PEP for primary care

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ABSTRACT

HIV prevention now involves pre-exposure and post-exposure prophylaxis, known as PrEP and PEP. While literature about how nurse practitioners can provide PrEP exists, there is none for PEP. This paper summarizes what is known about PEP and provides guidance for nurse practitioners who wish to include this intervention in their practice.

Introduction

While HIV prevention has historically focused on persons avoiding practices that transmit HIV, such as needle sharing and condomless sex, prevention now includes chemoprophylaxis, including pre- and post-exposure prophylaxis; known as PrEP and PEP, respectively, these interventions involve giving antiretroviral medications to HIV-negative patients.[1-3] Due to these changes, nurse practitioners' work has expanded; whereas previous prevention efforts mostly focused on counselling about testing and HIV transmission, they now include PrEP, for which guidelines exist.[1,2] Although PEP guidelines for nonoccupational HIV exposures also exist,[2,3] this intervention is less discussed in the primary care literature, despite being an important part of comprehensive HIV prevention services. This paper thus (1) includes a review of both the research on PEP and the CDC[3] and Canadian[2] PEP guidelines, and (2) serves as a starting point for nurse practitioners to consider how to integrate HIV PEP into their practice.

What Evidence Supports PEP?

The evidence on PEP mostly arises from animal model studies involving macaques, and shows that, when antiretroviral medications are administered to monkeys after parenteral or mucosal exposure, there are marked reductions in HIV seroconversion.[4,5] These studies also identified the required timing for PEP: fewer seroconversions occurred when PEP was administered as soon as possible after exposure, ideally within 24 hours, and continued for 28 days; shorter courses and later starting times corresponded with higher seroconversion rates.[6] One case-controlled trial using one antiretroviral medication (AZT) among humans subsequently identified an 81% reduction in seroconversion among hospital employees (primarily nurses) who were exposed to HIV via needlestick.[7] This high level of prevention made it unethical to withhold PEP in future studies. Data about maternal-child transmission further supported the utility of PEP, showing that PEP administration during childbirth correlated with less vertical transmission.[8,9] The outcome

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of these studies is that PEP is now standard-of-care for HIV exposures.

One limitation to PEP access is that, despite knowing it is effective, it remains mostly only available in emergency rooms and sexually transmitted infection (STI) clinics. While these settings are appropriate because STI clinic nurses have specialized knowledge and emergency rooms are always open, limiting access to these sites defies what is known about PEP: i.e., the time from HIV exposure to administering the first dose of PEP is centrally important to its effectiveness. It thus makes sense that the first dose of PEP could be administered in primary care settings where patients might present for care. Guidance about how to do this is detailed below.

Does my patient need PEP?

Based on available research, PEP is given to HIV-negative persons as soon as possible after HIV exposure.[2,3] As such, when considering PEP, the nurse practitioner's first step is to determine eligibility, which can occur by posing the following questions:

- Did the potential exposure to HIV occur within the preceding 72 hours?
- Was the potential exposure sufficient to cause HIV transmission?
- Is the person who may need PEP HIV-negative?
- Is the source of the potential exposure HIV-positive?

If the answer to any of these questions is no, PEP is not warranted. The time period has elapsed, the risk of transmission is minimal, the patient for whom PEP is being considered does not require it because s/he/they are already HIV-positive, and/or the source person is HIV-negative. Often, the timing and exposure questions are easily answered. Nurse practitioners need only ask patients about what occurred when. Although patients will not always provide these details (due to, for example, substance use or a reluctance to disclose), activities considered high-risk for HIV transmission include needle sharing and needlestick, condomless anal sex (receptive and penetrative), and condomless vaginal sex (receptive higher risk, but penetrative still an at-risk practice).[1,2,3] In contrast, determining the patient's and source person's HIV-status is often less clear, leaving nurse practitioners to decide if patients are likely HIV-negative and if the source person is potentially HIV-positive.

Is my Patient HIV-Negative?

To determine the patient's HIV-status, a three-part approach can be used. First, recent results should be sought. Although HIV results may not be valid due to testing window periods and ongoing risk, these results do reduce the period of potential new infection. Even a test from one year ago shortens the period of uncertainty to the time since testing plus the window period, which is 12 weeks for third-generation antibody tests and about 6 weeks for fourth generation antigen-antibody tests.[10] Second, if available, nurse practitioners should perform point-of-care HIV testing, with a positive result precluding PEP. In an STI clinic, this procedure identified patients who were unaware they were HIV-positive when seeking PEP.[11] This is unsurprising, considering that recent CDC[12] and

Canadian[13] estimates suggest that about 14% of persons living with HIV are undiagnosed. Third, nurse practitioners should assess patients for symptoms of seroconversion, including fever, chills, malaise, arthralgia, myalgia, rash, lymphadenopathy, abdominal pain, nausea, vomiting, and/or diarrhea.[1] Although up to 75-80% of persons experience these symptoms 10-28 days post-exposure, their presence does not preclude PEP initiation, as they are non-specific.[3] The presence of such symptoms may warrant more frequent testing to rule out seroconversion.

Although test results confirming an HIV-negative status with the last potential exposure being outside the window period would be ideal, due to the importance of initiating PEP quickly, nurse practitioners should prescribe PEP without delay for patients who are potentially HIV-negative. According to the CDC[3], when results are not available or are limited by window periods, decisions about PEP should be "based on the assumption that the potentially exposed patient is not infected". If tests determine otherwise, expert consultation should be sought, and discontinuation versus continuation of PEP at this point should occur under the guidance of an HIV specialist.[3]

One unique situation nurse practitioners may encounter is when patients who use PrEP request PEP. In this case, nurse practitioners should first assess patient's medication use; PEP is not indicated if the patient takes PrEP as prescribed. The CDC[3] is explicit on this point, stating that PEP is only indicated if the patient takes PrEP "sporadically" or not at all "within the week before recent exposure". Because this recommendation is only based on expert opinion, another option, based on the pharmacokinetic data of PrEP medication which shows a 72 hours intracellular half-life, is to provide PEP when all other conditions for PEP are fulfilled and the patient misses two consecutive pills.[14] While this approach has a lower threshold for PEP initiation, it more cautiously ensures PEP usage in the absence of evidence for when and how to use PEP in patients who are taking PrEP. It may, however, be needlessly conservative.

Is the Source Person HIV-Positive?

For the source's HIV-status, a few strategies can be used. The first is to test the source person and determine his/her/their HIV-status.[2,3] If positive, viral load and genetic testing should occur.[3] The outcome of such results raises the point of the *undetectable equals untransmittable* ("U=U") campaign, which is built on a robust body of evidence showing that HIV transmission becomes virtually zero once a person attains and sustains an undetectable viral load, which is <40-400 copies of HIV per mL of blood.[15] An important caveat in this body of work is that persons must actually have undetectable viral loads. Indeed, although no HIV transmissions occurred in a recent study about U=U, 55 participants were excluded from analysis because they did not maintain an undetectable viral load; these 55 patients constituted 5.5% of the entire study sample (n=1004) and 47.4% of those excluded (n=116).[16] In another study from San Francisco,[17] "Of the 118 HIV-positive men on ART, 92.4% reported they were virally suppressed at last clinic visit, 62.4% were actually virally suppressed as indicated by blood tests, and 77.8% of their partners reported that they believed their HIV-positive partner was virally suppressed". Thus, while a truly suppressed viral load would likely not warrant PEP, without the nurse practitioners being able to confirm such a viral load, it would be prudent to initiate PEP. If an undetectable viral load is confirmed later, PEP can be discontinued.[3] The same approach should be adopted for patients who report that their partner is HIV-positive, but confirmation of the viral load is not available.[2] In such cases, assume that a potential for transmission exists, and discontinue PEP later as needed.

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Alternatively, the patient may inform the nurse practitioners that the source person reported being HIV-negative, which is susceptible to the same limitations that apply to the patient's HIV test results. Another consideration is that the patient's assessment of HIV-negative status may be based on perceptions of the partner's appearance and social standing.[18] The nurse practitioners should thus inquire about how patients know their partners' HIV-status. Statements such as "he looked clean" and "he said he was on PrEP" may be uncovered, and are contextual interpretations of HIV-status, not explicit statements about HIV-status by the source person.[18]

> …PEP is indicated for HIV-negative patients who had exposures that transmit HIV with persons who are either known to be HIV-positive with detectable viral loads or unconfirmed undetectable viral loads or members of high-risk groups with unknown or reportedly negative HIV-status.[2,3]

Without direct confirmation of the source person's HIV-negative test results, PEP should be given if the risk of HIV transmission is enough based on what occurred and the risk of HIV exposure is sufficient, with HIV prevalence being a proxy measure for this level of risk. Following WHO[19] definitions, the HIV epidemic in the United States and Canada is "concentrated" because there is a <1% HIV prevalence among pregnant women and a >5% prevalence among specific sub-populations; this contrasts with generalized epidemics where HIV prevalence is >1% among pregnant women. In the United States and Canada, therefore, groups with an HIV prevalence >5% are considered high-risk based on prevalence; this includes men who have sex with men, persons who inject drugs, and persons who are Indigenous, African, Caribbean, or Black, or transgender.[12,13] The same approach of determining potential risk of HIV exposure based on group-level HIV prevalence would apply if the patient did not know the source person's HIV-status.

In summary, PEP is indicated for HIV-negative patients who had exposures that transmit HIV with persons who are either known to be HIV-positive with detectable viral loads or unconfirmed undetectable viral loads or members of high-risk groups with unknown or reportedly negative HIV-status.[2,3] (Table 1)

How do I Prescribe PEP?

What Should I Prescribe and for How Long?

According to CDC[3] and Canadian[2] guidelines, a first-line PEP regimen for adults includes 28 days of oral Emtricitabine-Tenofovir DF

Table 1.

HIV-Status		Transmission Risk	Recommendation
Positive	Viral load unknown	High risk*	PEP indicated
		Low risk†	PEP not indicated
	Viral load reportedly undetectable	High risk*	PEP indicated
		Low risk†	PEP not indicated
	Viral load confirmed undetectable	High risk*	PEP not indicated
		Low risk†	PEP not indicated
Negative	Laboratory results confirmed	High risk*	PEP not indicated (depending on window periods)
		Low risk†	PEP not indicated
	Laboratory results unconfirmed (high prevalence group)	High risk*	PEP indicated
		Low risk†	PEP not indicated
	Laboratory results unconfirmed (low prevalence group)	High risk*	PEP not indicated
		Low risk†	PEP not indicated
Unknown	High prevalence group	High risk*	PEP indicated
		Low risk†	PEP not indicated
	Low prevalence group	High risk*	PEP not indicated
		Low risk†	PEP not indicated

* High risk = percutaneous exposure (needlestick, needle sharing), anal sex (receptive/penetrative), vaginal sex (receptive/penetrative)

† Low risk = oral sex, spitting, biting, sharing sex toys

(FTC/TDF) 200/300mg fixed dose tablet once daily plus oral Raltegravir 400mg twice daily. Alternatively, oral Dolutegravir 50mg once daily can be used instead of Raltegravir, but should be avoided in pregnant women due to the risk of neural tube defects.[3] Contraindications to FTC/TDF include nephrotoxicity and an estimated creatinine clearance <60mL/min; there are no drug-drug interactions.[3] The side effects of FTC/TDF include asthenia, headache, and gastrointestinal upset, such as nausea, vomiting, and diarrhea.[3] There are no contraindications for Raltegravir, although dosage adjustment (doubling to 800mg po BID) is required if the patient takes Rifampin.[3] Polyvalent-cation antacids and laxatives should also be avoided due to the potential for chelation.[3] Raltegravir side effects include "insomnia, nausea, fatigue, and headache; severe skin and hypersensitivity reactions are also possible".[3]

Because there are no randomized controlled trials evaluating PEP medication, which agents to use is based on expert opinion.[3] Those that were selected are chosen because they are tolerable, require minimal dosing schedules, and have few drug-drug interactions.[3] The combination of three agents is similarly extrapolated from studies involving HIV-positive patients, among whom three medications yield high levels of viral suppression and little risk of resistance.[3]

The next consideration regarding PEP relates to providing the medication. The simplest approach is to administer the first dose immediately on-site and dispense the remainder of the 28 days

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of medication. This strategy corresponds with the fastest PEP initiation and the highest rates of continuation.[20] However, this approach requires that nurse practitioners both have PEP on-site and prescribe the full course of medication without follow-up or consultation before giving the full course of medication. Another approach is to provide a 3 to 6 day starter pack of medication, whether dispensed on-site or as a prescription to fill at the pharmacy, and have the remainder of the medication dispensed or given as a prescription once baseline laboratory results are available.[2] This approach ensures patient start PEP promptly, but only continue if it is were safe to do so. This approach also ensures a follow-up visit for PEP continuation, when the nurse practitioner can discuss side effects, adherence, and the results of the baseline testing; the nurse practitioner can provide additional supportive counselling at that time as well.[3] A third option is to provide a 3 to 6 day starter pack and refer the patient to an HIV specialist, as happens in many emergency departments. This approach might be ideal for nurse practitioners who are inexperienced with PEP, but requires multiple visits with multiple providers in multiple settings.[3] A fourth option is to send the patient to the local emergency department for immediate consultation with an infectious disease specialist. Examples of patients who would need to be referred out for management of PEP include: pregnancy, pediatrics, those with renal dysfunction (estimated creatinine clearance <60mL/min). Otherwise, provision of the full course of medication is within the scope of most nurse practitioners, and the first approach is the simplest for patients to obtain and continue PEP.

What Testing is Required?

In addition to HIV testing (ideally as a point-of-care and 4th generation serology test), nurse practitioners should test patients for whom PEP is considered for other bloodborne infections, such as syphilis, and hepatitis A, B, and C.[2,3] Hepatitis B testing, including surface antigen and surface antibody and core antibody, is important because FTC/TDF is partially active against hepatitis B infection and could induce reactivation in persons with active infection upon discontinuation.[2,3] Gonorrhea and chlamydia testing at urogenital, pharyngeal, and rectal sites should also occur, as indicated by the patient's practices.[2,3] Pregnancy testing should also occur as needed, even though pregnancy is not a contraindication to PEP.[2,3] Pregnant patients need only be given medications that are safe. (See above note about Dolutegravir.) Next, serum creatinine, alanine aminotransferase, and aspartate aminotransferase should be ordered to ensure patients can process PEP medication.[2,3] FTC/TDF is renally processed and requires an estimated creatinine clearance >60mL/min for use, and Raltegravir can cause elevated liver enzymes.[2,3] These serologic chemistry tests are ordered at baseline and repeated after two weeks if abnormal.[2] If the estimated creatinine clearance is <60mL/min, immediate consultation with an HIV specialist is required, so the patient can continue PEP with a non-renally processed medication. Otherwise, repeat testing after PEP completion is all that is required, and should include HIV testing using a fourth-generation test, unless follow-up is not guaranteed, in which case a point-of-care test could be used. The CDC[3] suggests this testing should occur after 4-6 weeks, and then after 3 and 6 months

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after PEP initiation. The Canadian guidelines[2], in contrast, recommend follow-up testing only after 3 months.

What Counselling Do I Provide?

Counselling is an essential component of PEP, and nurse practitioners should emphasize a few items. For one, patients need to be informed that PEP medications need to be taken everyday for 28 days.[2,3] Missing doses or not completing the course of medication undermines its efficacy. Next, nurse practitioners should ensure that patients are aware PEP can fail. Although current triple medication regimens likely have higher prevention outcomes than the 81% reduction in seroconversions identified in the single existing occupational case-control trial,[2] PEP failures still continue to occur.[21] Nurse practitioners should thus inform patients about the symptoms of HIV seroconversion and instruct them to return to clinic if such symptoms occur during, or up to one month after, PEP use.[2,3] Due to the risk of such failures, nurse practitioners should also instruct patients to eschew practices that transmit HIV until infection is ruled out after 6-12 weeks from the potential exposure that warranted PEP.[3] This approach would minimize onward HIV transmission in instances of PEP failure.

As another important item, nurse practitioners need to emphasize general risk reduction strategies for patients who request PEP. This would include a discussion about and the provision of condoms and sterile drug equipment, as well as discussions about HIV transmission and risk mitigation. As part of this, patients who warrant PEP should be offered PrEP. While the CDC[3] and Canadian[2] guidelines recommend PrEP after repeat instances of PEP use, other research has identified up to 10% seroconversion rates within one year after a single instance of PEP use, suggesting that multiple usages may not be required before initiating PrEP.[11,22] Following the CDC[3], provided that a patient has no contraindications to FTC/TDF and good adherence to PEP medication, s/he/they could initiate PrEP on the first day after completing PEP. Due to PEP failures, symptoms and missed pills may warrant expert consultation before proceeding with a PEP-to-PrEP transition, to reduce the risk of drug resistance. Otherwise, PEP-to-PrEP transitions can likely occur, and are included in the latest iterations of the CDC PEP[3] and PrEP[1] guidelines.

What Else Should I Consider?

Patients not known to be vaccinated for Hepatitis B should receive a single dose of vaccination at the time of PEP initiation.[3] Follow-up vaccination should be guided by baseline results. Hepatitis B immune globulin should also be provided if testing of the source person is possible and determines that this person is Hepatitis B antigen positive.[3] Moreover, patients who have negative pregnancy tests should be offered emergency contraception and ongoing contraception, as is appropriate and safe for them.[3]

Another important item is that, before providing PEP, patients need to know it exists and where to obtain it. Proactively, nurse practitioners should inform patients about PEP, especially those belonging to groups with elevated HIV prevalence, and, as part of this, instruct patients that they need to obtain PEP as soon as possible after potential HIV exposure, ideally within the first 24 hours, but up to 72 hours. The main

message is that PEP should be initiated rapidly because it likely becomes less effective as time passes.

Closing Remarks

PEP is an important HIV prevention tool that is often restricted to specialized settings, such as STI clinics and emergency departments. This, however, does not need to be the case: primary care nurse practitioners can initiate patients on PEP and perform all relevant monitoring. This builds on current evidence about the importance of rapid PEP initiation and guidelines which emphasize the need to have such HIV prevention be more broadly available within the healthcare system. This paper serves as a tool for nurse practitioners to consider how to implement PEP in their practice. In doing this, primary care nurse practitioners can provide their patients with comprehensive HIV prevention services, and ideally link these patients with the most appropriate services in the most convenient locations.

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