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Revised Surveillance Case Definition for HIV Infection — United States, 2014

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Revised Surveillance Case Definition for HIV Infection — United States, 2014

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Summary

Following extensive consultation and peer review, CDC and the Council of State and Territorial Epidemiologists have revised and combined the surveillance case definitions for human immunodeficiency virus (HIV) infection into a single case definition for persons of all ages (i.e., adults and adolescents aged ≥13 years and children aged <13 years). The revisions were made to address multiple issues, the most important of which was the need to adapt to recent changes in diagnostic criteria. Laboratory criteria for defining a confirmed case now accommodate new multitest algorithms, including criteria for differentiating between HIV-1 and HIV-2 infection and for recognizing early HIV infection. A confirmed case can be classified in one of five HIV infection stages (0, 1, 2, 3, or unknown); early infection, recognized by a negative HIV test within 6 months of HIV diagnosis, is classified as stage 0, and acquired immunodeficiency syndrome (AIDS) is classified as stage 3. Criteria for stage 3 have been simplified by eliminating the need to differentiate between definitive and presumptive diagnoses of opportunistic illnesses. Clinical (nonlaboratory) criteria for defining a case for surveillance purposes have been made more practical by eliminating the requirement for information about laboratory tests. The surveillance case definition is intended primarily for monitoring the HIV infection burden and planning for prevention and care on a population level, not as a basis for clinical decisions for individual patients. CDC and the Council of State and Territorial Epidemiologists recommend that all states and territories conduct case surveillance of HIV infection using this revised surveillance case definition.

Introduction

Since the first cases of acquired immunodeficiency syndrome (AIDS) were reported in the United States in 1981, surveillance case definitions for human immunodeficiency virus (HIV) infection (the cause of AIDS) and AIDS have undergone several revisions to respond to diagnostic advances (*1*–*5*). This document updates the surveillance case definitions published in 2008 (*5*). It addresses multiple issues, the most important of which was the need to adapt to recent changes in diagnostic criteria. Other needs that prompted the revision included 1) recognition of early HIV infection, 2) differentiation between HIV-1 and HIV-2 infections, 3) consolidation of staging systems for adults/adolescents and children, 4) simplification of criteria for opportunistic illnesses indicative of AIDS, and 5) revision of criteria for reporting diagnoses without laboratory evidence.

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Summary of Revisions to Surveillance Case Definition

The most important update is revision of the laboratory criteria for a confirmed case, which addresses the development of new diagnostic testing algorithms that do not use the Western blot or immunofluorescence HIV antibody assays. During 2009–2011, CDC and the Association of Public Health Laboratories proposed new diagnostic algorithms (*6*,*7*), and in June 2011 the Clinical and Laboratory Standards Institute (CLSI) published updated laboratory testing procedures for diagnosis of HIV infection (*8*). In these multitest algorithms, "supplemental" HIV tests (for confirming or verifying the presence of HIV infection after a positive [or "reactive"] result from an initial HIV test) can now include antibody immunoassays formerly used only as initial tests (e.g., conventional immunoassays or rapid tests) or can include nucleic acid tests (NAT). The 2008 surveillance case definition was not clearly consistent with the new algorithms because it specified that a test used for confirmation must be a "supplemental HIV antibody test (e.g., Western blot or indirect

immunofluorescence assay test)" (*5*). This revised surveillance case definition explicitly allows these new testing algorithms.

Some new multitest algorithms lead to a conclusion that laboratories might classify as a "presumptive positive" result. Persons with a presumptive positive test result are expected to receive subsequent tests, such as a quantitative viral load, to confirm their HIV diagnosis, but results of those tests might not be immediately available to surveillance programs. To avoid unnecessary complexity for surveillance, the revised surveillance case definition, like the earlier definition, does not make a distinction between presumptive and definitive diagnoses. If subsequent test results reveal that the person is not infected, the case and previous test results should be deleted from the surveillance database.

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 addition takes advantage of tests incorporated in the new algorithms that are more sensitive during early infection than previously used tests, and that together with a less sensitive antibody test, yield a combination of positive and negative results enabling diagnosis of acute (primary) HIV infection, which occurs before the antibody response has fully developed. The addition of stage 0 allows for routine monitoring of the number of cases diagnosed within several months after infection, which includes the most highly infectious period when viral loads are extremely high and intervention might be most effective in preventing further transmission. The definition of stage 0 also will 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+ T-lymphocyte values are usually persistently depressed (*9*).

The revised case definition adds other criteria and eliminates several criteria that were impractical or difficult to implement uniformly across all states and territories. Specifically, the revised case definition:

- Adds specific criteria for defining a case of HIV-2, which were not included in the 2008 case definition. The new definition incorporates criteria for HIV-2 infection used in a report of surveillance for HIV-2 infection (*10*) and included in one of the new CLSI testing algorithms (*8*).
- Eliminates the requirement to indicate if opportunistic illnesses (AIDS-defining conditions) indicative of stage 3 (AIDS) were diagnosed by "definitive" or "presumptive" methods. This requirement has been impractical to implement because the criteria to distinguish between "definitive" and "presumptive" methods were not interpreted in a standard, uniform way by state and local surveillance programs.
- Classifies stages 1–3 of HIV infection on the basis of the CD4+ T-lymphocyte count unless persons have had a stage-3–defining opportunistic illness. The CD4+ T-lymphocyte percentage is used only when the corresponding CD4+ T-lymphocyte count is unknown. This avoids overestimating the proportion of cases in stage 3, which occured when the stage was based on whichever CD4+ T-lymphocyte test result (count or percentage) indicated the more advanced stage. Clinical evidence suggests the percentage has little effect on prognosis after adjusting for the count (*11,12*).
- Removes the requirement that a "physician-documented" diagnosis must be based on laboratory evidence. This revision allows clinical evidence to be sufficient to define a case when it is impractical to retrieve laboratory test information regarding the initial diagnosis. The new definition also clarifies that the date of a physician-documented diagnosis is the diagnosis date recorded in a medical record note, rather than the date that the physician wrote the note.
- Combines the adult and pediatric criteria for a confirmed case of HIV infection and specifies different criteria for staging HIV infection among three age groups (<1 year, 1–5 years, and ≥6 years).
- Eliminates the distinction between definitive and presumptive diagnoses of HIV infection in children aged <18 months.
- Removes lymphoid interstitial pneumonia (pulmonary lymphoid hyperplasia) from the list of opportunistic illnesses indicative of stage 3 in children because this illness is associated with moderate rather than severe immunodeficiency (*4*).
- Eliminates the requirement that evidence of HIV infection in a child's biologic mother is needed to define a case of HIV infection in a child aged <18 months when laboratory testing of the infant independently confirms HIV infection. This change was recommended in a position statement approved at the June 2009 annual meeting of the Council of State and Territorial Epidemiologists (CSTE) (*13*).
- Extends the use of CD4+ T-lymphocyte counts and percentages for determining the stage of HIV infection to children as well as adults and adolescents, and now determines the stage in children aged 6–12 years the same way as in adults and adolescents. In the 2008 case definition, only the presence or absence of opportunistic illnesses was used as criteria for staging cases among children aged <13 years.

Scope and Applicability of the Surveillance Case Definition

This revised case definition, like the earlier one, is intended primarily for public health surveillance of HIV infection on a population level. Early diagnosis and viral suppression facilitate prevention of HIV transmission, morbidity, and mortality. This case definition's staging system allows for health departments to evaluate prevention and care, which can be measured by analyzing cases by their stage at diagnosis and how rapidly they progress to more advanced stages. For various reasons, it would be inappropriate for clinicians to use the surveillance staging system as a guide to manage patients. United States national panels on antiretroviral guidelines recommend antiretroviral therapy for all HIV-infected adults, adolescents, and infants, and the staging system does not include criteria strongly recommended as indicators for more rapid initiation of therapy (e.g., HIV nephropathy, hepatitis B coinfection, viral load >100,000 copies/mL, and a decline in CD4+ T-lymphocyte count by >100 cells/μL per year) (*14–16*). Treatment guidelines for children aged >1 year also recommend starting therapy on the basis of criteria other than stage, such as a viral load >100,000 copies/mL or conditions that are important (e.g., clinical category B [*13*]) but do not indicate stage 3, if treatment had been deferred after diagnosis (*16,17*).

Methods

The revised case definition was developed in several stages. First, in 2010, HIV surveillance experts at CDC convened six work groups that included both CDC and external subject matter experts, including health-care providers, surveillance health department staff, and representatives from academic institutions and public health and commercial laboratories. The names of work group members are listed at the end of this report. The six topic areas were new HIV testing algorithms, acute HIV infection, HIV-2 infection, opportunistic illnesses, pediatric HIV infection, and physician-documented diagnosis. Each work group examined research and program information about the topic areas and elicited experience and expert opinion from federal, state, and local HIV surveillance programs; clinicians who diagnose HIV infection; and laboratories that report HIV test results.

Second, all work groups presented a summary of their reports at a consultation convened by CDC in February 2012. The consultation included additional experts in HIV surveillance, laboratory testing, and clinical care, including members of CSTE.

Third, most of the recommendations from the consultation were incorporated in a position statement developed in collaboration with CDC that was approved at the June 2012 annual meeting of CSTE (*18*). The revisions of the surveillance case definition in this document are based largely on that position statement. Finally, this document underwent peer review (described at http://www.cdc.gov/hiv/pdf/policies_PRP_Revised_HIV_Case_Def.pdf) by health-care professionals in compliance with the Office of Management and Budget requirements for the dissemination of influential scientific information.

Revised Surveillance Case Definition

Section 1: Criteria for a Confirmed Case

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

1.1: Persons Aged ≥18 Months and Children Aged <18 Months whose Mothers were Not Infected

1.1.1: Laboratory Evidence

Laboratory criteria require reporting of the date of the specimen collection for positive test results in multitest algorithms or stand-alone virologic tests and enough information about the tests to determine that they meet any of the following criteria:

- A multitest algorithm consisting of
  - A positive (reactive) result from an initial HIV antibody or combination antigen/antibody test, and
  - An accompanying or subsequent positive result from a supplemental HIV test different from the initial test (*8*).

  The initial HIV antibody or antigen/antibody test and the supplemental HIV test that is used to verify the result from the initial test can be of any type used as an aid to diagnose HIV infection. For surveillance purposes, supplemental tests can include some not approved by the Food and Drug Administration (FDA) for diagnosis (e.g., HIV-1 viral load test, HIV-2 Western blot/immunoblot antibody test, and HIV-2 NAT). However, the initial and supplemental tests must be "orthogonal" (i.e., have different antigenic constituents or use different principles) to minimize the possibility of concurrent nonspecific reactivity. Because the antigenic constituents and test principles are proprietary information that might not be publicly available for some tests, tests will be assumed to be orthogonal if they are of different types. For example:
  - One test is a combination antigen/antibody test and the other an antibody-only test.
  - One test is an antibody test and the other a NAT.

– One test is a rapid immunoassay (a single-use analytical device that produces results in <30 minutes) and the other a conventional immunoassay.
– One test is able to differentiate between HIV-1 and HIV-2 antibodies and the other is not.

Tests also will be assumed to be orthogonal if they are of the same type (e.g., two conventional immunoassays) but made by different manufacturers. The type of HIV antibody test that verifies the initial test might be one formerly used only as an initial test (e.g., conventional or rapid immunoassay, HIV-1/2 type-differentiating immunoassay), or it might be one traditionally used as a supplemental test for confirmation (e.g., Western blot, immunofluorescence assay).

- A positive result of a multitest HIV antibody algorithm from which only the final result was reported, including a single positive result on a test used only as a supplemental test (e.g., HIV Western blot, immunofluorescence assay) or on a test that might be used as either an initial test or a supplemental test (e.g., HIV-1/2 type-differentiating rapid antibody immunoassay) when it might reasonably be assumed to have been used as a supplemental test (e.g., because the algorithm customarily used by the reporting laboratory is known).
- A positive result or report of a detectable quantity (i.e., within the established limits of the laboratory test) from any of the following HIV virologic (i.e., nonantibody) tests:
  – Qualitative HIV NAT (DNA or RNA)
  – Quantitative HIV NAT (viral load assay)
  – HIV-1 p24 antigen test
  – HIV isolation (viral culture) or
  – HIV nucleotide sequence (genotype).

1.1.2: Clinical (Nonlaboratory) Evidence

Clinical criteria for a confirmed case (i.e., a "physician-documented" diagnosis for which the surveillance staff have not found sufficient laboratory evidence described above) are met by the combination of:

- A note in a medical record by a physician or other qualified medical-care provider that states that the patient has HIV infection, and
- One or both of the following:
  – The laboratory criteria for a case were met based on tests done after the physician's note was written (validating the note retrospectively).
  – Presumptive evidence of HIV infection (e.g., receipt of HIV antiretroviral therapy or prophylaxis for an opportunistic infection), an otherwise unexplained low CD4+ T-lymphocyte count, or an otherwise unexplained diagnosis of an opportunistic illness (Appendix).

1.2: Children Aged <18 Months Born to Mothers Who Have an Unknown Infection Status or Were Known to be Infected

1.2.1: Laboratory Evidence

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-1 NAT (DNA or RNA)
  – HIV-1 p24 antigen test, including neutralization assay for a child aged >1 month
  – HIV isolation (viral culture) or
  – HIV nucleotide sequence (genotype).
- The test date (at least the month and year) is 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
  – No subsequent negative result on an HIV antibody test, and no subsequent negative result on an HIV NAT before age 18 months.

1.2.2: Clinical Evidence

- The same criteria as in section 1.1.2 or
- All three of the following alternative criteria:
  – Evidence of perinatal exposure to HIV infection before age 18 months
    ◦ A mother with documented HIV infection or
    ◦ A confirmed positive test for HIV antibody (e.g., a positive initial antibody test or antigen/antibody test, confirmed by a supplemental antibody test) and a mother whose infection status is unknown or undocumented.
  – Diagnosis of an opportunistic illness indicative of stage 3 (Appendix).
  – No subsequent negative result on an HIV antibody test.

1.3: Definition for Date of Diagnosis of a Confirmed Case for all Ages

1.3.1: Laboratory Criteria

If the diagnosis is based on laboratory evidence, the diagnosis date is defined as the earliest date on which the specimen was obtained for a positive HIV test result.

1.3.2: Clinical Criteria

If the diagnosis was based on clinical evidence ("physician-documented") rather than laboratory evidence, the diagnosis

date is defined as the date (at least the year) of diagnosis reported in the content of the medical record. If the diagnosis date was not reported in the note, the date when the note was written can be used as a proxy.

Section 2: Criteria for Classifying the HIV Type as HIV-2

All HIV infections in the United States should be assumed to be type 1 (HIV-1) unless laboratory test results are sufficient to classify the infection as type 2 (HIV-2), dual HIV-1 and HIV-2 infections, or undifferentiated HIV infection, as described below. Clinical or epidemiologic evidence might lead to laboratory testing for HIV-2 but is insufficient for classifying the HIV type as HIV-2.

2.1: Persons Aged ≥18 Months and Children Aged <18 Months Not Perinatally Exposed

HIV-2 infection

For HIV-2 infection, one or more of the following laboratory criteria are necessary and sufficient:

- FDA-approved HIV1/2 type-differentiating antibody test result positive for HIV-2 and negative for HIV-1.
- Positive HIV-2 Western blot (WB) (or immunoblot or line assay) result and negative or indeterminate HIV-1 WB result.
- Positive qualitative HIV-2 NAT result.
- Detectable quantitative HIV-2 NAT (viral load).
- Laboratory results interpreted as consistent with HIV-2 infection by a laboratory expert experienced in differentiating HIV-2 from HIV-1 if laboratory evidence for HIV-2 is ambiguous.

Dual infection with HIV-1 and HIV-2

The HIV type is classified as "dual" infection (both HIV-1 and HIV-2) if both an HIV-1 NAT and an HIV-2 NAT are positive.

Undifferentiated HIV type

The HIV type is classified as "undifferentiated" if there is no positive or detectable result from an HIV-1 NAT and a laboratory expert cannot resolve ambiguous evidence for HIV-2, such as:

- HIV-2 WB is positive and HIV-1 WB is HIV positive or
- HIV-1/HIV-2 type-differentiating antibody test result interpretation is "undifferentiated" (positive for both HIV-1 and HIV-2).

2.2: Difficulty of Diagnosing HIV-2 Infection in Children Aged <18 Months Born to Mothers Known to be HIV-infected or whose HIV Infection Status is Unknown

In perinatally exposed children aged <18 months, antibody tests are not used to diagnose HIV infection because of the expectation that they might be false indicators of infection in the child due to passive transfer of maternal antibody. The HIV-1 NAT routinely used to diagnose HIV-1 infection in children of this age is likely to be negative in an HIV-2-infected child because it is insensitive to HIV-2. A positive HIV-2 NAT result would satisfy the criteria for a case. Otherwise, the diagnosis of HIV-2 infection in a child will need to wait until the child is aged 18 months, when it can be based on antibody test results.

Section 3: Criteria for Uninfected and Indeterminate HIV Infection Status of Perinatally Exposed Children Aged <18 Months

3.1: Uninfected

A child aged <18 months who was born to an HIV-infected mother or had a positive HIV antibody test result is classified for surveillance purposes as not infected with HIV if all three of the following criteria are met:

- Laboratory criteria for HIV infection are not met (see section 1.2.1)
- No diagnosis of a stage-3-defining opportunistic illness (Appendix) attributed to HIV infection and
- Either laboratory or clinical evidence of absence of HIV infection as described below.

3.1.1: Laboratory Evidence

Definitively Uninfected

- No positive HIV NAT (RNA or DNA) and
- At least one of the following criteria:
  - At least two negative HIV NATs from specimens obtained on different dates, both of which were at age ≥1 month and one of which was at age ≥4 months.
  - At least two negative HIV antibody tests from specimens obtained on different dates at age ≥6 months.

Presumptively Uninfected

- Criteria for definitively uninfected with HIV are not met
- At least one of the following four laboratory criteria are met:
  - At least two negative NATs from specimens obtained on different dates, both of which were at age ≥2 weeks and one of which was at age ≥4 weeks.

- One negative NAT (RNA or DNA) from a specimen obtained at age ≥8 weeks.
- One negative HIV antibody test from a specimen obtained at age ≥6 months.
- If criteria for HIV infection had initially been met by one positive HIV NAT test then it must have been followed by at least two negative test results from specimens obtained on different dates, one of which is:
  - A NAT test from a specimen obtained at age ≥8 weeks, or
  - An HIV antibody test from a specimen obtained at age ≥6 months.

  and

- No subsequent positive NAT.

3.1.2: Clinical Evidence

A note in a medical record by a physician or other qualified medical-care provider states that the patient is not infected with HIV.

3.2: Indeterminate HIV infection status

A child aged <18 months born to an HIV-infected mother is categorized as having perinatal exposure with an indeterminate HIV infection status if neither the criteria for being HIV-infected nor the criteria for being uninfected are met.

Section 4: Criteria for Classifying the Stage of HIV Infection

The stages of HIV infection defined in this document are for surveillance staging of disease and might not be appropriate for patient care, clinical research, or other purposes. A confirmed case that meets the criteria for diagnosis of HIV infection can be classified in one of five HIV infection stages (0, 1, 2, 3, or unknown). Stage 0 indicates early HIV infection, inferred from a negative or indeterminate HIV test result within 6 months of a confirmed positive result, and these criteria supersede and are independent of the criteria used for later stages. Stages 1, 2, and 3 are based on the CD4+ T-lymphocyte count. If the CD4+ count is missing or unknown, the CD4+ T-lymphocyte percentage of total lymphocytes can be used to assign the stage. Cases with no information on CD4+ T-lymphocyte count or percentage are classified as stage unknown. If a stage-3–defining opportunistic illness has been diagnosed, then the stage is 3 regardless of CD4 T-lymphocyte test results, unless the criteria described below for stage 0 are met. CD4+ T-lymphocyte counts or percentages at the time of diagnosis allow classification of cases by stage at diagnosis. Subsequent CD4+ T-lymphocyte counts or percentages help monitor disease progression and whether the person is receiving on-going care.

The stage characterizes the status of HIV disease at a particular point in time. Of primary interest to surveillance 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. The stages are defined as follows:

Stage 0

The criteria for stage 0 consist of a sequence of discordant test results indicative of early HIV infection in which a negative or indeterminate result was within 180 days of a positive result. The criteria for stage 0 supersede and are independent of the criteria used for other stages.

Stage 0 can be established either:

- Based on testing history (previous negative/indeterminate test results): a negative or indeterminate HIV test (antibody, combination antigen/antibody, or nucleic acid test) result within 180 days before the first confirmed positive HIV test result of any type. The first positive test result could be any time before the positive supplemental test result that confirms it or
- Based on a testing algorithm: a sequence of tests performed as part of a laboratory testing algorithm that demonstrate the presence of HIV-specific viral markers such as p24 antigen or nucleic acid (RNA or DNA) 0–180 days before or after an antibody test that had a negative or indeterminate result. Examples of algorithms that would fulfill this requirement include:
  - A positive initial HIV immunoassay result (e.g., antigen/antibody or antibody only) followed by a negative or indeterminate supplemental antibody test result (e.g., HIV-1/HIV-2 antibody differentiation assay or Western blot) and a positive NAT result. All three tests are usually performed as part of the same testing algorithm but time might elapse between tests if additional specimens must be obtained for definitive supplemental testing.
  - A negative initial HIV immunoassay result followed by a positive NAT result that might have been done to evaluate the presence of acute HIV infection (*19,20*).

Exception

A confirmed case of HIV infection is not in stage 0 if the negative or indeterminate HIV test used as the criterion for it being a recent infection was preceded >60 days by evidence of HIV infection, such as a confirmed positive HIV test result, a clinical (physician-documented) diagnosis of HIV infection for which the surveillance staff have not found sufficient laboratory evidence, a CD4+ T-lymphocyte test result indicative of stage 3 (Table), or an opportunistic illness indicative of stage 3 (Appendix).

TABLE. 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 yr		1–5 yrs		≥6 yrs	
Stage	Cells/μL	%	Cells/μL	%	Cells/μL	%
1	≥1,500	≥34	≥1,000	≥30	≥500	≥26
2	750–1,499	26–33	500–999	22–29	200–499	14–25
3	<750	<26	<500	<22	<200	<14

* 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. There are three situations in which the stage is not based on this table: 1) if the criteria for stage 0 are met, the stage is 0 regardless of criteria for other stages (CD4 T-lymphocyte test results and opportunistic illness diagnoses); 2) if the criteria for stage 0 are not met and a stage-3-defining opportunistic illness has been diagnosed (Appendix), then the stage is 3 regardless of CD4 T-lymphocyte test results; or 3) if the criteria for stage 0 are not met and information on the above criteria for other stages is missing, then the stage is classified as unknown.

Classifying a case as stage 0 depends on documenting negative HIV antibody test results in the specific situations described above. Negative test results from testing algorithms that have concluded that the person is not infected need not be reported to HIV surveillance programs.

Progression of Stage After Initial Diagnosis in Stage 0

Although the stage at diagnosis does not change, if >180 days have elapsed after the stage was 0 at diagnosis, the stage at the later date is classified as 1, 2, 3, or unknown, depending on CD4+ T-lymphocyte test results (Table) or whether an opportunistic illness had been diagnosed >180 days after HIV infection diagnosis.

Stages 1, 2, 3, and unknown

If the criteria for stage 0 are not met, the stage is classified as 1, 2, 3, or unknown, depending on CD4+ T-lymphocyte test results or whether an opportunistic illness was diagnosed (Table). Infection among children aged 6–12 years is staged with the same criteria as infection among adults and adolescents, including opportunistic illnesses indicative of stage 3 (Appendix) that formerly applied only to adults and adolescents (i.e., pulmonary tuberculosis, recurrent pneumonia, and cervical cancer). Multiple or recurrent bacterial infections (other than recurrent salmonella septicemia), which formerly applied only to children aged <13 years, now apply only to children aged <6 years. Lymphoid interstitial pneumonia is no longer classified as indicative of stage 3 in children because it is associated with moderate rather than severe immunodeficiency (*4*). The diagnosis of any of the opportunistic illnesses, irrespective of diagnostic method used, will meet the criteria for staging, thereby eliminating the requirement in the 2008 case definition for some of them to be "definitively" diagnosed.

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Appendix: Stage-3-Defining Opportunistic Illnesses in HIV Infection

Bacterial infections, multiple or recurrent*
Candidiasis of bronchi, trachea, or lungs
Candidiasis of esophagus
Cervical cancer, invasive†
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1 month's duration)
Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy attributed to HIV§
Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1 month's duration)
Kaposi sarcoma
Lymphoma, Burkitt (or equivalent term)
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary, of brain
Mycobacterium avium complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
Mycobacterium tuberculosis of any site, pulmonary†, disseminated, or extrapulmonary
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis jirovecii (previously known as "*Pneumocystis carinii*") pneumonia
Pneumonia, recurrent†
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain, onset at age >1 month
Wasting syndrome attributed to HIV§

* Only among children aged <6 years.
† Only among adults, adolescents, and children aged ≥6 years.
§ Suggested diagnostic criteria for these illnesses, which might be particularly important for HIV encephalopathy and HIV wasting syndrome, are described in the following references:
CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 1994;43(No. RR-12).
CDC. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992;41(No. RR-17).

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