

## **Interim recommendations for the use of the BED capture enzyme immunoassay for incidence estimation and surveillance**

Statement from the Surveillance and Survey and the Laboratory working groups to the Office of the Global AIDS Coordinator.

### Overview

The BED capture enzyme immunoassay (BED-CEIA) measures the increasing proportion of HIV-1 IgG to total IgG after seroconversion to estimate HIV-1 incidence in a population.<sup>1</sup> In December 2005, the UNAIDS Reference Group on Estimates, Modeling and Projections issued a statement in response to preliminary data on the application of the BED-CEIA in HIV surveillance settings and selected validation studies which demonstrated that the assay overestimated HIV-1 incidence by misclassifying a number of individuals with long-term infection as recent infection in cross-sectional settings.<sup>2</sup> This misclassification effect is particularly severe in settings with high HIV prevalence and may vary by HIV-1 subtype. UNAIDS recommended that the assay not be used for routine HIV surveillance at present and called for further validation of the assay to improve specificity.

On May 9 – 10, 2006, the Surveillance and Survey and Laboratory working groups reviewed new study results and proposed adjustment factors to estimate HIV-1 incidence using the BED-CEIA. Data were presented from China, Cote d'Ivoire, South Africa, Thailand, Uganda, the United States, and Zimbabwe to address the concerns expressed by UNAIDS.

Based on its review of the study results, the working groups developed the following interim recommendations for organizations using the BED-CEIA for the estimation of HIV-1 incidence in cross-sectional serosurveys, intervention designs, and case-based surveillance in U.S. government-supported activities. In summary:

- The BED-CEIA can be used to estimate HIV-1 incidence if appropriate adjustments are made and appropriate experts consult on the methods in the following settings:
  - Sentinel or population-based serosurveys
  - Evaluation of HIV-1 prevention interventions
- The BED-CEIA can be used to estimate HIV-1 incidence in case-based HIV surveillance systems only under certain circumstances.

The working groups expect that both laboratory tests and the statistical methods which support the use of these tests will be improved substantially in coming months and years. Interim recommendations will be revised accordingly.

### Cross-sectional serosurveys

The BED-CEIA can be used to estimate HIV-1 incidence in cross-sectional serosurveys, including sentinel surveillance surveys among antenatal clinic (ANC) attendees or other populations, and population-based surveys. However, the data must be adjusted to account for the misclassification of individuals with long-term infection identified as recent infections (false recent) by the BED-CEIA.

The working groups reviewed two adjustment formulas. A summary of these adjustment formulas is included in Attachment #1.<sup>3,4</sup> The working groups advise use of both adjustments to develop separate incidence measures and allow for cross-checking of results for consistency.

The method described by McDougal et al. uses an adjustment for both short-term ( $\leq 310$  days) false long-term and recent cases, as well as an adjustment for longer term ( $>310$  days) false

recent individuals. The method by Hargrove et al. uses an adjustment for long-term (>365 days) false recent cases. The two sets of adjustments are expected to give similar results in most settings. Both adjustments have limited validation with only subtype B and C. In the event that they do not agree, the Surveillance and Survey and Laboratory Working groups will work with each country in interpreting results.

The adjustment factors are optimal in populations where no or few HIV-infected individuals are currently on antiretroviral therapy (ART). In populations where there is wide use of ART, every effort should be made to identify and exclude from the analysis all individuals using ART in the population, as ART use may be associated with substantial misclassification as recent infection. When analyzing trends over time in serial cross-sectional surveys (including from surveillance systems) the issue of misclassification of people on ART may be particularly relevant, as ART use is rapidly increasing in many countries.

Because the assay may vary with different HIV-1 subtypes, when possible, values for the adjustment factors should be estimated on populations with HIV-1 subtypes similar to the population under observation. This entails identification of long-term infections from other studies and application of the BED-CEIA to determine the proportion of false recent cases. When this cannot be done, the published adjustment factors may be used but should be interpreted cautiously as generalization to multiple countries and populations remains unclear.

Technical assistance (TA) is required to ensure proper application of the BED-CEIA. The Surveillance and Survey and the Laboratory working groups will provide the following TA:

- Assistance with the design of the survey to ensure that the appropriate population is sampled and data variables are collected;
- Identification of local factors contributing to misclassification of long-term infections as recent infections in the survey;
- Determination of appropriate values for local adjustment factors;
- Assistance in the application of adjustment factors to estimate HIV-1 incidence; and
- Development of quality control and quality assurance plans.

#### Intervention designs

The BED-CEIA can be used in intervention designs to measure the impact of a prevention intervention on HIV-1 incidence. Using the same methods described above for serosurveys, BED-CEIA data must be adjusted for the misclassification of individuals with long-term infection falsely identified as recent infections. The adjustment factors used should be consistent in each of the comparison arms. Adjustments may produce biased estimates for the study population; however, as long as the same adjustments are used for each intervention group and the interventions do not result in different levels of ART use, the biases are expected to be similar and the measured difference should reflect a difference in incidence.

Use of the BED-CEIA to estimate HIV-1 incidence in other specimen sets (e.g., voluntary counseling and testing sets, or blood donors) requires additional adjustments to remove biases caused by frequency and motivation for testing to avoid underestimating or overestimating HIV-1 incidence.

#### Case-based HIV surveillance

The BED-CEIA can be used to estimate HIV-1 incidence in case-based HIV-1 surveillance if the following conditions are met:

- High coverage (minimum of 85% of HIV-1 cases reported);

- Accurate coverage (<5% duplicate reports);
- Timely reporting (>66% within six months of diagnosis);
- Data are available on individual cases including clinical staging at diagnosis (CD4 results and AIDS status);
- Testing history (interval frequency and motivation); and
- Use of ARVs.<sup>5,6</sup>

If these essential conditions are not met, the working groups advise against using the case-based surveillance for estimating HIV-1 incidence and suggest using cross-sectional serosurveys instead.

#### Additional interim recommendations

- The BED-CEIA assay should never be used to determine the recency of infection in an individual. The method is appropriate only for larger scale studies of the types described here and data are to be interpreted only in aggregate. BED-CEIA incidence data will be particularly useful in comparing differences in HIV-1 incidence between sub-populations and changes in incidence over time.
- BED-CEIA incidence estimates should be applied only to the populations on which they are based. Extrapolation to larger populations should be done only when supported by ancillary data that show the extrapolations to be valid. At present, data are not currently available to allow incidence estimates from targeted surveys to be generalized to the entire population of a country.
- All studies, whether cross-sectional serosurveys, case-based surveillance, or serial cross-sectional studies must have an adequate sample size in order to provide a valid measure of HIV-1 incidence to support the conclusions to be drawn.
- Only specimens with confirmed HIV-1 infection should be tested with the BED-CEIA. Individuals with HIV-2 infection but without HIV-1 infection should be excluded from all studies to avoid the potential for even larger misclassification of results. Specimens should be collected, processed and stored optimally and cold chain should be maintained if transported to another laboratory for testing. Strict quality control and quality assurance measures should be adopted to ensure valid and accurate results.<sup>7,8</sup>
- When possible, serosurveys and studies should measure factors that may impact the interpretation of BED-CEIA results. These factors include long-term history of known HIV infection, symptoms of immunosuppression and use of ART. The BED-CEIA should not be used on specimens known to originate from persons known to be on treatment or to be severely immunosuppressed except as part of a validation study.

#### Future Research

Additional work is underway to improve the quality and reliability of the laboratory methods for the direct estimation of HIV-1 incidence. Further work also is being done to refine and validate the adjustments to estimate HIV-1 incidence in both simple and complex survey designs and to determine which factors most influence misclassification in different populations.

Validations of the adjustment factors are ongoing in cohort studies with directly observed incidence and individual-level data on ART use over time. Further validation is required for methods which attempt to correct for the misclassification of people on ART as recent infection in settings where individual-level data on ART use are not available.

#### Contact information

Please contact Dr. Bharat Parekh (BParekh@cdc.gov) of the CDC, Global AIDS Program, International Laboratory Branch or Dr. Andrea Kim (AAKim@cdc.gov) of the CDC, Global AIDS Program, Epidemiology and Strategic Information Branch for further information, including:

- Training on laboratory and epidemiological procedures for the BED-CEIA assay ;
- Incidence estimation; and
- In-country laboratory and epidemiological technical assistance for implementing the BED-CEIA assay for incidence estimation and surveillance and application of adjustment factors.

### References

1. Parekh B, Kennedy S, Dobbs T, et al. Quantitative Detection of Increasing HIV Type 1 Antibodies after Seroconversion: A Simple Assay for Detecting Recent HIV Infection and Estimating Incidence. *AIDS Research and Human Retroviruses* 2002; 18(4): 295-307.
2. UNAIDS. Statement on the use of the BED-assay for the estimation of HIV-1 incidence for surveillance or epidemic monitoring. Report of a meeting of the UNAIDS Reference Group for Estimates, Modelling and Projections. Athens, Greece, December 13-15th 2005. Geneva: [UNAIDS] 2005.
3. McDougal JS, Parekh, BS, Peterson ML, et al. Comparison of HIV-1 incidence observed during longitudinal follow-up with incidence estimated by cross-sectional analysis using the BED capture enzyme immunoassay. *AIDS Research and Human Retroviruses* 2006; 22(10): 945-52.
4. Hargrove J, Humphrey J, Mutasa K, et al. Improved HIV-1 incidence estimates using the BED Capture Enzyme Immunoassay (in CDC clearance review).
5. Mortality and Morbidity Weekly (MMWR). Guidelines for National Human Immunodeficiency Virus Case Surveillance, including Monitoring for Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome. Dec 10, 1999. 48 (RR13); 1-28.
6. Karon JM, Song R, Kaplan E, et al. Estimating HIV Incidence in the United States from HIV/AIDS surveillance data and less-sensitive HIV test results (Submitted to Statistics and Medicine).
7. Dobbs T, Kennedy S, Pau CP, et al. Performance Characteristics of the Immunoglobulin G-Capture BED-Enzyme Immunoassay, An Assay to Detect Recent Human Immunodeficiency Virus Type 1 Seroconversion. *Journal of Clinical Microbiology* 2004; 42(6):2623-2628.
8. Calypte® Biomedical Corporation. Package Insert: Calypte® HIV-1 BED Incidence EIA (IgG-Capture HIV-EIA), 2005.

### Attachments

1. BED-CEIA incidence and adjustment formula.doc