulnerable to HIV acquisition in the past, present, and future: (1) in the past—this is why PEP is used; (2) in the present—PEP can fail, and did so at a rate of 19% in the only case–control study to evaluate its efficacy,1 yet at rates of less than 5% to 10% in subsequent observation studies2; and (3) in the future—because studies have found diagnosis rates of up to 13% among gay men within 12 months of PEP use among patients who used this intervention.3 This last point has led some guidelines to suggest that PEP use more than once warrants pre-exposure prophylaxis (PrEP), which is the use antiretroviral medications before a potential HIV exposure to prevent seroconversion.4,5 The possibility of HIV acquisition in the near future (eg, less than 12-month period) after PEP use has also led the United States Centers for Disease Control and Prevention4 and the International Antiviral Association (USA Panel)6 to

What Do We Already Know about This Topic?
HIV PrEP is warranted after the use of HIV PEP.

How Does Your Research Contribute to the Field?
Immediate PEP2PrEP corresponded with decreased HIV seroconversion rates among persons who used PEP.

What Are Your Research’s Implications toward Theory, Practice, or Policy?
While more research is required to further show the safety and efficacy of PEP2PrEP, our findings provide proof-of-concept for this approach to HIV prevention and care.
recommend immediate PEP-to-PrEP (PEP2PrEP) transitions, such that persons who use PEP start PrEP without interruption in drug therapy. Other authors, however, caution against PEP2PrEP until patients are established as HIV-negative. This is because (1) persons use PEP due to an HIV exposure, (2) PEP is not guaranteed to prevent HIV acquisition, and (3) PrEP initiation during HIV seroconversion can produce drug resistance, and did so in PrEP trials at rates of about 41% among participants with acute HIV infections, compared to 3% among those who became HIV-positive due to PrEP failure. A more recent study identified a risk ratio of 3.34 (95% CI: 1.11-10.06) for drug resistance among persons starting PrEP during acute HIV infection compared to those without acute infection. Notably, despite this rate of occurrence for drug resistance, the iPrEx study identified that most drug resistance waned by 24 weeks of PrEP discontinuation.

The issue with the recommendations for and against PEP2PrEP is that little research supports both positions. Compounding this is that the real-world PEP delivery is often not clear-cut. Because Canadian and United States guidelines state that condomless anal sex between men of unknown HIV-status warrants PEP, many patients initiate PEP after unconfirmed exposures, of which an unknown subset would not actually have been bona fide exposures. While this point is important, in frontline clinical practices, such information often cannot be known. This is not to say that unconfirmed exposures do not warrant PEP, but that, because an unknown subset of patients use PEP when they did not actually have an HIV exposure, the concerns about PrEP after PEP may be smaller than anticipated because no harms would be possible. Compounding this situation is that, to then further delay PrEP in these cases could leave patients vulnerable to HIV acquisition until practitioners feel confident that patients do not have acute HIV infection, which may never occur if patients continue to engage in HIV practices that transmit HIV.

As such, the decision to start PEP2PrEP is a balance of stewardship (protecting against drug resistance) and ethics (withholding an intervention that prevents HIV seroconversion by 96%-99%). To inform this decision and address high seroconversion rates among PEP patients, we began offering PEP2PrEP to patients who (1) initiated PEP at our sexually transmitted infection (STI) testing clinic, (2) reported good adherence to the PEP, and (3) had no serologic or physical evidence of HIV infection. Our objective was to explore the uptake rate of PrEP after PEP, the relationships between specific patient characteristics and PrEP discontinuation of PrEP continuation, and the HIV seroconversion rate among our PEP patients overall and PEP2PrEP patients. We report here on the first 16 months of observational findings from a nurse-led PrEP clinic that is situated within the STI clinic in Ottawa, Canada.

Methods

Post-Exposure Prophylaxis, PrEP, and PEP2PrEP Protocols

Our STI clinic is located downtown Ottawa, Canada, which is a city of 1 million residents, with the greater region approaching 1.5 million residents. Ottawa Public Health operates this clinic, which has over 20 000 patient visits per year, and offers full STI screening, PEP, PrEP, and contraception services. This clinic is like most other publicly-funded public health STI clinics in Canada. While nurses, physicians, and nurse practitioners work in this STI clinic, nurses operate the PEP and PrEP projects under medical directives from nurse practitioners.

At this clinic, we offer nurse-led PEP and PrEP to patients who qualify based on guidelines and clinical judgement. For PEP, we use once-daily oral emtricitabine-tenofovir DF 200/300 mg plus raltegravir HD 1200 mg daily for 28 days. For PrEP, we use once daily oral emtricitabine-tenofovir DF 200/300 mg. We do not offer intermittent PrEP use and refer any patient who requests this to an alternate PrEP clinic where this is available. For PEP2PrEP, we offer patients an appointment to start PrEP at the point of PEP initiation and, if declined at first offer, again after 2 weeks during routine nursing follow-up. Patients who agree to PrEP are referred to our PrEP clinic for an initiation visit after approximately 3 weeks of PEP (see Figure 1). Patients who decline PEP2PrEP at both offers are informed they can request PrEP at any point. We also encourage these patients to do routine follow-up according to Canadian guidelines, and we follow these patients for up to 1 year after their PrEP use for routine HIV and STI screening.

Notably, in contrast to the Canadian PEP guidelines, we offer PrEP to anyone who uses PEP once. Our rationale is that, before PrEP, approximately 13.1% of gay men who obtained PEP from our STI clinic were diagnosed with HIV within 12 months of using PEP. We, therefore, feel that a single episode of PEP use justifies PrEP use.

At the first PrEP visit, we repeat HIV testing using the fourth-generation Abbott Architect (which has an estimated 85% sensitivity to detect acute HIV infection in persons using PrEP), do a thorough history and examination for signs/symptoms of HIV seroconversion, and collect blood for renal function testing. Once results show the patient has no HIV antigen/antibodies and adequate renal function for PrEP, we send the patient a prescription to start PrEP the day after completing PEP. We repeat these serologic and clinical assessments after 1 month of PrEP use and every 3 months thereafter. We also perform indicated STI testing at those visits (Figure 1).

We follow-up by telephone with all PrEP patients who do not attend scheduled appointments, and immediately offer them a new appointment that is convenient for them. We then continue with appointments as scheduled for such patients. We proceed in the same way for patients who sporadically miss appointments. Patients who miss 3 consecutive appointments, however, are informed that they can rebook for PrEP when it becomes more convenient for them and we offer immediate referrals to other PrEP clinics in the city.

Data Collection

Data for this study were extracted from our PEP2PrEP patients’ charts and input into Excel by the authors. We initiated our PEP2PrEP referrals August 5, 2018, and extracted data from
the files of patients who accessed PEP between that date and December 4, 2019. Extracted data focused on demographics (age, gender, income), sexual and drug use practices (sex practices, gender of partners, substance use), mental health (depression, anxiety, using the patient health questionnaire 9 [PHQ9], and generalized anxiety 7 scale [GAD7], respectively), reason for PEP use and follow-up details (practices that warranted PEP, symptoms, test results), and information on PrEP visits (attendance, symptoms, results). HIV diagnosis data were extracted from August 5, 2018, to March 4, 2020, with no subsequent data collection available due to COVID-19.

Data Analysis
Sociodemographic information was analyzed using descriptive statistics. The outcome of interest was PrEP discontinuation, defined as failing to present to clinical visit 3 (i.e., the 1 month PrEP recheck appointment). We were interested in exploring the relationships between specific patient characteristics and PrEP discontinuation. These variables included age (below versus above 25 years), income (high versus low), ethnicity (Caucasian versus visible minority), anxiety (any symptoms versus none), depression (any symptoms versus none), whether the patient accepted PEP2PrEP at the intake or follow-up visit, and previous STI (yes versus no). Thus, for each variable we conducted a bivariate \( \chi^2 \) test to identify the presence of a statistically significant relationship (in any direction) between it and the outcome of interest at \( P < .1 \). It was our intention to explore the direction of these relationships and to include all variables deemed significant in the bivariate analyses into a multivariable model; however, our results were not amenable to this (ie, there were no significant relationships). SPSS version 26 was used for this part of the analysis.

Ethical Approval and Informed Consent
The Ontario HIV Treatment Network funded this research, and the research ethics boards at the University of Ottawa and at Ottawa Public Health approved the project (ethics file numbers H-04-18-533 and 246-18, respectively). All participants in this study signed expressed consent for involvement in this project. Notably, a patient’s ability to obtain PEP or PrEP was not contingent upon study enrollment.

Results
During the 16-months of data collection, 61 patients presented to our STI clinic requesting PEP, 60.7\% (n = 37/61) were initiated and 81.1\% (n = 30/37) of those who used PEP agreed to PEP2PrEP. During the study period, 13.5\% (n = 5/37) patients accessed our clinic to initiate PEP more than once, which is similar to the average of 12.7\% (yearly range of 9.7-15.4\%) between 2015 and 2019. Of these patients, 31\% (n = 19/37) sought services at our clinic for the first time for PEP. This rate of access and uptake, plus the client demographics of these patients, also resembles our published data on this clinical service. For more information on this PEP program and its participants and outcomes, please see O’Byrne et al.3,14

No patient initiated on PEP, irrespective of PrEP use, was diagnosed with HIV since we implemented PEP2PrEP. Comparing PEP requests and initiations pre-/post-PEP2PrEP, 286 persons sought PEP in the 60 months before we started PEP2PrEP for a rate of 4.76/month, and 61 sought PEP in the 16 months after, for a rate of 3.81/month. For initiations, we gave PEP to 207 patients in the 60 months preceding PEP2PrEP, for a rate 3.45/month, compared to 46 initiations in the 16 months after, for a rate of 2.87/month. The observed changes in the rates of accessing and initiating PEP were not significant pre-/post-PEP2PrEP (\( P = .240 \) and \( P = .281 \), respectively). The HIV seroconversion rate before PEP2PrEP was 3.8\% (n = 11/286) and 0\% after. Of these 11 diagnoses, 6 occurred at intake when patients sought PEP, and 5 occurred within 12 months of using PEP; none of these 5 diagnoses were PEP failures, as all had tested negative after using PEP. The rate of HIV diagnosis after PEP before we implemented PEP2PrEP was thus 2.4\% (n = 5/207) for initiations, which, because we follow all PEP patients for 1 year after PEP use, equates to an HIV incidence of 5.4 per 100 person-years. Using this pre-PEP2PrEP seroconversion rate, from our 37 PEP initiations who generated 24.5 person-years of follow-up as of March 4, 2020, we would have expected 1.3 diagnosis during the PEP2PrEP study period.

Patients who agreed to PrEP after PEP use had a mean age of 30.3 years. They were 97\% male (n = 29/30), 61\% Caucasian (n = 17/28), and all reported sex with male partners. As well, 39\% screened positive for anxiety or
depression on the PHQ-9 or GAD-7—all of whom were already connected with mental health services. See Table 1 for more details.

All patients who agreed to PrEP after PEP use started PEP due to condomless anal sex with a male partner of unknown HIV-status, with 72% (n = 21/29, 1 unknown) of these contacts being receptive anal sex. As such, there were no confirmed HIV exposures. Of these patients, 93% (n = 28/30) completed PEP, with 1 lost to follow-up and 1 discontinuing. All had negative HIV test results at baseline and all but the 2 who did not follow-up had repeat negative test results at least 3 weeks later. Of the 30 patients who initiated PrEP due to PEP, 87% (n = 26/30) did immediate PEP2PrEP transitions; 13% (n = 4/30) had completed PEP for 4 to 16 weeks before PrEP.

One patient accepted PrEP when offered at PEP initiation but declined before starting.

For the 26 patients who did immediate PEP2PrEP transitions, 85% (n = 22/26) attended their second visit, and 66% (n = 14/21) of those eligible to do so attended their third visit (n = 3 had not reached this visit yet and n = 2 moved). Of those eligible to attend the fourth visit, 79% (n = 11/14) did so (n = 2 had not reached this visit yet, n = 1 was referred to another clinic). Of those eligible to attend the fifth visit, 87.5% (n = 7/8) did so (n = 2 had not reached this visit yet). Therefore, removing the 7 participants who had not yet progressed to visit 5, plus the 4 who continued at another clinic and the 2 who moved, we had 53.8% (n = 7/13) of participants retained on PrEP by visit 5. Table 2 and Figure 2 show the PEP2PrEP cascade. HIV tests at all visits were negative, and no patient reported symptoms of HIV seroconversion, although we diagnosed 16% (n = 4) of the 25 patients we tested for STIs with 5 STIs: 2 cases of syphilis, 2 cases of rectal gonorrhea, and 1 case of oral gonorrhea. These diagnoses occurred at the 1-month visit (n = 1 patient with rectal gonorrhea), the 4-month visit (n = 1 patient with syphilis and rectal gonorrhea), and the 7-month visit (n = 1 patient with syphilis and n = 1 patient with oral gonorrhea). Moreover, no one discontinued PrEP due to renal dysfunction.

Chi-square tests found no significant differences between the observed and expected frequencies for attendance at visit 3 (which was the largest drop-out point for PEP2PrEP) and the following items: age (below versus above 25 years), income (high versus low), ethnicity (Caucasian versus visible minority), anxiety (any symptoms versus none), depression (any symptoms versus none), whether the patient accepted PEP2PrEP at the intake or follow-up visit, and previous STI (yes versus no).

**Table 1. Participant Demographics.**

| Categories                  | Variables                      | N    | %   |
|-----------------------------|--------------------------------|------|-----|
| Patient demographics        |                                |      |     |
| Gender                      | Male                           | 29/30| 97% |
|                            | Trans female                   | 1/30 | 3%  |
| Sexual orientation          | Gay                            | 22/25| 88% |
|                            | Bisexual                       | 3/25 | 12% |
| Ethnicity                   | Caucasian                      | 17/28| 61% |
|                            | South Asian                    | 5/28 | 17% |
|                            | Latin American                 | 2/28 | 7%  |
|                            | Black                          | 2/28 | 7%  |
|                            | Southeast Asian                | 1/28 | 4%  |
|                            | Indigenous                     | 1/28 | 4%  |
| Education                   | University or College          | 24/26| 92% |
|                            | High school                    | 2/26 | 8%  |
| Medication insurance        | Private or public              | 22/30| 73% |
|                            | Uninsured                      | 8/30 | 27% |
| Income                      | <CA$10 000                     | 3/24 | 13% |
|                            | CA$10 000-CA$50 000            | 8/24 | 33% |
|                            | CA$50 000-CA$100 000           | 9/24 | 38% |
|                            | >CA$100 000                    | 4/24 | 17% |
| Risk behaviors              | History of sexually transmitted infections | 15/30 | 50% |
|                            | Receptive anal sex             | 27/29| 93% |
|                            | Penetrative anal sex           | 3/29 | 10% |
|                            | Substance use                  | 3/29 | 10% |
| Mental health screening     | No anxiety or depression       | 14/23| 61% |
|                            | Mild anxiety or depression     | 8/23 | 35% |
|                            | Moderate anxiety or depression | 3/23 | 13% |
|                            | Both anxiety and depression    | 9/23 | 39% |

Discussion

In this article, we reported on the findings of the first 16 months of our nurse-led PrEP clinic, focusing on the patients who agreed to PEP2PrEP. From 46 eligible PEP patients during the study period, 30 agreed to PrEP and 26 accepted immediate PrEP initiation after PEP completion. Notably, the rate of discontinuing PrEP was highest between visits two and three. For clinical outcomes, 16% of our PEP2PrEP patients were diagnosed with an STI while using PrEP, but none was diagnosed with HIV in our clinic or elsewhere in Ontario, although we do not have results for those who moved out of province or since the COVID-19 shutdowns (as testing was restricted during that time). Notably, nearly half of these participants reported mild or moderate anxiety and/or depression. These results raise a few points for discussion.

First, these results contribute generally to the ever-expanding literature on HIV PrEP and more specifically to the sparse literature on PEP2PrEP. Regarding the overall literature on PrEP, our findings add more data on the outcomes associated with nurse-led PrEP, showing its operational feasibility.15-20 While several studies confirm such findings about the functionality of nurse-led PrEP,15-20 much of this research has focused on evaluating if nurses can provide PrEP independently or in various collaborating roles and on the outcomes associated with nurses initiating and/or monitoring patients who use PrEP. Also unique to our study is that we
focused on PEP2PrEP and the outcomes associated with an immediate transition from one intervention to another. While our sample is small, our results suggest that this intervention is reasonable.

Second, the HIV positivity rate among our patients who used PEP was 0%, which decreased from the previous rate of 1.7% per year for the preceding 5 years. Based on historical data, we would have expected at least 1 HIV diagnosis during the 16-month study period. While the patients who accessed PEP before and after PEP2PrEP are not the same persons, it is the same clinic and there were no other changes to the PEP program during the study period. As well, that we diagnosed the 16% of PEP2PrEP patients with STIs during follow-up signals ongoing sexual practices that can result in HIV acquisition, which aligns with published literature. This lack of HIV diagnosis, however, could be coincidental or an artefact of missed diagnoses due to PrEP medication affecting diagnosis, although patients did seroconvert in the PrEP studies. It is also reassuring that missed diagnoses are not likely because our patients reported good PEP and PrEP adherence, had no signs/symptoms of HIV seroconversion, and all had negative HIV test results at PEP initiation, 1 week before starting PrEP, and 1 month after being on PrEP. However, longer-term follow-up may be required to better determine such outcomes.

That there were no HIV diagnoses among our PEP2PrEP patients suggests that this transition could be appropriate, which might help appease those who feel patients need to be established as HIV-negative through serologic testing after being off PEP for the duration of the HIV testing window. Seeing as 1.7% of our patients who used PEP had historically become HIV-positive (with this rate rising to 10% among gay men), delaying PrEP means depriving many highly vulnerable patients of an available intervention. Reinforcing the importance of PEP2PrEP is that other PEP studies have similarly found high rates of seroconversion after PEP use. Our findings thus suggest that withholding PEP2PrEP might not be ideal, although the lack of HIV diagnoses among our PEP2PrEP patients could be because no patient had a true HIV exposure; all sought PEP due to condomless anal sex with same-sex male partners of unknown HIV-status. As noted above, the point here is not that PEP was inappropriately initiated in such instances (it absolutely was warranted and appropriately provided); rather, our assertion is that, because an unknown subset of these instances of PEP use were possibly not required, in these unknown cases, there would be absolutely no harms of associated PrEP drug resistance because the person did not have a true exposure. This point is further reassuring for this transition.

Third, despite the potential success of this program, there was a high loss-to-follow-up rate between the PrEP initiation and follow-up visit after 1 month of PrEP use. Most who continued with PrEP after this visit continued thereafter, signaling a potential period to maintain retention in care. While patients may agree to initiate PrEP after PEP use, a substantial number may not continue PrEP after this time, as was the case in our study where over 4 of 5 eligible participants agreed to PrEP after PEP use, yet only 1 in 2 of participants who initiated PrEP were retained in care by visit 5. As was also found in other studies, offering PrEP is insufficient; additional efforts to increase retention are required. Without efforts to increase retention for PrEP use, the population-level success of this intervention will likely be limited. Moreover, that there were no clear sociodemographic factors associated with loss-to-follow-up suggests that this discontinuation may relate to the intervention itself, rather than it being a group-specific factor that makes people less willing and/or able to engage in treatment.

Alternatively, the loss-to-follow-up in our study, which is higher than in most published PrEP studies, may have arisen because our study was observational and involved routine clinical practices; in other words, our study was not a rigid clinical trial with study-funded retention strategies. As such, our findings might more accurately reflect real-world PrEP retention—and in fact do align with a published analysis of 16 907 participants from 95 studies, which identified that “by the end of 1 year, almost 40% of the participants who started...
treatment in these clinical trials had stopped taking the medication(s), despite the protocol-specific regimen of continuously maintained dosing. As such, our retention rate of 53.8% more closely aligns with this published rate of 60% continuation at 1 year, versus rates of 70% to 80% retention in the literature.

Fourth, that nearly half of the participants screened positive for mild-to-moderate anxiety or depression on the GAD7 and PHQ9 emphasizes the need for clinicians to assess for these disorders among persons who seek PEP and PrEP. Other studies have similarly found elevated rates of mood disorders among patients who use PEP and PrEP. Although no significant correlation was identified between anxiety or depression and PrEP discontinuation, previous studies have identified this relationship.

As such, mood disorders may be the reason PrEP is needed (in that sexual practices that can transmit HIV could be the manifestation of depression or anxiety) and might be reason it is not used in an ongoing fashion (in that these illnesses undermine retention in care). It is thus prudent for clinicians in PEP and PrEP programs to screen for, and provide services or referrals related to, mental health. Ignoring this may leave a driving force behind some sexual practices unaddressed and may undermine retention in care.

**Limitations**

Our findings must be interpreted considering certain limitations. For one, our sample was small and decreased over time. Whether these results would be maintained with a larger sample is unknown. It is also uncertain whether our results would translate to areas with different testing technologies and without nurses who are experts in HIV assessment—although the literature suggests that nurse-led PrEP is feasible. We also do not know whether patients who did not follow-up accessed PrEP elsewhere. Lastly, our sample was well-educated and insured, with most being Caucasian and identifying as gay. Whether these findings would apply to other groups is unclear.

**Conclusions**

Our PEP2PrEP study found that many patients who were eligible for PrEP declined this intervention and that many who started PrEP discontinued after 4 weeks. We also did not find any HIV diagnoses among PrEP2PEP patients, and the diagnosis rate among PEP patients decreased from 1.7% to 0% after starting PEP2PrEP. This is a reassuring finding considering that we would have expected at least 1 HIV diagnosis during our follow-up period; however, this finding could have been an artefact of a small study sample and disruptions caused by COVID-19. Nonetheless, despite these limitations, our results provide a proof-of-concept for PEP2PrEP as one strategy to reduce HIV transmission among a group with historically high rates of seroconversion. Now, larger scale studies need to determine if these results hold true for other populations. In the meantime, PEP2PrEP appears to be an appropriate intervention, and our findings support the Centers for Disease Control and Prevention guidelines to engage in this practice when clinicians can be reasonably certain that patients do not have acute HIV infection. Perhaps such an approach would yield similar outcomes that we observed, resulting in decreased HIV transmission more broadly.

**Authors’ Note**

Patrick O’Byrne and Lauren Orser have contributed equally to the work. All authors have read and approved the final manuscript. Patrick O’Byrne contributed to conceptualization, data extraction, analysis, and writing. Lauren Orser contributed to data extraction, analysis, and writing. Amanda Vandyk contributed to data analysis and editing. Patrick O’Byrne holds a research chair in public health and HIV prevention from the Ontario HIV Treatment Network (OHTN), Ministry of Health and Long Term Care, Government of Ontario.

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