06-ID-01

Committee: Infectious Disease

Title: Revision of the Surveillance Case Definition for HIV Infection Among Children age < 18 months

The purpose of this recommended revision to the surveillance case definition for perinatal HIV infection is to accommodate the advances and changes in clinical practice that have occurred in the evaluation and diagnosis of infants <18 months of age with perinatal exposure to HIV. Recommended revisions to the HIV surveillance case definition for children age <18 months at diagnosis primarily involve revisions to the presumptive uninfected category. No major revisions are proposed to the infected or definitively uninfected categories.

Exclusion of HIV infection either definitively or presumptively (see Appendix A) for surveillance purposes does not mean that one can absolutely rule out HIV infection clinically. These categories are used for surveillance classification purposes and statistical reporting and should not be used to guide clinical practice. A perinatally HIV-exposed child should continue to be followed clinically according to nationally accepted treatment and care guidelines (e.g., http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf and http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf). Follow up is needed for the purposes of 1) monitoring for potential complications of exposure to antiretrovirals during the perinatal period and 2) to definitively rule out HIV infection clinically.

Statement of problem:

Since the most recent revision in the HIV surveillance case definition in 1999 (1) HIV viral detection testing technologies have improved such that HIV can be diagnosed or ruled out sooner after the delivery of an infant by an HIV-infected mother. In addition, data from the Enhanced Perinatal Surveillance (EPS) system reveal that a large percentage of infants born to HIV-infected mothers were classified with an "indeterminate" HIV status using the then current surveillance definition (32% indeterminate among EPS births from 1999-2001) (2).

In light of these advances in diagnostic technology and the apparent inability of the current surveillance case definition to adequately classify a large proportion of HIV-exposed infants, the CDC held a perinatal HIV surveillance case definition consultation in April of 2005 to review the components of the perinatal HIV surveillance case definition for children age <18 months. The goals of this consultation were to:

a) review the current HIV perinatal surveillance case definition and the proposals for revision
b) review evidence for changes that would simplify and improve the perinatal HIV surveillance case definition based on current scientific evidence, and ultimately

c) provide recommendations for the revision of the perinatal HIV surveillance case definition.

Consultation participants included domestic and international experts in HIV surveillance, pediatric infectious disease, immunology, HIV testing technologies, and community advocacy. In addition to CDC participants, consultants represented CSTE; the World Health Organization; institutes, universities and schools of public health; hospitals; state health departments; national HIV/AIDS organizations; advocacy groups; and the Department of Health and Human Services. Upon conclusion of the consultation a plan was composed for guideline revision (see *Statement of Desired Action* below). If implemented, revisions applicable to this age group will supersede the 1999 *Revised Case Definition for HIV Infection* (accessible on the web at

http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4813a2.htm).

Statement of desired action to be taken:

CSTE recommends that CDC adopt the new HIV surveillance case definition for children age <18 months, as presented in Appendix A.

Public health impact:

All proposed changes to the HIV surveillance case definition for children <18 months of age are shown in Appendix A. The benefit of these changes is to reduce the number of indeterminate HIV cases among this age group. Minor formatting and wording modifications are proposed for the presumptive infected and definitive uninfected categories for children <18 months of age compared to the 1999 case definition. The only substantive changes are proposed for the presumptive uninfected category. The following paragraph compares the proposed HIV surveillance case definition for this category to the 1999 HIV surveillance case definition for children < 18 months of age.

For the presumptive uninfected category, CSTE proposes the inclusion of the following criterion:

1) Two negative RNA or DNA virologic tests, one of which was performed at ≥ 30 days of age (This criterion is not included in the 1999 case definition).

CSTE also proposes the modification of two criteria for the presumptive uninfected category:

1) One negative HIV virologic test performed at ≥ 8 weeks of age (1999 criteria: one negative HIV virologic test performed at ≥ 4 months of age);

or

2) One positive HIV virologic test with at least two subsequent negative tests, one of which is either a virologic test at ≥ 8 weeks or age, or a negative antibody test at ≥6 months of age (1999 criteria: One positive HIV virologic test with at least two subsequent negative virologic tests, at least one of which is ≥ 4 months or age; or negative HIV antibody test results, at least one of which is ≥ 6 months of age).

CSTE also proposes the addition of the phrase "with an indeterminate infection status" to proposed category IIC (1999 category IV) for perinatal exposure.

Table 1 indicates all definitive and presumptive infected (diagnosed HIV, not AIDS), definitive and presumptive uninfected, and indeterminate cases of HIV infection among children <18 months of age from 1999-2003 by birth year reported to the HIV/AIDS Reporting System. The table's "Current (before)" rows satisfy the current case definition based on infant HIV infection status and birth year. The "After Proposed Changes" rows take into account the proposed case definition changes (see Appendix A) based on infant HIV infection status and birth year. The highlighted rows indicate the impact of the proposed case definition changes by year. These data indicate that from 1999-2003, the percent of indeterminate cases would decrease from 28% to 20% with a corresponding increase in the number of presumptive uninfected cases (from 9% to 17%) when taking into account the proposed case definition changes. There are no changes to the definitive infected, presumptive infected and definitive uninfected cases with the proposed changes to the case definition. This suggests that a moderate reduction of children <18 months of age of indeterminate HIV status can be attained in the HIV/AIDS Reporting System with implementation of the proposed revision of the perinatal HIV surveillance case definition. This revision does not recommend a change in the AIDS case definition for children age < 18 months. Perinatally HIV-exposed children < 18 months of age who meet the AIDS case definition for this group will still be considered HIV-infected because of the greater ambiguity associated with diagnostic testing for HIV in this population.

Table 1. Number and percentage of infants <18 months of age by infant birth year and HIV infection status before and after proposed case definition changes —1996-2003

	Infection Status	Year of Birth										Total	
		1996-1999		2000		2001		2002		2003			
		N	%	N	%	N	%	N	%	N	%	N	%
Current (before)	Definitive +	857	8.65	142	4.57	120	4.20	85	3.34	55	2.50	1259	6.11
	Presumptive +	125	1.26	29	0.93	29	1.01	20	0.79	19	0.87	222	1.08
	Definitive -	5525	55.76	1857	59.73	1635	57.21	1417	55.63	1032	46.99	11466	55.61
	Presumptive -	**969**	**9.78**	**229**	**7.37**	**224**	**7.84**	**220**	**8.64**	**181**	**8.24**	**1823**	**8.84**
	Indeterminate	**2433**	**24.55**	**852**	**27.40**	**850**	**29.74**	**805**	**31.61**	**909**	**41.39**	**5849**	**28.37**
After Proposed Changes	Definitive +	857	8.65	142	4.57	120	4.20	85	3.34	55	2.50	1259	6.11
	Presumptive +	125	1.26	29	0.93	29	1.01	20	0.79	19	0.87	222	1.08
	Definitive -	5525	55.76	1857	59.73	1635	57.21	1417	55.63	1032	46.99	11466	55.61
	Presumptive -	**1652**	**16.67**	**461**	**14.83**	**509**	**17.81**	**411**	**16.14**	**441**	**20.08**	**3474**	**16.85**
	Indeterminate	**1750**	**17.66**	**620**	**19.94**	**565**	**19.77**	**614**	**24.11**	**649**	**29.55**	**4198**	**20.36**

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References

1. CDC. Guidelines for national human immunodeficiency virus case surveillance, including monitoring for human immunodeficiency virus infection and acquired immunodeficiency syndrome. MMWR 1999;48 (No. RR-13):1-32

2. CDC. Enhanced Perinatal Surveillance—United States, 1999–2001. Atlanta: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2004: [page 20]. Special Surveillance Report 4.

Attachment: Appendix A: Proposed surveillance case definition for HIV infection for children age <18 Months

Appendix A

Proposed Surveillance Case Definition for HIV Infection
For Children Age <18 Months

These revised definitions of HIV infection supersede those published in 1999 (1), apply to any variant of HIV (e.g., HIV-1 and HIV-2), and are intended for public health surveillance only. These definitions are not presented as a guide to clinical diagnosis or for other uses.

Revised laboratory criteria for children aged <18 months at diagnosis include revisions to the presumptive uninfected category. This revised definition takes into account more recent data related to use of newer testing technologies. No change was made to exclude conditions that meet criteria included in the 1987 pediatric surveillance case definition for AIDS for children aged less than eighteen months. Exclusion of HIV infection either definitively or presumptively (see boxes below) for surveillance purposes does not mean that one can absolutely rule out HIV infection clinically. In addition, for the purposes of calculating exact timing of tests based on the surveillance case definition, a one-month interval corresponds to 30 days.

II. For children under 18 months of age
A. A child aged less than 18 months born to an HIV-infected mother will be categorized for surveillance purposes as "HIV infected" if the child meets at least one of the following criteria:

Definitive Infected

Laboratory Criteria

Positive results on two separate specimens (excluding cord blood) using one or more of the following HIV virologic (nonantibody) tests:

- HIV nucleic acid (DNA or RNA) detection
- HIV p24 antigen test, including neutralization assay, in a child greater than or equal to 1 month of age
- HIV isolation (viral culture)

Presumptive Infected

Laboratory Criteria

A child who does not meet the criteria for definitive HIV infection but who has:

Positive results on only one specimen (excluding cord blood) using the above HIV virologic tests and no subsequent negative HIV virologic or negative HIV antibody tests

OR

Clinical or Other Criteria (if the above definitive or presumptive laboratory criteria are not met and child is born to an HIV-infected mother)

Diagnosis of HIV infection, based on the laboratory criteria above, that is documented in a medical record by a physician	or	When diagnostic testing for HIV infection or the results of such testing is not available, having conditions that meet criteria included in the 1987 pediatric surveillance case definition for AIDS

II. For children under 18 months of age (cont'd)

B. A child aged less than 18 months born to an HIV-infected mother will be categorized for surveillance purposes as "uninfected with HIV" if the child does not meet the criteria for HIV infection but meets the following criteria.

Definitive uninfected

Laboratory Criteria

Virologic testing: At least two negative HIV virologic tests*** from separate specimens, both of which were performed at greater than or equal to 1 month of age and one of which was performed at greater than or equal 4 months of age	or	Serologic testing: At least two negative HIV antibody tests from separate specimens obtained at greater than or equal to 6 months of age

AND

No other laboratory or clinical evidence of HIV infection (i.e., has not had any positive virologic tests, if performed, and has not had an AIDS defining condition)

Presumptive uninfected

Laboratory Criteria

A child who does not meet the above criteria for definitive "uninfected" status but who has:

Two negative RNA or DNA virologic tests* one of which was performed at greater than or equal to 30 days of age;	or	One negative RNA or DNA virologic tests* performed at greater than or equal to 8 weeks of age	or	One negative EIA HIV antibody test performed at greater than or equal to 6 months of age	or	One positive HIV virologic test with at least two subsequent negative tests, one of which is either a virologic test at greater than or equal to 8 weeks of age, or a negative HIV antibody test at greater than or equal to 6 months of age

AND

No other laboratory or clinical evidence of HIV infection (i.e., has not had an opportunistic infection for which there is no other underlying condition for immunosuppression and no subsequent positive virologic tests, if performed)

OR

Clinical or Other Criteria (if the above definitive or presumptive laboratory criteria are not met)

Determined by a physician to be "uninfected", and a physician has noted the results of the preceding HIV diagnostic tests in the medical record	**AND**	No other laboratory or clinical evidence of HIV infection (i.e., has not had any positive virologic tests, if performed, and has not had an opportunistic infection for which there is no other underlying condition for immunosuppression

II. For children under 18 months of age (cont'd)
C. A child aged less than 18 months born to an HIV-infected mother will be categorized as having perinatal exposure with an "indeterminate" infection status to HIV infection if the child does not meet the criteria for HIV infection (II.A) or the criteria for "uninfected with HIV" (II.B).

*HIV nucleic acid (DNA or RNA) detection tests are the virologic methods of choice for the diagnosis or exclusion of infection in children less than 18 months. Although HIV culture can be used for this purpose, it is more complex, less well standardized, and less sensitive than nucleic acid detection tests. The use of p24 antigen testing to exclude infection in children aged less than 18 months is not recommended because of poor sensitivity, especially in the presence of HIV antibody. Over the past decade, commercial tests for RNA and DNA detection have become available. Quantitative RNA tests are FDA-approved for monitoring HIV infection and qualitative RNA tests are approved for blood donor screening. The quantitative and qualitative RNA tests meet FDA standards of high analytic and clinical sensitivity and specificity [2-4]. All the commercial tests detect the major (M) subtypes of HIV-1 as well as most O-subtypes. They do not detect HIV-2. Because of the possibility of mutation/recombination involving the target sequences detected by a particular test, an occasional specimen in an individual may not be detected. If suspicion is high and results are negative, it may be prudent to test with another test.

Reference List

1. CDC. Guidelines for national human immunodeficiency virus case surveillance, including monitoring for human immunodeficiency virus infection and acquired immunodeficiency syndrome. MMWR 1999;48 (No. RR-13):1-32

2. Peter JB, Sevall JS. Molecular-based methods for quantifying HIV viral load. AIDS Patient Care and STDs 2004;18:75-79.

3. Lelie PN, van Drimmelen HAJ, Cuypers HTM, et al. Sensitivity of HCV RNA and HIV RNA blood screening assays. Transfusion 2002;42:527-536.

4. Gallarda JL, Dragon E. Blood screening by nucleic acid amplification technology: current issues, future challenges. Molecular Diagnosis 2000;5:11-22.