

**Notes for Reviewers of
“Response to Peer Reviewer Comments – nPEP Guidelines”
for posting on the OMB Peer Review Website**

Comments were copied to this document as noted in the peer reviewer documents or abridged when necessary for this document (e.g., track changes comments to tables and figures). I did not list all typos/rewording suggested when they did not affect the substance, intent, or meaning of the text.

The following pages are in the format used for the PrEP GL peer reviewer comments as previously cleared and posted. Note that names of reviewers associated with each comment have been removed for clearance/posting.

Responses to Peer Reviewer Comments

Updated Recommendations for Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States - 2015

4 May 2015

In compliance with the Peer Review Plan (available at http://www.cdc.gov/hiv/pdf/policies/PRP_nPEP_recommendations.pdf), we provided a draft of the document listed above to selected independent peer reviewers.)

We requested expert opinion from the peer reviewers on:

1. Whether any recommendations were based on studies that were inappropriate as supporting evidence or were misinterpreted
2. Whether there are significant oversights, omissions or inconsistencies that are critical for the intended audience of clinicians
3. Whether the recommendations for the intended audience of clinicians are justified and appropriate

Listed below are comments received from the peer reviewers and our responses.

1.whether any recommendations were based on studies that were inappropriate as supporting evidence or were misinterpreted

Reviewer 1

- a) Is this uniformly the case in all states? “HIV test results should be recorded separately from the findings of the sexual assault examination to protect patients' confidentiality in the event that medical records are later released for legal proceedings.”

We agree that this may vary by jurisdiction. This passage has been edited to be consistent with other CDC guidelines addressing sexual assault care (e.g., STD Treatment Guidelines)

Reviewer 2

No comments requiring a response

Reviewer 3

No comments requiring a response

Reviewer 4

- a) On page 18, and in the domestic studies (Mayer, et al) can you check to see if regimens included TDF + EFZ + raltegravir. I don't think they included EFZ.

These have been reviewed and indicated changes made in the text.

Reviewer 5

- a) False positive viral load levels vary with the sensitivity of the assay. What is the lowest acceptable false positive viral load level seen with current assays?

The limited literature in this area has been reviewed, citations added, and indicated changes in Figure 2 have been made.

Reviewer 6

No comments requiring a response

Reviewer 7

- a) Page 11. Reference 2 was updated Oct 2014. Please correct citation.

The citation was updated

2. whether there are significant oversights, omissions, or inconsistencies that are critical for the intended audience of clinicians

Reviewer 1

- a) Figure 1: This is could be less confusing. Language used needs consistency/clarification- Top: “Substantial exposure” but box below says ”Substantial risk for HIV acquisition” should these be the same/identical? Also, if they are but the HIV status of source is unknown, then according to definition it can never be “substantial”

The use of these two terms was reviewed and changed to be consistent. The substantial risk of HIV acquisition given a particular exposure is dependent on whether the source has HIV infection. For that reason, when the source is of unknown HIV status, we recommend a case-by-case determination.

- b) The way this is written is a bit ambiguous, it could be interpreted to mean that such a person would not receive nPEP following most recent exposure but would be referred to PrEP .

“Instead, healthcare 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 tenofovir and emtricitabine (Truvada®) for PrEP⁸⁻¹⁰ until effective changes in risk behavior occur”

Text was added to clarify as follows: 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.

- c) It should be pointed out that needle bore and hollow vs solid influence risk

Considered but no change made to text, bore refers to a hollow needle

- d) Table 2: Amend/annotate to include cbc and lfts as indicated in text below

We have amended table 2 to include recommendations specific to preferred regimens for non-pregnant adults. Information about additional testing for other drug regimens is provided in table 6 referenced in the text for this section.

- e) Figure 2: There are some conditions and decisions making that does not appear anywhere in text:.The issue of evaluating at presentation of presentation for signs and symptoms of acute HIV.

Text and Figure 2 were reviewed to be sure that acute HIV infection issues were described.

- f) Need to add summary text re Table 3. At the initial visit, patients should be instructed about the signs and symptoms associated with acute (primary) HIV infection (Table 3),

This direction is in the text immediately following Table 3.

- g) How would early detection avoid hepatic flare?

Added text to clarify...“if not detected and treated early”

- h) Include mention of unknown source....A 28-day course of nPEP is recommended ...

Change not made. For a source of unknown status, nPEP is not necessarily recommended, it should be a case by case determination.

- i) What is recommendation regarding STI testing [for sexually abused or assaulted children]?

Text added consistent with STD Treatment Guidelines as follows:

The details of the assessment and treatment of STDs in children being evaluated for sexual assault or abuse is beyond to scope of this guideline but is thoroughly addressed in the 2015 STD guidelines. In part, they state...The decision to obtain genital or other specimens from a child to conduct an STD evaluation must be made on an individual basis. Because STDs are not common in prepubertal children evaluated for abuse, testing all sites for all organisms is not routinely recommended.

- j) Another argument for starter pack vs prescribing is avoids delays related to lack of health insurance/\$\$, obtaining thru special order in non health facility based pharmacy

No change made. This would only be true when starter packs are provided free of charge.

- k) Prescription or starter pack?

Text revised to include either initial short-term prescription or starter pack

- l) Need to add duration [of patient practicing risk reduction] beyond nPEP

Reviewed, no change made. There is no specific duration for ongoing risk reduction behaviors after nPEP.

Reviewer 2

- a) Table 2: the above table is VAGUE in regards to Hep B testing. Is it recommending that ALL Source Pts and all Exposed Pts need to get the 4 serologies in Table 4? That seems wasteful and unnecessary. What would make the most sense would be to recommend the Source Pt get Hep B surface Ag; and the Exposed pt get Hep B surf Ab and Hep B surf Ag. Hep B core Ab Total seems unnecessary for the purpose of prescribing nPEP; and Hep B core IgM is truly unnecessary in this context]
- b) [the above table is also VAGUE on Hep C testing; this is compounded by the lack of a section in the text on Hep C testing (as Hep B has). Unclear what Hepatitis C serology is being recommended; presumably the recommendation is for Hep C Ab. However, whether a Hep C viral load is EVER indicated in the nPEP setting should be addressed, because it is commonly performed in the community (as per calls on the NCCC PEpline), at least for OCCUPATIONAL PEP]

In response to comments above (a-b), we have revised Table 2 to indicate the testing that should occur regardless of regimen chosen and the additional tests indicated for the preferred drug regimens for non-pregnant adults (including creatinine). We have clarified which hepatitis B and C serologic tests are indicated as recommended by CDC hepatitis screening guidelines.

- c) Therefore, for any person whose hepatitis C virus antibody test is negative at baseline but positive at 4-6 weeks [should this read 3 MONTHS? Because per Table 2, Hep C serology is NOT tested at 4-6wks] after the exposure,

We have reviewed and edited for consistency between revised table and text

- d) Consider adding a comment along the lines of “Expert consultation can be made with local experts or by calling the National Clinicians’ Post-Exposure Prophylaxis Hotline (PEpline) at 888-448-4911 – as in the Occupational PEP guidelines

Added the PEpline number

- e) A common question that comes up is “How do I transition from a 28-day course of PEP onto 2-drug PrEP?” In the absence of data one way or another, we usually advise them to go from TRV/RAL on Days 1-28 to TRV alone on D29. Since this is a common question, it is worth mentioning it, even if there is a comment that “there are no data to support this approach”]

Text added to indicate the possible need to transition to PrEP after completing 28 days of nPEP. Since only Truvada is recommended for PrEP and several nPEP regimens are possible, we did not specify further.

- f) In some persons, a high-risk exposure may be an exceptional occurrence and merit nPEP despite their ongoing general risk behavior.

Added clarifying text

Reviewer 3

- a) I don't have any substantive comments. The flow diagrams are very helpful, as is the checklist.

Thank you.

Reviewer 4

- a) Inclusion of discussion of PrEP for those at future risk of HIV should be included

We have added this

- b) For source patient testing, one should include viral load testing in addition to antibody testing if acute or recent HIV infection is suspected

We considered this suggestion but have not changed the text. We recommend 4th generation antibody/antigen testing for both source and exposed persons as viral load testing is not FDA approved for diagnosis of acute HIV infection.

- c) Table 2: You need to include calculated creatinine clearance in table. And it's a little confusing what is meant by HIV antigen testing versus viral load testing. Is it referring to 4th generation testing?

We have revised Table 2 to indicate the testing that should occur regardless of regimen chosen and the additional tests indicated for the preferred drug regimens for non-pregnant adults (including creatinine). We have clarified that antigen testing (e.g., p24) is a qualitative test (present or absent), usually as a component of the generation HIV tests, while viral load testing is quantitation of HIV virus.

- d) Figure 2, the cutoff threshold for viral load for acute HIV infection seems high at 50,000 copies. Is there data for this?

The limited literature in this area has been reviewed, citations added, and indicated changes in Figure 2 have been made.

- e) On page 51, you mention additional testing of liver and hematologic parameters but should be a little more clear on recommendations on when to do this.

We have amended table 2 to include recommendations specific to preferred regimens for non-pregnant adults. Information about additional testing for other drug regimens is provided in table 6 referenced in the text for this section.

- f) Both viral load and antibody testing may be indicated if recent or acute infection is suspected.

We have revised text to clarify that 4th generation antibody/antigen testing is preferred for detection of acute HIV infection in both source and exposed persons.

- g) Figure 2: 50,000 copies seems like a high threshold for false positive. Where's the data to support this??

The limited literature in this area has been reviewed, citations added, and indicated changes in Figure 2 have been made.

Reviewer 5

- a) Figure 1: Nice algorithm. Recommend adding under WHEN: in the box for substantial risk for HIV acquisition SP at high risk for HIV infection unknown SP HIV+ status occur the majority of the time during calls to the PEPLINE?

Thank you. We have added clarifying text.

- b) e.g. not oral [HIV antibody test] since less accurate.

Text edited throughout to indicate the use of blood tests for HIV, either antibody or antigen/antibody (preferred).

- c) Table 1: text changes not made to content that represents current CDC statement on transmission risks

Reviewed and updated as indicated

- d) Consider noting that testing such discarded needles [in public settings] is not recommended.

Considered. Since this test is not commonly done, suggested, or available outside of research, we elected not to discuss it here.

- e) Table 2.

- a. Might want to add that baseline HIV/HBV/HCV testing of EP should occur even if PEP not started based on text below,
- b. HIV Ab test should be at 6 and 12 months rather than 6 to 12 months—please clarify which is appropriate. If using more sensitive 4th gen, will testing out to 4 months be sufficient if HIV/HCV seroconversion occurs/
- c. Should this be a 4th gen HIV test that combines both HIV Ab and antigen testing as one test? if using multisport HIV test, do you still need to test out to 12 months
- d. Consider identifying specific HBV/HCV serology that is needed. Many PEpline callers often are confused about the specific HBV and HCV tests for the SP and EP. . I have gotten questions whether it is the HCV antigen that should be checked—of course, it is the HCV AB
- e. why repeat GT tests in EP after baseline testing. Makes sense to test EP at baseline if HIV+, then before starting ART but don't see need for testing at 3 and 6-12 mo after exposure

In response to comments a-e above, we have revised Table 2 to indicate the testing that should occur regardless of regimen chosen and the additional tests indicated for the preferred drug regimens for non-pregnant adults. We have also specified which hepatitis B and C serologic tests are indication and that Ag/Ab tests are preferred for HIV. We have deleted the 12 month testing.

- f) Figure 2: how was HIV viral load level determined

The limited literature in this area has been reviewed, citations added, and indicated changes in Figure 2 have been made.

- g) [hepatitis C testing] different than stated in Table 2 above.

Edited for consistency between revised table and text. We have revised Table 2 to indicate the testing that should occur regardless of regimen chosen and the additional tests indicated for the preferred drug regimens for non-pregnant adults (including creatinine). In the process, we reviewed table elements for consistency with the text

- h) Or lamivudine. First, several medications used for nPEP, including two in the preferred regimen (tenofovir and emtricitabine) are active against hepatitis B virus infection.

We have not added lamivudine as a component of the preferred regimen

- i) Should some discussion about HBIG be provided since this is identified in the occupational HBV guidelines?? What about HBsAg exposures to non-immune EP for HBV. Should the EP get HBIG if non-immune and SP is unknown HBV status. Might want to state that HBIG should be considered if the EP is not immune to HBV and the SP is HBsAg+ or unknown status.

The guidance in this document is consistent with the 2015 STD Treatment guidelines and so has not been changed. Consistent with the STD guideline we have added the caveat that if the source is available for testing and is HBsAg-positive then unvaccinated nPEP patients should receive both hepatitis B vaccine and HBIG at the time of initial evaluation.

- j) Table 4: Should HBIG be included in this table? Provide link to HBV guidelines for oPEP?

Table 4 is about hepatitis screening serology in the nPEP patient and we have not added reference to HBIG. See comment above about indications for HBIG.

- k) Consider providing example of where 2 drug regimen might be considered? Examples: oral receptive sex with ejaculation or insertive vaginal sex with unknown SP
- l) More toxic regimen [2-drug regimen] with NNRTI inclusion. Please provide example where this may be used ??NRTI toxicity . Is there any data with this regimen in nPEP?

Above bullets k-l, considered, but no revision made as three drugs are recommended.

- m) Even if the SP is HBSAG+???

All persons not known to be previously vaccinated against hepatitis B virus, should receive hepatitis B vaccination (without hepatitis B immune globulin); the first dose administered at the time of the initial examination. See STD Treatment Guidelines

- n) Consider deleting this since it is already in the table and indinavir is rarely used.
- o) Because the use of indinavir is associated with increased risk of nephrolithiasis in pregnant women and its use without co-administration of a ritonavir as a boosting agent can result in significantly decreased plasma levels of indinavir (the active agent) in pregnant women, indinavir should not be used as nPEP in pregnant women.

Considered (n-o above). No change made to recommendations for nPEP in pregnant women.

- p) Figure 3: this is a nice checklist. Is it possible to provide links to the specific tables in the document?

The checklist is intended to be a useful document in the absence of the guidelines. For that reason, we have not included links to guidelines content.

Reviewer 6

- k) My main comment would be perhaps adding a paragraph on the special consideration of transitioning from nPEP to PrEP. This is one of the areas where clinicians need guidance. I have found that nPEP helps move clients at continued high risk to PrEP.

This was added

- l) Table 2: This is going to confuse people particularly with many centers using 4th generation testing. Baseline would include a 4th generation test.

Changed HIV testing to specify preference for 4th gen (Ag/Ab) tests.

- m) Should emphasize that the priority should be to get ARVs in the body of exposed as examination of status of source is pursued

Have reviewed text to ensure that language emphasizing this priority is in relevant sections.

- n) Also adherence dialogue between provider and patient.

Modified text to include provider/patient communication about adherence.

Reviewer 7

- k) Overall I thought this was nicely written and informative. Not your typical guideline but can serve as a true literature background.

Thank you.

- l) One major theme I thought should be emphasized more is the possibility of acute asymptomatic HIV especially among those with high risk behaviors. Anecdotally, I have seen several pts present for nPEP whose rapid is negative yet have obtained HIV VL to find it greater than 10^5 so I believe there should be more emphasis to consider screening for primary HIV throughout the document.

Reviewed text to ensure mention of this in appropriate sections

- m) I would also do carve out for sexual assault as they should not be tested for STIs and just empirically treated. Also state laws vary on how PEP is prescribed as states may have different funding mechanisms that cover victims of assault.

This portion of the text was revised to be consistent with 2015 STD guidelines

- n) Page 8. Would add screening with HIV RNA for those who provide hx consistent with multiple potential exposures in past 6 weeks.

Considered but no change made. Viral load tests are not FDA approved for diagnosing acute HIV infection. Screening for acute infection is indicated for all persons for whom nPEP is being considered.

- o) Page 10. Delete bacterial in front of sexually transmitted infections. Should inquire about HSV too

Considered but no change made.

- p) Page 11. First paragraph. Consider adding sex in a mutually monogamous relationship with an HIV infected partner whose HIV VL is suppressed on ART and safer sex practices are advised. There should be some counseling included in the overall document for the sero-discordant couple

Considered but no change made because of the documented transmissions not linked to the HIV-positive partner in HPTN052 and other studies of HIV discordant couples.

- q) Page 38. I am concerned about the HIV status unknown being handled on a case by case basis. This does not provide advice to the providers evaluating the majority of patients presenting for nPEP. There needs to be solid advice for the ERs, urgent care, STD health centers and primary care providers. They need to at least start nPEP for anyone who has a high risk exposure regardless of known status. I would encourage you to consider the algorithm in NY State.

Considered but no change made for unknown HIV status of the source patient. Depending on the situation as evaluated at the time, persons of unknown HIV status may be considered high and low risk for prevalent HIV infection and so may or may not indicate a need for nPEP

- r) Page 39. VII-A1. Add sentence about obtaining HIV VL in pts with multiple risks within past 6 weeks. Start nPEP while waiting the results

Considered but no change made. Viral load tests are not FDA approved for diagnosing acute HIV infection. Antigen/antibody testing preferred for all persons for whom nPEP is being considered.

- s) Table 2. I would have serum creatinine for all because if not giving TDF, most likely still getting FTC, 3TC or AZT. Some would just get ALT and HCV RNA rather than serology. Also need to clarify what HBV and HCV tests should be ordered (HBsAg, SAb and total core Ab; HCV Ab with reflex HCV RNA) If only checking serology, all the more reason to check an ALT. Twelve months is a long window and would recommend 6 months as final visit. I also would add to check GC/C again at 6 months if ongoing risk. Also remember to back out STI testing for sexual assault.

We have revised Table 2 to indicate the testing that should occur regardless of regimen chosen and the additional tests indicated for the preferred drug regimens for non-pregnant adults (including creatinine). These are the minimum recommended tests. Providers may always obtain other testing when patient history, exam, or initial test results indicate their appropriateness. Our STD testing recommendations for sexual assault are consistent with CDC 2015 STD Treatment Guidelines. Our hepatitis screening recommendations are consistent with CDC hepatitis guidance.

- t) Figure 2 is troubling to me. If one does the algorithm for the initial exposure and assessing need for nPEP visit. One obtains a rapid test AND an HIV VL if they have had multiple risks within 6 weeks. If they have signs or sx of acute HIV, this is not a time for nPEP. They should be referred to an HIV expert for further diagnosis and treatment. For those who are asymptomatic but have had risks within 6 weeks, they should get their initial doses of 'nPEP' but also referred to an HIV expert. Here is where someone may prefer to use a PI based regimen. Then you have the person who does not have risks other than the encounter they came in for and is rapid test negative. They complete nPEP for 28 days and then have f/u testing.

These comments were considered. The figure and the recommended HIV diagnosis algorithm are not specific to categories of providers so no changes were made.

- u) What I am not following is the signs/sx yes category. This is potentially acute HIV and should be seen by an expert. There is not an immediate need to start ART without full evaluation. I am not sure where a VL of 50K comes from. If anyone's VL is greater than 500 copies, one should be obtaining a genotype and re-assess. The algorithm should be to obtain HIV test at completion of ART and 3 months. These patients should be referred to an HIV expert to decide if immediate ART is indicated. This patient needs more intensive counseling regarding that they may have acute HIV

The limited literature in this area has been reviewed, citations added, and indicated changes in Figure 2 have been made.

- v) For the follow up testing, the PEP would have been stopped. If the HIV test is positive, that person should be treated as any initial HIV diagnosis and obtain VL with genotype to determine best ART

options. Remember these people were on PEP so if they have breakthrough virus on PEP, then by definition you either have non-adherence or resistance.

The text was reviewed to be sure that this is clearly stated.

- w) Page 47. HIV becoming positive after 12 months is unlikely to be from that event. The HCV-HIV coinfection should be positive at 6 months by today's antibody tests.

While it has been reported to occur very late, we agree that this is extraordinarily uncommon and have changed the recommendation to 6 months.

- x) Page 48. I would not advise providing recommendations for continuing 3 drug PEP as treatment for those newly diagnosed HIV in these guidelines. I suggest re-word that pt should be immediately referred to HIV expert for access and engagement of care. The 3 drug PEP should not be discontinued by the PEP provider until the patient has been evaluated and treatment plan by HIV expert has been offered to patient

The text was revised to make clear the intent consistent with this comment.

- y) Page 49. Specify HBV tests. Discuss vaccination and immune globulin needs

Table 2 (Testing) has been revised. See response about HBIG below.

- z) Why no HB immune globulin. This is still recommended within 14 days of exposure but just should not be on same day as vaccination (although certainly is done in vertical transmission which we know can decrease effectiveness of vaccine).

The guidance in this document is consistent with the 2015 STD Treatment guidelines and so has not been changed. Consistent with the STD guideline we have added the caveat that if the source is available for testing and is HBsAg-positive then unvaccinated nPEP patients should receive both hepatitis B vaccine and HBIG at the time of initial evaluation.

- aa) Page 63: state laws vary on amount given to sex assault victims. Would make note to adhere to state laws

It is unclear what state laws are being referred to. No change made.

- bb) Page 64. Should highlight or make bold that nPEP should never be delayed waiting for advice or labs

We have reviewed the text to ensure that this advice is included in appropriate sections.

cc) Page 66. Again, emphasize no baseline STI testing in cases of sexual assault

Statements in these guidelines are consistent with 2015 STD Treatment Guidelines

dd) Page 71. Would add that although the decrease in methadone levels with DRVr is marginal and within acceptable clinical ranges, some patients may experience withdrawal and careful monitoring for methadone withdrawal is advised

Added text and a citation to this effect

3. whether the recommendations for the intended audience of health care providers are justified and appropriate
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Reviewer 1

a) Table 5: preferred regimen for adults/adolescents: Dolutegravir for wt > 40kg

Considered but no change made

b) Table 6: is there lower age limit for ZDV?

No. Per the pediatric HIV treatment guidelines, doses differ by gestational age at birth, time since birth, and weight. But there is no age at which ZDV cannot be safely administered for perinatal prophylaxis or treatment.

Reviewer 2

No comments requiring a response

Reviewer 3

No comments requiring a response

Reviewer 4

a) Including pre-exposure prophylaxis or PrEP [recommendation VII-E4]

Added

Reviewer 5

- a) I do agree with nPEP recommendations for starting Truvada + Raltegravir or dolutegravir as the preferred regimen based on tolerability and potency. Although, recommendations may be based on limited data, recommendations for using ritonavir boosted darunavir + Truvada would benefit from further discussion why this was selected as appropriate nPEP regimen (see comments) vs other ART regimens.

Considered but no changes made.

- b) One area of some controversy is the "window" for starting PEP. Although within 72 hours seems reasonable, most of the animal data strongly suggest a "tighter window" for starting PEP. Some discussion of this "window" would be helpful. This also contrasts with the NY State nPEP and PEP guidelines stating a "tighter" window of < 36 hours.

Considered but no change made. No informative human data for such a discussion.

- c) e.g. multispot . Oral rapid tests not recommended since less accurate

Specified blood tests throughout the document with preference for 4th generation antigen/antibody tests

- d) nPEP is recommended when the source of the body fluids is known to be HIV-positive or has significant risk factors (e.g. IDU, MSM with multiple partners) for HIV infection and the reported exposure would present a substantial risk of transmission.[VII-A]

Considered but no change made. nPEP is not recommended for all sources of unknown HIV status; instead a case-by-case determination is indicated based on identifiable risk factors.

- e) [case-by-case determination, VII-A] important since the majority of calls to the PEpline have no information about the SP and decision is to evaluate risks vs. benefits of nPEP based on the risk of the exposure

Agree that a case-by-case determination is indicated based on identifiable risk factors since nPEP is not indicated for all persons with a source of unknown HIV infection status.

- f) [include as preferred regimen] tenofovir DF (300 mg) with emtricitabine (200 mg) once daily plus darunavir (800 mg) and ritonavir (100 mg) once daily;[VII-C]

No change made in preferred regimens.

- g) Regimens are also provided for children and persons with decreased renal function and in pregnancy (see Table 6)[VII-C]

Pregnancy was added to the bullet as suggested

- h) 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 and C, pregnancy). [VII][VII-B][VII-D][VII-E]

Suggested change made.

- i) All persons who report behaviors or situations that place them at risk for future HIV exposures (e.g., injection drug use, sex without condoms) or who report past receipt of one or more courses of nPEP should be provided with risk-reduction counseling and intervention services, including the consideration of pre-exposure prophylaxis or PrEP[VII-E4]

Added

- j) dolutegravir + truvada is recommended, why not Stribild one daily? Both integrase will interfere with Scr excretion and lead to elevations in Scr. Also, since DRV/r is recommended as alternative, Stribild is not necessarily wrong although I would not recommend it if concern about drug interactions and unknown consequences of coBI in HIV negative persons

This was considered during development of the guidelines and decided otherwise. So no changes are made in preferred regimens

- k) Why not Stribild –tenofovir, emtricitabine, cobicistat, and elvitegravir? As I noted previously—not different in terms of Drug interactions from DRV/r

- l) can also use lamivudine if Truvada is not available

These (k-l) were considered during development of the guidelines and decided otherwise. So no changes are made in preferred regimens

Reviewer 6

No comments requiring a response

- a) Page 10. Alternative PrEP. You could also consider the fixed dose combination of TDF/FTC/EVG/cobi and ritonavir boosted atazanavir rather than limiting to only DRVr. While the rationale for DRVr is about not having drug interactions with methadone, there have been methadone withdrawal reported in the pk study with DRVr even though the decrease in methadone is marginally. Given all the drug metabolism polymorphisms, the package insert recommends careful monitoring. One could also consider Rilpivirine based on population resistance. The message that should be delivered is to give RAL or DTG as preferred and if for some reason, one needs an alternative is to obtain a consult and have an expert provide guidance.

This was considered during development of the guidelines and decided otherwise. So no changes are made in preferred regimens

- b) Page 10. Would add Prep to last bullet. ...and intervention services including pre-exposure prophylaxis (PrEP)

Added

- c) I found the last paragraph confusing in this section as the ARVs cited should not be used for anyone. EFV has not been recommended because of the significant CNS side effects including potential suicidality and depression, not just because of potential teratogenicity (which as later discussed is really less of an issue). I believe that this section would be better written as a few ARVs should be avoided as they are for ALL and not just have pregnant and nonpregnant women. Same for table 7. A table should be inclusive of avoidance of select ARVS for all, not just woman of child bearing age or pregnant or there needs to be two tables (which I prefer). One table for pregnancy and another for all.

This section is about pregnancy and so has not been amended.

- d) Should also include avoidance of abacavir because of hypersensitivity reactions without adequate time to screen.

We have added a statement about the inappropriateness of abacavir containing regimens for nPEP.

- e) I am not sure why table 5 has DRVr as alternate for aged 3-12 and LPVr for 2-12. This will be missed if because of the one year difference in FDA label. Suggest keeping as age 3-13 with all listed including DRVr and extend children 4 weeks to less than 3 or creating another 2-3 year if you want TDF/FTC/RAL

Considered but no change made.