CDC HIV/AIDS Science Facts:

Using the BED HIV-1 Capture EIA Assay to Estimate Incidence Using STARHS in the Context of Surveillance in the United States

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BACKGROUND

UNAIDS issued a statement in December 2005 stating that the BED HIV-1 Capture EIA should not be used for routine surveillance applications [1]. This statement was developed following release of data from Africa and Thailand comparing incidence rates using the BED assay with the serologic testing algorithm for recent HIV seroconversion (STARHS) compared with incidence rates using other methods including modeling and prospective studies. The comparisons suggest that the assay overestimates the proportion of specimens that are deemed "recent."

This document outlines concerns about the assay and how the circumstances in the US for using the assay with STARHS to estimate incidence of HIV in the US population address these concerns. Additional concerns not listed here may apply to international settings.

Overestimation may arise in the following areas:

1. The BED Assay: The assay detects levels of anti-HIV IgG relative to total IgG and is based on the observation that the ratio of anti-HIV IgG to total IgG increases with time after HIV infection. If a confirmed HIV-1 positive specimen is reactive on the standard sensitive EIA and has a normalized optical density of <0.8 on the BED assay, it is considered recently infected. A "false-recent" result can occur under the following circumstances:

   a. False-positive EIAs not confirmed with an HIV-1 Western blot or IFA (i.e., diagnostic algorithms with poor specificity)
      - Circumstances in the US surveillance system: STARHS (using BED) is done only on cases where the specimen is confirmed HIV-1 antibody positive using a Western blot or IFA confirmatory test.

   b. Poor specimen handling during processing or shipping
      - Circumstances in the US surveillance system: Laboratory quality control programs exist for laboratory accreditation in the US. Without this accreditation, laboratories cannot perform certain tests, including HIV antibody testing. Additionally, the HIV Incidence Surveillance System has detailed specimen storage, handling, and shipping procedures that laboratories follow in order to preserve specimen integrity.

   c. Chronic infection, inflammation, or hyper-gammaglobulinemia
      - Circumstances in the US surveillance system: Levels of chronic co-infection (and thus IgG) are low in the US. Therefore false-

recent results due to high IgG do not impact the assay's performance.

d. HIV subtype heterogeneity
   - Circumstances in the US surveillance system: HIV subtypes are relatively homogeneous in US population. Therefore false-recent results due to differences in window periods by subtype do not impact the assay's performance. Differences in window periods due to subtype heterogeneity are smaller for the BED compared with other assays used in STARHS.

e. Persons with advanced HIV disease (AIDS)
   - Circumstances in the US surveillance system: The US case-based surveillance system monitors several sentinel events over the life of an HIV case. In addition to HIV diagnosis, AIDS diagnosis is a reportable condition and is captured in the data collection system. STARHS results from cases with concomitant HIV and AIDS diagnoses are removed from the calculation of the incidence estimate.

f. Persons who have taken antiretroviral (ARV) agents 6 months before test
   - Circumstances in the US surveillance system: The US case-based surveillance system monitors several sentinel events over the life of an HIV case. In addition to HIV and AIDS diagnoses we collect information on ARV treatment. STARHS results from cases with a history of ARV use within 6 months before the diagnostic HIV test (for example, pre-exposure prophylaxis) are removed from the calculation of the incidence estimate.

2. Estimator: An additional source of error with STARHS is the estimator used to calculate incidence.

   a. An estimator must appropriately account for the type of sampling error present given the acquisition of specimens for STARHS testing. For example, specimens acquired from sexually transmitted disease clinics or antenatal care centers represent clients of those clinics and may not represent the general population or even the at-risk population. Specimens acquired from persons volunteering for HIV testing are likely not representative of persons who do not come forward for testing. It is important for the estimator to account for sampling bias.
      - Circumstances in the US surveillance system: The surveillance system in the US is case-based and receives data for all cases diagnosed regardless of clinic or venue of care. This yields a population-based sample of cases, eliminating the bias associated with clinic-based samples. However, bias can be introduced by differences among persons who volunteer for testing compared with those who do not. CDC statisticians have developed a method to accommodate our specific type of sampling bias. We will continue to evaluate the estimation method to ensure that it is providing the best possible estimate of the number of new HIV infections in the US.

   b. Additionally, measurement of the probability of being tested in the STARHS window period must be ascertained. This probability depends on testing behavior and is used in the calculation of incidence.

- Circumstances in the US surveillance system: CDC collects testing history information necessary to estimate the probability of being tested in the STARHS window period.

CONCLUSION

The BED HIV-1 Capture EIA was developed for and is solely used in the US in the context of HIV incidence surveillance. The BED in combination with the appropriate estimator is the preferred approach to calculating incidence of HIV infection in the US [2, without additional adjustment 3] and may be used in conjunction with information from additional sources (triangulation studies) to corroborate findings. The assay was validated in the laboratory, comparing favorably with the results of previous assays used in STARHS. The use of the assay must occur in the context of a case-based surveillance system where additional clinical and epidemiologic information is available for interpretation and estimation. It may be less successful in a specimen-based system where these critical data cannot be ascertained. Additional studies to determine false recent rates (e.g., among healthy, known long-term infected individuals who are not on ARV) may provide information to improve the accuracy of incidence estimates, and efforts to validate assay-based estimates with observed incidence will also continue.

REFERENCES

1. 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, Modeling and Projections. Athens, Greece, December 13-15th 2005. Geneva: [UNAIDS] 2005. Statement following a meeting of the UNAIDS Reference Group for Estimates, Modelling and Projections held in Athens, Greece, December 13th 2005. Uploaded December 2005.
2. Karon JM, Song R, Brookmeyer R, Kaplan EH, Hall HI. Estimating HIV incidence in the United States from HIV/AIDS surveillance data and biomarker HIV test results (in preparation).
3. McDougal JS, Parekh BS, Peterson ML, et al. Comparison of HIV type 1 incidence observed during longitudinal follow-up with incidence estimated by cross-sectional analysis using the BED capture enzyme immunoassay. *AIDS Res Hum Retroviruses* 2006; 22:945-952.

LINKS

UNAIDS Reference Group on Estimates, Modelling and Projections' Statement on the Use of the BED-Assay for the Estimation of HIV-1 Incidence for Surveillance or Epidemic Monitoring, available at http://data.unaids.org/pub/EPISlides/2006/Statement_BED_Policy_13Dec05_en.pdf

Statement from the Surveillance and Survey and the Laboratory Working Groups to the Office of the Global AIDS Coordinator: Interim Recommendations for the Use of the BED Capture Enzyme Immunoassay for Incidence Estimation and Surveillance, available at http://www.cdc.gov/nchstp/od/GAP/docs/surveillance/Interim%20Recommendations%20for%20the%20use%20of%20the%20BED%20capture%20enzyme%20immunoassay%20for%20incidence%20estimation%20and%20surveillance%20Approved%20November%2021%202006%20(2).pdf