Published in final edited form as:

AIDS. 2014 July 17; 28(11): 1545–1554. doi:10.1097/QAD.0000000000000301.

Practical guidance for nonoccupational postexposure prophylaxis to prevent HIV infection: an editorial review

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Abstract

Postexposure prophylaxis (PEP) with antiretroviral medication has been used as an HIV-prevention strategy for nearly 20 years. The fact that approximately 50 000 new HIV infections occur in the United States each year reflects marked underutilization of nonoccupational PEP (NPEP). There have been several advances in NPEP in the past 10 years. Clinical trials from different countries have demonstrated better tolerability, completion rates, and fewer drug–drug interactions with newer antiretroviral agents. Notably, there has been a shift from zidovudine-based to tenofovir-based regimens. Three-drug therapy is now favored for all potential HIV exposures. More recently, the US Public Health Service and the New York State Department of Health recommended tenofovir/emtricitabine and raltegravir as the first-line regimen universally for PEP. Advances in HIV testing technology may also allow shorter duration of follow-up HIV testing after a high-risk exposure. This review will discuss challenges with previously recommended regimens, newer potential candidate agents and the rationale for using them, intervals for laboratory monitoring, and cost considerations for NPEP. NPEP can be viewed as an educable moment and a potential bridge to preexposure prophylaxis, as part of a combination prevention package, for those who are likely to have recurrent higher-risk exposures. Thus, risk-reduction counseling should be an integral aspect of NPEP.

Keywords

biomedical HIV-prevention; nonoccupational postexposure prophylaxis; NPEP; postexposure prophylaxis

Introduction

Antiretroviral medication may be used for the prevention of HIV, as well as the treatment of HIV infection. On the basis of animal model data [1] and a retrospective case–control study of occupationally exposed healthcare workers [2], the US Centers for Disease Control and Prevention (CDC) first recommended the use of postexposure prophylaxis (PEP) to protect

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Conflicts of interest

There are no conflicts of interest.

occupationally exposed healthcare workers in 1998 [3]. This review will focus on management of nonoccupational PEP (NPEP) in adults. Data from several countries have demonstrated that NPEP following sexual exposure, including sexual assault, has been underutilized, and that the majority of such exposures are not brought to the attention of a medical provider [4–7]. A survey of New York State Emergency Department physicians in 2006 further indicated that a lack of resources and physician education were associated with low rates of provision of NPEP [8]. There are no recent longitudinal reports of trends in NPEP use in the United States, though other settings have been observing a rise in NPEP utilization over time [9–12].

Definitive recommendations about specific medications and duration of prophylaxis have been challenging because HIV is inefficiently transmitted, and the use of a placebo-controlled design would be deemed unethical by most experts. Hence, much of the current guidance is based on animal studies. The first studies that informed PEP protocols involved administration of (*R*)-9-(2-phosphonylmethoxypropyl) adenine, the derivative of tenofovir, to macaques for 28 days at different time intervals after being injected with simian immunodeficiency virus (SIV), which prevented ongoing infection after discontinuation of the drug [1,13]. A follow-up study was done by infecting female macaques intravaginally with HIV-2, which also demonstrated that earlier initiation of tenofovir and treatment duration of 28 days were necessary to prevent persistent infection [14]. Future studies in macaques by different groups have yielded similar results [15–17].

A case–control study of healthcare workers percutaneously exposed to HIV-infected blood demonstrated that those who took zidovudine had an 81% lesser risk of HIV seroconversion than those who did not [2]. The concept of PEP was further buttressed when zidovudine administered to HIV-infected women in the pre-HAART era resulted in markedly decreased rates of perinatal HIV transmission [18]. However, PEP has not been invariably successful in preventing transmission, as there are reported cases of HIV seroconversion despite PEP use [2,19,20], potentially because of late initiation of prophylaxis, exposure to particularly high viral inocula, and/or the use of insufficiently active regimens. Current first-line antiretrovirals for NPEP are better tolerated than those used in 2005, offering enhanced likelihood of medication regimen adherence. HIV testing technology has also seen many advances in recent years, including the development of point-of-care assays and later-generation platforms that narrow the time between infection and antibody or antigen detection. The CDC's NPEP guidelines in 2005 recommended using two-drug or three-drug antiretroviral therapy specifically after an HIV-uninfected person sustains a 'substantial' exposure to the blood or genital secretions of an HIV-infected person to an HIV-uninfected person [21]. More recent occupational PEP guidelines released by the US Public Health Service (USPHS) advocate for using a three-drug regimen after all risky exposures [22]. In this review, we will discuss the challenges of prior recommended regimens for NPEP, review data regarding newer candidate drugs for NPEP and the rationale for using them, and discuss the use of new HIV testing assays that might influence the duration and intervals of NPEP monitoring.

Who should receive nonoccupational postexposure prophylaxis?

The CDC recommends NPEP for patients after having a possible exposure to HIV-infected blood, genital secretions, rectal secretions, breast milk, or other bodily fluid visibly contaminated with blood [21]. Oftentimes, this occurs in the setting of unprotected sex, protected sex with condom failure, intravenous drug use, or other mucosal or wound exposure. Exposures involving the insertive oral partner and human bites do not require NPEP due to the extremely low risk for HIV acquisition, unless there are extenuating circumstances [21]. Often, the HIV status of the source is unknown, particularly if the exposure occurred with an anonymous partner, if HIV status was not discussed or disclosed, or if the source had not been recently tested. If the source has a recent documented negative antibody test or HIV plasma RNA result, then the exposed person does not need NPEP. Therefore, it is critical to obtain the source's HIV status whenever possible. Although source persons may be in a 'window period,' wherein HIV antibody is not detected after acute infection, the CDC does not currently recommend routine HIV RNA testing of the source or exposed person to guide whether or not patients should receive NPEP. However, the availability of information about the HIV RNA tests of either the source or exposed can aid in the risk assessment, if acute infection is suspected.

Initial management of nonoccupational postexposure prophylaxis

Animal data showed substantial attenuation in protective benefit when medication was administered 72 h after SIV inoculation [13], but because of the logistical challenges exposed individuals may experience, the CDC allows a 72-h postexposure window [21]. For high-risk exposures, the New York State AIDS Institute recommends that HIV medication should ideally be initiated within 2 h of exposure and preferably within the first 36 h [23]. NPEP should be discontinued if the source is deemed to be HIV-uninfected [21,23]. If the source is HIV-infected and is on treatment, information should be obtained about his or her resistance profile and treatment history to inform selection of the most potent NPEP regimen. The choice of specific HIV medications will be discussed in detail below. The source should also be tested for hepatitis B and hepatitis C if his or her status is unknown. Empiric treatment for gonorrhea and chlamydia should be given for survivors of sexual assault. Those who are not victims of sexual assault should be tested for gonorrhea, chlamydia, and syphilis, and treated if they test positive. Emergency contraception can be offered to female victims of sexual assault within 72 h of the exposure if a pregnancy test is negative.

Both the 2005 CDC NPEP guidelines and the 2013 New York State guidelines recommend that baseline laboratory tests should include: blood urea nitrogen, creatinine, complete blood count, liver function tests, HIV antibody, hepatitis C antibody, and hepatitis B surface antigen and antibody. If the hepatitis C serostatus of the source is unknown, the hepatitis C antibody should be repeated at 3 and 6 months after the exposure [21,23]. If the source is known to be infected with hepatitis C, the New York State additionally recommends that a viral hepatitis C RNA should be checked at 4 and 12 weeks, as well as an antibody test, with liver enzymes at 24 weeks [23]. If the source is either hepatitis B immune or uninfected, or the exposed is immune based on serology, then no hepatitis B prophylaxis is indicated. If the

source has a positive hepatitis B surface antigen or is high-risk for being infected, then the exposed should receive hepatitis B immunoglobulin if he or she is unvaccinated, a nonresponder to prior vaccination, or in the midst of the vaccine series [23]. Determination of hepatitis B core antibody status may be helpful in determining if individuals who are negative for hepatitis B surface antigen or surface antibody have been exposed to hepatitis B. There is no US Food and Drug Administration (FDA)-approved PEP for hepatitis C at the time of this review, though the advent of better tolerated oral regimens may allow postexposure prophylactic approaches in the future (see Table 1 for a summary of laboratory monitoring recommendations).

HIV nonoccupational postexposure prophylaxis treatment challenges: pill burden, cost

Postexposure prophylaxis regimens have entailed the use of two to three antiretrovirals because of presumed increased efficacy and enhanced protection (although there have not been any head-to-head comparisons of regimens containing different numbers of medications). However, there are a number of challenges for patients that may limit completion of currently available regimens. These include pill burden from having to take up to 4 pills per day, taking pills more than once daily, cost, and toxicities. Moreover, patients who are HIV-uninfected may respond differently to identical treatment regimens compared to HIV-infected patients. For instance, a group in Italy reported that HIV-uninfected patients had a six-fold higher rate of adverse effects and had to interrupt their treatment at an eight-fold higher rate compared to HIV-infected patients who used similar regimens [24]. One group of investigators designed a decision model that evaluated the tradeoffs of using either two or three drugs for occupational PEP, which took into account tolerability, efficacy, and potential resistance concerns, but the authors acknowledged that the model was constrained by limited available efficacy data [25]. They found that in many circumstances, two-drug regimens were more cost-effective because of decreased adherence with three-drug regimens. However, the study was initiated before several newer, better tolerated regimens were available. NPEP cost-effectiveness analyses have suggested that the intervention can be both cost-effective and cost-saving, albeit the estimates of various costs and PEP effectiveness were based on figures dating back to 1997 [26,27]. An Australian study demonstrated that NPEP is only cost-effective after unprotected receptive anal intercourse with an HIV-infected partner [28]. The most recent USPHS occupational PEP guidelines now recommend using three active drugs for all exposures that require antiretrovirals because of the availability of simpler and better tolerated regimens and the presumption of enhanced efficacy of triple-drug regimens, particularly if the source may have been antiretroviral-experienced [22].

HIV nonoccupational postexposure prophylaxis tolerability

The tolerability of specific PEP drug regimens has influenced the choice of medications since the ability to complete the prescribed 28-day course is very important. Table 2 summarizes PEP completion rates in various clinical trials. PEP regimens that included zidovudine have been associated with nausea, headaches, and anemia, which resulted in over 25% of patients failing to complete their 4-week course of medication [29]. A French study

observed adverse events in 59% of 98 participants who received zidovudine–lamivudine and lopinavir–ritonavir for occupational PEP or NPEP, including 20% that stopped treatment early due to side effects. Despite the frequency of adverse events, this regimen appeared to be better tolerated when compared to historical controls who used zidovudine–lamivudine with either indinavir or nelfinavir [30]. A later multicenter French trial studied zidovudine–lamivudine and fosamprenavir–ritonavir in 46 patients presenting for occupational PEP and NPEP, of whom 57% reported at least one adverse effect [31]. The study was terminated prematurely since 4 out of 26 patients at one of the participating sites reported advanced liver failure [32]. Another study evaluated 200 patients presenting for PEP at six emergency departments in Spain, 85% of which were nonoccupational exposures and 48% of whom were MSM [33]. Patients were randomized to receive zidovudine–lamivudine and either lopinavir–ritonavir or unboosted atazanavir. Occurrence of adverse events, and discontinuation or switching of the regimen, was similar both the groups.

More recent studies have focused on the use of tenofovir as a part of an NPEP regimen. Two Boston NPEP studies evaluated tenofovir with either lamivudine or emtricitabine without a third drug [34]. The majority of participants presented after receptive or insertive anal intercourse. Tenofovir-based NPEP regimens were associated with a much higher completion rate (72.7–87.5%) than historical controls who used zidovudine-based regimens (38.8–42.1%; $P < 0.0001$) at the same center. Of note, there was a higher rate of diarrhea in the tenofovir groups (31.3–37.5%) than the protease inhibitor-sparing zidovudine-based regimens (9.8%; $P < 0.01$). More nausea and vomiting were reported in the zidovudine groups than in the tenofovir groups (55.7 vs. 18.8–22.5%; $P < 0.01$). A tenofovir-based study in France administered tenofovir–emtricitabine and lopinavir–ritonavir to 188 patients presenting for occupational PEP and NPEP [35]. This group reported an 88% completion rate. The 12% of patients that stopped early did so due to adverse effects. Of the 166 patients who completed therapy, 42% had adverse effects, the most common being the following: diarrhea (78%), asthenia (78%), nausea and/or vomiting (59%), and headache (38%). There were no HIV seroconversions in this cohort. Overall, this study reinforced that tenofovir-based PEP regimens are well tolerated.

Two subsequent prospective, single-arm tolerability studies conducted in hospital emergency departments in France compared tenofovir and zidovudine–lamivudine to tenofovir–lamivudine and boosted atazanavir for patients presenting for occupational PEP and NPEP [36]. Completion rates were similar in both groups (21 and 18%, respectively; $P = 0.64$). Overall rate of adverse events was similar as well (45 and 43.5%, respectively; $P = 0.79$). The most common side effects included: nausea/vomiting (89 and 64%, respectively) and asthenia (78 and 77%, respectively). Although participants in the atazanavir group appeared to tolerate the regimen fairly well, this regimen was ultimately not recommended for PEP given the 87% rate of hyperbilirubinemia, 9% of which was either grade 3 or 4. Jaundice was seen in 66% of these cases, although only two persons discontinued PEP due to this symptom.

A recent Boston NPEP study reported on 100 patients who received tenofovir–emtricitabine and raltegravir, which is the first published tolerability study using an integrase inhibitor for PEP [37]. Medication was assessed by self-report, and 84% reported taking their daily dose

of tenofovir–emtricitabine every day of the course and at least one of the two daily doses of raltegravir. None of the patients stopped early due to side effects, but 27% occasionally missed the second daily dose of raltegravir. The most common adverse effects included: nausea or vomiting (27%), diarrhea (21%), and headache (15%). This regimen achieved similar completion rates as other tenofovir-based regimens, but it had a more favorable side effect profile than prior studies [37] (see Table 3 for a summary of side effects reported in clinical trials of NPEP regimens).

New HIV nonoccupational postexposure prophylaxis regimens

The USPHS [22] and the New York State Department of Health [23] recently recommended using tenofovir–emtricitabine and raltegravir as the preferred PEP regimen based on a recent study [37], as well as the theoretical advantage of blocking viral replication prior to integration within host DNA and few interactions with other medications compared to ritonavir-containing regimens. This regimen can be given in pregnancy. Although lopinavir-containing regimens have been associated with gastrointestinal side effects, its use for NPEP did not lead to many treatment discontinuations [33], leading many normative bodies to include it as an option for NPEP. Atazanavir, an alternative agent per CDC and New York State NPEP guidelines and a pregnancy class B drug, may also be considered for NPEP in pregnancy [21,23].

Since zidovudine has been found to have several side effects that have frequently led to premature PEP discontinuation, as discussed above, zidovudine-based regimens are not ideal for NPEP. Furthermore, multiple studies have demonstrated a significant level of transmitted antiretroviral drug resistance to non-nucleoside reverse transcriptase inhibitors in the United States [38–40]. Abacavir can cause a severe hypersensitivity reaction, and in the time-dependent setting of NPEP, there is not enough time to wait for HLA-B*5701 results that would indicate whether patients that are at increased risk for this reaction.

Certain non-nucleoside reverse transcriptase inhibitors have features that make them less desirable for NPEP. Efavirenz was recommended in the initial CDC NPEP guidelines in 2005, but its use can cause or exacerbate depression, anxiety, or other neuropsychiatric side effects, which may exacerbate the stress of the exposure itself. Efavirenz is also not preferable in early pregnancy due to risk for teratogenicity. Nevirapine can lead to acute liver failure and Stevens–Johnson syndrome in patients with preserved CD4⁺ cell counts and should be avoided for NPEP [41,42].

The majority of HIV transmission in treatment-naïve patients seems to be due to C-C chemokine receptor type 5 (CCR5)-tropic virus [43], allowing potential use of entry inhibitors for NPEP. As such, maraviroc is currently being studied for the use of preexposure prophylaxis (PrEP) through the HIV Prevention Trials Network 069 study [44]. However, CCR5 coreceptor antagonists may be ineffective against HIV strains that are tropic for CXCR4 or dual tropic, which cannot be assessed at the time of NPEP enrollment, barring rare situations in which information is available about the source's HIV genotype, tropism, or antiretroviral medication regimen.

As HIV treatment must be individualized for each patient, the choice of specific PEP regimens must consider side effects, comorbidities, drug–drug interactions, and hepatitis B or C coinfection. The USPHS Task Force’s most recent report about occupational PEP suggested that initial PEP regimens include tenofovir and emtricitabine with raltegravir, with darunavir, atazanavir, or fosamprenavir boosted with ritonavir to be considered as ‘preferred alternative’ agents if raltegravir is not used [22]. Although there are no case series describing the use of darunavir for PEP, it may have some advantages over other protease inhibitors since it can be given once a day and boosted with only 100 mg of ritonavir. Atazanavir appears to be well tolerated, but should be avoided for those who have a history of nephrolithiasis. Moreover, patients need to be counseled about the high incidence of hyperbilirubinemia and concomitant jaundice, which is readily reversible but may result in social harms [45]. Fosamprenavir for PEP was studied with zidovudine and lamivudine, so it is unclear how much of the toxicity noted in prior reports was attributable either zidovudine or fosamprenavir [31].

Concerns have been raised regarding the potential to select for drug-resistant virus by using HIV medication for perieposure prophylaxis [46], but modeling studies have estimated that the rate of such resistance in various populations is relatively low [47,48]. The twice-daily dosing of raltegravir presents some challenges since it intrinsically has a lower barrier to resistance than some of the newer integrase inhibitors and most of the protease inhibitors [49], and once-daily dosing resulted in statistically significantly lower rates of viral suppression compared to twice-daily dosing in HIV-infected treatment-naïve individuals [50]. Therefore, the current formulation of raltegravir must be used carefully in individuals who may not be fully adherent to the regimen because of intercurrent substance use or other behavioral health concerns. New formulations of raltegravir are under study and may allow effective once-daily dosing. Some of the newer antiretroviral agents are less likely to select for resistance. Several studies have shown that darunavir has a higher genetic barrier to HIV resistance compared to other protease inhibitors, including work involving isothermal titration calorimetry that has demonstrated that darunavir has a particularly high affinity to the HIV-1 protease-binding site [51–53]. Whereas nucleoside/nucleotide reverse transcriptase inhibitors have been shown to have particularly favorable penetration ratios in the genital tract [54], several studies have also demonstrated good penetration of darunavir in the male genital tract [55,56]. These features of darunavir make it an attractive third agent for NPEP.

There are also promising NPEP agents among the newer integrase strand inhibitors. Whereas elvitegravir and raltegravir share similar genetic mechanisms of resistance [49,57], elvitegravir is now available in a one-daily pill coformulation with tenofovir and emtricitabine that may optimize adherence to a daily regimen. An NPEP tolerability trial evaluating the fixed-dose combination of tenofovir–emtricitabine–elvitegravir–cobicistat is underway, the results of which may help guide potential future use of this medication for NPEP. Dolutegravir has been recently US FDA-approved, and earlier studies have demonstrated that it is well tolerated and has a much higher barrier to resistance than raltegravir [58,59], which would be ideal for high-risk exposures to highly treatment-experienced individuals. In addition, it can be administered once daily and does not require metabolic boosting. Tolerability studies in HIV-uninfected patients and long-term clinical

experience are needed to guide whether this agent or other new compounds should be considered for routine use in NPEP.

Drug interactions during nonoccupational postexposure prophylaxis

It is important to note that emergency hormonal contraception administered concomitantly with prophylaxis and/or treatment for sexually transmitted infections (i.e. intramuscular ceftriaxone and high-dose oral azithromycin) may induce profound nausea when given as part of a postexposure 'package'. In addition, studies have demonstrated that nausea, headache, abdominal pain, and other somatic complaints can be frequent sequelae after sexual assault, even in the absence of new medications [60–62]. Coupled with the fact that tenofovir-based NPEP regimens are also associated with nausea [34–37], there is a high potential for nausea during a course of NPEP, particularly after sexual assault. Patients should receive counseling about this and be treated symptomatically with antiemetics. Raltegravir and tenofovir–emtricitabine can be safely used with hormonal contraceptives and gastric acid-lowering agents without dose adjustments. Of note, women should be instructed not to breastfeed while taking tenofovir–emtricitabine. Ritonavir-based regimens have the potential for a wide range of drug interactions with different classes of medications, so a thorough medication history is necessary before prescribing ritonavir [63]. Rifampin can increase metabolism of raltegravir, thereby reducing its plasma concentrations. If a patient is on rifampin therapy, either raltegravir should be avoided or the raltegravir dose should be 800 mg twice daily.

Duration of HIV testing after nonoccupational postexposure prophylaxis

Current CDC guidelines recommend follow-up HIV testing for NPEP through 24 weeks after the initial exposure [21]. A recent study reported the performance of six different rapid HIV antibody tests in known HIV-infected patients that were either on or off treatment, which had a sensitivity of 97–100% for all of the tests [64]. However, the performance of rapid tests in acute HIV infection was markedly lower [65,66]. The CDC Acute HIV Infection analysis compared the performance of fourth-generation HIV assays, which can detect both antibody and p24 antigen, to earlier-generation assays at three different sites using 62 positive nucleic acid amplification specimens (NAAT) as the gold standard. The sensitivities were as follows: 76–88% for fourth-generation tests, 55–57% for third-generation tests, and 22–33% for the rapid antibody tests [67]. On the basis of these data, the CDC recently proposed a new HIV testing algorithm that utilizes fourth-generation antigen/antibody testing as the screening test and obviates the need for western blot [68], although this sequence of testing has not yet been universally implemented. HIV RNA testing should be used if there is clinical suspicion for acute HIV infection, but expense and low positive predictive value in low probability settings should not make it a routine screening test. In light of recent advances in the sensitivity and specificity of HIV testing, the New York State AIDS Institute has recommended curtailing follow-up HIV testing for HIV-exposed persons using NPEP from 24 to 12 weeks postexposure [23]. On the contrary, the 2013 occupational PEP guidelines maintain that testing should continue through 24 weeks in most cases [22]. One specific exception to this is if an exposed patient seroconverts to hepatitis C after exposure to a source known to be coinfecting with HIV and hepatitis C, in

which case providers should extend HIV testing through 12 months. Otherwise, if a fourth generation is negative 3 months after completing the PEP medication course (i.e. at 4 months postexposure), then the USPHS guidance does not suggest additional HIV testing [22]. Further experience and data regarding the sensitivity and cost-effectiveness of fourth-generation testing will inform an appropriate necessary testing schedule. More sensitive HIV testing will help distinguish acute infections from rare PEP failures in patients presenting for NPEP. Any patient with signs or symptoms consistent with acute retroviral syndrome should be tested for HIV on an urgent basis with an RNA test, regardless of the timing of the exposure.

HIV risk counseling and preexposure prophylaxis

Prevention counseling is an essential component of any NPEP protocol. In a Boston NPEP study of 108 MSM, 21% reported unprotected sex while receiving NPEP, and 11% reported unprotected anal intercourse with a high-risk partner during follow-up [69]. Multiple studies have shown that patients may present for NPEP multiple times, ranging from 9 to 28%, depending on the setting [19,70–72]. However, studies that have primarily followed high-risk MSM have dispelled preconceptions that NPEP increases sexual behavior disinhibition [70,73]. On the contrary, these studies have demonstrated that effective counseling can be a powerful tool for reduction in risk-taking behavior and adherence to follow-up HIV testing. Therefore, providers should view NPEP as an educable opportunity for behavioral and biomedical risk-reduction counseling.

There are multiple potential evidence-based counseling opportunities for behavior change in high-risk individuals [74–76]. Providers should screen patients for high-risk sexual practices, such as unprotected sex, having multiple sex partners, and having HIV-infected partners. Patients should be informed that specific behaviors portend a higher cumulative risk of HIV acquisition, such as unprotected receptive anal intercourse as compared to other methods. Patients who use injection drugs should be encouraged to use sterile equipment when possible. The NPEP encounter can also be a key time to perform screening and counseling for sexually transmitted infections, substance use, and mental health conditions. If brief counseling sessions do not achieve risk reduction, then a referral to a behavioral specialist for intensive risk-reduction interventions may be considered [74–76]. These topics should be discussed with the source partner involved in the exposure if he or she is available for counseling. Source or exposed persons found to be HIV-infected should be promptly referred to an HIV provider to initiate antiretroviral therapy. For those individuals who believe they may have recurrent high-risk HIV exposures in the future, providers should consider engaging in a discussion about PrEP. Individuals who are unable to obtain insurance or state-based coverage of PrEP may be directed to Gilead's medication assistance program [77]. Additional research is needed to inform providers about how to optimize the transition from NPEP to PrEP for patients engaging in recurrent HIV risks.

In conclusion, since the introduction of recommendations for the use of PEP to prevent HIV transmission [3,21], understanding of optimal practices has expanded tremendously due to several PEP trial advances in HIV treatment research from the past 10 years. From the medication standpoint, there has been a shift from using zidovudine-based regimens to

tenofovir-based regimens, which has resulted in much lower toxicity and far better completion rates of the 28-day course. Additional tolerability and efficacy trials examining single daily dose regimens and newer agents are necessary to guide future NPEP practices, including situations in which clinical data raise concerns for possible transmission of resistant HIV. The fact that there are still nearly 50 000 new HIV infections in the United States annually [78] reflects marked underutilization of NPEP. Therefore, institutions should strive to educate providers and at-risk patients and about the rationale for NPEP in order to improve access to and delivery of services in settings in which patients may present after high-risk exposures. For those who continue to have high-risk exposures, programs that facilitate a seamless transition from NPEP to PrEP should be strongly considered, in concert with other prevention modalities.

Acknowledgements

S.J. and K.H.M. contributed to drafting and editing the manuscript.

Funding: K.H.M. receives funding from the Harvard University Center for AIDS Research (CFAR), an NIH-funded program (P30 AI060354; PI: Walker).

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Table 1

Nonoccupational postexposure prophylaxis laboratory monitoring (for exposed patients).

	Baseline	2 weeks after exposure	4 weeks after exposure	6 weeks after exposure	12 weeks after exposure	16 weeks after exposure	24 weeks after exposure
HIV Ab or Ag-Ab	CDC; NYSDOH; USPHS		CDC ^a ; NYSDOH	CDC ^a ; USPHS	CDC; NYSDOH; USPHS	USPHS ^b	CDC; USPHS ^c
Blood urea nitrogen, complete blood count, creatinine	CDC; NYSDOH; USPHS	CDC; NYSDOH; USPHS	NYSDOH				
Liver enzymes	CDC; NYSDOH; USPHS	CDC; NYSDOH; USPHS	NYSDOH				NYSDOH
Hepatitis C antibody (if source negative or unknown)	CDC; NYSDOH				CDC; NYSDOH		CDC; NYSDOH
Hepatitis C RNA, liver enzymes (if source seropositive)			NYSDOH		NYSDOH		
Hepatitis B surface antigen and antibody	CDC; NYSDOH		CDC ^a	CDC ^a	CDC		
GC, Chlamydia NAAT at site of exposure, rapid plasma reagent (RPR) (not for sexual assault)	CDC; NYSDOH	CDC; NYSDOH	CDC ^a	CDC ^a			

CDC, 2005 CDC NPEP guidelines [21]; NYSDOH, 2013 New York State DOH NPEP guidelines [23]; USPHS, 2013 USPHS HIV PEP guidelines [22].

^aFour or 6 weeks postexposure.^bOnly if fourth-generation test is used.^cOnly if fourth-generation test is not used.

Table 2

Completion rates of various postexposure prophylaxis regimens over past 10 years.

	Enrollment (N)	Inclusion criteria	Regimen(s)	Results
Rabaud <i>et al.</i> , 2005 [30]	121	Exposure within 48 h (or 140 h if rape); occupational and nonoccupational exposures; age 18	ZDV/3TC + LPV/RTV for 4 weeks	16.5% stopped early due to adverse effects; 64.5% completed therapy, 48.7% of whom reported adverse effects
Burty <i>et al.</i> , 2008 [31]	46	Exposure within 48 h; occupational and nonoccupational exposures; age 18	ZDV/3TC + FPV/RTV for 4 weeks	13.0% stopped early due to adverse effects; 47.8% completed therapy, 54.5% of whom reported adverse effects; no HIV seroconversions
Diaz-Brito <i>et al.</i> , 2012 [33]	ZDV/3TC + LPV/RTV: 102; ZDV/3TC + ATZ: 98	Age > 18; met criteria for Spain's PEP program; occupational and nonoccupational exposures	ZDV/3TC + LPV/RTV for 4 weeks; OR ZDV/3TC + unboosted ATZ for 4 weeks	LPV arm: 63.7% completed therapy; 15.7% stopped or switched due to adverse effects; ATZ arm: 64.3% completed therapy; 17.3% stopped or switched due to adverse effects; no HIV seroconversions in either arm
Mayer <i>et al.</i> , 2008 [34]	ZDV/3TC: 122; ZDV/3TC+PI: 119; TDF/3TC: 68; TDF/FTC: 44	Exposure within 72 h; sexual exposures; age 18	January 2000–May 2004: ZDV/3TC for low-risk exposures; ZDV/3TC + PI (mostly NFV) for high-risk exposures; May 2004–March 2005: TDF/3TC; March 2005–March 2006: TDF/FTC (N = 44); all groups treated for 4 weeks	ZDV/3TC: 42.1% completion; ZDV/3TC + PI: 38.8% completion; TDF/3TC: 87.5% completion; TDF/FTC: 72.7% completion; No HIV seroconversions in the TDF groups; 3 HIV seroconversions in the ZDV groups
Tosini <i>et al.</i> , 2010 [35]	188	Exposure within 48 h; occupational and nonoccupational exposures; age 18	TDF/FTC + LPV/RTV for 4 weeks	11.7% stopped early due to adverse effects; 88.3% completed therapy, 42.2% of whom reported adverse effects; No HIV seroconversions
Burty <i>et al.</i> , 2010 [36]	ZDV/3TC + TDF: 171; TDF/3TC + ATZ/RTV: 152	Exposure within 48 h; occupational and nonoccupational exposures; age 18	ZDV/3TC + TDF for 4 weeks; OR TDF/3TC + ATZ/RTV for 4 weeks	12.9% and 14.5%, respectively, stopped early due to adverse effects; ZDV/3TC + TDF: 81.5% completion; TDF/3TC + ATZ/RTV: 79.0% completion; no HIV seroconversions
Mayer <i>et al.</i> , 2012 [37]	100	Exposure within 72 h; sexual exposures; age 18	TDF/FTC + RAL for 4 weeks	84% completed regimen, 32% of whom occasionally missed second daily dose of RAL; none stopped early due to side effects; no HIV seroconversions

3TC, lamivudine; ATZ, atazanavir; FPV, fosamprenavir; FTC, emtricitabine; LPV, lopinavir; NFV, nelfinavir; PI, protease inhibitor; RAL, raltegravir; RTV, ritonavir; TDF, tenofovir; ZDV, zidovudine.

Table 3

Most common side effects of postexposure prophylaxis regimens over the past 10 years.

	Adverse effect							
	Nausea/ vomiting	Diarrhea	Headache	Fatigue/ weakness	Abdominal pain/bloating	Rash	Neuropsychiatric	Hyperbilirubinemia
ZDV/3TC + LPV/RTV [30]	66%	67%	NR	47%	NR	11%	NR	NR
ZDV/3TC + FPV/RTV [31]	73%	58%	NR	62%	NR	12%	NR	NR
ZDV/3TC + LPV/RTV [33]	48%	22%	NR	17%	(Included in nausea/ vomiting total)	1%	11%	NR
ZDV/3TC + unboosted ATZ [33]	34%	7%		23%		0%	16%	
TDF/3TC [34]	18.8%	31.3%	18.8%	28.1%	20.3%	NR	NR	NR
TDF/FTC [34]	22.5%	47.5%	22.5%	30.0%	47.5%	NR	NR	
TDF/FTC + LPV/RTV [35]	59%	78%	38%	78%	NR	2%	NR	NR
ZDV/3TC/TDF [36]	89%	40%	NR	78%	NR	NR	NR	NR
TDF/3TC + ATZ/RTV [36]	64%	38%		77%				87%
TDF/FTC + RAL [37]	27%	21%	15%	14%	16%	NR	NR	NR

3TC, lamivudine; ATZ, atazanavir; FPV, fosamprenavir; FTC, emtricitabine; LPV, lopinavir; NFV, nelfinavir; NR, not reported; PI, protease inhibitor; RAL, raltegravir; RTV, ritonavir; TDF, tenofovir; ZDV, zidovudine.