Updated Guidelines for Antiretroviral Postexposure Prophylaxis After Sexual, Injection Drug Use, or Other Nonoccupational Exposure to HIV—United States, 2016

from the
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U.S. Department of Health and Human Services

Update: Interim Statement Regarding Potential Fetal Harm from Exposure to Dolutegravir – Implications for HIV Post-exposure Prophylaxis (PEP). Please see attached file.

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CONTENTS

I. List of Tables and Figures

II. Abbreviations and Acronyms

3TC	lamivudine
Ab	antibody
Ag	antigen
Ag/Ab	antigen/antibody combination test
AIDS	acquired immunodeficiency syndrome
Anti-HBc	hepatitis B core antibody
Anti-HBs	hepatitis B surface antibody
aOR	adjusted odds ratio
ATV	atazanavir
ATV/r	ritonavir-boosted atazanavir
CAI	condomless anal intercourse
CA-NSI	community-acquired needlestick injury
CD4	CD4 T lymphocyte
CDC	Centers for Disease Control and Prevention
CI	confidence interval
d4T	stavudine
DDI	didanosine
DNA	deoxyribonucleic acid
DRV	darunavir
DRV/r	ritonavir-boosted darunavir
DTG	dolutegravir
DHHS	U.S. Department of Health and Human Services
ED	emergency department
EFV	efavirenz
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
FTC	emtricitabine
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HIV	human immunodeficiency virus
IDV	indinavir
IDV/r	ritonavir-boosted indinavir
IFA	indirect fluorescent antibody
LPV	lopinavir

LPV/r	ritonavir-boosted lopinavir
MSM	gay, bisexual, and other men who have sex with men
NAAT	nucleic acid amplification test
NFV	nelfinavir
NIH	National Institutes of Health
NNRTI	non-nucleoside reverse transcriptase inhibitors
NRTI	nucleoside reverse transcriptase inhibitors
NVP	nevirapine
nPEP	nonoccupational postexposure prophylaxis
oPEP	occupational postexposure prophylaxis
PCR	polymerase chain reaction
PI	protease inhibitor
PrEP	preexposure prophylaxis
PWID	persons who inject drugs
OR	odds ratio
PCR	polymerase chain reaction
PEP	postexposure prophylaxis
PrEP	preexposure prophylaxis
QALY	quality-adjusted life year
RAL	raltegravir
RNA	ribonucleic acid
RPV	rilpivirine
RTV	ritonavir
SANE	Sexual Assault Nurse Examiner
SD	standard deviation
SIV	simian immunodeficiency virus
SHIV	simian human immunodeficiency virus
STI	sexually transmitted infection
TDF	tenofovir disoproxil fumarate
ZDV	zidovudine

III. Disclosure of Potential Competing Interest

nPEP Guidelines Consultants and Working Group Potential Competing Interest. The federal government employees who prepared this report have no competing interests with the manufacturers of the products discussed herein. See Appendixes 1A, 1B, and 1C for the definition of competing interests for persons involved in guidelines development and procedures for managing conflicts of interest, lists of names and affiliations of the nPEP guidelines development teams and consultants, and financial disclosures of potential competing interests.

IV. Summary

The purpose of these guidelines is to provide health care providers in the United States with updated guidelines to the 2005 U.S. Department of Health and Human Services nonoccupational postexposure prophylaxis (nPEP) recommendations[1] on the use of antiretroviral nPEP and other aspects of case management for persons with isolated exposure outside health care settings to blood, genital secretions, or other potentially infectious body fluids that might contain human immunodeficiency virus (HIV). The use of occupational PEP (oPEP) for case management for persons with possible HIV exposures occurring in health care settings are not addressed in this guideline; updated oPEP guidelines have been published separately.[2]

IV-A. What Is New in This Update

This update incorporates additional evidence regarding use of nonoccupational postexposure prophylaxis (nPEP) from animal studies, human observational studies, and consideration of new antiretroviral medications that were approved since the 2005 guidelines, some of which have improved tolerability. New features are inclusion of guidelines for the use of rapid antigen/antibody (Ag/Ab) combination HIV tests, for revised preferred and alternative 3-drug antiretroviral nPEP regimens, an updated schedule of laboratory evaluations of source and exposed persons, updated antimicrobial regimens for prophylaxis of sexually transmitted infections and hepatitis, and a suggested procedure for transitioning patients between nPEP and HIV preexposure prophylaxis (PrEP), as appropriate.

IV-B. Summary of Guidelines

- Health care providers should evaluate persons rapidly for nPEP when care is sought ≤72 hours after a potential nonoccupational exposure that presents a substantial risk for HIV acquisition.[a] [VI-A4] [VII-A2][b]
    - All persons considered for nPEP should have determination of their HIV infection status by HIV testing, preferably by using rapid combined Ag/Ab, or antibody blood tests. [VII-A1] [VII-B1]
    - If rapid HIV blood test results are unavailable, and nPEP is otherwise indicated, it should be initiated without delay and can be discontinued if the patient is later determined to have HIV infection already or the source is determined not to have HIV infection. [VII-A1]

[a] See Figure 1.

[b] Numbers in brackets refers readers to the section in these guidelines that provides the basis for the recommendation.

- nPEP is recommended when the source of the body fluids is known to be HIV-positive and the reported exposure presents a substantial risk for transmission. [VII-A]

- nPEP is not recommended when the reported exposure presents no substantial risk of HIV transmission. [VII-A]

- nPEP is not recommended when care is sought > 72 hours after potential exposure. [VI-A4] [VII-A] [VII-A2]

- A case-by-case determination about the nPEP is recommended when the HIV infection status of the source of the body fluids is unknown and the reported exposure presents a substantial risk for transmission if the source did have HIV infection. [VII-A]

- All persons offered nPEP should be prescribed a 28-day course of a 3-drug antiretroviral regimen.[a] [VII-B1] [VII-C]

    - The preferred regimen for otherwise healthy adults and adolescents
        - tenofovir disoproxil fumarate (tenofovir DF or TDF) (300 mg) with emtricitabine (200 mg) once daily ***plus***

          raltegravir (RAL) 400 mg twice daily or dolutegravir (DTG) 50 mg daily. [VI-A2ci] [VII-C]

    - Alternative regimen for otherwise healthy adults and adolescents is
        - tenofovir DF (300 mg) with emtricitabine (FTC) (200 mg) once daily ***plus***

          darunavir (DRV) (800 mg) and ritonavir[a] (RTV) (100 mg) once daily. [VII-C]

    - Regimens are also provided for children, persons with decreased renal function, and pregnant women (see Table 6). [VII-C]

    - Health care providers considering using antiretroviral regimens for nPEP other than those listed in these guidelines as preferred or alternative are encouraged to consult with other health care providers who have expertise in antiretroviral medication use for similar patients (e.g., children, pregnant women, or those with such comorbid conditions as impaired renal function). [VII-C] [VII-E2]

- All persons evaluated for possible nPEP should be provided any indicated prevention, treatment, or supportive care for other exposure-associated health risks and conditions (e.g., bacterial sexually transmitted infections, traumatic injuries, hepatitis B virus and hepatitis C virus infection, or pregnancy). [VII] [VII-B3] [VII-B4] [VII-B5] [VII-D]

- All persons who report behaviors or situations that place them at risk for frequently recurring HIV exposures (e.g., injection drug use, or sex without condoms) or who report receipt of ≥ 1 course of nPEP in the past year should be provided risk-reduction counseling and intervention services, including consideration of preexposure prophylaxis. [VII-E4] [VII-E5]

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[a] Ritonavir is used in clinical practice as a pharmacokinetic enhancer to increase the trough concentration and prolong the half-life of darunavir and other protease inhibitors; it was not considered an additional drug when enumerating drugs in a regimen.

V. INTRODUCTION

The most effective methods for preventing human immunodeficiency virus (HIV) infection are those that protect against exposure. Antiretroviral therapy cannot replace behaviors that help avoid HIV exposure (e.g., sexual abstinence, sex only in a mutually monogamous relationship with an HIV-uninfected partner, consistent and correct condom use, abstinence from injection drug use, and consistent use of sterile equipment by those unable to cease injection drug use). Provision of antiretroviral medication after isolated sexual, injection drug use, or other nonoccupational HIV exposure, known as nonoccupational postexposure prophylaxis (nPEP), is less effective at preventing HIV infection than avoiding exposure.

In 2005, the U.S. Department of Health and Human Services (DHHS) released its first recommendations for nPEP use to reduce the risk for HIV infection after nonoccupational exposures to blood, genital secretions, and other body fluids that might contain HIV.[1] In 2012, updated guidelines on the use of occupational PEP (oPEP) for case management for persons with possible HIV exposures occurring in health care settings were published and are not addressed in this guideline.[2] Other organizations, including health departments, professional medical societies, and medical institutions, have developed guidelines, recommendations, and protocols for nPEP delivered to adults and children.[3-10]

This document updates the 2005 DHHS nPEP recommendations in response to new information regarding clinical experience for delivering nPEP, including using newer antiretroviral regimens and their side-effect profiles and cost-effectiveness of nPEP to prevent HIV infection for different exposure types. We describe in more detail the goals for the new guidelines, funding source of the guidelines, persons involved in guidelines development, definition of competing interest for persons involved in guidelines development and procedures for managing competing interest (Appendix 1A).

CDC scientists selected nPEP subject matter experts from the Food and Drug Administration (FDA), the National Institutes of Health (NIH), hospitals, clinics, health departments, and professional medical societies to participate as panelists to discuss recent developments in nPEP practice by CDC teleconferences in December 2011, and April 2012 (Appendix 1B). Any potential conflicts of interests reported by persons involved in developing the guidelines and the determination made for each of those potential conflicts are listed in Appendix 1C.

A working group of CDC HIV prevention scientists and other CDC scientists with expertise pertinent to the nPEP guidelines conducted nPEP-related systematic literature reviews. Appendix 2 summarizes the methods used to conduct that review, including databases queried, topics addressed, search terms, search dates, and any limitations placed on the searches (i.e., language, country, population, and study type). All studies identified through the literature search were reviewed and included in the body of evidence. Appendix 3 includes a summary of the key observational and case studies among humans that comprise the main body of evidence.

These nPEP guidelines are not applicable for occupational exposures to HIV; however, we attempted to standardize the selection of preferred drugs for nPEP and occupational postexposure prophylaxis (oPEP).[2] These guidelines also do not apply to continuous daily oral antiretroviral prophylaxis that is initiated before potential exposures to HIV as a means of reducing the risk for HIV infection among persons at high risk for its sexual acquisition (preexposure prophylaxis or PrEP[11]).

Among the limitations of these guidelines is that they are based on a historical case-control study related to occupational PEP among hospital workers, observational and case studies examining nPEP's effectiveness among humans, animal studies related to PEP's efficacy among primates, and expert opinion on clinical practice among humans related to nPEP. Because of concerns about the ethics and feasibility of conducting large-scale prospective randomized placebo-controlled nPEP clinical trials, no such studies have been

conducted. Additionally, although nPEP failures were rare in the observational studies we reviewed, those studies often have inadequate follow-up testing rates for HIV infection; therefore, nPEP failures might be underestimated. Because these guidelines represent an update of previous guidelines about a now established clinical practice, we elected not to use a formal grading scheme to indicate the strength of supporting evidence.

VI. Evidence Review

VI-A. Possible Effectiveness of nPEP

No randomized, placebo-controlled clinical trial of nPEP has been conducted. However, data relevant to nPEP guidelines are available from animal transmission models, perinatal clinical trials, observational studies of health care workers receiving prophylaxis after occupational exposures, and observational and case studies of nPEP use. Although the working group mainly systematically reviewed studies conducted after 2005 through July 2015, we also include findings from seminal studies published before 2005 that help define key aspects of nPEP guidelines. Newer data reviewed in this document continue to support the assertion that nPEP initiated soon after exposure and continued for 28 days with sufficient medication adherence can reduce the risk for acquiring HIV infection after nonoccupational exposures.

V1-A1. oPEP Studies

A case-control study demonstrating an 81% (95% confidence interval [CI] = 48%–94%) reduction in the odds of HIV transmission among health care workers with percutaneous exposure to HIV who received zidovudine (ZDV) prophylaxis was the first to describe the efficacy of oPEP.[12] Because of the ethical and operational challenges, no randomized controlled trials have been conducted to test the efficacy of nPEP directly. In the absence of a randomized controlled trial for nPEP, this case-control study reports the strongest evidence of benefit of antiretroviral prophylaxis initiated after HIV exposure among humans.

V1-A2. Observational and Case Studies of nPEP

The following is a synopsis of domestic and international observational studies and case reports that have been published since the 2005 U.S. nPEP guidelines were issued. In the majority of studies, failure of nPEP, defined as HIV seroconversion despite taking nPEP as recommended, was typically confirmed by a seronegative HIV enzyme-linked immunosorbent assay (ELISA) at baseline visit, followed by a positive ELISA and Western blot or indirect fluorescent antibody (IFA) during a follow-up visit.

VI-A2a. Men Who Have Sex with Men

Based on 1 case report[13] and 6 studies[14-19] reporting results exclusively or separately among men who have sex with men (MSM), 49 seroconversions were reported after nPEP use. The case report from Italy described an nPEP failure in an MSM despite self-reported 100% adherence to his 3-drug medication regimen consisting of ZDV, lamivudine (3TC), and indinavir (IDV) and denial of ongoing HIV risk transmission behaviors after completing nPEP; concomitant hepatitis C virus (HCV) seroconversion was also diagnosed.[13] In the 6 studies, 48 of 1,535 (31.3 seroconverions/1,000 persons) MSM participants became HIV infected despite nPEP use. At least 40 of the 48 seroconversions likely resulted from ongoing risk behavior after completing nPEP. Thirty-five of these 40 seroconversions occurred ≥ 180 days subsequent to nPEP initiation and are unlikely to constitute nPEP failures.[16,18] The remaining 8 seroconverters among 1,535 MSM participants (5.2 seroconverions/1,000 persons) may be classified as potential nPEP failures. This included 1 recipient with an indeterminate HIV test result and isolation of an M184 mutation resistant virus on the last day of his 28-day regimen despite initiating

nPEP ≤ 48 hours after exposure,[20] indicating that seroconversion was occurring during the 28-day period of nPEP administration. Another 4 patients seroconverted at 91 days, 133 days, 160 days, and 168 days after nPEP initiation, including 3 who reported completing the 28-day regimen; however, there was no description of the presence or lack of ongoing sexual risk behaviors after nPEP completion.[18] Among the remaining 3 men who seroconverted after taking nPEP, taking nPEP was not associated with any suggestion of change in seroconversion risk, although no information was reported regarding the nPEP regimen prescribed, adherence to nPEP, delay in nPEP initiation or timing of HIV-positive results.[15]

In a 2-year prospective study in Brazil, investigators provided 200 seronegative MSM at high risk with education regarding nPEP and a 4-day starter pack with instructions to initiate its use for a suspected eligible exposure.[16] A follow-up 24-day pack (to complete a 28-day course) was provided only for those men with eligible exposures. Sixty-eight of 200 MSM initiated nPEP. Adherence to nPEP medications was estimated on the basis of questions at the 28-day visit and remaining pill counts. The entire 28-day nPEP regimen was completed by 89% of men with eligible exposures including 1 participant who seroconverted. Ten of 11 seroconversions occurred among men who did not initiate nPEP.[16]

VI-A2b. Sexual Assault

VI-A2bi. General Population (all ages). Globally, 3 systematic reviews[20-22] and 1 prospective *cohort* study[23] spanning childhood through adulthood reported wide-ranging proportions of participants being eligible for nPEP (range, 6%–94%), being offered nPEP (range, 5%–94%), accepting nPEP (range, 4%–100%), or completing nPEP (range, 9%–65%). Among the 3 systematic reviews, none reported HIV screening results or the number of nPEP failures.[20-22]

VI-A2bii. Adults and Adolescents. Although nPEP use for sexual assault survivors has been widely encouraged both in the United States and elsewhere,[24-27] documented cases of HIV infection resulting from sexual assault of women or men rarely have been published.[25,28,29] Of 5 individual retrospective studies of nPEP limited to adult and/or adolescent sexual assault survivors that the working group reviewed, 3 reported no seroconversions at baseline or at follow-up among those sexual assault survivors who completed nPEP,[30-32] and 2 did not report any information about HIV screening results or the number of nPEP failures.[33,34]

VI-A2biii. Children and Adolescents. Studies of nPEP also have focused on children or adolescents evaluated for sexual assault. In a pooled analysis based on 10 studies of 8,336 children or adolescents evaluated for sexual assault or abuse, at least 1,362 were determined to be nPEP eligible. Twenty-four of the remaining 6,974 (3.4 seroconversions/1,000 persons) children or adolescents who were not eligible for nPEP were found to be HIV infected at baseline testing.[35-44] Among 672 children or adolescents reported to have been offered nPEP, 472 were known to have initiated nPEP, and 126 were reported to have completed a 28-day nPEP course. No new HIV infections were documented among these 472 (0.0 seroconversions/1,000 persons) children/adolescents in the pooled analysis who initiated nPEP. New HIV infections might have been underestimated as return rates for children or adolescents attending at least 1 follow-up visit during which an HIV test might have been conducted after initiating nPEP ranged from 10%[40] to 76%.[44]

VI-A2c. Mixed or Other Populations

VI-A2ci. Mixed populations. Eighteen studies, including 9 international studies[45-54] and 9 domestic studies[55-63] examined multiple routes of HIV risk exposure among adults, adolescents, and children with sexual and nonsexual exposures, including consensual sexual relations, sexual assault, injection drug use, and needlestick exposures.

Fifteen of the 19 studies reported both the number of participants who completed 28 days of nPEP and the number of participants who HIV seroconverted after initiating nPEP.[46-58,62,63] In these 15 studies, 2,209 participants completed 28 days of nPEP, of whom, at least 19 individuals HIV seroconverted,[45-48,52,54,56,62,63] but

only 1 seroconversion[47] (8.6/1,000) was attributed to nPEP failure. This seroconversion occurred 6 weeks after nPEP initiation in a sexually assaulted female who presented ≤ 4 hours after assault and completed nPEP.[47] She had a positive HIV RNA polymerase chain reaction (PCR) test but no confirmatory HIV ELISA test documented during the 5–6 week follow-up HIV testing period after initiating nPEP. Among the other 18 seroconversions that occurred during follow-up HIV testing among participants who completed 28 days of nPEP, 5 occurred ≥6 months after nPEP completion and were likely associated with ongoing sexual risk behavior after nPEP completion.[45,54] One seroconversion occurred after a participant reported poor adherence to nPEP, ongoing sexual risk behavior, and multiple nPEP courses after the initial course of nPEP, however, the timing of seroconversion was not clearly specified.[63] One seroconversion occurred in an MSM presenting with acute retroviral syndrome 3 weeks after condomless anal sex with an anonymous partner and no receipt of nPEP.[48] One seroconversion occurred in a woman during the 6-month follow-up period after completing nPEP and it was attributed to ongoing sharing of injection drug use equipment.[48] One seroconversion occurred in a patient who started nPEP > 72 hours after a high-risk exposure.[46] Additional seroconversions occurred at various time periods after initiation of nPEP without detailed information about ongoing sexual exposure or adherence to nPEP (2 and 5 months [n=2 participants][62]; 3 and 6 months [n=2 participants][52]; 5 months [n=1 participant][62]; and 12 months [n=1 participant]).[62] Among 3 participants who seroconverted while taking or shortly after taking ZDV-containing nPEP regimens, there was a lack of information about ongoing sexual exposure or detailed information about strict adherence to the full 28-day nPEP regimen.[56] However, only 33.8%–42.1% of all patients who were administered ZDV-containing nPEP regimens in this study completed their regimens as prescribed.[56]

In the remaining 4 of 19 studies, 2 studies did not report rates of HIVseroconversion[59,60] and 2 studies did not report rates of completion of the 28-day nPEP regimen,[45,61] including a study that reported 7 seroconversions that occurred at unspecified time periods during the 6 months after nPEP initiation among 649 users of nPEP.[61]Of all nPEP clients in this study, 18.5% had previously used nPEP between 1 and 5 times.[61]

In 3 domestic studies, participants who were administered tenofovir (TDF)-containing nPEP regimens were substantially more likely than historical control subjects in studies consisting of ZDV-containing regimens to complete their prophylaxis as prescribed and less likely to experience common side effects.[49,56,57,60] In two studies, the highest completion rates were observed for the TDF-3TC (87.5%) and TDF-emtricitabine (FTC) (72.7%) arms followed by the TDF-FTC-raltegravir (RAL) (57%) and ZDV-3TC-3rd drug arms (the 3rd drug was mainly a protease inhibitor [PI]) (38.8 %).[57] In addition to the 57% of patients who completed all 3 drugs of the TDF-FTC-RAL arm, 27% of patients took their TDF-FTC and first RAL dose daily, but sometimes missed the second dose of RAL.[57] In another study, the completion rates were highest in the TDF-FTC-ritonavir (RTV)-boosted lopinavir (LPV/r) arm (88.3%) compared with the TDF-3TC-RTV-boosted atazanavir (ATV/r) arm (79%), ZDV-3TC-LPV/r arm (77.5%), or ZDV-3TC-nelfinavir (NFV) arm (65.5%).[49] In the last domestic study, TDF-containing compared with ZDV-containing regimens were associated with significantly higher completion rates in the bivariate analysis (OR 2.80 [95% CI = 1.69–1.18]) but not in the multivariate analysis (OR 1.96 [95% CI = 0.73–5.28]).[60]

VI-A2cii. Other Populations. Data for 438 persons with unintentional nonoccupational needlestick or other sharps exposures described in 7 published reports were reviewed, including data for 417 children and 21 adults.[64-70] Childhood and adolescent exposures were characterized as community-acquired exposures occurring in public outdoor places (e.g., playgrounds, parks, or beaches) or by reaching into needle disposal boxes at home or in a hospital. Adult exposures were often similar to occupational exposures occurring while handling needles or disposing of needles in a sharps container. In all cases, the HIV status of the source person was unknown except in 1 report[64] involving multiple percutaneous exposures with lancets among 21 children while playing with discarded needles in a playground. Some of the lancets had been used multiple times to stick different children. One of the children stuck with a lancet was known to be HIV infected before the incident, not receiving antiretroviral therapy, and documented to have an HIV-1 plasma viral load of 5,250,000 copies/mL; the other 20 children were considered potentially exposed to HIV.[64] Additionally, in 1 of the studies, 2 children

were hepatitis B surface antigen (HBsAg)-positive at baseline before starting prophylaxis.[66] Among 155 children offered nPEP, 149 accepted and initiated nPEP, and 93 completed their 28-day nPEP course.[64-70] Antiretroviral prophylaxis with either ZDV and 3TC or ZDV, 3TC plus a PI (IDV, NFV, LPV/r) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) (nevirapine [NVP]) was used for those 149 children or adults accepting and initiating nPEP. No seroconversions for HIV, hepatitis B virus (HBV), or HCV were reported among those receiving or not receiving nPEP.[64-70]

In the case report of a 12-year old girl in Saudi Arabia with sickle-cell disease who was inadvertently transfused with a large volume of packed red blood cells, the use of a 13-week, 4-drug nPEP regimen of TDF, FTC, ritonavir-boosted darunavir (DRV/r) (later changed to LPV) and RAL resulted in loss of presence of detectable HIV-1 antibodies.[71] No HIV-1 DNA or plasma HIV-1 RNA was detected by PCR testing during the 8-month follow-up period.

VI-A3. Postnatal Prophylaxis of Infants Born to HIV-infected Mothers

Data regarding the efficacy of infant PEP to prevent mother-to-child HIV transmission provides only limited, indirect information about the efficacy of antiretroviral medications for nPEP. Postpartum antiretroviral prophylaxis is designed to prevent infection after contact of mucosal surfaces (ocular, oral, rectal, or urethral) or broken skin in the infant with maternal blood or other fluids that are present at time of labor and delivery, especially during vaginal births. Trials in which the infant was provided postpartum prophylaxis but the mother received neither prepartum or intrapartum antiretroviral prophylaxis provide the most relevant indirect data regarding nPEP after exposure to a source who did not have suppressed viral load secondary to antiretroviral therapy. Although a combination of prophylaxis during the prenatal, intrapartum, and postpartum periods offers the most effective reduction of perinatal transmission, postpartum prophylaxis alone also offers reduction.[72-75]

A randomized open-label clinical trial of antiretrovirals provided to infants born to breastfeeding HIV-infected women demonstrated an overall reduction in postnatal HIV infection at 14 weeks (the end of the period of prophylaxis) by approximately 70% (95% CI unreported). The trial compared a control group receiving a short-arm postnatal prophylaxis regimen and 2 comparison groups, each receiving different extended-arm postnatal prophylaxis regimens.[76] The control group received the short-arm regimen consisting of single-dose NVP plus 1-week ZDV and the 2 comparison groups received the control regimen and either 1) extended daily NVP for 14 weeks or 2) extended daily NVP and ZDV for 14 weeks. The corresponding HIV infection rates at 14 weeks were 8.5% in the control group, and 2.6% and 2.5% in the 2 extended arms comparison groups, respectively.

An observational study documented a potential effect of ZDV prophylaxis initially started postnatally compared with the prepartum and intrapartum periods. A review of 939 medical records of HIV-exposed infants in New York State indicated that the later the prophylaxis was started after the prepartum period, the higher the likelihood of perinatal transmission and that a benefit existed to postnatal prophylaxis alone (without maternal intrapartum or prepartum medication). Perinatal prophylaxis started during the prepartum, intrapartum, early postpartum ($\leq$48 hours after birth), and late postpartum (3 days–42 days) periods resulted in corresponding transmission rates of 6.1%, 10.0%, 9.3%, and 18.4%, respectively.[77] A perinatal transmission rate of 31.6% was observed when no perinatal prophylaxis was provided; the study included data from patients who had pregnancies early in the epidemic when HIV perinatal prophylaxis was first being implemented, and it was uncertain whether using intrapartum and/or postnatal prophylaxis alone was beneficial among mothers without prenatal care.

VI-A4. Animal Studies

Macaque models have been used to assess potential PEP efficacy. These studies examined artificial exposures to simian immunodeficiency virus (SIV) which varied by modes of exposure, virus innocula, and drug

regimens. The parameters imposed by those animal studies might not reflect human viral exposures and drug exposures, and those differences should be considered when interpreting their findings. Nevertheless, macaque models have provided important proof-of-concept data regarding PEP efficacy. More recent animal studies have tested the effectiveness of newer antiretrovirals and alternate routes of PEP administration. Subcutaneous tenofovir was reported to block SIV infection after intravenous challenge among long-tailed macaques if initiated ≤ 24 hours after exposure and continued for 28 days.[78] All 10 macaques initiated on PEP at 4 or 24 hours post inoculation were documented to be SIV-uninfected at 36–56 weeks post inoculation compared with all 10 macaques that failed to receive any prophylaxis and became SIV infected within 20–36 weeks post-inoculation. In a study of 24 macaques, TDF was less effective if initiated 48 or 72 hours post-exposure or if continued for only 3 or 10 days.[79] In contrast, all 11 macaques became SIV infected in a study involving 3 control macaques receiving no prophylaxis and 8 macaques receiving a combination of ZDV, 3TC, and IDV administered orally through nasogastric catheter after intravenous virus inoculation at 4 or 72 hours post-SIV inoculation.[80] High virus innocula and drug exposures that are lower than those achieved among humans as a result of inadequate interspecies adjustment of drug dosing might have contributed to the lack of protection reported for that study. However, a macaque study designed to model nPEP for vaginal HIV exposure demonstrated that a combination of ZDV, 3TC and a high dose of IDV protected 4 of 6 animals from vaginal SIV infection when initiated ≤ 4 hours after vaginal exposure and continued for 28 days, whereas 6 of 6 animals in the control group receiving a placebo became SIV infected.[81] In another study, after 20 vaginal simian/human immunodeficiency virus infection (SHIV) challenges and a 10-week follow-up period, 5 of 6 macaques were protected when treated with topically applied gel containing 1% RAL 3 hours after each virus exposure compared with none of four macaques treated with placebo gel.[82] Likewise, macaques administered subcutaneous TDF for 28 days, beginning 12 hours (4 animals) or 36 hours (4 animals) after vaginal HIV-2 exposure, were protected from infection. Three of 4 animals treated 72 hours after exposure were also protected.[83] Three of 4 untreated animals in the control group became infected with HIV-2. Overall, data from these macaque studies demonstrate that PEP might be effective among humans if initiated ≤ 72 hours and continued daily for 28 days. In a systematic review and meta-analysis of 25 nonhuman primate studies, including rhesus macaques in10 studies and cynomolgus monkeys in 5 studies, use of PEP was associated with an 89% lower risk of seroconversion compared with nonhuman primates who did not use PEP. Also, use of tenofovir compared with other drugs was associated with lower seroconversion.[84]

VI-B. Possible Risks Associated with nPEP

Concerns regarding potential risks associated with nPEP as a clinical HIV prevention intervention include the occurrence of serious adverse effects from the short-term use of antiretroviral medications by otherwise healthy persons without HIV infection, and potential selection for drug-resistant strains of virus among those who become HIV infected despite nPEP use (particularly if medication adherence is inconsistent during the 28-day course or if the source transmits resistant virus). An additional concern is that persons engaging in consensual sex or nonsterile injection drug use may rely solely on PEP instead of adopting more long-term risk-reduction behaviors such as safer sexual and drug-injecting behaviors.

VI-B1. Antiretroviral Side Effects and Toxicity

In a meta-analysis[20] of 24 nPEP-related studies, including 23 cohort studies and 1 randomized clinical trial (behavioral intervention to improve nPEP adherence), of 2,166 sexually assaulted persons, clinicians prescribed 2-drug regimens,[36,38,40,42,85-88] 3-drug regimens,[23,31,58,89-92] 2- and 3-drug regimens,[30,32,50,93,94] or an unknown number of drugs.[46,95-97] ZDV was a part of all the regimens and all 2-drug regimens contained ZDV and 3TC, except 1 study in which ZDV and zalcitabine were prescribed.[88] Antiretrovirals provided as a part of 3-drug regimens included ZDV, 3TC, NFV, IDV, LPV/r, NVP, efavirenz (EFV), or co-formulated FTC/TDF with co-formulated LPV/r. Nausea, vomiting, diarrhea, and fatigue were the most commonly reported side effects.[20]

Serious side effects have been reported occasionally (e.g., nephrolithiasis and hepatitis) in the literature.[98-100] Rarely, severe hepatotoxicity has been observed among patients administered NVP-containing regimens for both oPEP and nPEP, including a female health care worker who required a liver transplantation after taking oPEP[101]; therefore, CDC advises against use of NVP forPEP.[1,99] Also, since January 2001, product labeling for NVP states that using it as part of a PEP regimen is contraindicated.[102]

A retrospective study in western Kenya involved 296 patients who were eligible for and initiated nPEP, including 104 who completed a 28-day course of nPEP; patients received either stavudine (d4T), 3TC and NVP or ZDV, 3TC, and LPV/r.[47] Neither the proportion of patients reporting side effects (14% [LPV-containing arm] and 21% [NVP-containing arm]) nor antiretroviral therapy completion rates differed substantially between the 2 arms. The most commonly reported side effects included epigastric pain, skin rash, and nausea among patients receiving NVP-containing regimens and diarrhea, dizziness, and epigastric pain among those receiving LPV/r-containing regimens. However, 1 hepatitis-related death of a sexual assault survivor taking a NVP-containing regimen prompted investigators to change to a new PEP regimen containing ZDV, 3TC, and LPV/r. Inclusion of NVP and d4T were initially included in nPEP regimens because of availability and cost but were discontinued in 2005 as a result of adverse events and toxicities among healthy patients. This change was also influenced by a black box warning in the drug labeling for NVP describing increased toxicity among patients on NVP with higher CD4 T lymphocyte (CD4) cell counts.

Commonly used medications in the observational studies of nPEP published after 2005 included ZDV, 3TC, LPV/r, TDF, FTC, and RAL. The majority of regimens involved using 3 drugs (range, 2–4 drugs) with a daily 2-pill burden (range, 1–3 pills). The side-effect profile that included fatigue, nausea, headache, diarrhea, and other gastrointestinal complaints was similar across studies of MSM having mainly consensual sex and studies of sexual assault survivors, including mainly women, children, and a limited proportion of men.[20,23,31,44,55-57,103]

Two trials, including a total of 602 participants, compared TDF- versus ZDV-containing nPEP regimens; both reported better medication tolerability among participants taking TDF-containing regimens.[49,56] Another study reported fewer side effects among 100 adult participants prescribed a 3-drug nPEP regimen that included RAL, TDF, and TDF compared to historical controls using a 3-drug PEP regimen including ZDV, 3TC, and a RTV-boosted PI.[57]

In an open-label, nonrandomized, prospective cohort study comparing RAL-FTC-TDF in 86 MSM and FTC-TDF in 34 MSM, 92% and 91% of participants completed 28 days of treatment, respectively, with mean adherences of 89% and 90%, respectively.[17] Use of RAL rather than a PI was associated with the avoidance of 8 prescribed drug, and 37 potential illicit drug, interactions. However, in the RAL arm, 8 recipients (9%) developed mild myalgias, and 4 recipients developed grade 4 elevations in creatinine kinase. Both the myalgias and creatinine kinase elevations improved to grade 2 or less by week 4 without RAL discontinuation.

Among 100 MSM in an open-label, single-arm study at 2 public health clinics and 2 hospital EDs in urban areas in Australia, a once daily 28-day nPEP single-pill combination regimen of FTC-rilpivirine (RPV)-TDF was well tolerated with 98.5% adherence by self-report and 92% completion of the 28-day regimen.[19] However, within 1 week of completing nPEP, 1 patient developed acute abdominal pain, vomiting, and grade 4 laboratory evidence of acute pancreatitis (lipase 872 IU/L). The pancreatitis resolved ≤ 21 days without need for hospitalization.[19]

In a 2-arm open label randomized multicenter clinical trial in EDs in 6 urban hospitals in Barcelona, Spain, comparing ZDV/3TC + LPV/r with ZDV/3TC + atazanavir (ATV), 64% of nPEP recipients in both arms completed the 28-day course and 92% of patients reported taking > 90% of scheduled doses (without difference between arms).[53] Adverse events were reported in 46% of patients overall (49%, LPV/r arm; 43%, ATV arm). Gastrointestinal problems were more common in the LPV/r arm.

A pooled series of case reports revealed that 142 (67%; range, 0%–99%) of 213 children and adolescents who initiated nPEP and who had ≥1 follow-up visit, reported adverse effects and 139 of 465 (30%; range, 0%–64.7%) children and adolescents who initiated nPEP, completed their course of nPEP.[32,35-44] Most commonly reported nPEP regimens included ZDV + 3TC or ZDV + 3TC + (NFV or IDV or LPV/r). Most common adverse events among the 213 participants included nausea (n = 83; 39%), fatigue (n = 58; 27%), vomiting (n = 38; 18%), headache (n = 26; 12%), diarrhea (n = 25; 12%), and abdominal pain (n = 15; 7%).

V1-B2. Selection of Resistant Virus

In instances where nPEP fails to prevent infection, selection of resistant virus by the antiretroviral drugs is theoretically possible. However, because of the paucity of resistance testing in documented nPEP failures, the likelihood of resistance occurring is unknown.

A case report from Brazil documented a 3TC-resistance mutation on day 28 of therapy in a man treated with ZDV and 3TC who subsequently underwent HIV seroconversion.[16] Although the patient was noted to have taken nPEP, detailed information regarding adherence was unreported. Because the source-person could not be tested, whether the mutation was present at the time of transmission or whether it emerged during nPEP use is unknown.

Rationale for the concern regarding acquiring resistant virus from the exposure that leads to nPEP prescription includes data from an international meta-analysis of 287 published studies of transmitted HIV-1 drug resistance among 50,870 individuals during March 1, 2000–December 31, 2013, including 27 studies and 9,283 individuals from North America.[104] The study-level estimate of transmitted drug resistance in North America was 11.5% (resistance to any antiretroviral drug class), 5.8% (resistance to NRTIs), 4.5% (resistance to NNRTIs, and 3.0% (resistance to PIs).

VI-B3. Effects of nPEP on Risk Behaviors

The majority of studies examining the association between use and availability of nPEP and sexual risk behaviors during or after its use have been conducted in developed countries, primarily among MSM; no studies related to risk compensation were conducted among persons with injection-related risk factors.[14,16,105-111] The majority of these studies did not report increases in high-risk sexual behaviors after receipt of nPEP[14,16,106,110,111] and participants sometimes reported a decrease in sexual risk-taking behavior.[16,106] However, in 3 studies, nPEP users were more likely than persons who did not use nPEP to report having multiple partners and engaging in condomless receptive or insertive anal sex with HIV-infected partners or partners with unknown serostatus after completing nPEP.[14,108,110] In 2 of these studies, nPEP users were also more likely to subsequently become HIV infected than patients who did not use nPEP.[108,110] During 2000–2009 in the Amsterdam Cohort Study, MSM who were prescribed nPEP, compared with a reference cohort of MSM, had an incidence of HIV infection approximately 4 times as high (6.4 versus 1.6/100 person-years).[108] During 2001–2007, MSM in a community cohort study in Sydney, Australia reported continued, but not increased, high-risk sexual behaviors among nPEP users; more specifically, no change in sexual behavior was reported at 6 months after 154 incident nPEP uses and after ≥18 months for 89 incident nPEP uses. Among those MSM who received nPEP, the hazard ratio of subsequent HIV infection was 2.67 (95% CI = 1.40, 5.08).[110] The authors did not attribute this elevated risk for HIV seroconversion among users of nPEP to nPEP failure but rather to a documented higher prevalence of condomless anal intercourse (CAI) with HIV-infected partners among users of nPEP, compared with persons who did not use nPEP. In summary, users of nPEP, compared with participants who did not use nPEP had a continued higher prevalence of ongoing CAI with HIV-infected persons resulting in a greater likelihood of HIV seroconversion during all periods, especially after completing nPEP. In another study, repeated courses of nPEP were unassociated with risk for subsequent HIV infection.[45] In a study of 99 patients who attended a clinic in Toronto to be evaluated for nPEP during January 1, 2013–September 30, 2014, 31 (31%) met CDC criteria for

PrEP initiation.[112] PrEP candidacy in this study was associated with sexual exposure to HIV, prior nPEP use, and lack of drug insurance. Those studies[14,108,110,112] demonstrate that certain nPEP users with ongoing high-risk sexual behaviors might need additional behavioral and biomedical prevention interventions, including PrEP, instead of nPEP.[11,113]

One U.S.-based study among 89 MSM that examined risk behavior during the 28-day course of nPEP reported that among participants, 21% reported having insertive or receptive CAI, and 43% reported engaging with ≥ 1 partner known to be HIV-positive or of unknown serostatus (i.e., a high-risk partner).[105] Ninety-four percent of participants reporting having high-risk partners also reported having insertive or receptive anal intercourse. Of participants with high-risk partners and who practiced insertive or receptive anal intercourse, 26% reported CAI with their high-risk partner while receiving nPEP. The strongest predictor of CAI during nPEP in that study was HIV engagement, defined as receiving services from an HIV-related organization, donating money to or volunteering for an HIV-related cause, or reading HIV-related magazines and online sites. A nearly 5-fold chance of reporting condomless sex with a high-risk partner during nPEP was associated with each standard deviation increase in HIV engagement (OR 4.7 [95% CI = 1.3–17.04]). Investigators hypothesized that persons who are more involved with HIV-related services or organizations might be more informed about the effectiveness of nPEP and more likely to perceive themselves to be at less risk for HIV transmission while receiving nPEP and therefore more likely to have CAI.[105]

Awareness of nPEP availability, defined as general knowledge of availability of nPEP as a tool for preventing HIV infection after a potential HIV exposure[107] or nPEP use more than once in 5 years,[103] was associated with condomless sex among MSM.[103,107] Additionally, a longitudinal study of MSM in the Netherlands reported no associations existed between any nPEP-related beliefs (e.g., perceiving less HIV or acquired immunodeficiency syndrome (AIDS) threat, given the availability of nPEP, or perceiving high effectiveness of nPEP in preventing HIV) and the incidence of sexually transmitted infections (STIs) or new HIV infection.[109]

VI-C. Antiretroviral Use During Pregnancy

No trials have been conducted to evaluate use or the maternal or fetal health effects of short-term (i.e., 28-day) antiretroviral use as nPEP among pregnant women without HIV infection. However, clinical trials have been conducted and extensive observational data exist regarding use of specific antiretrovirals during pregnancy among HIV-infected women both when initiated as treatment for health benefits to the women and when initiated to reduce mother-to-child HIV transmission. Although duration of antiretroviral use during pregnancy has varied in these trials, it often spans months of pregnancy. Only ZDV is specifically approved for use in pregnancy, but as a result of data from clinical trials, other antiretroviral drugs have been reported to have short-term safety for pregnant women and their fetuses, and therefore can be considered for nPEP in women who are or who might become pregnant. See *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States* for information regarding use of specific antiretrovirals during pregnancy.[114] Additionally, results from ongoing surveillance of major teratogenic effects related to antiretroviral use during pregnancy are described in the Antiretroviral Pregnancy Registry International Interim Report every 6 months.[115]

Certain antiretrovirals have been associated with severe side effects, toxicity, potential for teratogenicity, or other untoward effects among pregnant and non-pregnant women with HIV infection[114] and therefore are not recommended for nPEP use (see section VII-F2b. Pregnant Women and Women of Childbearing Potential for a list of antiretroviral medications that should not be used for nPEP in pregnant women). These include EFV, NVP, and d4T plus didanosine (DDI).[114] Using IDV without RTV-boosting demonstrated altered drug metabolism during pregnancy.[116,117] No severe side effects, toxicity, or adverse pregnancy outcomes have been reported to occur among HIV-uninfected women taking antiretrovirals for oPEP or nPEP.

Reports are conflicting regarding whether an association exists of substantial malformations with use of EFV during the first trimester among humans. Studies using cynomolgus monkeys reported a potential association between neurologic congenital malformations and first-trimester use of EFV.[118] Although case reports exist of neurologic defects among infants of women receiving EFV,[119,120] no elevated risk for overall congenital malformations associated with first-trimester EFV exposure have been reported in either prospectively reported pregnancies from the Antiretroviral Pregnancy Registry[115] or from a meta-analysis of 23 studies with birth outcomes from 2,026 live births among women receiving EFV during the first trimester.[121]

HIV-infected pregnant women receiving combination antiretroviral regimens that included NVP have been reported to suffer severe hepatic adverse events, including death. However, whether pregnancy increases the risk for hepatotoxic events associated with NVP therapy is unknown. Use of NVP in HIV-infected women (regardless of pregnancy status) with high CD4 counts > 250 cells/mm^3[102] or elevated transaminase levels at baseline[122] has been associated with potentially life-threatening rash and hepatotoxicity. NVP use in 3 HIV-infected women with CD4 counts <100 cells/mm^3 at baseline has been associated with death among those also taking anti-tuberculosis therapy.[122]

Among antiretroviral medication combinations no longer recommended, regimens containing d4T with DDI have been associated with severe maternal lactic acidosis among pregnant HIV-infected women,[123,124] including severe necrotic pancreatic and hepatic steatosis and necrotic cellulitis of the abdominal wall in 1 woman,[123] 1 fetal demise (normal for gestational age) at 38 weeks gestation,[124] and 1 postnatal death at age 2 weeks in a 1,000 gram infant with trisomy 18.[123] Additionally, using IDV without RTV-boosting during pregnancy results in substantially lower antepartum exposures of IDV, compared with use of RTV-boosted IDV.[116,117]

VI-D. Behavioral Intervention to Support Risk Reduction During nPEP Use

Study findings from 2 randomized control trials underscore the importance of combining nPEP with behavioral interventions[125] to support continuing risk reduction. In a randomized controlled counseling intervention trial among nPEP recipients at a single U.S. site, investigators compared behavioral effects among those who received 2 (standard) versus 5 (enhanced) risk-reduction counseling sessions. Both interventions were based on social cognitive theory, motivational interviewing, and coping effectiveness. Compared with baseline, a reduction occurred at 12 months in the reported number of condomless sex acts for both intervention arms. The group reporting ≤ 4 condomless sex acts during the previous 6 months at baseline benefitted more from the 2-session intervention, while persons reporting ≥ 5 condomless sex acts during the previous 6 months at baseline revealed a greater reduction of condomless sex acts after receiving the 5-session intervention.[126] These findings demonstrate that more counseling sessions might be necessary for persons reporting higher levels of sexual risk behavior when initiating nPEP. In another randomized control trial, MSM who received contingency management, a substance abuse intervention providing voucher-based incentives for stimulant-use abstinence, had greater nPEP completion rates, greater reductions in stimulant use, and fewer acts of condomless anal intercourse compared with control participants who received incentives that were not contingent on their substance abstinence.[127]

VI-E. Adherence to nPEP Regimens and Follow-up Visits

Difficulties in adherence have been noted in both maintaining adherence to daily doses of antiretroviral medication for 28 days among the majority of populations and adherence to follow-up clinical visits for HIV testing and other care. Such adherence difficulties appear particularly severe in studies of nPEP for sexually assaulted persons. Methods for measuring completion of nPEP medication regimen differed across studies, and loss to follow-up was a major hindrance to assessing medication adherence for the majority of studies.

In a systematic review and meta-analysis of 34 nPEP studies not including sexual assault and 26 nPEP studies including only sexual assault, nPEP completion rates were lowest among persons who experienced sexual assault (40.2% [95% CI = 31.2%, 49.2%]) and highest among persons who had other nonoccupational exposures (65.6% [95% CI = 55.6%, 75.6%]).[128] In a separate meta-analysis of 24 nPEP-related studies, including 23 cohort studies and 1 randomized behavioral intervention to improve nPEP adherence, of 2,166 sexually assaulted persons receiving nPEP and pooled across the 24 studies, 40.3% (95% CI = 32.5%–48.1%; range, 11.8%–73.9%) adhered to a 28-day course of nPEP, and 41.2% (95% CI = 31.1%–51.4%; range, 2.9%–79.7%) did not return to pick up their prescribed medication or did not return for follow-up appointments.[20] Medication adherence was measured in 24 studies by using varying methodology, including pill count, volume of syrup remaining, self-report, counts of number of pharmacy visits, recall of number of doses taken by notation on a calendar, number of prescriptions filled, and number of weekly clinic appointments kept. Reported medication adherence was lower in developed countries (n=15 studies, 5 countries)[23,30-32,36,38,46,50,58,88-92,94,97] compared with developing countries (n=8 studies, three countries)[40,42,85-87,93,95,96] (33.3% versus 53.2%, respectively; *P*=0.007), possibly due to higher awareness of HIV transmission risk in countries with a high HIV prevalence.[20] Eight of the 24 (33%) studies[30,32,46,86-89,97] provided nPEP medications at time of initiation of prophylaxis as starter packs including 4–7 days of medication, and 1 study provided either a starter pack of medications or a full 28-day supply of nPEP at initiation.[96] In this latter study, the proportion who adhered to the 28 days of nPEP was 29% for patients initially receiving the starter pack and 71% for patients receiving a full 28-day supply.[96]

Although sexually assaulted persons are sometimes at risk for HIV transmission, they often decline nPEP, and many who do take it do not complete the 28-day course. This pattern has been reported in multiple countries and in programs in North America. In Ontario, for example, 798 of 900 eligible sexually assaulted persons were offered nPEP, including 69 and 729 at high or unknown risk for HIV transmission due to the factors associated with their sexual assault, respectively.[23] Forty-six (67%) of 69 persons at high risk for HIV transmission and 301 (41%) of 729 persons with unknown risk accepted and initiated nPEP. Twenty-four percent of patients at high risk and 33% of patients with unknown risk completed the 28-day course. Reasons for discontinuing treatment were documented in 96 cases and included adverse effects (81%), interference with routine (42%), inability to take time away from work or school (22%), and reconsideration of HIV risk (19%).

Of the observational studies of sexually assaulted persons provided nPEP, the majority identified similar challenges. Studies have demonstrated that early discontinuation of medication and a lack of follow-up pose challenges to providing nPEP to sexually assaulted persons.[31,33,47,50]

Four international studies examined adherence among both men and women with non-assault sexual and injection drug use risk exposures.[46,48,49,51] Full medication adherence in these studies ranged from 60%–88%; 60%[48] and 79%[51] completed therapy (without specifying how completion was defined) and 67%[48] and 88%[49] completed 28 days or 4 weeks of nPEP. The proportion of MSM who adhered to nPEP medication for 28 days reported in those studies ranged from 42%–91%.

Studies that used a fixed dose combination of ZDV/3TC and LPV/r as primary components in the nPEP drug regimen reported low medication adherence for 28 days (24%–44%).[23,44,47] A study among MSM compared use of a fixed-dose combination regimen containing TDF/FTC with or without RAL (an integrase inhibitor) with ZDV/3TC and a RTV-boosted PI; adherence rates were superior for the TDF-containing regimens (57% [with RAL]–72.7% [without RAL]) compared with the PI-containing regimen (46%). Although 57% of the TDF/FTC/RAL arm reported taking their medications as directed, an additional 27% took their once daily medication, but sometimes missed their second daily dose of RAL.[57]

VI-F. nPEP Cost-effectiveness

Estimates of cost-effectiveness of nPEP as an HIV prevention method reported in the literature vary by HIV exposure route and estimated prevalence of infection among source persons. A study using data from the San Francisco nPEP program estimated the cost-effectiveness of hypothetical nPEP programs in each of the 96 metropolitan statistical areas in the United States.[129] It included 3 different data sources, including data from clinical care and drug cost data from the San Francisco Department of Public Health nPEP program,[130] estimates of the per-act probability of HIV transmission associated with different modes of sexual and parenteral HIV exposure,[131-133] and HIV prevalence data from 96 U.S. metropolitan statistical areas.[134] Investigators estimated the cost-effectiveness of hypothetical nPEP programs as an HIV prevention method in each area compared with no intervention. By defining cost-effective programs as those costing <$60,000/quality-adjusted life year (QALY), that study found nPEP programs were cost-effective across the combined metropolitan statistical areas with a cost utility ratio of $12,567/QALY saved (range, $4,147–$39,101). nPEP was most cost-effective for MSM ($4,907/QALY). It was not cost-effective for needle-sharing persons who inject drugs (PWID) ($97,867/QALY), persons sustaining nonoccupational needlesticks ($159,687/QALY), and receptive female partners ($380,891/QALY) or insertive male partners ($650,792/QALY) in penile-vaginal sex. The hypothetical nPEP program would be cost-saving (cost-utility ratio, <$0) only for men and women presenting with receptive anal intercourse or if nPEP use was limited to clients with known HIV-infected partners.[129] In another study limited to San Francisco, the overall cost-utility ratio for the existing nPEP program was $14,449/QALY saved and for men experiencing receptive anal sex, the nPEP program was cost-saving.[130]

Studies in Australia and France reported similar results. For example, in Australia, using a threshold for cost-effectiveness of $50,000/QALY, nPEP was cost-effective among persons having CAI with an HIV-infected source ($40,673/QALY).[135] In France, using thresholds for cost-saving and cost-effectiveness of €0/QALY saved and <€50,000/QALY saved, respectively, nPEP was cost-saving among men and women who had receptive anal intercourse with an HIV-infected man (-€22,141/QALY saved [men]; and -€22,031/QALY saved [women]) and cost-saving among PWID having shared needles with an HIV-infected person (-€1,141/QALY saved).[136]

Additionally, these same French and Australian studies, and a Swiss study, reported that HIV testing to determine the status of the source person (when possible) was determined to reduce costs associated with nPEP programs by avoiding unnecessary prophylaxis.[48,135,136]

VI-G. Attitudes, Policies, and Knowledge About nPEP Use Among Health Care Providers and Candidates for nPEP

Since 1997, certain health care providers, health policy makers, and scientific investigators of nPEP have recommended wider availability and/or use of nPEP,[24,131,137-144] while others have been more cautious about implementing it in the absence of definitive evidence of efficacy or effectiveness.[145,146] Multiple public health jurisdictions in the U.S., including the New York State AIDS Institute, the San Francisco County Health Department, the Massachusetts Department of Public Health, the Rhode Island Department of Health, and the California State Office of AIDS, have issued policies or advisories for nPEP use.[3,4,147,148]

Surveys of health care providers and facilities indicate a low level of awareness and capacity to provide nPEP as well as a lack of access for nPEP for those for whom it is recommended need for more widespread dissemination and implementation of guidelines and protocols for nPEP use and a need for improved access. In a study of 181 patients presenting to the emergency department (ED) who had been sexually assaulted, lack of insurance, older patient age, and acquaintance rape were factors associated with not being offered nPEP.[30] A study evaluating access to nPEP services in 117 health care sites in Los Angeles County through use of Internet

searches and telephone surveys, determined that only 14% offered nPEP to clients regardless of insurance status, and an even lower percentage, 8%, offered nPEP to uninsured clients, indicating the need to improve access to such services.[149] A survey in New York State (NYS) reported that among 184 EDs, 88% reported evaluating patients with possible nonoccupational exposures to HIV in accordance with NYS guidelines, however, full implementation of NYS nPEP guidelines was incomplete with 4% neither supplying nor prescribing antiretroviral drugs in the ED and only 22% confirming whether linkage to follow-up care was successful.[150] Screening of STIs, risk-reduction counseling, and education about symptoms of acute HIV seroconversion were not consistently performed according to the NYS guidelines.[150] Additionally, in a survey of 142 HIV health care providers in Miami and the District of Columbia, prescribing nPEP was associated with having patients request nPEP, or having a written nPEP protocol, although most providers reported not having a written nPEP protocol and that patients rarely or never requested nPEP.[151] Lack of prescribing nPEP was associated with believing that nPEP would lead to antiretroviral resistance.[151] More health care providers in the District of Columbia compared with those in Miami, prescribed nPEP (59.7% versus 39.5%, respectively $P < 0.048$).[152] In a cross-sectional study describing program practices related to HIV testing and nPEP among 174 sexual assault nurse examiner (SANE)/forensic nurse examiner (FNE) programs in the U.S. and Canada, 75% had nPEP policies, 31% provided HIV testing, and 63% offered nPEP routinely or based on patient request.[153] Medication cost was the most important barrier to providing nPEP in these programs.

Awareness, knowledge, and use of nPEP has been described among MSM.[14,15,106,108,110,154] Evidence indicates awareness of nPEP and interest in its use among potential patients. When nPEP studies were established in San Francisco, approximately 400 persons sought treatment during December 1997–March 1999.[106,154] In an HIV prevention trial of 4,295 MSM in 6 U.S. cities during 1999–2003, a total of 2,037 (47%) had heard of nPEP at baseline and 315 (7%) reported using nPEP on ≥1 occasion.[14] Predictors of nPEP use included having multiple partners, engagement in condomless sex with a known HIV-infected partner or with a partner of unknown HIV status, and use of illicit drugs. Among 1,427 MSM in a community cohort of HIV-negative men in Sydney, Australia, during 2001–2007, knowledge of nPEP increased from 78.5% at baseline to 97.4% by the fifth annual interview, and nPEP use increased from 2.9/100 person-years in 2002 to 7.1/100 person-years in 2007.[110] During 2006–2009, knowledge of nPEP among MSM from urban areas in the Netherlands increased from 46% to 73%.[108] Also, the annual number of PEP prescriptions to MSM in Amsterdam increased 3-fold, from 19 in 2000 to 69 in 2007.[15]

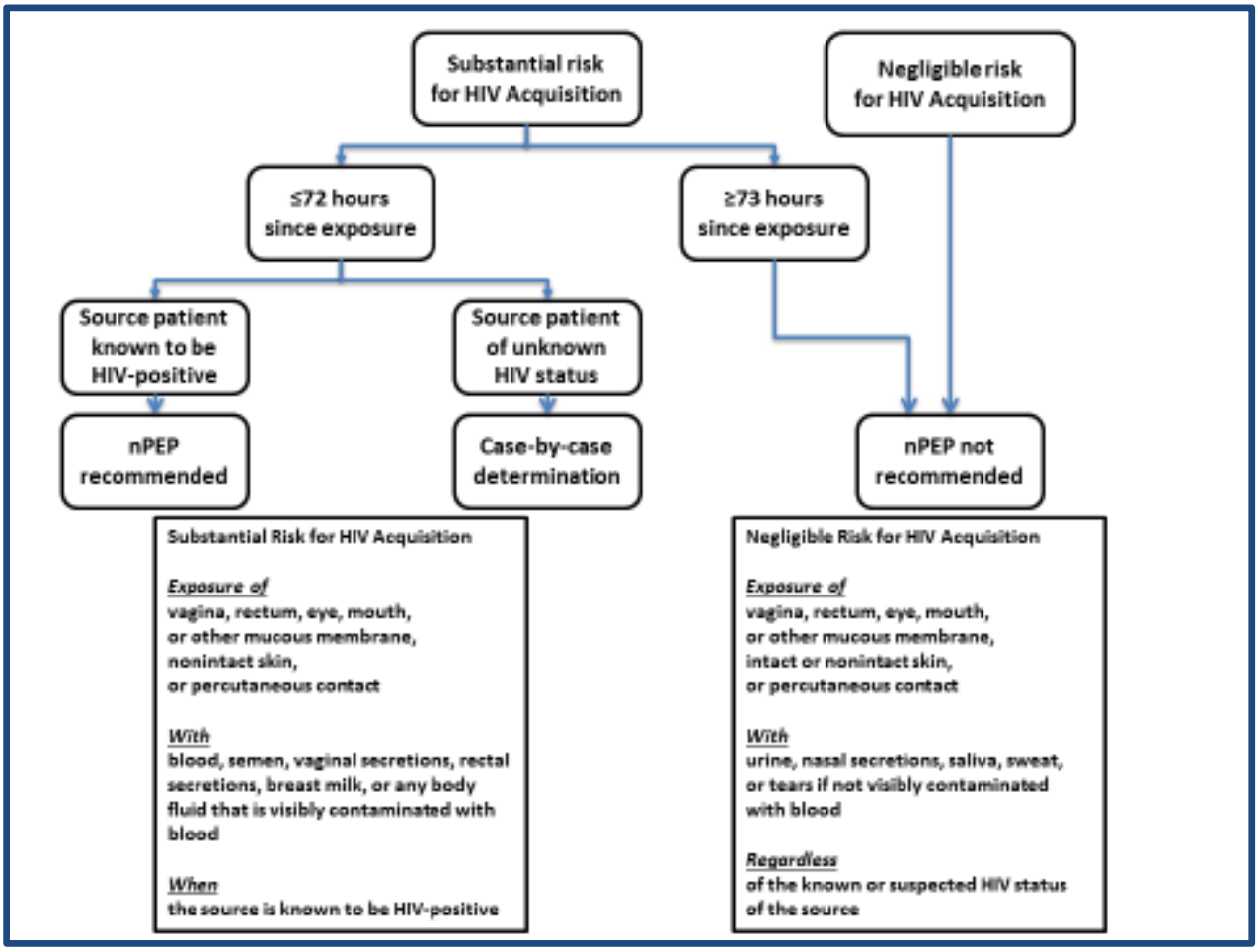
In a study of 227 pediatric and adolescent patients aged 9 months–18 years who were evaluated for sexual assault in Atlanta, Georgia, 40% of patients were examined ≤ 72 hours after the sexual assault, of whom 81% reported a history of genital or anal trauma.[41] In that study, patients aged 13–18 years and those who reported sexual assault by a stranger were more likely to present to the ED ≤ 72 hours after the sexual assault. Health care providers in the hospital's ED where this nPEP study was conducted expressed reluctance to prescribe nPEP to pre-pubertal children. For example, of 87 children and adolescents seen in the ED ≤ 72 hours after the assault, 23 had anogenital trauma or bleeding, and 5 were offered nPEP.

VII. Patient Management Guidelines

VII-A. Initial Evaluation of Persons Seeking Care After Potential Nonoccupational Exposure to HIV

Effective delivery of nPEP after exposures that carry a substantial risk for HIV infection requires prompt evaluation of patients and consideration of biomedical and behavioral interventions to address current and ongoing health risks. The initial evaluation provides the information necessary for determining if nPEP is indicated (Figure 1).

Figure 1. Algorithm for evaluation and treatment of possible nonoccupational HIV exposures



Procedures at the evaluation visit include determining the HIV infection status of the potentially exposed person and the source person (if available), the timing and characteristics of the exposure for which care is being sought, and the frequency of possible HIV exposures. Additionally, to determine whether other treatment or prophylaxis is indicated, health care providers should assess the likelihood of STIs, infections efficiently transmitted by injection practices or needlesticks (e.g., hepatitis B or hepatitis C virus), and pregnancy for women.

VII-A1. HIV Status of the Potentially Exposed Person

nPEP is only indicated for potentially exposed persons without HIV infection. Because potentially exposed persons might have acquired HIV infection already and be unaware of it, routine HIV antibody testing should

be performed on all persons seeking evaluation for potential nonoccupational HIV exposure. If possible, this should be done with an FDA-approved rapid antibody or Ag/Ab blood test kit with results available within an hour. If HIV blood test results will be unavailable during the initial evaluation visit, a decision whether nPEP is indicated should be made based on the initial assumption that the potentially exposed patient is not infected. If medication of HIV prophylaxis is indicated by the initial evaluation and started, it can be discontinued if the patient is later determined to already have HIV infection.

VII-A2. Timing and Frequency of Exposure

Available data from animal studies indicate that nPEP is most effective when initiated as soon as possible after HIV exposure; it is unlikely to be effective when instituted > 72 hours after exposure.[83] Therefore, persons should seek nPEP as soon as possible after an exposure that might confer substantial risk and health care providers should evaluate such patients rapidly and initiate nPEP promptly when indicated.

nPEP should be provided only for infrequent exposures. Persons who engage in behaviors that result in frequent, recurrent exposures that would require sequential or near-continuous courses of antiretroviral medications (e.g., HIV-discordant sex partners who inconsistently use condoms or PWID who often share injection equipment) should not be prescribed frequent, repeated courses of nPEP. Instead, health care providers should provide persons with repeated HIV exposure events (or coordinate referrals for) intensive sexual or injection risk-reduction interventions, and consider the prescription of daily oral doses of the fixed-dose combination of TDF and FTC (Truvada, Gilead Sciences, Inc., Foster City, California) for PrEP.[11] However, if the most recent recurring exposure is within the 72 hours prior to an evaluation, nPEP may be indicated with transition of the patient to PrEP after completion of 28 days of nPEP medication.

In the special case of children with evidence of chronic sexual abuse who come to the attention of a health care provider ≤ 72 hours after their most recent exposure, nPEP can be considered on a case-by-case basis. In addition, child protective services should be engaged for consideration of removal of the child from exposure to the perpetrator of the sexual abuse.

VII-A3. HIV Acquisition Risk from the Exposure

In addition to determining when the potential exposure occurred, determining whether nPEP is indicated requires assessing if the reported sexual, injection drug use, or other nonoccupational exposure presents a substantial risk for HIV acquisition. Health care providers should consider 3 main factors in making that determination: (1) whether the exposure source is known to have HIV infection, (2) to which potentially infected body fluid(s) the patient was exposed, and (3) the exposure site or surface.

The highest level of risk is associated with exposure of susceptible tissues to potentially infected body fluid(s) from persons known to have HIV infection, particularly those who are not on antiretroviral treatment. Persons with exposures to potentially infectious fluids from persons of unknown HIV status are at unknown risk for acquiring HIV infection. When the source of exposure is known to be from a group with a high prevalence of HIV infection (e.g., a man who has sex with men or a PWID who shares needles or other injection equipment), the risk for unrecognized HIV infection in the source is increased.

The estimated per-act transmission risk, when exposed to infectious fluid(s) from a person with HIV infection, varies considerably by exposure route (Table 1).[155] The highest estimated per-act risks for HIV transmission are associated with blood transfusion, needle sharing during injection drug use, receptive anal intercourse, and percutaneous needlestick injuries. Insertive anal intercourse, insertive penile-vaginal intercourse, and oral sex represent substantially lower per-act transmission risk.

Table 1. Estimated per-act risk for acquiring human immunodeficiency virus (HIV) from an infected source, by exposure act[a]

Exposure type	Rate for HIV acquisition per 10,000 exposures
Parenteral	
Blood transfusion	9,250
Needle sharing during injection drug use	63
Percutaneous (needlestick)	23
Sexual	
Receptive anal intercourse	138
Receptive penile-vaginal intercourse	8
Insertive anal intercourse	11
Insertive penile-vaginal intercourse	4
Receptive oral intercourse	Low
Insertive oral intercourse	Low
Other[b]	
Biting	Negligible
Spitting	Negligible
Throwing body fluids (including semen or saliva)	Negligible
Sharing sex toys	Negligible

Source: http://www.cdc.gov/hiv/policies/law/risk.html

[a] Factors that may increase the risk of HIV transmission include sexually transmitted diseases, acute and late-stage HIV infection, and high viral load. Factors that may decrease the risk include condom use, male circumcision, antiretroviral treatment, and preexposure prophylaxis. None of these factors are accounted for in the estimates presented in the table.

[b] HIV transmission through these exposure routes is technically possible but unlikely and not well documented.

A history should be taken of the specific sexual, injection drug use, or other exposure events that can lead to acquiring HIV infection. Eliciting a complete description of the exposure and information about the HIV status of the partner(s) can substantially lower (e.g., if the patient was exclusively the insertive partner or a condom was used) or increase (e.g., if the partner is known to be HIV-positive) the estimate of risk for HIV transmission resulting from a specific exposure.

Percutaneous injuries from needles discarded in public settings (e.g., parks and buses) sometimes result in requests for nPEP. Although no HIV infections from such injuries have been documented, concern exists that syringes discarded by PWID might pose a substantial risk. However, such injuries typically involve small-bore needles that contain only limited amounts of blood, and the infectiousness of any virus present might be low.[156,157] Saliva that is not contaminated with blood contains HIV in much lower titers and constitutes a negligible exposure risk,[158] but saliva that is contaminated with HIV-infected blood poses a substantial exposure risk. HIV transmission by this route has been reported in ≥ 4 cases.[159-162]

VII-A4. HIV Status of the Exposure Source

When the exposure source's HIV status is unknown, that person's availability for HIV testing should be determined. When the source person is available and consents to HIV testing, a clinical evaluation visit should be arranged that includes HIV testing by using a fourth-generation combined Ag/Ab test. The risk for transmission might be especially great if the source person has been infected recently because the viral burden in blood and semen might be particularly high.[163,164] However, ascertaining this in the short time available for the initial nPEP evaluation might not be possible. If the risk associated with the exposure is high, starting nPEP and then making a decision whether to continue nPEP after the source's HIV status is determined is recommended.

If the exposure source is known to have HIV infection at the time of the nPEP evaluation visit and consents, the health care provider should attempt to interview that person or that source person's health care provider to determine the history of antiretroviral use and most recent viral load. That information might help guide the choice of nPEP medications to avoid prescribing antiretroviral medications to which the source-virus is likely to be resistant. If the person with HIV infection is willing, the clinician might consider drawing blood for viral load and resistance testing, the results of which might be useful in modifying the initial nPEP medications if the results can be obtained promptly.[165]

VII-B. Laboratory Testing

Laboratory testing is required to (1) document the HIV infection status of the person presenting for nPEP evaluation (and the exposure source when available and consent has been granted), (2) identify and clinically manage any other conditions potentially resulting from sexual- or injection-related exposure to potentially infected body fluids, (3) identify any conditions that would affect the nPEP medication regimen, and (4) monitor for safety or toxicities related to the regimen prescribed (Table 2).

Table 2. Recommended schedule of laboratory evaluations of source and exposed persons for providing nPEP with preferred regimens

Test	Source	Exposed persons			
	Baseline	Baseline	4–6 weeks after exposure	3 months after exposure	6 months after exposure
		For all persons considered for or prescribed nPEP for any exposure			
HIV Ag/Ab testing[a] (or antibody testing if Ag/Ab test unavailable)	✓	✓	✓	✓	✓[b]
Hepatitis B serology, including: hepatitis B surface antigen hepatitis B surface antibody hepatitis B core antibody	✓	✓	—	—	✓[c]
Hepatitis C antibody test	✓	✓	—	—	✓[d]
		For all persons considered for or prescribed nPEP for sexual exposure			
Syphilis serology[e]	✓	✓	✓	—	✓
Gonorrhea[f]	✓	✓	✓[g]	—	—
Chlamydia[f]	✓	✓	✓[g]	—	—
Pregnancy[h]	—	✓	✓	—	—
		For persons prescribed tenofovir DF+ emtricitabine + raltegravir or tenofovir DF+ emtricitabine + dolutegravir			
Serum creatinine (for calculating estimated creatinine clearance[i])		✓	✓	—	—
Alanine transaminase, aspartate aminotranferase		✓	✓	—	—
	For all persons with HIV infection confirmed at any visit				
HIV viral load	✓	✓[j]			
HIV genotypic resistance	✓	✓[j]			

Abbreviations: Ag/Ab, antigen/antibody combination test; HIV, human immunodeficiency virus; nPEP, nonoccupational postexposure prophylaxis; tenofovir DF, tenofovir disoproxil fumarate.

[a] Any positive or indeterminate HIV antibody test should undergo confirmatory testing of HIV infection status.

[b] Only if hepatitis C infection was acquired during the original exposure; delayed HIV seroconversion has been seen in persons who simultaneously acquire HIV and hepatitis C infection.

[c] If exposed person susceptible to hepatitis B at baseline.

[d] If exposed person susceptible to hepatitis C at baseline.

[e] If determined to be infected with syphilis and treated, should undergo serologic syphilis testing 6 months after treatment

[f] Testing for chlamydia and gonorrhea should be performed using nucleic acid amplification tests. For patients diagnosed with a chlamydia or gonorrhea infection, retesting 3 months after treatment is recommended.

- For men reporting insertive vaginal, anal, or oral sex, a urine specimen should be tested for chlamydia and gonorrhea.
- For women reporting receptive vaginal sex, a vaginal (preferred) or endocervical swab or urine specimen should be tested for chlamydia and gonorrhea.
- For men and women reporting receptive anal sex, a rectal swab specimen should be tested for chlamydia and gonorrhea.
- For men and women reporting receptive oral sex, an oropharyngeal swab should be tested for gonorrhea. (http://www.cdc.gov/std/tg2015/tg-2015-print.pdf)

[g] If not provided presumptive treatment at baseline, or if symptomatic at follow-up visit.

[h] If woman of reproductive age, not using effective contraception, and with vaginal exposure to semen.

[i] eCrCl = estimated creatinine clearance calculated by the Cockcroft-Gault formula; eCrClCG = [(140 − age) x ideal body weight] ÷ (serum creatinine x 72) (x 0.85 for females).

[j] At first visit where determined to have HIV infection.

VII-B1. HIV Testing

All patients initiating nPEP after potential HIV exposure should be tested for the presence of HIV-1 and HIV-2 antigens and antibodies in a blood specimen at baseline (before nPEP initiation), preferably using a rapid test. Patients with baseline rapid tests indicating existing HIV infection should not be started on nPEP. Patients for whom baseline HIV rapid test results indicate no HIV infection or rapid HIV test results are not available should be offered nPEP. There should be no delay in initiation of nPEP while awaiting baseline HIV test results. Repeat HIV testing should occur at 4–6 weeks and 3 months after exposure to determine if HIV infection has occurred. See http://www.cdc.gov/hiv/testing/laboratorytests.html regarding information on approved HIV tests. Oral HIV tests are not recommended for use among persons being evaluated for nPEP.

Additionally, persons whose sexual or injection-related exposures results in concurrent acquisition of HCV and HIV infection might have delayed HIV seroconversion. This has been documented among MSM with sexual exposure[13] and health care personnel receiving oPEP for needlestick exposures.[166,167] Therefore, for any person whose HCV antibody test is negative at baseline but positive at 4–6 weeks after the exposure, HIV antibody tests should be conducted at 3 and 6 months to rule out delayed seroconversion (see Table 2).

VII-B2. Recognizing Acute HIV Infection at Time of HIV Seroconversion

Persons initiating nPEP, if it fails, may experience signs and symptoms of acute HIV infection while on nPEP. At the initial visit, patients should be instructed about the signs and symptoms associated with acute (primary) HIV infection (Table 3), especially fever and rash,[168] and asked to return for evaluation if these occur during the 28 days of prophylaxis or anytime within a month after nPEP concludes.

Table 3. Clinical signs and symptoms of acute (primary) human immunodeficiency virus infection[169,170]

		Sex		Mode of HIV acquisition	
Features	**Overall (n = 375), %**	**Male (n = 355), %**	**Female (n = 23), %**	**Sexual (n = 324), %**	**Injection drug use (n = 34), %**
Fever	75	74	83	77	50
Fatigue	68	67	78	71	50
Myalgia	49	50	26	52	29
Skin rash	48	48	48	51	21
Headache	45	45	44	47	30
Pharyngitis	40	40	48	43	18
Cervical adenopathy	39	39	39	41	27
Arthralgia	30	30	26	28	26
Night sweats	28	28	22	30	27
Diarrhea	27	27	21	28	23

Acute HIV infection is associated with high viral load. However, health care providers should be aware that available assays might yield low viral-load results (e.g., <3,000 copies/ml) among persons without HIV infection (i.e., false-positives). Without confirmatory tests, such false-positive results can lead to misdiagnoses of HIV infection.[171] Transient, low-grade viremia has been observed among persons exposed to HIV who were

administered antiretroviral nPEP[172] and did not become infected. In certain cases, this outcome might represent aborted infection rather than false-positive test results, but this can be determined only through further testing.

All patients who have begun taking nPEP and for whom laboratory evidence later confirms acute HIV infection at baseline or whose follow-up antibody testing indicates HIV infection, should be transferred rapidly to the care of an HIV treatment specialist (if nPEP was provided by another type of health care provider). If the patient is taking a 3-drug antiretroviral regimen for nPEP at the time of HIV infection diagnosis, the 3-drug regimen should not be discontinued by the nPEP provider until the patient has been evaluated and a treatment plan initiated by an experienced HIV care provider.[173]

VII-B3. STI Testing

Any sexual exposure that presents a risk for HIV infection might also place a person at risk for acquiring other STIs.[174] For all persons evaluated for nPEP because of exposure during sexual encounters, STI-specific nucleic acid amplification (NAAT) testing is recommended for gonorrhea and chlamydia,[174] by testing first-catch urine or with swabs collected from each mucosal site exposed to potentially infected body fluids (oral, vaginal, cervical, urethral, rectal).[174,175] Additionally, blood tests for syphilis should be conducted for all persons evaluated for nPEP.

VII-B4. HBV Testing

HBV infection is of specific concern when considering nPEP for 2 reasons. First, multiple medications used for nPEP, including 2 in the preferred regimen (TDF and FTC) are active against HBV infection. For safety reasons, health care providers need to know if a patient has active HBV infection (positive hepatitis B surface antigen [HBsAg]) so that the patient can be closely monitored for reactivation "flare ups" when nPEP is stopped, and treatment for HBV infection is discontinued. Although this is rare, it can result in substantial hepatic dysfunction if not detected and treated early. Additionally, obtaining hepatitis serology (HBsAg, hepatitis B surface antibody [anti-HBs], and hepatitis B core antibody [anti-HBc]) will identify nonimmune persons who should be provided hepatitis B vaccination Table 4).[176]

Table 4. Hepatitis B virus screening serology[177]

HBsAg	Anti-HBc	Anti-HBs	IgM Anti-HBc	Interpretation	Action
Negative	Negative	Negative	—	Susceptible	Vaccinate
Negative	Positive	Positive	—	Immune (natural infection)	Document
Negative	Negative	Positive	—	Immune (prior vaccination)	Document
Positive	Positive	Negative	Negative	Chronic hepatitis B virus infection	Evaluate for treatment
Positive	Positive	Negative	Positive	Acute hepatitis B virus infection	Follow and evaluate for treatment
Negative	Positive	Negative	—	Unclear—might be: • resolved infection (most common) • false-positive anti-HBc; susceptible • "low level" chronic infection • resolving acute infection	Case-by-case evaluation
Abbreviations: HBsAg, hepatitis B surface antigen; anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody.					

VII-B5. Pregnancy Testing

nPEP is not contraindicated for pregnant women. Moreover, because pregnancy has been demonstrated to increase susceptibility to sexual HIV acquisition,[178] nPEP can be especially important for women who are pregnant at the time of sexual HIV exposure.

For women of reproductive capacity who have had genital exposure to semen and a negative pregnancy test when evaluated for possible nPEP, current contraception use should be assessed, and if a risk for pregnancy exists, emergency contraception should be discussed with the patient.

VII-B6. Baseline and Follow-up Testing to Assess Safety of Antiretroviral Use for nPEP

All patients who will be prescribed nPEP should have serum creatinine measured and an estimated creatinine clearance calculated at baseline to guide selection of a safe and appropriate antiretroviral regimen for nPEP. Also, health care providers treating patients with nPEP should monitor liver function, renal function, and hematologic parameters when indicated by the prescribing information for the antiretrovirals prescribed. Drug-specific recommendations are available at the online AIDS*Info* Drugs Database at: http://aidsinfo.nih.gov/drugs or the antiretroviral treatment guidelines.[114,173,179]

Unusual or severe toxicities from antiretroviral drugs should be reported to the manufacturer or FDA (http://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm, or 1-800-FDA-1088 [1-800-332-1088]).

If nPEP is prescribed to a woman who is pregnant at the time of exposure or becomes pregnant while on nPEP, health care providers should enter the patient's information (anonymously) into the Antiretroviral Pregnancy Registry (http://www.apregistry.com).

VII-C. Recommended Antiretroviral nPEP Regimens

A 28-day course of nPEP is recommended for HIV-uninfected persons who seek care ≤ 72 hours after a nonoccupational exposure to blood, genital secretions, or other potentially infected body fluids of persons known to be HIV infected or of unknown HIV status when that exposure represents a substantial risk for HIV acquisition. Since adherence is critical for nPEP efficacy, it is preferable to select regimens that minimize side effects, number of doses per day and the number of pills per dose.

No strong evidence exists, based on randomized clinical trials, that any specific combination of antiretroviral medication is optimal for nPEP use. Although a limited number of studies have evaluated the penetration of antiretroviral medications into genital tract secretions and tissues,[180-182] evidence is insufficient for recommending a specific antiretroviral medication as most effective for nPEP for sexual exposures. Therefore, the recommended regimens for nPEP in these guidelines are based on expert opinion from the accumulated experience with antiretroviral combinations that effectively suppress viral replication among HIV-infected persons for the purpose of HIV treatment and mainly observational studies of the medication tolerance and adherence when these same drugs are taken for nPEP.

The recommendation for a 3-drug antiretroviral regimen is based on extrapolation of data demonstrating that the maximal suppression of viral replication occurs among persons with HIV infection when combination antiretroviral therapy with ≥3 drugs is provided. Also, the likelihood of protection against acquiring resistant virus would be greater with a 3-drug regimen compared with a 2-drug regimen. Recommending a 3-drug regimen for all patients who receive nPEP will increase the likelihood of successful prophylaxis in light of potential exposure to virus with resistance mutation(s) and will provide consistency across PEP guidelines for

both nPEP and oPEP.[2] Additionally, if infection occurs despite nPEP, a 3-drug regimen will more likely limit emergence of resistance than a 2-drug regimen.

Table 5. Preferred and alternative antiretroviral medication 28-day regimens for nPEP[a,b]

Age group	Preferred/ alternative	Medication
Adults and adolescents aged ≥ 13 years, including pregnant women, with normal renal function (creatinine clearance ≥ 60 mL/min)	**Preferred**	A 3-drug regimen consisting of tenofovir DF 300 mg ***and*** fixed dose combination emtricitabine 200 mg (Truvada[c]) once daily ***with*** raltegravir 400 mg twice daily ***or*** dolutegravir 50 mg once daily
	Alternative	A 3-drug regimen consisting of tenofovir DF 300 mg ***and*** fixed dose combination emtricitabine 200 mg (Truvada) once daily ***with*** darunavir 800 mg (as 2, 400-mg tablets) once daily ***and*** ritonavir[b] 100 mg once daily
Adults and adolescents aged ≥ 13 years with renal dysfunction (creatinine clearance ≤59 mL/min)	**Preferred**	A 3-drug regimen consisting of zidovudine ***and*** lamivudine, with both doses adjusted to degree of renal function ***with*** raltegravir 400 mg twice daily ***or*** dolutegravir 50 mg once daily
	Alternative	A 3-drug regimen consisting of zidovudine ***and*** lamivudine, with both doses adjusted to degree of renal function ***with*** darunavir 800 mg (as 2, 400-mg tablets) once daily ***and*** ritonavir[b] 100 mg once daily
Children aged 2–12 years	**Preferred**	A 3-drug regimen consisting of tenofovir DF, emtricitabine, and raltegravir, with each drug dosed to age and weight[d]
	Alternative	A 3-drug regimen consisting of zidovudine ***and*** lamivudine ***with*** raltegravir ***or*** lopinavir/ritonavir[b], with raltegravir and lopinavir/ritonavir dosed to age and weight[d]
	Alternative	A 3-drug regimen consisting of tenofovir DF ***and*** emtricitabine ***and*** lopinavir/ritonavir[b], with each drug dosed to age and weight[d]

Age group	Preferred/ alternative	Medication
Children aged 3–12 years	Alternative	A 3-drug regimen consisting of tenofovir DF **and** emtricitabine **and** darunavir[e]/ritonavir[b], with each drug dosed to age and weight[d]
Children aged 4 weeks[f]–< 2 years	**Preferred**	A 3-drug regimen consisting of zidovudine oral solution ***and*** lamivudine oral solution ***with*** raltegravir ***or*** lopinavir/ritonavir[b] oral solution (Kaletra[g]), with each drug dosed to age and weight[d]
Children aged 4 weeks[f]–< 2 years	Alternative	A 3-drug regimen consisting of zidovudine oral solution ***and*** emtricitabine oral solution ***with*** raltegravir ***or*** lopinavir/ritonavir[b] oral solution (Kaletra), with each drug adjusted to age and weight[d]
Children aged birth–27 days	Consult a pediatric HIV-specialist	

Abbreviations: HIV, human immunodeficiency virus; nPEP, nonoccupational postexposure prophylaxis; tenofovir DF, tenofovir disoproxil fumarate.

[a] These recommendations do not reflect current Food and Drug Administration-approved labeling for antiretroviral medications listed in this table.

[b] Ritonavir is used in clinical practice as a pharmacokinetic enhancer to increase the trough concentration and prolong the half-life of darunavir, lopinavir, and other protease inhibitors. Ritonavir is not counted as a drug directly active against HIV in the above "3-drug" regimens.

[c] Gilead Sciences, Inc., Foster City, California.

[d] See also Table 6.

[e] Darunavir only FDA-approved for use among children aged ≥ 3 years.

[f] Children should have attained a postnatal age of ≥ 28 days and a postmenstrual age (i.e., first day of the mother's last menstrual period to birth plus the time elapsed after birth) of ≥ 42 weeks.

[g] AbbVie, Inc., North Chicago, Illinois.

Table 6. Formulations, cautions, and dose adjustments for antiretroviral medications in preferred and alternative nPEP regimens[a]

Drug	Formulation	Side effects, contraindications, and cautions	Dose adjustments
Tenofovir disoproxil fumarate (TDF) (Viread, Gilead Sciences, Inc., Foster City, California) Also available as component of fixed-dose combination, Truvada (Gilead Sciences, Inc., Foster City, California) (emtricitabine + TDF)	150-mg tablet 200-mg tablet 250-mg tablet 300-mg tablet 40-mg/gm powder	**Side effects:** Asthenia, headache, diarrhea, nausea, vomiting **Contraindications:** Nephrotoxicity; for nPEP, should not be administered to persons with acute or chronic kidney injury or those with eCrCl < 60 mL/min **Cautions:** TDF can be used in nPEP regimens for patients with chronic hepatitis B infection, but hepatic function tests should be closely monitored when regimen is stopped because withdrawal of this drug may cause an acute hepatitis exacerbation.	**Children aged 2–11 years (powder)** • 8 mg/kg body weight • Not to exceed adult dose (300 mg qd) **Children aged 2–11 years (tablet), per body weight** • 17 to < 22 kg, 150 mg-tablet once daily • 22 to < 28 kg, 200 mg-tablet once daily • 28 to < 35 kg, 250-mg tablet once daily • ≥ 35 kg, 300-mg tablet once daily • Not to exceed adult dose (300 mg once daily)
Emtricitabine (FTC) (Emtriva, Gilead Sciences, Inc., Foster City, California) Also available as component of fixed-dose combination, Truvada (FTC + TDF)	200-mg capsule 10-mg/mL oral solution	**Side effects:** Hyperpigmented rash or skin discoloration **Cautions:** FTC can be used in nPEP regimens for patients with chronic hepatitis B infection, but hepatic function tests should be closely monitored when regimen is stopped because withdrawal of this drug might cause an acute hepatitis exacerbation. **Contraindications:** Do not administer with lamivudine	**Children aged 0–3 months (oral solution)** • 3 mg/kg once daily • Not to exceed 240 mg once daily **Children aged 3 months–17 years, per body weight** • 6 mg/kg once daily (oral solution) • ≥ 33 kg 200-mg tablet once daily • Not to exceed 240 mg once daily
Raltegravir (RAL) (Isentress, Merck & Co., Inc., Kenilworth, New Jersey)	400-mg tablet 100-mg chewable, scored tablet 25-mg chewable tablet	**Side effects:** Insomnia, nausea, fatigue, headache; severe skin and hypersensitivity reactions have been reported **Cautions:** Dosage adjustment required if co-administered with rifampin (800 mg twice daily for adults). Co-administration with antacids, laxatives, or other products containing polyvalent cations (Mg, Al, Fe, Ca, Zn), including iron, calcium, or magnesium supplements; sucralfate; buffered medications; and certain oral multivitamins can reduce absorption of RAL. RAL should be administered ≥ 2 hours before or ≥ 6 hours after administration of cation-containing medications or products, however, RAL can be co-administered with calcium carbonate-containing antacids.[154] **Contraindications:** None	**Children aged 6–12 years and weighing > 25 kg** • 400 mg-tablet twice daily **Or** • Chewable tablets twice daily. See table below for chewable tablet dose. **Children aged 2–12 years (chewable tablets), per body weight** • 11 to < 14 kg, 75-mg twice daily • 14 to < 20 kg, 100-mg twice daily • 20 to < 28 kg, 150-mg twice daily • 28 to < 40 kg, 200-mg twice daily • ≥ 40 kg, 300-mg twice daily

Drug	Formulation	Side effects, contraindications, and cautions	Dose adjustments
Dolutegravir (DTG) (Tivicay, ViiV Healthcare, Brentford, Middlesex, United Kingdom)	50-mg tablet	**Side effects:** Insomnia, headache **Cautions:** Dosage adjustment required if co-administered with rifampin, fosamprenavir/ritonavir, tipranvir/ritonavir, or efavirenz (50 mg twice daily for adults). Co-administration with antacids, laxatives, or other products containing polyvalent cations (Mg, Al, Fe, Ca, Zn), including iron, calcium, or magnesium supplements; sucralfate; buffered medications; and some oral multivitamins can reduce absorption of DTG. DTG should be administered ≥ 2 hours before or at ≥ 6 hours after administration of cation-containing medications or products.[151] **Contraindications:** Do not administer with dofetilide.	**Children aged 12 years old and older and weighing ≥ 40 kg** • 50-mg tablet once daily
Darunavir (DRV)/ritonavir(RTV) (Prezista, Janssen Therapeutics, Titusville, New Jersey)	75-mg tablet 150-mg tablet 400-mg tablet 600-mg tablet 100-mg/mL oral suspension	**Side effects:** Rash (sulfonamide allergy), diarrhea, nausea, headache **Cautions:** Must be administered with food; must be co-administered with ritonavir; can cause hepatotoxicity. Use with caution with persons with known allergy to sulfonamide medications **Contraindications:** Co-administration of ritonavir with certain sedative hypnotics, antiarrhythmics, sildenafil, or ergot alkaloid preparations is contraindicated and might result in potentially life-threatening adverse events.	**Children aged 3 to < 18 years and weight > 10 kg** WEIGHT (KG) — DOSE (TWICE DAILY WITH FOOD) 10 to < 11 kg* — darunavir 200 mg (2.0 mL) plus ritonavir 32 mg (0.4 mL†) 11 to < 12 kg* — darunavir 220 mg (2.2 mL) plus ritonavir 32 mg (0.4 mL†) 12 to < 13 kg* — darunavir 240 mg (2.4 mL) plus ritonavir 40 mg (0.5 mL†) 13 to < 14 kg* — darunavir 260 mg (2.6 mL) plus ritonavir 40 mg (0.5 mL†) 14 to < 15 kg* — darunavir 280 mg (2.8 mL) plus ritonavir 48 mg (0.6 mL†) 15 to < 30 kg — darunavir 375 mg (combination of tablets or 3.8 mL‡) plus ritonavir 48 mg (0.6 mL†) 30 to < 40 kg — darunavir 450 mg (combination of tablets or 4.6 mL‡) plus ritonavir 100 mg (tablet or 1.25 mL†) ≥ 40 kg — darunavir 600 mg (tablet or 6 mL) plus ritonavir 100 mg (tablet or 1.25 mL†) * The dose in children weighing 10–15 kg is 20 mg/kg darunavir and 3 mg/kg ritonavir per kg body weight per dose, which is higher than the weight-adjusted dose in children with higher weight. † Ritonavir 80 g/mL oral solution ‡ The 375-mg and 450-mg darunavir doses are rounded for suspension-dose convenience.

Drug	Formulation	Side effects, contraindications, and cautions	Dose adjustments
Lopinavir (LPV)/ritonavir (RTV) (Kaletra, AbbVie Inc., North Chicago, Illinois)	200/50-mg tablets 100/25-mg tablets 80/20-mg/mL oral solution	**Side effects:** Nausea, vomiting, diarrhea **Cautions:** PR and QT interval prolongation have been reported. Use with caution with patients at risk for cardiac conduction abnormalities or receiving other drugs with similar effect. Do not administer to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of ≥ 42 weeks and a postnatal age of ≥ 14 days. **Contraindications:** Co-administration of ritonavir with certain sedative hypnotics, antiarrhythmics, sildenafil, or ergot alkaloid preparations is contraindicated and might result in potentially life-threatening adverse events.	**Children aged 14 days–12 months, per body weight** Suspension (lopinavir/ritonavir) • 16/4 mg/kg or 300/75 mg/m^2 twice daily **Children aged > 12 months–18 years, per body weight** Suspension (lopinavir/ritonavir) • < 15 kg, 12/3 mg/kg twice daily • ≥ 15 kg to 40 kg, 10/2.5 mg/kg twice daily • > 40 kg, 400/100 mg twice daily • not to exceed the recommended adult dose (400/100 mg [5 mL] twice daily **Children aged > 12 months–18 years** Tablet, weight-based dosing (lopinavir/ritonavir) • 15 to 25 kg, 2 100/25-mg tablets twice daily • > 25 to 35 kg, 3 100/25-mg tablets twice daily • > 35 kg, 4 100/25-mg tablets twice daily or 2 200/50-mg tablets twice daily
Ritonavir[b](RTV) (Norvir, AbbVie, Inc., North Chicago, Illinois)	100-mg tablets 100-mg soft gelatin capsules 80-mg/mL oral solution	**Side effects:** Abdominal pain, asthenia, headache, malaise, anorexia, diarrhea, dyspepsia, nausea, vomiting, circumoral paresthesia, peripheral paresthesia, dizziness, and taste perversion. **Cautions:** PR and QT interval prolongation have been reported. Use with caution with patients at risk for cardiac conduction abnormalities or receiving other drugs with similar effect. Can cause hepatotoxicity, pancreatitis, or hyperglycemia **Contraindications:** Co-administration of ritonavir with certain sedative hypnotics, antiarrhythmics, sildenafil, or ergot alkaloid preparations is contraindicated and might result in potentially life-threatening adverse events.	• See pediatric dosage for use as a boosting agent with darunavir or lopinavir in respective darunavir and lopinavir sections of this table.

Drug	Formulation	Side effects, contraindications, and cautions	Dose adjustments
Zidovudine (ZDV; AZT) (Retrovir, ViiV Healthcare, Brentford, Middlesex, United Kingdom)	100-mg capsule 300-mg tablet 10-mg/mL oral syrup 10-mg/mL intravenous infusion	**Side effects:** Nausea, vomiting, headache, insomnia, and fatigue **Cautions:** Can cause anemia and neutropenia	**Infants aged birth–41 days** **Full term (aged ≥ 35 weeks gestation at birth), per body weight** Syrup • 4 mg/kg orally twice daily Intravenous[c] • 3.0 mg/kg, infused over 30 minutes, every 12 hours **Premature (aged ≥ 30 to 35 weeks gestation at birth; from birth through day 14 of life; switch to full term infant dose at 15 days of life), per body weight** Syrup • 2 mg/kg orally twice daily Intravenous[c] • 1.5 mg/kg, infused over 30 minutes, every 12 hours **Premature (aged < 30 weeks gestation at birth; day 14–28 of life; switch to full term infant dose at 29 days* of life), per body weight** Syrup • 2 mg/kg orally twice daily Intravenous[c] • 1.5 mg/kg, infused over 30 minutes, every 12 hours **Infants and children aged ≥35 weeks post-conception and at least 4 weeks post-delivery, per body weight** Syrup or Capsules • 4 to < 9 kg, 12 mg/kg twice daily • 9 to < 30 kg, 9 mg/kg twice daily Tablet • ≥ 30 kg, 300-mg tablet twice daily * Note: Premature infants exposed to HIV after day 1 of life are switched to full-term infant dose at 29 days of life.

Drug	Formulation	Side effects, contraindications, and cautions	Dose adjustments
Lamivudine (3TC) (Epivir, ViiV Healthcare, Brentford Middlesex, United Kingdom)	150-mg scored tablet 100-mg tablet 300-mg tablet 10-mg/mL oral solution	**Side effects:** Headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea, and cough **Cautions:** 3TC may be used in nPEP regimens for patients with chronic hepatitis B infection, but hepatic function tests should be closely monitored when regimen is stopped since withdrawal of this drug may cause an acute hepatitis exacerbation. **Contraindications:** Do not administer with emtricitabine	**Neonates and infants, aged ≤ 27 days** Oral solution • 2 mg/kg twice daily **Children, aged ≥ 4 weeks** Oral solution • 4 mg/kg (maximum dose 150 mg) twice daily **Children aged < 16 years and weighing ≥ 14 kg** Scored 150-mg tablet • 14 to < 20 kg, 75 mg (1/2 tablet) AM + 75 mg (1/2 tablet) PM • 20 to < 25 kg, 75 mg (1/2 tablet) AM + 150 mg (1 tablet) PM • ≥ 25 kg, 150 mg tablet twice daily **Adolescents (aged ≥ 16 years) and adults, per body weight** • < 50 kg, 4 mg/kg (up to 150 mg) twice daily • ≥ 50 kg, 150 mg twice daily or 300 mg once daily

Abbreviations: eCrCl = estimated creatinine clearance calculated by the Cockcroft-Gault formula; eCrClCG = [(140 − age) x ideal body weight] ÷ (serum creatinine x 72) (x 0.85 for females); nPEP, nonoccupational postexposure prophylaxis.

[a] For most current dosing regimens for treatment naïve children, see 1) AIDSInfo Drugs Database at http://aidsinfo.nih.gov/drugs, 2) Drugs@FDA (FDA approved drug products index) at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/, 3) Pediatric ARV treatment guidelines at http://aidsinfo.nih.gov/guidelines/html/2/pediatric-treatment-guidelines/0#, and 4) Perinatal guidelines at http://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/0

[b] Ritonavir is used in clinical practice as a pharmacokinetic enhancer to increase the trough concentration and prolong the half-life of darunavir, lopinavir, and other protease inhibitors

[c] Infants unable to receive oral dosing may receive intravenous dosing

Health care providers might consider using antiretroviral regimens for nPEP other than those listed as preferred or alternative because of patient-specific information (e.g., an HIV-infected exposure source with known drug-resistance or contraindications to ≥1of the antiretrovirals in a preferred regimen). In those cases, health care providers are encouraged to seek consultation with other health care providers knowledgeable in using antiretroviral medications for similar patients (e.g., children, pregnant women, those with comorbid conditions) (Appendix 4).

> Providers should be aware that abacavir sulfate (Ziagen, ViiV Healthcare, Brentford, Middlesex, United Kingdom) should not be prescribed in any nPEP regimen. Prompt initiation of nPEP does not allow time for determining if a patient has the *HLA-B*5701* allele, the presence of which is strongly associated with a hypersensitivity syndrome that can be fatal.[183]

Health care providers and patients who are concerned about potential adherence and toxicity or the additional cost associated with a 3-drug antiretroviral regimen might consider using a 2-drug regimen (i.e., a combination of 2 NRTIs or a combination of a PI and a NNRTI). However, this DHHS guideline recommends a 3-drug regimen in all cases when nPEP is indicated.

VII-D. Prophylaxis for STIs and Hepatitis

All adults and adolescents with exposures by sexual assault should be provided with prophylaxis routinely for STIs and HBV,[174] as follows:

- For gonorrhea, (male and female adults and adolescents),
  - ceftriaxone 250 mg intermuscular, single dose;
  - ***plus*** azithromycin, 1 g, orally, single dose;
- For chlamydia (male and female adults and adolescents),
  - azithromycin, 1 g, orally, single dose
  - ***or*** doxycycline, 100 mg, orally, twice a day for 7 days.
- For trichomonas (female adults and adolescents),
  - metronidazole, 2 g, orally, single dose
  - ***or*** tinidazole, 2 g, orally, single dose

All persons not known to be previously vaccinated against HBV, should receive hepatitis B vaccination (without hepatitis B immune globulin),[174] with the first dose administered during the initial examination. If the exposure source is available for testing and is HBsAg-positive, unvaccinated nPEP patients should receive both hepatitis B vaccine and hepatitis B immune globulin during the initial evaluation. Follow-up vaccine doses should be administered during 1–2 months and at 4–6 months after the first nPEP dose. Previously vaccinated sexually assaulted persons who did not receive postvaccination testing should receive a single vaccine booster dose.

HPV vaccination is recommended for female survivors aged 9–26 years and male survivors aged 9–21 years. For MSM with who have not received HPV vaccine or who have been incompletely vaccinated, vaccine can be

administered through age 26 years. The vaccine should be administered to sexual assault survivors at the time of the initial examination, and follow-up dose administered at 1–2 months and 6 months after the first dose.[174]

Routine use of STI prophylaxis is not recommended for sexually abused or assaulted children.[174]

VII-E. Considerations for All Patients Treated with Antiretroviral nPEP

The patient prescribed nPEP should be counseled regarding potential associated side effects and adverse events specific to the regimen prescribed. Any side effects or adverse events requiring immediate medical attention should be emphasized.

VII-E1. Provision of nPEP Starter Packs or a 28-day Supply at Initiation

Patients might be under considerable emotional stress when seeking care after a potential HIV exposure and might not be attentive to, or remember, all the information presented to them before making a decision regarding nPEP. Health care providers should consider giving an initial prescription for 3–7 days of medication (i.e., a starter pack) or an entire 28-day course and scheduling an early follow-up visit. Provision of the entire 28-day nPEP medication supply at the initial visit rather than a starter pack of 3–7 days has been reported to increase likelihood of adherence, especially when patients find returning for multiple follow-up visits difficult.[96,184] Routinely providing starter packs or the entire 28-day course requires that health care providers stock nPEP drugs in their practice setting or have an established agreement with a pharmacy to stock, package and urgently dispense nPEP drugs with required administration instructions. At the patient's second visit, health care providers can discuss the results of baseline HIV blood testing (if rapid tests were not used), provide additional counseling and support, assess medication side effects and adherence, or provide an altered nPEP medication regimen if indicated by side effects or laboratory test results. nPEP starter packs or 28-day supplies might also include such medications as antiemetics to alleviate recognized side effects of the specific medications prescribed, if they occur. Health care providers should counsel patients regarding which side effects might occur (Table 6), how to manage them, and when to contact the provider if they do not resolve.[173]

VII-E2. Expert Consultation

When health care providers are inexperienced with prescribing or managing patients on antiretroviral medications or when information from persons who were the exposure source indicates the possibility of antiretroviral resistance, consultation with infectious disease or other HIV-care specialists, if available immediately, is warranted before prescribing nPEP to determine the correct regimen. Similarly, consulting with specialists with experience using antiretroviral drugs is advisable when considering prescribing nPEP for certain persons—pregnant women (infectious disease specialist or obstetrician), children (pediatrician), or persons with renal dysfunction (infectious disease specialist or nephrologist). However, if such consultation is not available immediately, nPEP should be initiated promptly and, if necessary, revised after consultation is obtained. Expert consultation can be obtained by calling the PEPline at the National Clinician's Consultation Center at 888-448-4911 (additional information is available at http://nccc.ucsf.edu/clinician-consultation/pep-post-exposure-prophylaxis/).

VII-E3. Facilitating Adherence

Observational studies have reported that adherence to nPEP regimens is often inadequate and has been especially so among sexual assault survivors. Medication adherence can be facilitated by (1) prescribing medications with fewer side effects, fewer doses per day, and fewer pills per dose; (2) educating the patient

regarding potential side effects of the specific medications prescribed and providing medications to assist if side effects occur (e.g., antiemetics); (3) recommending medication adherence aids (e.g., pill boxes); (4) helping patients incorporate doses into their daily schedules; and (5) providing a flexible and proactive means for patient–health care provider contact during the nPEP period.[185,186] Also, establishing a trusting relationship and maintaining good communication about adherence can help to improve completion of the nPEP course. Adherence to the nPEP medications prescribed to children will depend on the involvement of and support provided to parents and guardians.

VII-E4. HIV Prevention Counseling

The majority of persons who seek care after a possible HIV exposure do so because of failure to initiate or maintain effective risk-reduction behaviors. Notable exceptions are sexual assault survivors and persons with community-acquired needlestick injuries.

Although nPEP can reduce the risk for HIV infection, it is not always effective. Therefore, patients should practice protective behaviors with sex partners (e.g., consistent condom use) or drug-use partners (e.g., avoidance of shared injection equipment) throughout the nPEP course to avoid transmission to others if they become infected and after nPEP to avoid future HIV exposures.

At follow-up visits, when indicated, health care providers should assess their patients' needs for behavioral intervention, education, and services. This assessment should include frank, nonjudgmental questions about sexual behaviors, alcohol use, and illicit drug use. Health care providers should help patients identify ongoing risk concerns and develop plans for improving their use of protective behaviors.[187]

To help patients obtain indicated interventions and services, health care providers should be aware of local resources for high-quality HIV education and ongoing behavioral risk reduction, counseling and support, inpatient and outpatient alcohol and drug-treatment services, family and mental health counseling services, and support programs for HIV-infected persons. Information regarding publicly funded HIV prevention programs can be obtained from state or local health departments.

VII-E5. Providing PrEP After nPEP Course Completion

Persons who engage in behaviors that result in frequent, recurrent exposures that would require sequential or near-continuous courses of nPEP should be offered PrEP[11] at the conclusion of their 28-day nPEP medication course. Because no evidence exists that prophylactic antiretroviral use delays seroconversion and nPEP is highly effective when taken as prescribed, a gap is unnecessary between ending nPEP and beginning PrEP. Upon documenting HIV-negative status, preferably by using an Ag/Ab test, daily use of the fixed dose combination of TDF (300mg) and FTC (200 mg) can begin immediately for patients for whom PrEP is indicated. Clinicians with questions about prescribing PrEP, are encouraged to call the PrEPline 855-448-7737 at the National Clinician Consultation Center or go to their website (http://nccc.ucsf.edu/clinician-consultation/prep-pre-exposure-prophylaxis/).

VII.E6. Providing nPEP in the Context of PrEP

Patients fully adhering to a daily PrEP regimen as recommended by their health care practitioner are not in need of nPEP if they experience a potential HIV exposure while on PrEP. PrEP is highly effective when taken daily or near daily.[11,188] For patients who report that they take their PrEP medication sporadically and those who did not take it within the week before the recent exposure, initiating a 28-day course of nPEP might be indicated. In

that instance, all nPEP baseline and follow-up laboratory evaluations should be conducted. After the 28-day nPEP regimen is completed, if confirmed to be HIV uninfected, the daily PrEP regimen can be reinitiated.

VII-E7. Management of Source Persons with HIV Infection

When persons who were the exposure source are present during the course of evaluating a patient for potential HIV exposure, health care providers should also assess that person's access to relevant medical care, behavioral intervention, and social support services. If needed care cannot be provided directly, health care providers should help HIV-infected source persons obtain care in the community (http://locator.aids.gov/).

VII-F. Additional Considerations

VII-F1. Reporting and Confidentiality

As with all clinical care, health care providers should handle nPEP evaluations with confidentiality. Confidential reporting of STIs and newly diagnosed HIV infections to health departments should occur as indicated by that jurisdiction's local laws and regulations.

For cases of sexual assault, health care providers should document their findings and assist patients with notifying local authorities.[174] How health care providers should document and report their findings is beyond the scope of these guidelines. Laws in all 50 states strictly limit the evidentiary use of a survivor's previous sexual history, including evidence of previously acquired STIs, to avoid efforts to undermine the credibility of the survivor's testimony. Evidentiary privilege against revealing any aspect of the survivor's examination or medical treatment also is enforced in the majority of most states.

Certain states and localities have special programs that provide reimbursement for medical therapy, including antiretroviral medication after sexual assault, and those areas might have specific reporting requirements. In all states, sexually assaulted persons are eligible for reimbursement of medical expenses through the U.S. Department of Justice Victim's Compensation Program in cases where the sexual assault is reported to the police (http://www.ojp.usdoj.gov/ovc/map.html).When the sexual abuse of a child is suspected or documented, the clinician should report it in compliance with that jurisdiction's laws and regulations.

VII-F2. Special Populations

VII-F2a. Sexually Assaulted Persons

Eighteen percent of a national sample of adult women in the United States reported having ever been raped, and approximately 1 in 10 women (9.4%) has been raped by an intimate partner during her lifetime.[189] Sexual assault also occurs among men. Approximately 1 in 71 men (1.4%) in the United States has been raped at some time in his life.[189] In 1 series from an ED, 5% of reported rapes involved men sexually assaulted by men.[190]

Sexual assault typically has multiple characteristics that increase the risk for HIV transmission if the assailant is infected. In 1 prospective study of 1,076 sexually assaulted person, 20% had been attacked by multiple assailants, 39% had been assaulted by strangers, 17% had had anal penetration, and 83% of females had been penetrated vaginally. Genital trauma was documented among 53% of those assaulted, and sperm or semen was detected in 48%.[191] Often, in both stranger and intimate-partner rape, condoms are not used[192,193] and STIs are frequently contracted.[194-197] In the largest study[198] examining prevalence of HIV infection among sexual assailants, 1% of men convicted of sexual assault in Rhode Island were HIV infected when they entered prison, compared with 3% of all prisoners and 0.3% of the general male population.

Persons provided nPEP after sexual assault or child sexual abuse should be examined and co-managed by professionals specifically trained in assessing and counseling patients and families during these circumstances (e.g., Sexual Assault Nurse Examiner [SANE] program staff). Local SANE programs can be located at http://www.sane-sart.com/. Patients who have been sexually assaulted will benefit from supportive services to improve adherence to nPEP if it is prescribed, and from crisis, advocacy, and counseling services provided by sexual assault crisis centers.

VII-F2b. Pregnant Women and Women with Childbearing Potential

Information is being collected regarding safe use of antiretroviral drugs for pregnant and breastfeeding women who do not have HIV infection, particularly those whose male partners have HIV infection and who use antiretrovirals as PrEP.[114] Because considerable experience has been gained in recent years in the safe and recommended use of antiretroviral medications during pregnancy and breastfeeding among women with HIV infection—either for the benefit of the HIV-infected woman's health or to prevent transmission to newborns—and because of the lack of similar experience in HIV-uninfected pregnant women, nPEP drug recommendations (Table 5) rely on those used for HIV-infected women during pregnancy and breastfeeding.

Health care providers should be aware that certain medications are contraindicated for use as nPEP among potentially or actually pregnant women as follows (Table 7):

- Efavirenz (EFV) is classified as FDA pregnancy Category D because of its potential teratogenicity when used during the first 5–6 weeks of pregnancy.[199] It should be avoided in nPEP regimens for HIV-uninfected women during the first trimester and should not be used for women of childbearing age who might become pregnant during an antiretroviral prophylaxis course. For all women with childbearing potential, pregnancy testing must be done before the EFV initiation, and women should be counseled regarding potential risks to the fetus and the importance of avoiding pregnancy while on an EFV-containing regimen.[114]

- Prolonged use of stavudine (d4T) in combination with didanosine (DDI) for HIV-infected pregnant women has been associated with maternal and fetal morbidity attributed to lactic acidosis; therefore, this combination is not recommended for use in an nPEP regimen during pregnancy.[123,124]

- Because using indinavir (IDV) is associated with increased risk for nephrolithiasis among pregnant women and its use without co-administration of a ritonavir as a boosting agent can result in substantially decreased plasma levels of IDV (the active agent) among pregnant women, IDV should not be used as nPEP for pregnant women.

- Severe hepatotoxicity has been observed among patients administered nevirapine (NVP)-containing nPEP regimens (regardless of pregnancy status); therefore, NVP is contraindicated for nPEP, including for pregnant women.[83]

Table 7. Antiretroviral medications that should not be used for nPEP among pregnant women

Antiretroviral	Risk in pregnancy	Concern
Efavirenz	Teratogenicity	Fetal safety
Nevirapine	Hepatotoxicity	Maternal safety
Stavudine and didanosine	Mitochondrial toxicity and lactic acidosis	Maternal safety
Indinavir (without co-administration with ritonavir) during second or third trimester	Substantially decreased plasma concentration; risk for nephrolithiasis	Efficacy and maternal safety
Abbreviation: nPEP, nonoccupational postexposure prophylaxis.		

If nPEP is prescribed to a woman who is pregnant at the time of exposure or becomes pregnant while on nPEP, health care providers should enter the patient's information (anonymously) into the Antiretroviral Pregnancy Registry (http://www.apregistry.com).

VII-F2c. Incarcerated Persons

Approximately 2 million persons are incarcerated in jails and prisons and can be at risk for HIV infection acquisition during incarceration. Studies have indicated that the risk for becoming infected while incarcerated is probably less than the risk outside a facility[200-202]; nevertheless, correctional facilities should develop protocols for nPEP to help reduce the legal, emotional and medical problems associated with an exposure event for this vulnerable population. As foundation for nPEP provision when it is indicated, correctional facilities should provide HIV education, voluntary HIV testing, systems to assist in identifying potential HIV exposures without repercussion for inmates, and provision of nPEP evaluation and medication. Sexual assaults in particular can put inmates at risk for HIV acquisition and inmates may engage in behaviors that put them at risk for HIV acquisition both prior to being incarcerated and upon reentry into the community. A 15-minute interactive educational program designed to educate inmates about nPEP resulted in a 40% increase in knowledge compared to baseline regardless of inmate-related demographics or HIV-risk characteristics.[203]

The federal Bureau of Prisons has published a clinical practice guideline that integrates guidance for nonoccupational and occupational HIV-related exposures.[204] Those guidelines specific to nPEP represent an adaptation of the 2005 CDC nPEP guidelines and outline HIV postexposure management recommendations for the different exposure types. The federal Bureau of Prisons nPEP recommendations can be modified for use in correctional facilities of varying sizes and resources. The Bureau of Prisons guidelines provide practical materials for both correctional health care providers and inmates and include worksheets to assist health care providers in systematically documenting HIV exposures and nPEP therapy management, and sample patient consent forms. They recommend that each correctional facility develop its own postexposure management protocol. The CDC recommends that health care providers should make every effort to use of current CDC guidelines related to selection of nPEP antiretrovirals.

VII-F2d. PWID

A history of injection drug use should not deter health care providers from prescribing nPEP if the exposure provides an opportunity to reduce the immediate risk for acquisition of HIV infection. A survey of health care providers who treat PWID determined a high degree of willingness to provide nPEP after different types of potential HIV exposure.[202]

When evaluating whether exposures are isolated, episodic, or ongoing, health care providers should assess whether persons who continue to engage in injecting or sexual HIV risk behaviors are practicing risk reduction (e.g., not sharing syringes, using a new sterile syringe for each injection, and using condoms with every partner or client). For certain persons, a high-risk exposure might be an exceptional occurrence and merit nPEP despite their ongoing general risk behavior. For other persons, the risk exposures might be frequent enough to merit consideration of PrEP either instead of nPEP or after a 28-day nPEP course.

PWID should be assessed for their interest in substance abuse treatment and their knowledge and use of safe injecting and sexual practices. Patients desiring substance abuse treatment should be referred for such treatment. Persons who continue to inject or who are at risk for relapse to injection drug use should be instructed regarding use of a new sterile syringe for each injection and the importance of avoiding sharing injection equipment. In areas where programs are available, health care providers should refer such patients to sources of sterile injection equipment. When sexual practices can result in ongoing risk for HIV acquisition, referral for sexual risk-reduction interventions is recommended.

None of the preferred or alternative antiretroviral drugs recommended for nPEP in Table 5 have substantial interactions with methadone or buprenorphine. However, other antiretrovirals might decrease or increase methadone levels; therefore, health care providers electing to use antiretrovirals not specifically recommended for nPEP should check for interactions before prescribing to persons on opiate substitution therapy. For example, RTV-boosted DRV can decrease methadone levels marginally (within acceptable clinical range), and careful monitoring for signs and symptoms of withdrawal is advised.[205]

VII-F3. Special Legal and Regulatory Concerns

VII-F3a. HIV Testing of Exposure Source Patients

When approaching persons who were the exposure source for patients being considered for nPEP, health care providers should be aware of potential legal concerns related to requesting them to undergo HIV testing. During 2011, a total of 33 states had ≥ 1 HIV-specific criminal exposure laws.[206] These laws focus explicitly on persons living with HIV. HIV-specific criminal laws criminalize or impose additional penalties on certain behaviors (e.g., sexual activity or needle-sharing without disclosure of HIV-positive status) and sex offenses. In jurisdictions where consent to HIV testing might invoke legal repercussions (see http://www.cdc.gov/hiv/policies/law/states/), the exposure source person should be made aware of possible legal jeopardies. Health care providers can opt instead to make nPEP treatment decisions without HIV testing of the source.

VII-F3b. Adolescents and Clinical Preventive Care

Health care providers should be aware of local laws and regulations that govern which clinical services adolescent minors can access with or without prior parental consent. In certain jurisdictions, minors of particular ages can access contraceptive services, STI diagnosis and treatment, or HIV testing without parental or guardian consent. In fewer settings, minors can access clinical preventive care (e.g. vaccines, nPEP, or PrEP).[207] To provide and coordinate care when a minor presents for possible nPEP, health care providers should understand their local regulations and institutional policies guiding provision of clinical preventive care to adolescent minors.

VII-F4. Potential Sources of Financial Assistance for nPEP Medication

Antiretroviral medications are expensive, and certain patients are unable to cover the out-of-pocket costs. When public, privately purchased, or employer-based insurance coverage is unavailable, health care providers can assist patients with obtaining antiretroviral medications through the medication assistance programs of the pharmaceutical companies that manufacture the prescribed medications. Applications are available online that can be faxed to the company or certain companies can be called on an established phone line. Requests for assistance often can be handled urgently so that accessing medication is not delayed. Information for specific medications and manufacturers is available at http://www.pparx.org/en/prescription_assistance_programs/list_of_participating_programs.

Additionally, persons being prescribed nPEP after sexual assault can be reimbursed for medications and clinical care costs through state Crime Victim's Compensation Programs funded by the U.S. Department of Justice. Contact information for each state is available at http;//www.ojp.usdoj.gov/ovc/map.html or http;//www.nacvcb.org/index.asp?bid=16.

VIII. CONCLUSION

Accumulated data from human clinical and observational studies, supported by data from animal studies, indicate that using antiretroviral medication initiated as soon as possible ≤72 hours after sexual, injection drug use, or other substantial nonoccupational HIV exposure and continued for 28 days might reduce the likelihood of HIV acquisition. Because of these findings, DHHS recommends prompt initiation of nPEP with a combination of antiretroviral medications when persons seek care ≤72 hours after exposure, the source is known to be HIV infected, and the exposure event presents a substantial risk for HIV acquisition by an exposed, uninfected person. When the HIV status of the source is unknown and the patient seeks care ≤72 hours after exposure, DHHS does not recommend for or against nPEP, but encourages health care providers and patients to weigh the risks and benefits on a case-by-case basis. When the HIV acquisition risk is negligible or when patients seek care > 72 hours after a substantial exposure, nPEP is not recommended. A 3-drug nPEP regimen is recommended for all persons for whom nPEP is indicated. Providing a 28-day nPEP supply or a 3–7 day nPEP starter pack at initiation of nPEP might improve adherence. Providing medications to ameliorate specific side effects for the antiretrovirals prescribed might improve adherence to the nPEP regimen. Figure 2 includes a summary of key nPEP considerations.

Figure 2. nPEP considerations summary

Initial nPEP Evaluation

- Obtain history of potential exposure event
  - HIV and HBV status of exposed person and source person, if available
  - Timing of most recent potential exposure
  - Type of exposure event and risk for HIV acquisition
  - Make determination if nPEP is indicated
- If nPEP is indicated
  - Conduct laboratory testing
    - HIV blood test (rapid combined Ag/Ab test, if available)
    - STIs, HBV, HCV, pregnancy, and chemistries, as indicated
  - Prescribe 28-day nPEP course
    - Educate patient about potential regimen-specific side effects and adverse events
    - Counsel patient about medication adherence
    - Provide patient with nPEP prescription or full 28-day nPEP course or nPEP starter pack and prescription
  - When necessary, assist patients with obtaining nPEP medication through a medication assistance program for the prescribed regimen
- For all persons evaluated
  - Prescribe prophylaxis for STIs and HBV infection, if indicated
  - Provide counseling related to HIV prevention strategies, as appropriate
  - Document sexual assault findings and fulfill local reporting requirements
  - Conduct confidential reporting of newly diagnosed STIs and HIV infection to health department
  - Link HIV-infected persons to relevant medical and psychosocial support services

Follow-up evaluations for persons prescribed nPEP

- Conduct HIV and any other indicated laboratory testing
- Consider changing nPEP regimen if indicated by side effects or results of initial testing
- Provide additional counseling and support for medication adherence and HIV prevention, if indicated

Abbreviations: Ag/Ab, antigen/antibody combination test; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; nPEP, nonoccupational postexposure prophylaxis; STI, sexually transmitted infection.

VIII-A. Plans for Updating These Guidelines

These guidelines are intended to assist U.S. health care providers in reducing the occurrence of new HIV infections through the effective delivery of nPEP to the patients most likely to benefit. As new medications and new information regarding nPEP become available, these guidelines will be revised and published.

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X. APPENDICES

Appendix 1A

Summary of Methods for nPEP Guidelines Development and Roles of Teams and Consultants

Topic	Comment
The guidelines' goal	Provide guidance for medical practitioners regarding nPEP use for persons in the United States.
nPEP Working Group	The nPEP Working Group is composed of 13 members from the Centers for Disease Control and Prevention (CDC) with expertise in nPEP or other subject areas pertinent to the guidelines (e.g., cost-effectiveness, sexual assault, or nPEP adherence), including certain members who were involved in the writing of the previous version(s) of the CDC nPEP guidelines.
nPEP Writing Group	The nPEP Writing Group is composed of 12 members from CDC with expertise in nPEP or other subject areas pertinent to the guidelines (e.g., cost-effectiveness, sexual assault, or nPEP adherence, etc.), including 1 member who was involved in the writing of the previous version of CDC's nPEP guidelines.
nPEP external consultants	External consultants were selected from government, academia, and the health care community by CDC to participate in 2 consultations by telephone conference call regarding nPEP on the basis of the member's area of subject matter expertise. Each consultation was chaired by 1 of the CDC nPEP co-chairs. The list of the external consultants is available in Appendix 2B.
Competing interests and management of conflicts of interest	All internal CDC staff and external consultants involved in developing the guidelines or who served in the external consultations submitted a written financial disclosure statement reporting any potential conflicts of interest related to questions discussed during the consultations or concerns involved in developing of the nPEP guidelines. A list of these disclosures and their last update is available in Appendix 2C. The nPEP co-chairs reviewed each reported association for potential competing interest and determined the appropriate action, as follows: disqualification from the panel, disqualification/recusal from topic review and discussion; or no disqualification needed. A *competing interest* is defined as any direct financial interest related to a product addressed in the section of the guideline to which a panel member contributes content. *Financial interests* include direct receipt by the panel member of payments, gratuities, consultancies, honoraria, employment, grants, support for travel or accommodation, or gifts from an entity having a commercial interest in that product. *Financial interest* also includes direct compensation for membership on an advisory board, data safety monitoring board, or speakers bureau. Compensation and support that filters through a panel member's university or institution (e.g., grants or research funding) is not considered a competing interest.

Topic	Comment
OMB Peer Review and OMB Public Engagement	As recommended by the Office of Management and Budget for scientific documents fitting the classification of Influential Scientific Information, during Oct. 2014–December 2015, the draft nPEP guidelines underwent peer review by independent scientific and technical experts. They were asked to review the scientific and technical evidence that provides the basis for the nPEP guidelines and to provide input on the draft guidelines before they were finalized. Peer reviewers were asked whether any recommendations are based on studies that were inappropriate as supporting evidence or were misinterpreted, whether there are significant oversights, omissions, or inconsistencies that are critical for the intended audience of clinicians, and whether the recommendations for the intended audience of health care providers are justified and appropriate. In addition, the recommendations from the draft nPEP guidelines were presented to the public through 2 public engagement webinars on November 14 and 17, 2014. Based on the responses from both peer review and public engagement, updates were made to the nPEP guidelines prior to their publication. CDC's responses to the comments were also posted on the CDC/ATSDR Peer Review Agenda website at http://www.cdc.gov/od/science/quality/support/peer-review.htm and the CDC Division of HIV/AIDS Prevention Program Planning Scientific Information Quality—Peer Review Agenda website at http://www.cdc.gov/hiv/policies/planning.html.
Guidelines users	Health care providers
Developer	The CDC nPEP Working Group
Funding source	Epidemiology Branch, Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, TB Prevention, CDC
Recommendation ratings	Because none of the evidence is based on randomized clinical trials, but rather observational studies or expert opinion, we have elected not to provide graded recommendations for these guidelines.
Abbreviations: AIDS, acquired immunodeficiency virus; CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus; nPEP, nonoccupational postexposure prophylaxis.	

Appendix 1B

nPEP Guidelines Development Teams and Consultants

CDC nPEP Guidelines Writing Team

Kenneth L. Dominguez, MD, MPH (lead author), Dawn K. Smith, MD, MS, MPH, Vasavi Thomas, RPh, MPH; Nicole Crepaz, PhD; Karen S. Lang, MSW; Walid Heneine, PhD; Janet McNicholl, MD; Laurie Reid, RN, MS; Brandi Freelon, MD; Steven Nesheim, MD; Ya-lin (Aileen) Huang, PhD; and Paul J. Weidle, PharmD, MPH.

CDC nPEP Working Group

Ken Dominguez, MD, MPH (Co-lead); Vasavi Thomas, RPh, MPH (Co-lead), Dawn K. Smith, MD, MS, MPH; Steve Nesheim, MD; Walid Heneine, PhD; Lauri Reed, Brandi Freelon, MD; Nicole Crepaz, PhD; Karen S. Lang, MSW; Ya-lin (Aileen) Huang, PhD; Kathleen Irwin, MD, MPH; Gema Dumitru, MD; David Kuhar, MD; and Lynn Paxton, MD, MPH.

Federal Consultants

CDC: Norma Harris, PhD; John Brooks, MD; Pragna Patel, MD, MPH; and Philip J. Peters, MD.

Other Federal Agencies

Holly Van Lew, PharmD, Indian Health Service; Newton Kendig, MD, Bureau of Prisons; David Burns, MD, National Institutes of Health; Laura Cheever, MD, Health Resources and Services Administration; Maggie Czarnogorski, MD, Department of Veterans Affairs; Heather Huentelman, PharmD, Indian Health Service; Kimberly Struble, PharmD, Food and Drug Administration; Rohan Hazra, MD, National Institutes of Health; Lynne Mofenson, MD, National Institutes of Health; and Steve George Siberry, MD, MPH, National Institutes of Health.

Nonfederal External Consultants

Jeffrey Beal, MD, Florida Department of Health; Ronald H. Goldschmidt, MD, University of California, San Francisco; Donna Greco, MSW, Pennsylvania Coalition Against Rape/National Sexual Violence Resource Center; Angela Kashuba, BScPhm, PharmD, University of Northern Carolina Center for AIDS Research, Chapel Hill; Sally Laskey, MA, National Sexual Violence Resource Center, Enola, Pennsylvania; Kenneth Mayer, MD, Fenway Health Center, Boston, Massachusetts; Thera Meehan, MS, MPH, Massachusetts Department of Public Health, Boston; Jennifer Sayles, MD, Los Angeles County Public Health Department, California; Barbara Sheaffer, MA, Pennsylvania Coalition Against Rape, Enola, Pennsylvania; Lyn Stevens, MS, ACRN, NP, New York State Department of Health, Albany; Elaine Abrams, MD, Columbia University College of Physicians & Surgeons, New York, New York; Michael Brady, MD, Columbus Children's Hospital, Ohio; Ellen Chadwick, MD, Northwestern University's Feinberg School of Medicine, Chicago, Illinois; Rana Chakraborty, MD, Emory University School of Medicine, Atlanta, Georgia; Ellen Cooper, MD, Boston University School of Medicine, Massachusetts; Peter Havens, MD, MPH, Children's Hospital of Wisconsin, Milwaukee; Daniel Johnson, MD, Comer Children's Hospital, University of Chicago, Illinois; Paul Krogstad, MD, University of California at Los Angeles–David Geffen School of Medicine; Natalie Neu, MD, MPH, Columbia University Medical Center, New York, New York; Vicki Peters, MD, New York City Department of Health and Mental Hygiene, New York; Russ van Dyke, MD, Tulane University School of Medicine. New

Orleans, Louisiana; and Geoffrey Weinberg, MD, University of Rochester Medical Center, School of Medicine and Dentistry, New York.

CDC Scientific Support Staff

Beverly Bohannon, RN, MS; and Wayne Hairston II, MPH, MBA, ICF International, Atlanta, Georgia.

CDC editor

C. Kay Smith, Med

Abbreviation: nPEP, nonoccupational postexposure prophylaxis.

Appendix 1C

Financial Disclosures of Potential Competing Interest
nPEP Guidelines Consultants and Working Group

Member (affiliation)	Role	Company	Relationship	Determination
Elaine Abrams, MD, Columbia University College of Physicians & Surgeons	Non-federal external consultant	None		
Jeffrey Beal, MD, Florida Department of Health	Non-federal external consultant	CDC Flow Through Money—Perinatal Transmission Project	Principal Investigator	No disqualification needed
Beverly Bohannon, RN, MS, CDC	CDC scientific support staff	None		
Michael Brady, MD, Columbus Children's Hospital	Non-federal external consultant	None		
John Brooks, MD, CDC	Other CDC consultant	None		
David Burns, MD, NIH	Other federal consultant	None		
Ellen Chadwick, MD, Northwestern University's Feinberg School of Medicine	Non-federal external consultant	Abbott Labs	Spouse—Abbott retiree; Spouse—owner of stocks and stock options	Recusal from topic review and discussion of selection of antiretrovirals for nPEP use
Rana Chakraborty, MD, Emory University School of Medicine	Non-federal external consultant	None		
Laura Cheever, MD, HRSA	Other federal consultant	None		
Ellen Cooper, MD, Boston University School of Medicine	Non-federal external consultant	None		
Nicole Crepaz, PhD, CDC	nPEP Writing Team, nPEP Workgroup	None		
Maggie Czarnogorski, MD, Department of Veterans Affairs	Other federal consultant	None		
Kenneth L. Dominguez, MD, MPH, Co-lead, CDC	nPEP Writing Team and nPEP Workgroup (co-lead)	None		
Gema Dumitru, MD, CDC	nPEP Workgroup	None		
Brandi Freelon, MD, CDC	nPEP Writing Team and nPEP Workgroup	None		
Ronald H. Goldschmidt, MD, University of California, San Francisco	Non-federal external consultant	CDC funding PEPline	Director—National HIV/AIDS Clinician's Consultation Center	No disqualification needed
Wayne Hairston II, MPH, MBA, CDC	CDC scientific support staff	None		
Norma Harris, PhD, CDC	Other CDC consultant	None		

Member (affiliation)	Role	Company	Relationship	Determination
Peter Havens, MD, MPH, Children's Hospital of Wisconsin	Non-federal external consultant	None		
Rohan Hazra, MD, NIH	Other federal consultant	None		
Walid Heneine, PhD, CDC	nPEP Writing Team and nPEP Workgroup	None		
Ya-lin (Aileen) Huang, PhD, CDC	nPEP Writing Team and nPEP Workgroup	None		
Heather Huentelman, PharmD, IHS	Other federal consultant	None		
Kathleen Irwin, MD, MPH, CDC	nPEP Workgroup	None		
Daniel Johnson, MD, Comer Children's Hospital; University of Chicago	Non-federal external consultant	None		
Angela Kashuba, BScPhm, PharmD, University of North Carolina Center for AIDS Research	Non-federal external consultant	None		
Newton Kendig, MD, Bureau of Prisons	Other federal consultant			
Paul Krogstad, MD, University of California Los Angeles—David Geffen School of Medicine	Non-federal external consultant	None		
David Kuhar, MD, CDC	nPEP Workgroup	None		
Karen S. Lang, MSW, CDC	nPEP Writing Team and nPEP Workgroup	None		
Sally Laskey, MA, National Sexual Violence Resource Center	Non-federal external consultant	None		
Janet McNicholl, MD, CDC	nPEP Writing Team	None		
Thera Meehan, MS, MPH, Massachusetts Department of Public Health	Non-federal external consultant	None		
Lynne Mofenson, MD, NIH	Other federal consultant	None		
Steven Nesheim, MD, CDC	nPEP Writing Team and nPEP Workgroup	None		
Natalie Neu, MD, MPH, Columbia University Medical Center	Non-federal external consultant	None		
Pragna Patel, MD, CDC	Other CDC consultant	None		
Lynn Paxton, MD, MPH, CDC	nPEP Workgroup	None		
Philip J. Peters, MD, CDC	Other CDC consultant	None		
Vicki Peters, MD, New York City Department of Health and Mental Hygiene	Non-federal external consultant	None		

Member (affiliation)	Role	Company	Relationship	Determination
Laurie Reid, RN, MS, CDC	nPEP Writing Team and nPEP Workgroup	None		
Jennifer Sayles, MD, Los Angeles County Public Health Department	Non-federal external consultant	None		
Barbara Sheaffer, MA, Pennsylvania Coalition Against Rape	Non-federal external consultant	CDC funding—National Sexual Violence Resource Center	Medical Advocacy Coordinator	No disqualification needed
George Steve Siberry, MD, MPH, NIH	Other federal consultant	None		
Dawn Smith, MD, MS, MPH, CDC	nPEP Writing Team and nPEP Workgroup	Salaried by CDC to do nPEP work	Medical Epidemiologist, Biologic Intervention	No disqualification needed
Lyn Stevens, MS, ACRN, NP, New York State Department of Health	Non-federal external consultant	CDC Grant (Adult Viral Hepatitis)	Adult Viral Hepatitis Prevention Coordinator	No disqualification needed
Kimberly Struble, PharmD, FDA	Other federal consultant	None		
Vasavi Thomas, RPh, MPH, CDC	nPEP Writing Team and nPEP Workgroup (co-lead)	None		
Russ van Dyke, MD, Tulane University School of Medicine	Non-federal external consultant	None		
Holly Van Lew, PharmD, Indian Health Service	Other federal consultant	None		
Paul J Weidle, PharmD, MPH, CDC	nPEP Writing Team	None		
Geoffrey Weinberg, MD, University of Rochester Medical Center, School of Medicine and Dentistry	Non-federal external consultant	None		

Abbreviations: CDC, Centers for Disease Control and Prevention; nPEP, nonoccupational postexposure prophylaxis.

Appendix 2

Literature Search Methods for the nPEP Guidelines

Topic	Databases	Research Question	Keywords	Dates of Search	Search Limits
Animal Studies	PubMed	Which studies related to PEP involving animal models were published since 2005?	SIV post exposure prophylaxis, post-exposure prophylaxis, antiretroviral prophylaxis in macaques	January 2005 to July 2015	No limitations
Observational Studies, Case Reports	Web of Knowledge, PubMed, Google Scholar	Which are the results of latest nPEP observational and case studies since 2005 with a focus on populations studied, drug regimens used, completion rates, side effects of medications, number of breakthrough infections?	nPEP, nonoccupational postexposure or post-exposure prophylaxis, and HIV postexposure or post-exposure prophylaxis	January 2005 to July 2015	Excluded opinion pieces; no other limitations
Effects on Risk-Reduction Behaviors	MEDLINE, EMBASE, CINAHI [EBSCOhost]	What are the potential behavioral implications of offering nPEP?	HIV infections, acquired immune deficiency syndrome, seropositivity, serodiagnosis, HIV, AIDS, post exposure or post-exposure prophylaxis, post exposure or post-exposure prevention, non-occupational, non pep, NOPEP, nPEP, PEP	January 1996 to July 2015	No limitations
Cost Effectiveness	PubMed	The cost-effectiveness evaluation of nPEP in the United States and other resource-rich countries.	HIV, post exposure post-exposure prophylaxis, PEP, nPEP, economic evaluation, cost utility, cost-benefit analysis, cost benefit, cost effectiveness	January 2005 to July 2015	English only; excluded occupational exposure; not an economic evaluation; no other limitations
Pregnant Women, Women of Childbearing Potential	PubMed	Which nPEP studies involving pregnant women and women of childbearing potential were conducted since 2005?	pregnant women, women of reproductive age, PEP, nPEP, postexposure or post-exposure HIV prophylaxis	January 2005 to July 2015	No limitations
Children/Adolescents	PubMed	Which nPEP studies involving children or adolescents were conducted since 2005?	Children, pediatrics, adolescents, PEP, nPEP, postexposure or post-exposure HIV prophylaxis	January 2005 to July 2015	No limitations
Sexual Assault Survivors	PubMed	Which nPEP studies involving sexual assault survivors were conducted since 2005?	Sexual assault, sexual abuse, PEP, nPEP, postexposure or post-exposure HIV prophylaxis	January 2005 to July 2015	No limitations
Incarcerated Populations	PubMed	Which nPEP studies involving incarcerated populations were conducted since 2005?	Incarcerated, jail, prison, correctional facility, nPEP, PEP	January 2005 to July 2015	No limitations

Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; nPEP, non-PEP, or NOPEP, nonoccupational postexposure prophylaxis; PEP, postexposure prophylaxis.

Appendix 3

Studies Reviewed for the nPEP Guidelines

MSM Studies

Authors, year: Donnell et al, 2010[14]

Type of study: Randomized behavioral intervention trial to assess perceptions and nPEP use over a 4-year period

Location: 6 U.S. cities

Sample size: n=4,295 MSM

Risk: HIV uninfected men who reported unprotected anal sex in the past year

Intervention: Behavioral intervention vs. standard risk-reduction counseling (accompanying nPEP drug regimen not reported)

Drug regimen: Not reported

Time from exposure to nPEP: Not reported

Completion of nPEP: Not reported

HIV seroconversions: 3

Conclusion: Increased odds of nPEP use was observed in participants with multiple partners and participants who had unprotected anal sex with HIV infected and unknown status partners. The availability of nPEP did not lead to an increase in high-risk sex.

Authors, year: Foster et al, 2015[19]

Type of study: Open-label, single-arm nonrandomized trial at 2 public sexual health clinics and 2 hospital EDs during December 23, 2012–June 12, 2014.

Location: Melbourne, and Sydney, Australia

Sample size: n=100 MSM

Risk: Sexual 65% failed to use a condom after anal intercourse; 29% used a condom but it tore or slipped off; 6% source partner removed condom

Intervention: 3-drug single tablet once daily dose regimen

Drug regimen: RPV + FTC + TDF

Time from exposure to nPEP: ≤72 hours; presentation for nPEP initiation at a mean=30 hours; nPEP initiated at a mean of 2 hours after presentation

Completion of nPEP: 92%

HIV seroconversions: 0 seroconversions occurred through week 12 after initiation of nPEP. Adherence was 98.6% by pill count and 98.5% by self–report; 88% tested had plasma TDF levels suggesting full adherence. 88% experienced ≥1 clinical adverse events. Adverse events included mainly fatigue (34%) and nausea (23%); one participant developed acute abdominal pain and vomiting and grade 4 laboratory evidence of acute pancreatitis ≤1 week of completing nPEP.

Conclusion: A triple ARV regimen of RPV, FTC, and TDF administered once daily as a single combination tablet was well tolerated as nPEP with high levels of adherence and regimen completion.

Authors, year: Jain et al, 2015[18]

Type of study: Retrospective medical record review in a large community health center during July1997–August 2013

Location: Boston, Massachusetts

Sample size: n=788 MSM; median age=32.9 years; 21.2% presented for nPEP 2 or more times (range, 1–15 times)

Risk: Consensual unprotected sex most common n=726 (62.2%); n=425 (58.5%) receptive anal; n=277 (38.2%) insertive anal; n=157 (21.6%) receptive oral intercourse; n=351 (31.1%) condom failure or removal; (35.6%) HIV-positive partner

Intervention: nPEP (number of drugs not reported in this study, however, previous studies from this site have reported 2 or 3 drugs)

Drug regimen: Not reported

Time from exposure to nPEP: Not reported but assume 72 hours based on previously published studies from this site

Completion of nPEP: Not reported

HIV seroconversions: 39 seroconversions occurred at >90 days after initially presenting for nPEP; 4 occurred at <180 days: 91, 133, 160, 168 days; 3 of 4 reported completing 28-day regimen; adherence or ongoing sexual risk behavior not reported; 35 (89.7%) seroconversions occurred at ≥180 days after nPEP initiation; seroconversion associated with younger age and/or being African American or Latino; almost 90% of post-nPEP infections were probably due to subsequent risk-taking and not a failure of the initial nPEP regimen

Conclusion: Younger age, being Latino and/or being African American, but not repeated nPEP use, were associated with incident HIV infection. Younger MSM of color who are nPEP users may benefit from early HIV risk reduction and PrEP.

Authors, year: McAllister et al, 2014[17]

Type of study: Nonrandomized, open-label, prospective cohort study at two urban hospital centers

Location: Sydney, Australia

Sample size: n=125 MSM enrolled; n=91 prescribed 3-drug regimen; n=34 prescribed 2-drug regimen; mean age 32–34 years

Risk: Sexual

Intervention: 2-drug or 3-drug regimen

Drug regimen: TDF + FTC or RAL+ TDF + FTC; Mean Adherence to each arm: TDF + FTC (90%); RAL-FTC-TDF (89%); 8 patients reported myalgia on the 3-drug regimen vs. none on the 2-drug regimen; Grade 4 creatinine kinase elevations occurred in 5 subjects on the 3-drug regimen vs. none on the 2-drug regimen. All Grade 4 creatinine kinase elevations resolved to ≤grade 2 after desisting from exercise and increasing oral fluids intake

Time from exposure to nPEP: Not reported

Completion of nPEP: 86/91 (95%) participants prescribed a 3-drug regimen met criteria to stay on nPEP; 79/86 (92%) completed 28-day 3-drug regimen; 31/34 (91%) participants prescribed 2-drug regimen completed 28-day 2-drug regimen; overall 110/120 (91.7%) who met criteria to stay on nPEP completed 28-day regimen; overall 110/125 (88%) who were prescribed nPEP, completed the 28-day regimen

HIV seroconversions: 0

Conclusion: Although the 3-drug and 2-drug arms had similar percentages of patients completing their 28-day regimens, 9% of the 3-drug arm experienced grade 4 creatinine kinase elevations which subsequently resolved with increased fluid intake and desisting exercise. If a RAL-TDF-FTC regimen is used, a preferred nPEP regimen, authors recommend (1) asking patients about concomitant medications associated with rhabdomyolysis (i.e. statins); (2) patient education about possible association between RAL-containing nPEP, exercise, and rhabdomyolysis and the need to report myalgia; (3) laboratory monitoring of serum creatinine

kinase at baseline; if myalgia or weakness develops, conduct additional during treatment and clinical examination for proximal muscle weakness. Completion rates were higher for this study compared to those in other studies, including similar nPEP regimens. This may have been due to a high level of support provided by the study team including an experienced nPEP nurse, 24-hour contact with the nurse consultant, text reminders of appointments, proactive recall after missed appointments and frequent adherence education.

Authors, year: Schechter et al, 2004[16]

Type of study:

Location: Rio de Janeiro, Brazil

Sample size: n=200 participants; median age, 28 years; n=68 received nPEP

Risk: Sexual exposure (gay or bisexual)

Intervention: 2-drug regimen

Drug regimen: ZDV + 3TC

Time from exposure to nPEP: ≤48 hours

Completion of nPEP: 11 (1 among nPEP users, 10 among patients not using nPEP)

HIV seroconversions:

Conclusion: nPEP was safely tolerated and did not appear to be associated with either increases in reported high-risk behavior or HIV transmission; such findings may limit its impact as a public health intervention

Authors, year: Sonder et al, 2010[15]

Type of study: Observational study comparing 2 nPEP regimens

Location: Amsterdam

Sample size: n=309 MSM

Risk: Sexual exposure

Intervention: One 4-drug regimen and one 3-drug regimen; 2- or 3-pill burden

Drug regimen: Single-dose NVP + ZDV+ 3TC+ NFV or ZDV + 3TC + ATV

Time from exposure to nPEP: Seroconverters presented between 5–36 hours post exposure

Completion of nPEP: 237/261 (91%)

HIV seroconversions: 5 (likely due to ongoing risk behavior)

Conclusion: Common side effects were fatigue, nausea, and diarrhea (worse in regimen 1). There was no significant difference in completion rates of the two regimens. Strategies are needed to prevent subsequent HIV exposures in nPEP-treated individuals

Authors, year: Terzi et al, 2007[13]

Type of study: Case report

Location: Italy

Sample size: n=1 MSM
Risk: Receptive anal intercourse with HIV + male
Intervention: 3-drug regimen; 2-pill burden
Drug regimen: ZDV + 3TC (Combivir) + IDV
Time from exposure to nPEP: 30 hours
Completion of nPEP: Complete adherence
HIV seroconversions:
Conclusion: Sexual exposures to HIV and HCV require prolonged follow-up due to the risk of late seroconversion.

Sexual Assault Studies—Adults, Adolescents, and Children (combined)

Authors, year: Chacko et al, 2012[20]
Type of study: Systematic review of nPEP adherence among victims of sexual assault
Location: U.S. and International
Sample size: n=24 studies of adults, adolescents, and children
Risk: Sexual assault
Intervention: Various 2- and 3-drug regimens
Drug regimen: Most regimens included ZDV
Time from exposure to nPEP: Not reported
Completion of nPEP: 40%
HIV seroconversions: Not reported
Conclusion: Overall adherence was poor but was higher in developing countries compared to developed countries. Common side effects were: nausea and vomiting, diarrhea, and fatigue. More interventions are needed to improve adherence. Standard methods of conducting and reporting nPEP programs are needed.

Authors, year: Draughon and Sheridan, 2011[21]
Type of study: Systematic review spanning 10 years
Location: Sub-Saharan Africa (Kenya, Malawi, and South Africa)
Sample size: n=studies of adults, adolescents, and children
Risk: Sexual assault
Intervention: Not reported
Drug regimen: Not reported
Time from exposure to nPEP: Not reported
Completion of nPEP: 0%–65% (most studies reported >35%)

HIV seroconversions: Not reported

Conclusion: Overall adherence was low, but was higher in locations where the full 28-day PEP regimen was given up front.

Authors, year: Draughon and Sheridan, 2012[22]

Type of study: Systematic review

Location: Low HIV prevalence countries

Sample size: n=34 studies of adults, adolescents, and children

Risk: Sexual assault

Intervention: nPEP (number of drugs not reported by reviewers)

Drug regimen: Not reported

Time from exposure to nPEP: 24–96 hours

Completion of nPEP: 0%–63%

HIV seroconversions: Not reported

Conclusion: There was wide variation in the provision, acceptance, and adherence to nPEP programs. Anywhere from 5%–100% of eligible patients received nPEP across studies. Further research is needed to understand the experience of sexual assault survivors with the health care system and nPEP following an attack

Authors, year: Loutfy et al, 2008[23]

Type of study: Prospective cohort study

Location: Ontario, Canada

Sample size: n=798 sexual assault survivors presented to sexual assault treatment centers and offered nPEP; females (n=775 [97.1%]), age 4–17 years (n=190 [23.8%]), age 18–80 years (n=608 [77.2%]); 347 accepted nPEP

Risk: Sexual assault

Intervention: 3-drug regimen; 2-pill burden

Drug regimen: Combivir + Kaletra

Time from exposure to nPEP: ≤72 hours

Completion of nPEP: 111/347 (31.9%) completed nPEP including (11/46 [23.9%]) of participants at high risk completed therapy and (100/301 [33.2%]) of unknown risk participants completed therapy

HIV seroconversions: Not reported

Conclusion: The PEP program for sexual assault survivors in Ontario proved to be feasible and acceptable among participants. The most common side effects were fatigue, nausea, and diarrhea. Further research is needed to improve loss to follow-up and completion rates of nPEP.

Sexual Assault Studies—Adults and/or Adolescents

Authors, year: Carrieri et al, 2006[33]

Type of study: Retrospective survey of nPEP consultations

Location: Southeastern France

Sample size: n=94 persons, aged 18 years or older, presented to AIDS centers for nonoccupational HIV exposure (female n=88 [93.6%], male n=6 [6.4%]); nPEP prescribed to 86 persons

Risk: Sexual assault

Intervention: 2 and 3 drug regimens

Drug regimen: Not reported

Time from exposure to nPEP: 72% (n=77) ≤48 hours

Completion of nPEP: 25% (n=23) >3 months follow-up

HIV seroconversions: Not reported

Conclusion: Half of all participants were lost to follow-up after the first consultation. During the study period there were 600 additional sexual assaults that were reported to police but did not receive nPEP consultation. Prompt HIV medical assessment is needed for sexual assault survivors as well as strategies to improve nPEP adherence.

Authors, year: Griffith et al, 2010[31]

Type of study: Retrospective chart review in an urban county hospital from June 2007–June 2008

Location: Dallas, TX

Sample size: n=151 adolescent and adult women (151 prescribed nPEP, 62 received follow-up of which 58 self-reported taking nPEP); aged 13–17 years, n=43 (28%); 18–61 years, n=108 (72%)

Risk: Sexual assault

Intervention: 3-drug regimen; 2-pill burden

Drug regimen: Kaletra + Truvada or Combivir

Time from exposure to nPEP: ≤72 hours

Completion of nPEP: 62/151 (41%) of women presented for a follow-up visit. 37 of the 62 (60%) took nPEP for ≥21 days or completed prescribed course of therapy

HIV seroconversions: 0 (36 of 58 women who reported taking nPEP at follow-up were HIV screened at week 12 or 24 of follow-up)

Conclusion: Full medication compliance and follow-up counseling remain challenges for sexual assault survivors and providers. A detailed nPEP protocol and continuity of care promotes quality patient management.

Authors, year: Krause et al, 2014[34]

Type of study: Retrospective cohort study of medical records from a level 1 trauma center participating in the Sexual Assault Nurse Examiner (SANE) Program

Location: Northeastern, United States

Sample size: n=179 cases of sexual assault among 171 unique female patients, aged ≥16 years (median: 26 years); nPEP offered to 138 patients for whom PEP was appropriate within the 72-hour window period; an additional 5 patients outside the 72-hour window period were offered PEP; 86% or 124/143 cases who were offered PEP, accepted PEP

Risk: Sexual assault

Intervention: 2-drug or 3-drug regimen

Drug regimen: Either FTC/TDF and LPV/r) (n=85, 59.4%) or FTC/TDF alone (n=32, 22.4%)

Time from exposure to nPEP: ≤72 hours (for most cases; 5 cases were given nPEP outside the 72-hour window)

Completion of nPEP: 34 of 124 (27.4%) cases who followed up with an infectious disease specialist completed nPEP

HIV seroconversions: Not reported

Conclusion: All 138 sexual assault case patients who were eligible for nPEP were offered nPEP. Only a minority of those who were documented to have followed up with an infectious disease specialist completed nPEP. There is a need for a better system for post-assault follow-up.

Authors, year: Linden et al, 2005[30]

Type of study: Retrospective medical record review of female sexual assault survivors presenting to an urban ED during 10/1/99–9/30/2002

Location: Boston, MA

Sample size: n=292 charts reviewed; n=181 in final sample size; mean age 29.1 years (range, 18–82); n=89 patients offered nPEP; n=85 patients accepted

Risk: Sexual assault

Intervention: 2-drug or 3-drug regimen; 1- or 2-pill burden

Drug regimen: Initiated in ED, ZDV + 3TC (Combivir) (n=78); Combivir + NFV (n=4); Initiated in referral clinic: 2-drugs (unspecified) (n=2); 3-drugs (unspecified) (n=1)

Time from exposure to nPEP: Median time from assault to presentation in ED (10.1 hours; range, 0–24 hours)

Completion of nPEP: Overall 18 of 85 (21%), including 15 of 82 (18%) of those initiated on nPEP in ED and 3 of 3 initiated on nPEP after being referred to another clinical care site

HIV seroconversions: No seroconversions during follow-up period in 38 patients with at least 1 follow-up visit

Conclusion: A minority of sexual assault survivors were offered nPEP and few completed full nPEP course.

Authors, year: Olshen et al, 2006[32]

Type of study: Retrospective medical record review of adolescents presenting to urban pediatric EDs ≤72 hours of penetrating sexual assault in 2 academic medical centers during July 1, 2001 to June 30, 2003

Location: Boston, MA

Sample size: n=177 adolescents aged 12–22 years; n=145 adolescents with adequate documentation; n=129 eligible for nPEP; n=110 accepted nPEP; n=85 initiated nPEP

Risk: Sexual assault

Intervention: 2-drug or 3-drug regimen

Drug regimen: 3TC + ZDV (94%); 3TC +ZDV + NFV (3%); 3TC + ZDV + IDV (2%)

Time from exposure to nPEP: ≤72 hours

Completion of nPEP: 13/85 (15%) who initiated nPEP completed 28-day course; 37 returned for first follow-up visit

HIV seroconversions: No seroconversions among 23 tested for HIV

Conclusion: Poor rates of nPEP completion among adolescent sexual assault survivors. May be due to uncertainties regarding exposure, high rates of psychiatric comorbidity, and low rates of return for follow-up care.

Sexual Assault Studies Including Children and/or Adolescents

Authors, year: Chesshyre et al, 2009[43]

Type of study: Retrospective review of medical records from January 2005–February 2007

Location: Blantyre, Malawi

Sample size: n=217 children and adolescents presented with history of sexual abuse; ages: n=62 (29%)<5 years; n=113 (52%) 5–10 years; n=42 (19%) 11–16 years; n=92 children were eligible for and received nPEP; n=153 children were not offered nPEP because they presented >72 hours or had chronic history of abuse

Risk: Child sexual abuse

Intervention: 2-drug regimen

Drug regimen: ZDV + 3TC

Time from exposure to nPEP: ≤72 hours

Completion of nPEP: Not reported

HIV seroconversions: No HIV seroconversions in any of the 92 children initiated on nPEP; 7/153 (5%) children who were not offered nPEP tested HIV+

Conclusion: The initiation of an nPEP program for child victims of sexual abuse led to increased numbers of such children presenting for nPEP services and is likely to have resulted in decreased HIV acquisition in this population.

Authors, year: Collings et al, 2008[42]

Type of study: Prospective observational cohort of 200 consecutive cases of child rape referred for assessment to a state hospital, Oct–Dec 2004

Location: KwaZulu-Natal, South Africa

Sample size: n=200 children and adolescents presenting with history of child rape; mean age 10.6 years (range, 1–17 years); 120 children eligible and offered nPEP; n=64 children not eligible due to presentation >72 hours; n=113 followed by hospital; n=7 referred to another nPEP provider

Risk: Child sexual abuse

Intervention: 2-drug regimen

Drug regimen: ZDV + 3TC

Time from exposure to nPEP: ≤72 hours

Completion of nPEP: 40/113 (35.5%) followed by hospital completed 28-day course

HIV seroconversions: No seroconversions among 13/40 children returning for 3-month follow-up and 4/40 children returning at 6-month follow-up.

Conclusion: Poor nPEP adherence and return for follow-up existed; further research is needed to identify reasons for such nonadherence and identify interventions to improve adherence.

Authors, year: Du Mont et al, 2008[44]

Type of study: Retrospective analysis of data on female adolescent sexual assault survivors from the HIV PEP Project, an implementation and evaluation of a program of universal offering of nPEP to sexual assault victims of all ages in 18 hospital-based sexual treatment centers

Location: Ontario, Canada

Sample size: n=386 sexually assaulted female adolescents; mean age 16.7 years (range, 12–19 years); n=325 eligible for nPEP; 307 offered nPEP; n=131 accepted nPEP; the most common reason for declining nPEP was lack of concern about acquiring HIV; students, survivors with marked anxiety, and those encouraged by a health professional were more likely to accept PEP

Risk: Sexual assault

Intervention: 3-drug regimen; 2-pill burden

Drug regimen: Combivir and Kaletra

Time from exposure to nPEP: ≤72 hours

Completion of nPEP: 34% (44/131) completed 28-day course nPEP; 47% (61/131) adhered to day 14; the most common side effects were nausea, fatigue, vomiting, and diarrhea; survivors who were white and had known their assailant<24 hours were more likely to complete nPEP; most common reasons for stopping nPEP early: ARV side effects (73%), including most often nausea and fatigue

HIV seroconversions: Permission not obtained to provide results of HIV testing

Conclusion: Stronger health care provider recommendations needed for nPEP; need for training of health care providers to consistently offer and recommend nPEP to all those meeting established risk criteria.

Authors, year: Ellis et al, 2005[37]

Type of study: Prospective study of children presenting to hospital with history of child sexual abuse during January, 1 2004 through December 31, 2004

Location: Blantyre, Malawi

Sample size: n=64 children presented with history of sexual assault; median age 83 months (range, 22–180 months); n=17 children eligible for, offered, and accepted nPEP

Risk: Sexual assault

Intervention: 2-drug regimen

Drug regimen: AZT+3TC

Time from exposure to nPEP: ≤72 hours

Completion of nPEP: 11/17 (65%) accepting nPEP completed 28-day course

HIV seroconversions: Among nPEP users, no seroconversions among 11 who returned after 1 month, 7 who returned after 3 months, and 2 who returned at 6 months; 1 of 4 children who did not receive nPEP was screened for HIV and was HIV+

Conclusion: The study found nPEP to be safe, acceptable, and feasible. The authors recommend routine offering of nPEP to all eligible children.

Authors, year: Fajman et al, 2006[41]

Type of study: Retrospective study of medical records of children presenting with child sexual abuse to inner-city pediatric ED in 2002

Location: Atlanta, GA

Sample size: n=227 sexually assaulted children and adolescents with adequate data; age range, 9 months–18 years; n=87 presented ≤72 hours of assault; n=5 sexually assault adolescent survivors were prescribed nPEP; being assaulted by a stranger associated with receiving nPEP (PR=11.9, 95% CI=1.4, 100.2, *P*=0.02).

Risk: Sexual assault

Intervention: 3-drug regimen; 2-pill burden

Drug regimen: Combivir (ZDV + 3TC) + nelfinavir

Time from exposure to nPEP: Within 72 hours

Completion of nPEP: 0 completed 28-day course

HIV seroconversions: No seroconversions reported among the 3 nPEP recipients who were tested, or among the 82 patients who presented within 72 hours but did not receive nPEP

Conclusion: nPEP for pediatric HIV exposures was underutilized in a hospital in a large urban center with high HIV prevalence and underscores the need for physician education about nPEP for children.

Authors, year: Girardet et al, 2009[35]

Type of study: Retrospective medical record review of children and adolescents presenting at a sexual abuse clinic during a 38-month period (January 2001–March 2004)

Location: Houston, Texas

Sample size: Of 4,234 cases of child or adolescent sexual assault, 1,750 (41%) were tested for HIV; n=879 aged<13 years, n=871 adolescents; n=303 were nPEP eligible; 16/303 (5%) were offered nPEP (aged 3–17 years); n=15 accepted nPEP

Risk: Sexual assault

Intervention: 2- or 3-drug regimen

Drug regimen: ZDV + 3TC (14 cases); ZDV + 3TC +LPV/r (1 case of acute genital trauma)

Time from exposure to nPEP: ≤96 hours

Completion of nPEP: Inconsistent reporting; none of the children completed follow-up; no reported significant side effects among the 9 patients reporting for at least 1 follow-up visit

HIV seroconversions: No seroconversions among 9 children who returned for ≥1 follow-up visit

Conclusion: Only 5% of those children or adolescents who were eligible for nPEP were offered nPEP. Adherence was difficult to document based on limited adherence to follow-up visits. Need for research to better define nPEP efficacy in children and adolescents.

Authors, year: Merchant et al, 2004[39]

Type of study: Retrospective medical record review of female adolescents presenting at an urban pediatric ED (January 1999 to December 2000)

Location: New York, New York

Sample size: n=25 adolescent females aged 12–19 years presenting with history of sexual assault; n=15 eligible for and offered nPEP; n=14 accepted nPEP

Risk: Sexual assault

Intervention: 1- or 3-drug regimen

Drug regimen: 1 received ZDV in 1999; 13 received 3-drug regimen, ZDV + 3TC + 3rd drug (n=12); d4T + 3TC + 3rd drug (n=1); (3rd drug was NFV [n=9] or IDV [n=4])

Time from exposure to nPEP: ≤72 hours; nPEP ordered an average of 218 minutes after patient presented to the ED; patient received drugs on average 58 minutes after nPEP was ordered

Completion of nPEP: No patients completed 28-day course

HIV seroconversions: Not reported (efficacy not studied in this study)

Conclusion: There was a significant delay in ordering nPEP and administering nPEP in the emergency room. Highlights importance of expediting nPEP in that setting.

Authors, year: Neu et al, 2007[38]

Type of study: Prospective nonrandomized observational study of children and adolescents presenting to the pediatric ED during March 1999–September 2002

Location: New York City, New York

Sample size: n=70 patients (aged 11–19 years) evaluated for sexual assault; n=33 enrolled in the study (94% female; mean age 15.3 years)

Risk: Sexual assault

Intervention: 2-drug regimen; 1-pill burden

Drug regimen: Combivir

Time from exposure to nPEP: ≤72 hours

Completion of nPEP: 8/33 (24%); return rate for follow-up visits: 1st visit, 23/33 (70%); week 2, 20/33 (60%); week 4–6, 11/33 (33%); 12 weeks, 9/33 (27%); 24 weeks, 6/33 (18%)

HIV seroconversions: No seroconversions in those presenting for follow-up at 4–6 weeks (11/33), 12 weeks (9/33), or 24 weeks (6/33)

Conclusion: Inadequate adherence to medications and follow-up were significant problems in this nPEP program for sexually assaulted children and adolescents.

Authors, year: Schremmer et al, 2005[36]

Type of study: Retrospective medical record review of children presenting for evaluation of suspected sexual abuse who were provided nPEP during February 1999–March 2001.

Location: Kansas City, Missouri

Sample size: n=2,865 evaluated for suspected sexual abuse; n=34 children and adolescents received nPEP (aged 12 weeks to 18 years, mean age 13 years); nPEP use associated with stranger assault

Risk: Sexual abuse

Intervention: 1-, 2-, and 3-drug regimens

Drug regimen: ZDV (n=1); ZDV + 3TC (n=32); ZDV+3TC+NFV (n=1)

Time from exposure to nPEP: ≤73 hours (range, 2–73 hours)

Completion of nPEP: 8/34 (24%) patients completed 28-day course

HIV seroconversions: No seroconversions among 33 patients tested at initial evaluation or among the 16 patients who had at least 1 subsequent HIV test after initial evaluation

Conclusion: Inadequate adherence to medication regimen and follow-up in child and adolescent survivors of suspected sexual abuse who received nPEP were noted.

Authors, year: Speight et al, 2006[40]

Type of study: Retrospective medical record review of children presenting with suspected childhood rape to a sexual assault care center during July 2003–March 2004

Location: Thika, Kenya

Sample size: n=48 children aged<18 years (96.8% female) presenting with suspected rape; n=33 eligible for, offered, and accepted nPEP

Risk: Sexual assault

Intervention: 2-drug regimen

Drug regimen: ZDV + 3TC

Time from exposure to nPEP: ≤72 hours

Completion of nPEP: 15/33 (45%) completed 28-day course

HIV seroconversions: No seroconversions among 3 patients tested for HIV; 3 seroconversions among 15 who were not eligible for nPEP

Conclusion: Majority (86%) of children presented within the 72-hour window period. Providing post-rape care is feasible and acceptable but requires special training for counselors, and providers, including training related to pediatric dosing.

Pediatric and Adolescent Community-acquired Needlestick Injury (CA-NSI) Studies

Authors, year: de Waal et al, 2006[66]

Type of study: Case report of nPEP use among children involved in a mass needlestick injury (1999)

Location: Tygerberg, South Africa

Sample size: n=54 children involved in mass needlestick exposure from discarded needles on a soccer field; n=44 were administered nPEP

Risk: CA-NSI

Intervention: 2-drug regimen

Drug regimen: ZDV + 3TC

Time from exposure to nPEP: ≤72 hours

Completion of nPEP: ARV adherence declined from 64% at week 3 to 52% at week 4; 7 patients on nPEP experienced nausea at 3 weeks

HIV seroconversions: No seroconversions to HIV, HBV, or HCV were noted in 44 children tested at 6 months

Conclusion: Follow-up of patients after mass exposure was difficult and adherence to nPEP was poor. Fewer follow-up visits are probably adequate in a non-mobile community (might consider eliminating the 3-month follow-up visit).

Authors, year: Papenburg et al, 2008[65]

Type of study: Combination of prospective and retrospective case series describing community acquired needle stick injuries in children at 2 pediatric tertiary care teaching hospitals (1988–2006 for one hospital and 1995–2000 at another hospital)

Location: Montreal, Canada

Sample size: n=274 pediatric patients with community acquired needlestick injuries; 73% of patients sought care on day of injury; n=210 injuries occurred during an era when nPEP was available; n=87 patients offered nPEP; n=82 patients accepted nPEP

Risk: CA-NSI; blood reported on needle or syringe in 36 injuries; n=71 reported an injury that bled

Intervention: 2-drug or 3-drug regimen

Drug regimen: ZDV + 3TC (n=74); ZDV + 3TC + NFV (n=4); ZDV + 3TC + IDV (n=3); ZDV + 3TC + RTV (n=1)

Time from exposure to nPEP: Not specified

Completion of nPEP: 10/82 (12%) patients discontinued nPEP; unclear from report if remaining 72 completed the full 28-day course

HIV seroconversions: 0 HIV seroconversions occurred at 6 month follow-up visit among 189/274 (nPEP and non-nPEP) patients tested for HIV

Conclusion: There were no seroconversions for HIV, HBV, or HCV among the 274 pediatric, community-acquired needlestick injuries, adding evidence that suggests the risk of transmission of bloodborne viruses in these exposures is low.

Authors, year: Russell et al, 2002[67]

Type of study: Prospective study of children with community-acquired needlestick injuries (published 2002)

Location: Melbourne, Australia

Sample size: n=50 cases of CA-NSI; median age=6.9 years (range, 1.8–14.3 years)

Risk: CA-NSI

Intervention: No nPEP offered

Drug regimen: Not applicable

Time from exposure to nPEP: Not applicable

Completion of nPEP: Not applicable

HIV seroconversions: No seroconversions among 36 children tested for HIV, HBC, HBC

Conclusion: No seroconversions to HIV, HBV, or HCV occurred among 50 cases of CA-NSI; HBV prophylaxis and vaccination was administered and no nPEP for HIV was administered.

Authors, year: Thomas et al, 2006[64]

Type of study: Case report of CA-NSIs sustained by 21 children on primary school playground, including an HIV-infected source patient

Location: London, England

Sample size: n=20 children exposed and started on nPEP; 1 child already known to be HIV infected at baseline, not started on nPEP

Risk: CA-NSI

Intervention: 3-drug regimen

Drug regimen: ZDV + 3TC + NVP

Time from exposure to nPEP: Within 72 hours

Completion of nPEP: 10/20 (50%)

HIV seroconversions: None

Conclusion: Was logistically difficult to provide nPEP under such circumstances, however, it seemed to be effective.

Mixed Populations Studies

Authors, year: Babl et al, 2000[58]

Type of study: Retrospective medical record review of children and adolescents presenting with CA-NSI in to the pediatric emergency room of an urban hospital during June 1997–June 1998

Location: Boston, Massachusetts

Sample size: n=10 pediatric and adolescent patients offered nPEP; n=8 started on nPEP

Risk: Sexual assault (n=6); CA-NSI (n=4)

Intervention: 3-drug regimens

Drug regimen: ZDV + 3TC+ Indinavir (n=7); ZDV + 3TC+ NFV (n=1)

Time from exposure to nPEP:

Completion of nPEP: 2/8 (25%) completed 28-day course; financial concerns, side effects, additional psychiatric and substance abuse issues, degree of parental involvement influenced adherence to nPEP and follow-up

HIV seroconversions: No seroconversions among 5 tested at 4 to 28 weeks.

Conclusion: HIV nPEP presented medical and management challenges and requires coordinated effort. Need for written protocol, coordinated approach, and national guidelines.

Authors, year: Beymer et al, 2014[61]

Type of study: Retrospective medical record review of clients receiving PEP services at LGBT community-based clinic (May 2011–December 2012)

Location: Los Angeles

Sample size: n=649 nPEP clients (n=529 [81.5%] first PEP use, n=120 [18.5%] PEP use 1–5 times previous to current nPEP initiation); whites, Hispanics, and blacks made up 42.5%, 35.4%, and 8.8% of nPEP users, and 30.4%, 42.4%, and 16.7% of HIV-infected persons, respectively

Risk: Gay/homosexual 75.5%, bisexual 11.9%, heterosexual 10.6%, other 1.9%

Intervention: 2-drug regimen

Drug regimen: TDF/FTC

Time from exposure to nPEP: ≤72 hours; mean time from exposure to first PEP medication dose 38.5 hours (SD=19 h)

Completion of nPEP: 93% self-reported taking all 4 pills in the previous 4-day medication recall period at 2 weeks after nPEP initiation

HIV seroconversions: 7 seroconversions occurred during the 6-month study period after nPEP initiation (including the 5 months after completing nPEP; exact timing not described)

Conclusion: 18.5% repeat nPEP users may benefit from PrEP; racial/ethnic inequities found in nPEP use compared with corresponding HIV prevalence deserves attention.

Authors, year: Bogoch et al, 2014[59]

Type of study: Prospective longitudinal study of referrals to nPEP programs in 2 emergency rooms and 2 academic medical centers

Location: Boston, MA

Sample size: n=180 persons referred for nPEP; median age 28 years (interquartile range, 23–35 years); 65.6% women; n=98 (54.4%) attended first nPEP visit

Risk: Sexual (57.2%), 72% nonconsensual, 1% MSM; nonsexual (42.8%), 17.8% injecting-drug use, 40% accidental needlestick injuries, 42.2% accidental mucous membrane or non-needle percutaneous exposures

Intervention: 3-drug regimen

Drug regimen: First line regimen: co-formulated TDF and FTC (Truvada) and LPV/r (Kaletra); RAL was substituted for LPV/r with drug interactions or side effects preventing adherence

Time from exposure to nPEP: Not reported

Completion of nPEP: 43/177 (46%) patients had documented completion of a 28-day course of nPEP; women were less likely to complete a 28-day course of nPEP

HIV seroconversions: Not reported

Conclusion: There were significant attrition rates between the emergency department and nPEP follow-up clinic. Older patients and persons without insurance were significantly less likely to attend initial clinic for nPEP care after presenting to the emergency department. Individuals with exposure to a known HIV-positive source individual were more likely to attend their initial clinic appointment. Women accounted for the majority of nonconsensual sexual exposures and were less likely to have documented completion of their 28-day nPEP regimen.

Authors, year: Chan et al, 2013[52]

Type of study: Retrospective cohort study with medical record review at large urban hospital emergency room, January 1, 2008–December 31, 2010

Location: Toronto, Canada

Sample size: n=241 patients

Risk: All were sexual exposures; MSM 76.8%, heterosexual 23.2%, non-consensual 5.0% of 236 with documentation about whether sex was consensual; HIV-positive source n=102

Intervention: 2-drug regimen (for lower risk exposures), 3-drug regimen (for higher risk exposures)

Drug regimen: Not specified

Time from exposure to nPEP: ≤72 hours; among 205 with known timing of exposure: <24 hr, 70 (34.1%); 24–48 hr, 68 (33.2%); 48–72 hr, 28 (13.7%); >72 hr, 7 (3.4%); not documented, 32 (15.6%)

Completion of nPEP: Of 205 patients given nPEP, n=71 (34.6%) completed a 28-day course; n=20 (9.8%) stopped medications early due to patient preference, cost, low HIV risk, source patient tested HIV negative; n=114 (55.6%) unknown completion status; n=55 with adverse effects, diarrhea (n=20), nonspecific gastrointestinal upset (n=14), nausea (n=13)

HIV seroconversions: Two patients who initially tested HIV negative at baseline subsequently tested HIV-positive at 3-month and 6-month visits; data regarding ongoing sexual exposure was incomplete

Conclusion: While it was encouraging that 92.6% of patients presented within the 72-hour window period, only 34.6% were known to have completed the full 28-day course. It is unclear whether the 2 HIV seroconversions that occurred during the 3-month and 6-month follow-up visits were nPEP failures as sexual histories were incomplete during follow-up.

Authors, year: Diaz-Brito et al, 2012[53]

Type of study: Open label randomized multicenter clinical trial comparing 2 nPEP regimens in patients presenting to emergency rooms in 6 urban hospitals

Location: Barcelona, Spain

Sample size: n=255 patients presenting for nPEP evaluation randomized into ZDV/3TC + LPV/r twice daily arm (n=131) or ZDV/3TC + atazanavir (n=124)

Risk: n=200; nonoccupational n=170 (85%); sexual n=156 (78%); occupational n=30 (1%)

Intervention: 3-drug regimen

Drug regimen: ZDV/3TC + LPV/r or ZDV/3TC + atazanavir

Time from exposure to nPEP: Median interval between exposure and presentation=18h (IQR 5–32); nonoccupational (median=20 hours); occupational (median=5 hours)

Completion of nPEP: 64% completed 28-day course in both arms; 92% of patients reported taking >90% of scheduled doses (without difference between arms); adverse events reported in 46% of patients (49% LPV/r arm and 43% atazanavir arm); gastrointestinal problems more common in LPV/r arm

HIV seroconversions: 0

Conclusion: Rate of completion was similar for both arms; almost 50% of patients of both arms suffered side effects. Strategies to improve adherence are needed.

Authors, year: Fletcher et al, 2013[63]

Type of study: Prospective cohort study

Location: Los Angeles, California

Sample size: n=35 patients; gay n=30; not gay=5; mean age=34.1 years (SD 7.4)

Risk: Not clearly defined; however, participants reported mean of 11.9 (SD 26.5) episodes of unprotected anal intercourse in past 6 months

Intervention: 2-drug regimen

Drug regimen: TDF + FTC (Truvada)

Time from exposure to nPEP: ≤72 hours

Completion of nPEP: 25/35 (71.4%) completed the 28-day course; 48.6% took all 28 doses; 14.3% took > 90% of doses; at baseline, higher number of lifetime STDs and recent episodes of unprotected anal intercourse were associated with reductions in medication adherence

HIV seroconversions: 1 (participant reported nonadherence to nPEP and multiple subsequent sexual exposures)

Conclusion: There was a significant indirect association between sexual risk taking and nPEP adherence. Interventions to reduce sexual risk taking will reduce risk for HIV acquisition and may play a role in improving nPEP adherence.

Authors, year: Gulholm et al, 2013[54]

Type of study: Retrospective medical record review at urban hospital sexual health clinic (1/2008–12/2011)

Location: Sydney, Australia

Sample size: n = 282 patients on 319 occasions presented for nPEP; n = 262 (94.3%) male

Risk: n = 260 (99.2%) participants had homosexual exposure; of 319 presentations, 203 (63.6%) receptive unprotected anal intercourse, 87 (27.4%) insertive anal intercourse, 12 (3.8%) receptive vaginal intercourse, 5 (1.6%) penile-vaginal sexual assault, 5 (1.6%) receptive fellatio, 5 (1.6%) needlestick injuries, 4 (1.3%) needle-sharing episodes

Intervention: 2-drug or 3-drug regimen

Drug regimen: Mainly TDF/FTC-containing regimens; TDF + FTC (n = 136 [42.6%]), TDF + FTC + d4T (n = 149 [46.7%])

Time from exposure to nPEP: ≤ 72 hours; < 4 hours (16 [5.1%]), 4–12 hours (59 [19.0%]), 12–24 hours (82 [26.5%]), 24–48 hours (96 [31.0%]), 48–72 hours (57 [18.4%])

Completion of nPEP: 228/319 (71/%) completed nPEP; completion associated with reporting AEs and changing the nPEP regimen; adverse events associated with being prescribed a regimen other than TDF/FTC, younger age, earlier year of nPEP prescription, and changing the nPEP regimen

HIV seroconversions: 2 seroconversions more than 6 months after NPEP due to ongoing high-risk behavior

Conclusion: nPEP was appropriately targeted to highest risk patients. HIV seroconversions due to ongoing high-risk sexual behavior highlight importance of integrating counseling regarding safer sexual behaviors as an integral component of nPEP care.

Authors, year: Jain et al, 2015[60]

Type of study: Retrospective longitudinal study of electronic medical records of nPEP users (1999–2013)

Location: Boston, Massachusetts

Sample size: n = 894 patients; n = 1,244 nPEP courses; mean age at PEP enrollment = 33.9 years

Risk: MSM = 788; heterosexual = 91; sexual assault = 66; transgender = 15; injection drug use = 14; sexual exposure (non-assault) = 1,152

Intervention: n = 927 TDF-based treatment regimen; N = 592 3-drug regimen

Drug regimen: Either an AZT/3TC or TDF/FTC backbone with or without a third drug.

Time from exposure to nPEP: ≤ 72 hours

Completion of nPEP: 85.7% completion rate overall (463 of 540 with documented completion status); reasons for discontinuing: medication intolerance (48.1%) due to nausea (43.2%), diarrhea (13.5%), rash (13.5%), HIV negative partner (9.1%); increased completion rates associated with having HIV-infected partner or fewer drugs in regimen (2 vs.3)

HIV seroconversions: Not reported

Conclusion: nPEP use increased over time. nPEP users demonstrated recurrent high-risk behavior. A defined group of nPEP users may benefit from earlier, targeted HIV risk-reduction and PrEP counseling.

Authors, year: Mayer et al, 2008[56]

Type of study: Two phase 4 studies of TDF-containing regimens compared to historical controls who took ZDV-containing regimens

Location: Boston, Massachusetts

Sample size: n=353 enrollees; n=44 (TDF/FTC arm); n=68 (TDF/3TC arm); control arms: n=122 ZDV/3TC arm, n=119 ZDV/3TC + 3rd drug arm

Risk: Sexual exposure; TDF/FTC arm, n=41 (93.2%) male (MSM/bisexual), n=41 male (100%); TDF/3TC arm, n=66 (97.1 %) male, n=56 (82.4% MSM/bisexual); ZDV/3TC arm, n=98 (80.3%) male; ZDV/3TC + 3rd drug arm, n=88 (73.9%)

Intervention: 3 separate 2-drug regimens and one 3-drug regimen; 1-, 2-, or 3-pill burden

Drug regimen: TDF + 3TC, TDF + FTC, or ZDV + 3TC (with or w/o a PI)

Time from exposure to nPEP: ≤72 hours

Completion of nPEP: 42–87.5% completed nPEP (highest completion in TDF regimens): 72.7% (n=32 TDF/FTV arm), 87.5% (n=63 TDF/3TC arm), 42.1% (n=53 ZDV/3TC arm), 38.8% (n=50 ZDV/3TC + 3rd drug arm [3rd drug was mainly PI])

HIV seroconversions: In TDF arms, n=0 seroconversions; in AZT arms, n=3 (during or shortly after their course of nPEP); Note: Level of adherence in seroconverters not described.

Conclusion: Participants taking TDF-containing regimens for nPEP demonstrated greater adherence and tolerability, with milder side effects than those taking ZDV-containing regimens.

Authors, year: Mayer et al, 2012[57]

Type of study: Evaluation of a novel 3-drug nPEP regimen

Location: Boston, MA

Sample size: TDF-FTC-RAL arm (n=100); control arms: TDF/FTV arm, n=44; AZT/3TC +3rd drug arm, n=119; overall age range, 18–61 years; males (73.9%–100%—all arms); MSM/bisexual (70.5%–71.5% in TDF arms)

Risk: Sexual exposure to HIV-infected partner or partner of unknown HIV status

Intervention: 3-drug regimen; 2-pill burden

Drug regimen: RAL + fixed dose combination TDF and FTC (Truvada)

Time from exposure to nPEP: ≤72 hours

Completion of nPEP: 57% (n=57) completed TDF-FTC-RAL arm (an additional 27% completed a modified regimen.); 72.7% (n=32) completed TDF/FTV arm; 38.8% (n=46) completed AZT/3TC arm

HIV seroconversions: 0

Conclusion: Tolerability to the 3-drug regimen, with integrase inhibitor, RAL, was high. The most common side effects were nausea and vomiting, diarrhea, abdominal discomfort, headache, and fatigue.

Authors, year: McDougal et al, 2014[62]

Type of study: Retrospective medical record abstraction of patients attending a publicly funded HIV clinic between 2000 and 2010

Location: Seattle, Washington

Sample size: 360 evaluated for nPEP; 324 prescribed nPEP; median age 30 years (range, 14 years–68 years)

Risk: Among patients evaluated for nPEP: sexual exposures (928%), MSM (59%), sexual assault (22%)

Intervention: 66% (n=214) 3-drug regimen

Drug regimen:

Time from exposure to nPEP: 334/260 (93%) initiated ≤72 hours, 177/360 (49%) within 24 hours

Completion of nPEP: 287/324 (89%) completed nPEP

HIV seroconversions: n=4; 2 tested positive at 2 and 5 months; 1 tested negative at baseline and 11 days and positive at 5 months; 1 tested positive at 12 months after nPEP initiation; adherence to nPEP and history of ongoing sexual exposures not described

Conclusion: Must increase education and promotion of HIV prevention, including nPEP for populations who would benefit most. Established nPEP service sites may have added benefit of also serving as locations for HIV case-finding and PrEP referrals.

Authors, year: Olowookere et al, 2010[51]

Type of study: Retrospective medical record abstraction of clients presenting for HIV nPEP at an antiretroviral therapy clinic during January 2005–December 2006

Location: Ibadan, Nigeria

Sample size: n=48 clients received nPEP; mean age 27.9 years ± 12.3 years (n=6, <15 years); about 1/3 were children and adolescents

Risk: Nonoccupational exposures: sexual assault (50%); occupational exposures: needlesticks (25%), blood splash into mucous membranes (25%)

Intervention: 3-drug regimen

Drug regimen: Either ZDV + 3TC + 3rd drug or D4T + 3TC + 3rd drug; 3rd drug=EFV, IDV or LPV/r

Time from exposure to nPEP: Not reported

Completion of nPEP: 38/48 (79%) completed therapy

HIV seroconversions: No seroconversions among 40 clients at 6 months of follow-up

Conclusion: 24% of clients receiving nPEP could not complete therapy due to side effects.

Authors, year: Pierce et al, 2011[45]

Type of study: Data linkage study using an nPEP service database and an HIV surveillance registry

Location: Australia

Sample size: n=1,420 male nPEP recipients; age range, 14–78 years; median=34.5 years

Risk: Indirect data suggest most participants presenting for NPEP are MSM, but risk behaviors were not collected for these participants

Intervention: Number of drugs in nPEP regimen not reported.

Drug regimen: Not reported

Time from exposure to nPEP: ≤72 hours

Completion of nPEP: Not reported

HIV seroconversions: n=3 nPEP related failures; n=34 additional seroconversions >6 months after nPEP initiation and deemed related to ongoing risk behavior

Conclusion: Frequency of nPEP use was not associated with risk of HIV seroconversion. Note: Data on nPEP adherence and completion were not available, but may have provided an explanation for drug failure.

Authors, year: Rey et al, 2008[46]

Type of study: Retrospective medical record abstraction of all consultations for nPEP in three consultation centers January 2001–December 2002

Location: Southeastern France

Sample size: n=910 exposures; age range, 15–18 yr (5.9%), 19–35 yr (68.6%), 36–50 yr (21.4%), >50 yr (4.1%); men=60.4%; female=39.2%; transsexual=0.3%; n=800 given initial nPEP prescription; n=776 accepted nPEP; n=527 received remaining nPEP prescription to complete 28-day course

Risk: n=910 sexual exposures, including 108 sexual assaults, 220 homosexual contacts among men

Intervention: 2- or 3-drug regimen

Drug regimen: Not reported

Time from exposure to nPEP: nPEP given before and after the 72 hour window period

Completion of nPEP: 355/776 (44%) who accepted nPEP completed 28-day course

HIV seroconversions: 1 seroconversion occurred in a patient after completing nPEP but who presented >72 hours after a high-risk exposure (not considered an nPEP failure)

Conclusion: Follow-up rates were poor; strategies need to improve follow-up, including a tracking process and psychosocial support for youngest patients and survivors of sexual assault.

Authors, year: Shoptaw et al, 2008[55]

Type of study: Biobehavioral HIV prevention intervention

Location: Los Angeles

Sample size: n=100 enrollees

Risk: High-risk sexual or drug-related exposure; n=45 drug use, n=1 injection drug use, n=63 MSM, n=9 bisexual, n=9 heterosexual; mean age 31.8 years

Intervention: 2-drug regimen; 1-pill burden

Drug regimen: ZDV + 3TC

Time from exposure to nPEP: ≤72 hours

Completion of nPEP: n=84 individuals received the full 28-day supply of study drug; 63/84 (75%) completed nPEP

HIV seroconversions: 0

Conclusion: nPEP provision for persons at high risk for HIV is feasible and safe at the community level. The most common adverse events were fatigue, nausea, headache, and gastrointestinal complaints.

Authors, year: Siika et al, 2009[47]

Type of study: Retrospective cohort study of electronic medical records of patients enrolled for HIV nonoccupational and occupational PEP during November 2001–December 2006 (Note: Only results for nPEP patients summarized in this table)

Location: Eldoret, Kenya

Sample size: n=355 nPEP exposures among children, adolescents, and adults; 100% accepted nPEP; n=296 advised to continue nPEP after testing HIV negative at baseline

Risk: Sexual assault (n=292 [82%]; female adult [n=189], female child [n=91], male child [n=15]); unprotected consensual sex, condom malfunction, human bites, exposure to body fluids of individuals suspected to be HIV infected, and barber cuts (n=63 [18%])

Intervention: 3-drug regimen; 2- or 3-pill burden

Drug regimen: D4T + 3TC + NVP; ZDV + 3TC + LPV/r (Note: Authors do not distinguish between ARVs used for nPEP or oPEP)

Time from exposure to nPEP: Median time=19 hours (range, 1–672 hours; 86% <72 hours)

Completion of nPEP: 104/296 (35%) completed nPEP. No statistically significant difference in reported side effects between NVP arm (21%) and LPR/r arm (14%) (P=0.44). No difference in completion rates for two arms (P=0.91). 1 death related to ARV-associated acute hepatitis associated with NVP arm.

HIV seroconversions: 1 HIV seroconversion at 6 weeks after nPEP initiation using RNA PCR test among 129 patients; seroconversion occurred in sexually assaulted child who presented ≤4 hours of assault and completed nPEP. HIV ELISA tests were negative in 87 patients; however, child who seroconverted did not undergo ELISA testing as well.

Conclusion: It is feasible to provide nPEP and oPEP in resource-constrained settings. Lack of HIV testing, delayed presentation, ARV discontinuation, and loss to follow-up are challenges in Western Kenya. Centralization of PEP services may improve coordination and supervision.

Authors, year: Tissot et al, 2010[48]

Type of study: Retrospective medical record abstraction of nPEP administrations during 1998–2007

Location: Lausanne, Switzerland

Sample size: n=1,233 consultations for potential HIV exposure; n=910 exposures among 867 persons included in final analysis; n=830 individuals requested nPEP at least once; n=710 initiated nPEP; 64% male, median age 30 years (range, 14–87 years)

Risk: 58%=heterosexual; 15%=homosexual; 6%=sexual assault; 20%=nonsexual (mainly CA-NSI or sharing of injection drug equipment)

Intervention: 3-drug regimen

Drug regimen: Mainly ZDV + 3TC + NFV (n=548, 77%) or ZDV + 3TC + LPV/r (n=108, 15%)

Time from exposure to nPEP: 60% sought care ≤24 hours after exposure and 82% sought care ≤48 hours

Completion of nPEP: 423/710 (60%) completed 28-day course; 396/620 (64%) for which data were available, reported side effects (mainly gastrointestinal disturbance and fatigue)

HIV seroconversions: 2 seroconversions occurred during follow-up, not attributable to nPEP failures

Conclusion: HIV testing in source persons avoided nPEP in 31% of exposures.

Authors, year: Tosini et al, 2010[49]

Type of study: Multi-site prospective study to evaluate the tolerability of nPEP with TDF/FTC +LPV/r

Location: France

Sample size: n=249 men and women; mean age 31.5 years; n=166 completed 28 days of PEP (tolerability good in 58%)

Risk: Nonoccupational exposures: sexual intercourse n=204 (82%), other n=5 (2%); occupational exposures (n=40)

Intervention: One 3-drug regimen; 2-pill burden

Drug regimen: TDF + FTC + LPV/r vs. historical controls taking ZDV containing regimens or TDF + ATV

Time from exposure to nPEP: ≤48 hours

Completion of nPEP: 166/188 (88%)

HIV seroconversions: No HIV seroconversions were recorded during the study

Conclusion: The TDF/FTC + LPV/r regimen proved easy to use, well-tolerated, and had less participants to discontinue medications secondary to adverse effects when compared with historical controls. The authors recommend this regimen as standard of care for HIV nPEP. Among those with ≥1 side effect, 78% diarrhea, 78% asthenia, 59% nausea and/or vomiting.

Authors, year: Wong et al, 2010[50]

Type of study: Observational study of nPEP use following nPEP protocol and guidelines development in one Canada province

Location: Alberta, Canada

Sample size: n=174 persons received nPEP (135 females, 39 males); median age 24 years (range 4–69 years)

Risk: Sexual assault (68%, n=118), percutaneous (21%, n=36), consensual sex (7%, n=12), mucosal (3%, n=5), other (0.6%, n=1), not documented (1%, n=2)

Intervention: Primarily 2 and 3-drug regimens, one 4-drug regimen

Drug regimen: Not explicitly reported; most regimens included ZDV

Time from exposure to nPEP: 86% of cases ≤48 hours

Completion of nPEP: 86/174 (49%)

HIV seroconversions: 0 of 143

Conclusion: The majority of nPEP cases were sexual assaults in young women. No seroconversions were observed, however, lack of follow-up and early discontinuation of medication were problematic. NPEP programs need to better address adherence and follow-up.

Blood Transfusion Study

Authors, year: Al-Hajjar et al, 2014[71]

Type of study: Case report of nPEP use following inadvertent HIV-infected blood transfusion

Location: Riyadh, Saudi Arabia

Sample size: One 12 year old girl with sickle cell disease

Risk: Child was inadvertently transfused with large volume of HIV-infected packed red blood cells

Intervention: 4-drug regimen

Drug regimen: TDF, FTC, DRV/r and RAL (DRV/r subsequently changed to LPV)

Time from exposure to nPEP: At 24 hours after transfusion

Completion of nPEP: Completed 13 weeks of ARV PEP

HIV seroconversions: Patient did not seroconvert (negative for HIV-1 DNA and plasma HIV-1 RNA by PCR through 8 months following exposure)

Conclusion: Authors report successful use of combination ART nPEP after a large volume transfusion of HIV-contaminated blood despite detection initially of HIV antibodies immediately after the transfusion. The fact that antibodies disappeared after nPEP initiation cautions against not starting or stopping nPEP in patients with detectable antibodies immediately after a contaminated blood transfusion.

Abbreviations

3TC, lamivudine; ATV, atazanavir; AZT, zidovudine; CA-NSI, community-acquired needlestick injury; d4T, stavudine; DRV/r, darunavir + ritonavir; ED, emergency department; ELISA, enzyme-linked immunosorbent assay; EFV, efavirenz; FTC, emtricitabine; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDV, indinavir; LPV, lopinavir; LPV/r, lopinavir/ritonavir; MSM, men who have sex with men; NFV, nelfinavir; nPEP, nonoccupational postexposure prophylaxis; NVP, nevirapine; oPEP, occupational postexposure prophylaxis; PEP, postexposure prophylaxis; PI, protease inhibitor; PrEP, preexposure prophylaxis; RAL, raltegravir; RNA PCR, ribonucleic acid polymerase chain reaction; RPV, rilpivirine; SD, standard deviation; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine.

Trade-named Drug Compositions

Combivir, ZDV+3TC; Kaletra, LPV/r (lopinavir + ritonavir); Truvada, TDF + FTC.

Appendix 4

Consideration of Other Alternative HIV nPEP Antiretroviral Regimens[a]

Create a combination regimen alternative to those in Table 5: May combine 1 drug or drug pair from Column A with 1 pair of nucleoside/nucleotide reverse transcriptase inhibitors from Column B.

Or

Use an existing fixed-dose combination alternative to those in Table 5.

Prescribers unfamiliar with these medications should consult physicians familiar with the agents and their toxicities.

Column A	Column B
Raltegravir Darunavir + ritonavir Etravirine Rilpivirine Atazanavir + ritonavir Lopinavir/ritonavir Dolutegravir	Tenofovir DF+ emtricitabine Tenofovir DF + lamivudine Zidovudine + lamivudine Zidovudine + emtricitabine

Fixed-dose combinations

The fixed-dose combinations Stribild (elvitegravir, cobicistat, tenofovir DF, emtricitabine) and Complera (rilpivirine, tenofovir DF, and emtricitabine) are complete regimens and no additional antiretrovirals are needed.

ALTERNATIVE ANTIRETROVIRAL MEDICATIONS FOR USE AS nPEP ONLY WITH EXPERT CONSULTATION

Efavirenz
Enfuvirtide
Fosamprenavir
Maraviroc
Saquinavir
Stavudine

ANTIRETROVIRAL MEDICATIONS GENERALLY NOT RECOMMENDED FOR USE AS nPEP

Didanosine
Nelfinavir
Tipranavir
Abacavir

ANTIRETROVIRAL MEDICATIONS CONTRAINDICATED AS nPEP

Nevirapine
Efavirenz (not for pregnant women)
Tenofovir (not for persons with eCrCl < 60 ml/min)

Abbreviations: DF, disoproxil fumarate; eCrCl, estimated creatinine clearance; nPEP, nonoccupational postexposure prophylaxis; TM, trademark.

[a] These antiretrovirals can be considered for use in regimens alternative to those in Table 5. For detailed information on each drug, please refer to individual drug package inserts available at: AIDSInfo Drugs Database at: http://aidsinfo.nih.gov/drugs. For consultation or assistance with HIV nPEP, contact PEPline (telephone 888-448-4911; internet site: http://www.nccc.ucsf.edu/about_nccc/pepline/).