CDC Responses to External Peer Reviewers' Comments on the Draft 2013 Revised Surveillance Case Definition for HIV Surveillance

The following is an explanation of responses to external peer reviewers' comments on the draft manuscript "Revised Surveillance Case Definition for HIV Infection—United States, 2013".

Comments from Reviewer A

1. **Comment**: Regarding the statement that "Published treatment guidelines recommend antiretroviral therapy for all HIV-infected adults, adolescents, and infants," which is located in the subsection on "Limitations and applicability of surveillance case definition" in the introduction: "Some important and influential treatment guidelines (e.g., European AIDS Clinical Society) still recommend that the treatment decision should be based on CD4 count. This sentence should be clarified to reflect this."

   Response: This sentence was clarified by specifying that the sources of these guidelines were USA panels:

   > "USA panels on antiretroviral guidelines recommend antiretroviral therapy for all HIV-infected adults, adolescents, and infants, …."

2. **Comment**: Section 4, regarding the definition of stage 0 "based on a testing algorithm," and the examples given: "Another common scenario is a patient receiving frequent testing (e.g., 3-monthly) for PREP. The patient may have a negative serologic test followed by a positive (and then confirmed) serologic test on a subsequent sample."

   Response: This scenario is covered under the definition of stage 0 "based on testing history (previous negative/indeterminate test results" [from an earlier testing algorithm, not part of the same algorithm that concluded with a positive result]).

3. **Comment**: Regarding the description of stage 0: "Is 'earliness' a word?"

   Response: According to www.dictionary.com, "earliness" is a noun derived from the adjective "early". It is the opposite of "lateness." The "criterion for the earliness of infection" is intended to distinguish between infections that are early and those that are not. Possible synonyms (e.g., "punctuality", "suddenness", "prematurity"), suggested by www.thesaurus.com, are not preferable substitutes.

4. **Comment**: Regarding section 4, concerning staging based on CD4 counts: "The previous guidelines stipulated that HIV stage is based on lowest CD4 count. Is this no longer the case? Is the new definition intended to be more dynamic? This point should be clarified."

   Response: The stage is no longer necessarily based on the lowest CD4 count that the person has experienced in his/her life. This was clarified in the second paragraph of section 4:

"Of primary interest is the stage at initial diagnosis, but the stage can change in either direction after diagnosis, and might be defined with reference to dates of interest, such as the most advanced stage recorded through a particular date."

5. **Comment**: Regarding the staging table: "Is there a reference to justify the pediatric values? These do not seem to correspond to any current guidelines as far as I can see."

   Response: The threshold values chosen for the staging system for children <6 years of age were based primarily on the values used in Table 2 of the "1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age" (*MMWR* 1994;43[No. RR-12]). That publication includes the following description of the methods used to select the threshold values in that table: "To establish the age-specific values of CD4+ percent that correlate with the CD4+ count thresholds, CDC compiled data from selected clinical projects in the United States and Europe. The data included >9,000 CD4+ counts, with the corresponding CD4+ percent determinations, from both HIV-infected and uninfected children <13 years of age. Nonparametric regression modeling was used to establish the CD4+ percent boundaries that best correlated with the CD4+ count boundaries in the classification system." The threshold values are also consistent with some of those in Table 1 of the article entitled "Discordance between CD4 cell count and CD4 cell percentage: implications for when to start antiretroviral therapy in HIV-1 infected children" by David Dunn et al. (*AIDS* 2010;24[8]:1213–1217). These values were also based on an unpublished analysis of data collected by CDC regarding the CD4 percentages that correspond to threshold values of CD4 counts (200, 500, 750, 1000, and 1500 cells/µL). The choice of threshold values was also informed by the opinions of more than a dozen clinical experts on pediatric HIV infection who participated in a workgroup convened by CDC for revising the surveillance case definition.

6. **Comment**: Regarding the threshold values for the CD4 percent in the staging system in the table below:

Table 1. HIV infection stage, based on age-specific CD4+ T-lymphocyte count or CD4+ T-lymphocyte percentage of total lymphocytes*

	Age on date of CD4 T-lymphocyte test					
	<1 year		1–5 years		6 years through adult	
Stage*	Cells/µL	%	Cells/µL	%	Cells/µL	%
1	≥1,500	≥30	≥1,000	≥26	≥500	≥26
2	750–1,499	25–34	500–999	20–29	200–499	14–25
3	<750	<20	<500	<14	<200	<14

* The stage is based primarily on the CD4+ T-lymphocyte count; it is based on the CD4 percentage only if the count is missing ….

"It seems anomalous that 1–5 and 6+ [age] groups have same value of CD4 percentage [threshold] (26%) but different values of CD4 count [threshold] (1000 vs 500). I think there is a case for

dropping CD4 percent altogether. It is very rare that CD4 percent is available but not CD4 count. And in children as well as adults CD4 count is the stronger individual predictor."

Response: Based on an updated analysis of CDC data that has not yet been published, the threshold values for the CD4 percentage in children <6 years old have been revised to show an inverse correlation of the CD4 percentage with age, similar to that of the CD4 count with age, as shown in the table below.

Table 1. HIV infection stage, based on age-specific CD4+ T-lymphocyte count or CD4+ T-lymphocyte percentage of total lymphocytes*

	Age on date of CD4 T-lymphocyte test					
	<1 year		1–5 years		6 years through adult	
Stage*	Cells/µL	%	Cells/µL	%	Cells/µL	%
1	≥1,500	≥34	≥1,000	≥30	≥500	≥26
2	750–1,499	25–34	500–999	20–29	200–499	14–25
3	<750	<26	<500	<22	<200	<14

* The stage is based primarily on the CD4+ T-lymphocyte count; it is based on the CD4 percentage only if the count is missing….

These revised threshold values are consistent with thresholds used in the 2006 "WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-related Disease in Adults and Children" (http://www.who.int/hiv/pub/guidelines/WHO%20HIV%20Staging.pdf), except that the WHO immunological classification used 4 age groups and 4 CD4 result categories, whereas the CDC staging system uses 3 age groups and 3 CD4 result categories, and for the oldest age group, the WHO classification used CD4 percent thresholds of 25% and 15%, whereas the CDC classification uses 26% and 14%. Since the CD4 percent would rarely be available without a CD4 count, any problems with the thresholds chosen for the CD4 percent will be mitigated, because the count will take precedence over the percentage in determining the stage, and the CD4 percent will be used only in the rare instances when the count is unavailable.

Comments from Reviewer B

7. **Comment**: Regarding section 1, the criteria for a confirmed case: "I would suggest a table as well as the text to summarize, as you did for the CD4 and staging table."

   Response: Unfortunately the criteria for a confirmed case are too complex for a publishable table. They are best organized by using an outline structure rather than a table.

8. **Comment**: Regarding criteria 1 through 3 for laboratory evidence for infection among persons 18 months old through adult [section 1.1.1]: "I suggest a footnote indicating that these criteria are not in any rank order; or, if they are in order 1-3 of strength, then state so."

Response: Criteria 1 through 4 are not in a rank order. They are preceded by the phrase "any of the following criteria," which should make clear that any of them would suffice without the need for a footnote.

9. **Comment**: Regarding laboratory evidence (section 1.1.1): "Is there any quality control or requirement of evidence of the laboratory proficiency of the persons doing, reading, or reporting the tests?"

   Response: No, it would be impractical for HIV surveillance programs to ascertain the proficiency of laboratories or other testing facilities. They must trust the agencies that have that responsibility. Laboratories generally must be licensed by the states in which they operate. This question is most relevant for CLIA-waived tests done by HIV screening centers in venues that might not be considered laboratories. Even in such circumstances, for surveillance purposes, the test results will be accepted at face value. If subsequent testing reveals that the patient is actually not infected, the records will be deleted from the surveillance database.

10. **Comment**: Regarding clinical evidence (section 1.1.2): "What about lab tests done before [a physician note was written,] but uncovered after the physician note? Would they not also be considered?"

    Response: If lab test results were found after a physician note, but pertained to tests done before the physician note, then these test results would be considered laboratory evidence, which is covered in section 1.1.1. They would take precedence over the physician note in determining the diagnosis date, because they were done earlier, regardless of whether they were discovered later.

11. **Comment**: Regarding section 4: "I am concerned that acute infection in a perinatally infected infant has been disregarded in this CDC surveillance staging. An HIV-exposed newborn negative at birth and then positive within 180 days has an acute infection and should meet the criteria for stage 0. What was the reason to not include? …. [Such children] clearly represent acute infection and are a group [in which] we can define the time of infection as during labor delivery if they are not breastfed and negative on their birth PCR. While I realize the numbers are not large, they still seem important to include in the acute infection group."

    Response: The criteria for stage 0 have been expanded to include such children by deleting the following sentences from the description of stage 0:

    > "Stage 0 may apply to adults, adolescents, and children known not to have acquired HIV infection perinatally from their mother. Classifying stage of infection among children aged <18 months, would require evidence that the biologic mother was uninfected after the child was born or that the child was definitively uninfected (see section 3.1.1 above) before becoming infected after birth."

    Thus, the criteria for stage 0 may now apply to all children, regardless of whether they were perinatally exposed to HIV.

12. **Comment**: "The references appear sparse, particularly for pediatric HIV NAT diagnosis; and [for] the rationale for moving away from CD4% in infants as preferred over the CD4 absolute count."

    Response: The criteria for diagnosis of HIV infection in perinatally exposed children <18 months of age by means of NATs is essentially unchanged from those used in the 2008 case definition. The only difference is that, in the 2013 case definition, the distinction between definitive and presumptive diagnosis is eliminated, thereby allowing the criteria for presumptive diagnosis (which are more inclusive than those for definitive diagnosis) to be used for all cases in perinatally exposed children of this age.

    The rationale for using the absolute CD4 count, rather than the CD4 percentage, is based on the findings in papers by David Dunn, et al. In his 2010 paper, he states, "Models suggested that CD4 percentage had little or no prognostic value over and above that contained in CD4 cell count, irrespective of age. … More emphasis should be placed on CD4 cell count than on CD4 percentage in deciding when to start ART in HIV-1-infected children." It is true that references are sparse to support this, but it is difficult to find data from cohorts that include data on both CD4 test results and clinical manifestations in children at all stages of disease.

Comments from Reviewer C

13. **Comment**: Regarding section 1.1.2 on Clinical (Non-Laboratory) Evidence, which includes the following criterion: "A note written by a physician or other qualified medical-care provider that does not meet the laboratory criteria described above but states that the patient has HIV infection":

    > "This change may need a little more clarification. Is the physician note based on information taken directly from the patient's recollection and told to the physician, or based on what the physician knows of the patient from his … medical records? Clear training to surveillance workers will be needed so uniform interpretation occurs."

    Response: This criterion includes any note in which the physician appears to accept the diagnosis, regardless of whether based primarily on a history given orally by the patient or based on other information. Generally, it may be impossible to determine from the note whether the physician based the diagnosis solely on what the patient said. As long as the physician does not express doubt about the diagnosis by modifying "HIV infection" with terms such as "possible" or "rule out," acceptance of it by surveillance staff will be accurate enough for surveillance purposes. CDC will provide training on this issue for surveillance staff, and guidance in the "Technical Guidance for HIV Surveillance Programs."

14. **Comment**: Regarding section 2 (about HIV-2 infection), in which the term "laboratory expert" is used twice: "Surveillance programs may ask about 'laboratory expert.' [What does this term mean? How can surveillance programs know who is such an expert?]"

    Response: The meaning of this term is clarified by the words that follow its first mention: "a laboratory expert experienced in differentiating HIV-2 from HIV-1." In practice, the surveillance staff of health departments will not have to make this decision, because guidance will be provided by the CDC coordinator of investigations of "cases of public health importance" (COPHI), to whom

state/local HIV surveillance personnel are reporting possible cases of HIV-2 infection. The laboratory experts on whose judgment the CDC COPHI coordinator has relied to make such diagnoses have generally been in CDC's retrovirology laboratory or in a state or municipal public health laboratory that has had a large amount of experience in diagnosing HIV-2 infection.

15. **Comment**: Also regarding section 2: "there is no mention of history of travel to HIV-2 prevalent countries."

    Response: The case definition does not mention risk factors for HIV-2 infection, such as travel to countries in which HIV-2 infection is prevalent, because HIV-2 infection may occur in someone without any apparent risk factors for it. Risk factors should guide testing for HIV-2 infection, but should not be used as criteria for making the diagnosis. The last sentence of the introductory paragraph for section 2 explains this: "Clinical or epidemiologic evidence may lead to laboratory testing for HIV-2, but are insufficient for classifying the HIV type as HIV-2." Risk factors for HIV-2 infection were not mentioned in the 2008 surveillance case definition of HIV infection either.

16. **Comment**: Regarding the definition of stage 0 in section 4: "I see several operational issues for high-volume reporting states that would have to be dealt with by training and eHARS re-programming. It will be difficult to operationalize this section based on the lack of reporting of negative test results. I don't see states requiring that by rule or law."

    Response: CDC recognizes the difficulty of operationalizing the identification of stage 0 and will address it in training for surveillance staff and modification of eHARS. Detection of stage 0 is expected to vary among health departments, depending on their arrangements for laboratories to report the necessary negative test results to them.

    Related to this issue, the following paragraph will be removed from the case definition because it is more appropriate in a document for training surveillance staff, such as CDC's "Technical Guidance for HIV Surveillance Programs," than in the case definition:

    "*Note on obtaining negative/indeterminate test results*:

    HIV surveillance programs will be challenged to learn of the negative or indeterminate test results required for cases to meet the stage-0 definition. Surveillance staff could review medical records of confirmed cases to find previous negative/indeterminate test results, but surveillance programs may find it more practical for laboratories automatically to report a negative/indeterminate antibody test result from a supplemental immunoassay done between an algorithm's initial positive immunoassay and concluding positive nucleic acid test. Automatic reporting of such negative/indeterminate test results would also be more likely to happen soon enough after infection to provide time for intervention to prevent further transmission. Some states may also choose to require laboratories to report negative test results after initial positive results for unconfirmed potential cases; this could enable the health department to help the patient obtain additional testing needed to distinguish acute infection from absence of infection. The great majority of negative test results, which are from testing algorithms that have already concluded that the patient is not infected, need not be reported to surveillance programs."

Comments from Reviewer D

17. **Comment**: Regarding the following sentence in the section on "limitations and applicability of surveillance case definition" in the introduction: "These can be measured by analyzing cases by their stage at diagnosis and how rapidly they progress to more advanced stages.":

    "Once a certain stage is assigned, can a patient revert to an earlier stage or, once assigned at a stage, does the person always stay at that stage?"

    Response: The sentence cited above answers part of this question by saying that a case may progress from the stage at diagnosis to a more advanced stage later. However, this sentence did not say whether the case can later revert to a less advanced stage in response to successful therapy. To remedy that omission, the following was added to the end of the second paragraph in section 4:

    "Of primary interest is the stage at initial diagnosis, but the stage can change in either direction after diagnosis, and might be defined with reference to dates of interest, such as the most advanced stage recorded through a particular date."

18. **Comment**: Regarding criteria for a confirmed case in section 1, "Somewhere it needs to be explicit that [either] lab evidence or clinical evidence is sufficient to meet case definition ('or,' not 'and')."

    Response: To make clear that a case does not need both lab evidence and clinical evidence, the following was added to the introduction to section 1:

    "Criteria for a confirmed case may be met by either laboratory evidence or clinical evidence, as described below. Laboratory evidence is preferred over clinical evidence."

    CDC recommends that surveillance programs collect data on clinical evidence in addition to available laboratory evidence if the clinical evidence indicates an earlier diagnosis date than the laboratory evidence.

19. **Comment**: Regarding section 1.1.1.1: "need to add an 'and' here to make it explicit that both criteria denoted by open circles bullets need to be met to satisfy case definition via algorithm 1."

    Response: An "and" was added, shown below:

    "1) A multi-test algorithm consisting of

    - a positive result on an initial HIV antibody or combination antigen/antibody test

      and

    - an accompanying or subsequent positive result on a supplemental HIV test different from the initial test (*4*)."

20. **Comment**: Regarding section 1.1.1.2, where it says, "when it may reasonably be assumed to have been used as a supplemental test":

    "Is it written elsewhere who makes this decision? CDC or local public health? Will there be guidelines to ensure consistency in this decision?"

Response: The following parenthetical expression was added to the sentence for clarification:

"(e.g., because the algorithm customarily used by the reporting laboratory is known)."

21. **Comment**: Regarding section 1.1.2, where it says, "an otherwise unexplained low CD4+ T-lymphocyte count or diagnosis of an opportunistic illness":

    "To be more clear, [you] should repeat [the] word "unexplained" in this phrase to emphasize that only the OIs occurring in [the] absence of a known cause of immunodeficiency can be counted."

    Response: This criterion was reworded to make clear that "otherwise unexplained" applies to both a low CD4 count and an OI diagnosis:

    "Circumstantial evidence of HIV infection (e.g., receipt of HIV antiretroviral therapy, prophylaxis for an opportunistic infection), an otherwise unexplained low CD4+ T-lymphocyte count [see Table 1], or an otherwise unexplained diagnosis of an opportunistic illness [see Appendix A])"

22. **Comment**: Regarding the negative antibody test criterion in section 1.2.1 that says, "A child aged <18 months is categorized for surveillance purposes as HIV infected if all of the following criteria are met:

    - Positive results on at least one specimen (not including cord blood) from any of following HIV virologic tests
      - HIV nucleic acid (DNA or RNA) test (NAT)
      - HIV p24 antigen test, including neutralization assay, for a child aged >1 month
      - HIV isolation (viral culture)
      - HIV nucleotide sequence (genotype)
    - Reporting of the date of the test (at least the year and month); this should be the date of specimen collection, if known
    - No subsequent negative result on an HIV antibody test
    - No subsequent negative result on an HIV NAT unless at >18 months of age and an HIV antibody test was also positive at >18 months of age (to allow for an undetectable viral load due to effective antiretroviral therapy)":

    "Until what age [must there be no subsequent antibody test]? If an age [limit for a negative antibody test] is not specified [as it is specified for a negative HIV NAT], this criterion will never be met."

    Response: This section has been revised as follows:

    "A child aged <18 months is categorized for surveillance purposes as HIV infected if all of the following criteria are met:

    - Positive results on at least one specimen (not including cord blood) from any of following HIV virologic tests
      - HIV nucleic acid (DNA or RNA) test (NAT)
      - HIV p24 antigen test, including neutralization assay, for a child aged >1 month

- HIV isolation (viral culture)
- HIV nucleotide sequence (genotype)

- Reporting of the date of the test (at least the year and month); this should be the date of specimen collection, if known
- One or both of the following:
  - Confirmation of the first positive result by another positive result on one of the above virologic tests from a specimen obtained on a different date

    or
  - Both of the following:
    - No subsequent negative result on an HIV antibody test

      and
    - No subsequent negative result on an HIV NAT before 18 months of age"

Thus, the absence of negative test results is required only if the diagnosis is based on a single positive virologic test. It is not required if there are two or more positive NATs. It would be extremely rare for an HIV-infected child to have negative HIV antibody test results, even after passively acquired maternal antibodies have disappeared. The only circumstances where this might occur would be either in end-stage disease in which the child's ability to make antibodies has been lost, or in a so-called "functional cure" resulting from unusually aggressive treatment with highly active antiretroviral agents very soon after birth, as was recently reported at the 2013 CROI by Dr. Deborah Persaud. In cases of "functional cure," infection is likely to be confirmed by multiple positive results on HIV NATs. According to Dr. Persaud's CROI abstract, for example, "infection was confirmed by positive HIV DNA and RNA testing on 2 separate blood samples obtained on the 2nd day of life. 3 additional plasma viral load tests (days of life 7, 12, and 20) were positive before reaching undetectable levels at age 29 days." Therefore, it is unnecessary to place an age limit on the requirement for absence of a negative antibody test when the child has only a single positive NAT. Doing so would risk classifying as cases some uninfected children with falsely positive NATs. An age limit is placed on the requirement for a negative NAT because viral nucleic acid may be expected to have become undetectable in response to therapy, but this is generally not true of HIV antibody.

23. **Comment**: Regarding the introductory part of section 3.1: "Indent this section to make it clear that either one of these criteria [laboratory or clinical] is sufficient to satisfy the "and" part of this section."

    Response: Instead of indenting, this ambiguity was eliminated by rewording as follows:

    - "Laboratory criteria for HIV infection are not met (see section 1.2.1)

    and

    - No diagnosis of a stage-3-defining opportunistic illness (see Appendix A) attributed to HIV infection.

    and

    - Either laboratory or clinical evidence as described below"

24. **Comment**: Regarding the footnote to Table 1 that says, "The change in the upper CD4 percentage threshold from 29% (as in the case definition of 2008) to 26% (as in the revision above) is contingent on data being published that support it, to corroborate unpublished analyses of surveillance data.":

    "So, when will this change take effect? What if no such data are forthcoming in the next 5 years?"

    Response: An updated analysis of CD4 test data from two sources—national HIV surveillance and the NA-ACCORD cohort study—have both shown that the CD4 percent that corresponds to a CD4 count of 500 cells/µL is 26% rather than 29%. Therefore, the upper CD4 percentage threshold for this age group has been changed from 29% to 26%, and the footnote regarding this change has been deleted.

Comments from Reviewer E

25. **Comment**: Regarding the words, "immunoassays formerly used only as initial tests (e.g., conventional enzyme immunoassay [EIA], rapid test, …)" in the introduction:

    "Would consider also referring to 'ELISA' since that term is still commonly used."

    Response: Abbreviations such as "EIA" have been eliminated from the parentheses.

26. **Comment**: Regarding the term "rapid test," in the sentence to which the preceding comment referred: "immunoassays formerly used only as initial tests (e.g., conventional enzyme immunoassay [EIA or ELISA], rapid test, …)":

    "Consider specifying both oral fluid and blood rapid tests."

    Response: No change was made in response to this suggestion because the intent of the sentence is to contrast initial/screening tests with supplemental/confirmatory tests, and "rapid tests" have previously been used only as initial/screening tests, not as supplemental/confirmatory tests, regardless of whether the test specimen was oral fluid or blood. Therefore, there is no need to clarify that the rapid tests include both oral fluid tests and blood tests.

27. **Comment**: Regarding the term "serologic test" used in Section 1.1.1: "It states 'serologic,' but shouldn't the rapid oral fluid test also be added here and throughout?"

    Response: The term "serologic" was meant to include both antibody tests and combination antigen/antibody tests; it was not meant to exclude tests on specimens other than serum, such as oral fluids or whole blood. To reduce potential confusion about the meaning of "serologic." it has been replaced by the expression "antibody or antigen/antibody" wherever it had been used throughout the document.

28. **Comment**: In the introduction, regarding the following sentence: "Second, another important change is the addition of 'stage 0' based on a sequence of negative and positive test results indicative of early HIV infection. This takes advantage of tests incorporated in the new algorithms

that are more sensitive during early infection than tests previously in use, enabling diagnosis of acute (primary) HIV infection, which occurs before the antibody response has fully developed.":

> "[It] seems confusing to use both the terms 'early' and 'acute' HIV infection interchangeably in this paragraph. Many define 'acute' as the period of time before antibody can be detected, and 'early' as within 6 months of infection."

Response: A later sentence in the same paragraph has been revised to make clear by the words "acute HIV infection (part of stage 0)" that stage 0 (which approximates "early HIV infection" if the latter is defined as "within 6 months of onset of infection") includes but is not the same as the shorter period of "acute" infection:

> "The definition of stage 0 will also reduce confusion between acute HIV infection (part of stage 0), when CD4+ T-lymphocyte counts can be transiently depressed, and stage 3 (AIDS), an advanced stage of HIV infection when CD4 and T-lymphocyte values are usually persistently depressed (*5*)."

An alternative usage of "early infection" that excludes the period of acute infection would be more confusing because acute infection implies very early infection, and "early" should be interpreted as including "very early."

29. **Comment**: In the introduction, in the section subtitled "Limitations and applicability of surveillance case definition," regarding the following sentence: "Published treatment guidelines recommend antiretroviral therapy for all HIV-infected adults, adolescents, and infants, and the staging system does not include some criteria strongly recommended as indicators for more rapid initiation of therapy (e.g., HIV nephropathy, hepatitis B coinfection, viral load >100,000 copies/ml, a decline in CD4 T-lymphocyte count by >100 cells/µL per year) (*11–13*).":

> "Updated treatment guidelines no longer list conditions favoring 'more rapid initiation of therapy'—[I] would take [them] out."

Response: No change was made in response to this comment because re-examination of the updated treatment guidelines (on July 11, 2013) showed that the guidelines still list conditions favoring "more rapid initiation of therapy" on pages E-10 and E-11 (http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf). The guidelines explain that these conditions should be considered when obstacles to adherence may be a reason for deferring treatment, and in resource-limited settings where there is a need to prioritize treatment to the patients who need it most. Likewise, the latest pediatric treatment guidelines continue to recommend that a high viral load be an indicator for more urgent initiation of treatment if treatment had been deferred: "In children with lower-strength (B level) recommendations for treatment, plasma HIV RNA levels >100,000 copies/mL provide stronger evidence for initiation of treatment (BII)." (http://aidsinfo.nih.gov/contentfiles/lvguidelines/PediatricGuidelines.pdf; Table 7, page F-2, accessed July 11, 2013, updated November 5, 2012)

30. **Comment**: Regarding the references cited for treatment guidelines: "[You] need to update references to DHHS adult and pediatric guidelines which have both been updated: adult 2/12/13, peds 11/5/12."

    Response: The AIDSINFO.NIH.GOV treatment guideline references were accessed on July 11, 2013, and the last date they were updated by the guidelines panel was added to each of those citations.

31. **Comment**: Regarding the description of "orthogonal" tests for criterion #1 in Section 1.1.1: "Would 2 different positive rapid tests also meet the definition? This is used commonly in developing countries, and I suspect could be used commonly in the U.S. as well."

    Response: Yes, two different positive rapid tests would also meet the case definition.

32. **Comment**: Regarding the use of detectable viral loads as a sufficient criterion for diagnosis in criterion #3 in Section 1.1.1): "What about the issue of false positive HIV RNA results (typically with levels <100 copies/ml)?"

    Response: False positive viral loads are a recognized possibility, and must be considered by clinicians. However, the scenario in which the patient's first positive HIV test is a detectable viral load is probably unusual, because approved testing algorithms generally do not use a NAT until after at least one positive antibody test. A detectable viral load as the first positive test would be likely to occur only in suspected acute infection. The option of requiring a second test after a viral load below a low threshold (e.g., <100) was considered by the CDC surveillance workgroups on new HIV testing algorithms and acute infection, but was rejected as impractical for surveillance. Often viral loads are reported to surveillance only as "detectable" without the number of copies/ml specified. It may be better for surveillance to include a small number of false cases based on a low viral load than to miss a possibly larger number of true cases due to patients not promptly returning for further testing to confirm the initial detectable viral load.

33. **Comment**: Regarding the following sentence in the introduction to Section 4, "Cases with no information on CD4+ T-lymphocyte count or percentage can be classified as stage unknown.":

    "Should 'can be' instead be 'will be'?"

    Response: No, because a case without information on CD4 test results could be classified in stage 3 if an AIDS-defining opportunistic infection had been diagnosed or in stage 0 if the first confirmed positive test was within 180 days after a negative test. Only the cases that do not meet the criteria for stage 0 and that have had no diagnosis of a stage-3-defining opportunistic illness would be classified as being in stage "unknown" if there were no information on CD4 test results.

34. **Comment**: Regarding Table 1: "This table may be confusing because it lists staging both by CD4 count and CD4 %. Although the footnote states 'use the % only if the count is missing,' it may be confusing if there are discordant results between count and %. Suggest clarifying by stating that the count takes precedence over %."

    Response: To make this clearer, the first sentence of the footnote has been rewritten as follows:

“The stage is based primarily on the CD4+ T-lymphocyte count; the CD4+ T-lymphocyte count takes precedence over the CD4 T-lymphocyte percentage, and the percentage is considered only if the count is missing.”