CDC Response to Peer Review of the Draft
Antiretroviral Postexposure Prophylaxis After Sexual, Injection Drug Use, or Other Nonoccupational Exposure to HIV—United States, 2025 Update

Background:

With effective HIV prevention and care interventions, the estimated annual number of persons with new HIV infections in the United States (U.S.) has declined from a peak of 130,000 in the mid-1980s to 32,800 in 2022.(*1*) These ongoing efforts are critical to ending the HIV epidemic. Non-occupational HIV post-exposure prophylaxis (nPEP) is an effective intervention that uses antiretroviral (ARV) medications to reduce the likelihood of HIV acquisition after sexual, injection drug use, or other non-occupational exposures.

The U.S. Department of Health and Human Services (HHS) initial nPEP recommendations were published in 2005 and updated in 2016 to include newer ARV regimens and the cost-effectiveness of nPEP to prevent HIV infection by exposure type.(*2*) The 2025 update of the nPEP guidelines includes recommendations for use of nPEP in the U.S. including newer ARV regimens, updates to nPEP indications, and emerging nPEP implementation strategies. These recommendations are intended to inform U.S. healthcare professionals who provide clinical management of adults and children potentially exposed to HIV in nonoccupational settings. The nPEP guidelines cannot provide recommendations for every individual clinical circumstance and are not a substitute for medical evaluation and advice.

Methods:

The HIV nPEP guidelines process included a systematic literature review, categorization and evaluation of the evidence quality, recommendation development, external input, and peer review. The draft updated nPEP guideline document underwent peer review through the Office of Management and Budget (OMB). Three non-CDC peers reviewed the draft and provided input for CDC consideration.(*3*) These peer reviewers were selected based on their clinical expertise in HIV prevention and care and their infectious disease clinical training and experience in infectious disease, HIV prevention, HIV care, and nPEP. External peer reviewers were asked to objectively review the draft guideline document and appendices, provide feedback where indicated to increase accuracy, clarity, and usability, and to assess that the type and strength of each recommendation is appropriate for the evidence that served as the basis of the recommendation. CDC reviewed all comments from the peer reviewers, organized topically, and considered in draft revisions. Decisions to make changes in the nPEP guidelines were made by the CDC nPEP guideline workgroup.

Summary of Findings and CDC Responses

Below is a summary of the main comments and suggested edits by peer reviewers, organized by topic. Each peer reviewer comment is followed by the CDC response. Peer reviewer comments were generally very positive; CDC greatly appreciates the reviewers' time and effort to review. Because this is a summary, not all edits made are listed below. Most of the suggested edits and clarifications suggested by the reviewers were made.

General comments:
All reviewers suggested CDC update language throughout the guidelines to avoid stigmatizing language when referring to persons with HIV and in describing PrEP users taking medication as prescribed.

> CDC Response: *Based on guidance from Division of HIV and the National Institute of Allergy and Infectious Diseases HIV Language Guide, the language was updated. For example, "infection" following the word HIV when referring to persons with HIV was removed to avoid potentially stigmatizing language.*

One reviewer suggested we combine the nPEP and occupational postexposure prophylaxis (oPEP) guidelines so that clinicians and public health officials can access both PEP guidelines in one place.

- CDC Response: *An update to the oPEP guidelines is in development and publication is expected in 2025. As a result, the two guidelines cannot be combined at this time. CDC will consider combining nPEP and oPEP guidelines for future updates.*

Reviewers suggested updated studies and their references throughout the guidelines.

- CDC response: *All references were reviewed and updated accordingly.*

Rating schema and literature review:
Reviewers suggested various changes to the rating schema which was based on the strength of the recommendation and the quality of the evidence. For example, one reviewer suggested changing the statement, "There is insufficient evidence to recommend nPEP >72 hours after the time of exposure" from a CIII to BIII.

- CDC Response: *CDC updated the rating scheme/scale overall to be consistent with current CDC quality standards and practices. As a result, many of the rating recommendations were changed to "Good Practice Statements.*

One reviewer questioned the reason nPEP studies done outside of the United States were excluded from the literature review.

- CDC Response: *CDC decided to exclude nPEP studies done outside of the United States due to the concern that the study populations were not generalizable to the U.S.*

population. However, some exceptions were made for studies that included information on drug regimens, and their side effects and toxicity.

Laboratory testing:
One reviewer questioned the utility of obtaining a HIV NAT at 12 weeks after nPEP initiation in someone who is not on preexposure prophylaxis (PrEP) since they would have been off antiretroviral treatment (ART) for 8 weeks. NOTE: CDC recommends a 28-day course of nPEP so an HIV NAT is recommended 8 weeks after the completion of the nPEP course.

- CDC Response: *CDC will recommend HIV NAT at 12 weeks after nPEP initiation to account for the possibilities of either a false negative initial HIV test or of a subsequent HIV exposure. The draft nPEP guidelines state that this "…timing is recommended based on data about the timeline for ARV washout and the window period of the HIV tests.(4, 5) Most laboratory-based Ag/Ab tests should be able to detect HIV acquisition from the initial exposure; however, many observational studies have demonstrated nPEP failures attributable to subsequent exposures (which may not be disclosed).(6)"*

Two reviewers recommended specifying in the text which sexually transmitted infections (STI) to test for as well as in Table 8 and to specify which labs should be done to screen for Hepatitis B virus (HBV).

- CDC Response: *CDC discussed obtaining testing for gonorrhea, chlamydia, and syphilis in the text and in Table 8. CDC's recommendation for HBV testing includes obtaining hepatitis B surface antibody, hepatitis B core antibody, and hepatitis B surface antigen.*

PEP regimen drug tables:
One reviewer recommended emphasizing that nPEP should be started as soon as possible. Even though there is a 72-hour window to start nPEP, it would be beneficial to start the medication earlier in the window as opposed to later.

- CDC Response: CDC*'s recommendation states, "Initiate nPEP as soon as possible, but no later than 72 hours after exposure."*

One reviewer encouraged CDC to list drug combinations in alphabetical order based on their proper name. In previous guidelines, drug combinations that were tenofovir-based were listed first which is the format used also by the International Antiviral Society–USA Panel.

- CDC Response: *CDC reviewed drug combination orders and alphabetized them to align with the manufacturer's stated drug combination order.*

One reviewer requested clarity on how creatinine clearance was calculated in the Tables 6 and 7.

- CDC Response: *CDC updated the definition of creatine clearance to include, "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)"*

One reviewer recommended including examples of nPEP regimen medications that providers could consider prescribing to ameliorate GI effects.

- CDC Response: *CDC edited the guidelines to state, "Potential side effects of antiretroviral agents should be discussed with the nPEP recipient, and, when anticipated, preemptive prescribing of agents to ameliorate side effects (e.g., prescribing an anti-emetic or anti-spasmodic for regimens including zidovudine and ritonavir) might improve PEP regimen…"*

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1. Centers for Disease Control and Prevention. HIV Surveillance Report: Diagnoses, Deaths, and Prevalence of HIV in the United States and 6 Territories and Freely Associated States, 2022. Report. 2024 05/21/2024.
2. Dominguez KL, Smith DK, Thomas V, Crepaz N, Lang K, Heneine W, et al. Updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection drug use, or other nonoccupational exposure to HIV—United States, 2016. 2016.
3. Office of Management and Budget. Final Information Quality Bulletin for Peer Review 2005 [updated January 14, 2005. Available from: https://www.federalregister.gov/documents/2005/01/14/05-769/final-information-quality-bulletin-for-peer-review.
4. Delaney KP, Hanson DL, Masciotra S, Ethridge SF, Wesolowski L, Owen SM. Time until emergence of HIV test reactivity following infection with HIV-1: implications for interpreting test results and retesting after exposure. Clinical infectious diseases. 2016:ciw666.
5. Taylor D, Durigon M, Davis H, Archibald C, Konrad B, Coombs D, et al. Probability of a false-negative HIV antibody test result during the window period: a tool for pre-and post-test counselling. International journal of STD & AIDS. 2015;26(4):215-24.
6. Beymer MR, Weiss RE, Bolan RK, Kofron RM, Flynn RP, Pieribone DL, et al., editors. Differentiating nonoccupational postexposure prophylaxis seroconverters and non-seroconverters in a community-based clinic in Los Angeles, California. Open forum infectious diseases; 2017: Oxford University Press US.