Seroincidence of Recent Human Immunodeficiency Virus Type 1 Infections in China

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A subtype B, E, and D immunoglobulin G capture immunoassay shows promise as a tool for estimating human immunodeficiency virus type 1 seroincidence from cross-sectional surveys, but the test-specific limitations suggest that an adjustment is necessary, and further validation of the assay with populations with divergent subtypes is needed.

Knowledge of human immunodeficiency virus (HIV) seroincidence could help in distinguishing between recent and long-term HIV infections, identifying recent trends or “hot spots,” guiding better-informed prevention, care, and treatment, and determining areas or populations that are appropriate for vaccine, microbicide, and other prevention clinical trials; therefore, measuring HIV seroincidence has become increasingly important. However, the seroincidence is difficult to measure, and this has traditionally relied on the prospective testing and longitudinal follow-up of people at risk (2, 9, 20, 24). Estimation of the incidence by prospective studies faces challenges of bias, logistics, and high cost (2, 17). Laboratory assays to determine recent infection, such as p24 or HIV-1 RNA assays, require screening of large numbers of seronegative individuals to identify those in the very short “window period” (2). The less-sensitive enzyme immunoassays (EIAs) for detection of recent HIV type 1 (HIV-1) infection using cross-sectional surveys were designed based only on subtype B antigens (15, 18, 21, 26). An HIV-1 subtypes B, E, and D immunoglobulin G capture immunoassay (BED-CEIA) overcomes the disadvantages of less-sensitive EIAs and is designed to detect various HIV-1 subtypes (4, 12, 22, 23). Data demonstrated that this assay was useful for estimating seroincidence from a range of different HIV-1 subtypes using cross-sectional surveys (3, 6, 10, 13, 14, 15a, 19, 25; E. Karita, O. Manigart, G. Stevens, S. Allen, E. Hunter, M. Price, P. Fast, W. Stevens, N. Ketter, and the Rwanda-Zambia HIV Research Project, presented at the AIDS Vaccine Conference, Montréal, Canada, 6 to 9 September 2005). BED-CEIA has not been validated in China, where many disparate HIV-1 subtypes are circulating, including A, B, B’ (Thai B), C, D, F, G, circulating recombinant form 01_AE (CRF01_AE), CRF07_BC, and CRF08_BC (27). Therefore, we evaluated the performance of BED-CEIA among injection drug users (IDUs) in China.

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A total of 1,955 serospecimens from IDUs who tested HIV-1 seropositive from 2002 to 2005 were tested using the BED-CEIA. The 1,955 specimens included 29 from known seroconverters identified by weekly EIA (Kinghawk, Beijing, China) and reverse transcription-PCR (HIV-1/2 antibody assay; Kinghawk, Beijing, China) tests and 300 seropositive specimens from persons known to be infected for ≥2 years. All seropositive specimens were prescreened by EIA (Vironostica HIV-Uni-Form II plus 0; BioMerieux) and confirmed with Western blotting (HIV Blot 2.2; Genelabs Diagnostics). CD4+ cell counts were determined using flow cytometric analysis (FACScan, Becton-Dickinson, Heidelberg, Germany) (5, 8). We performed BED-CEIA (Cyntel Biomedical Corporation, Rockville, MD) using the algorithm of a single screening test and triple confirmatory tests to determine recent seroconversions. (11, 16, 19, 22). We calculated the cumulative, annualized incidence observed in the HIV Prevention Trials Network (HPTN) 033 Xinjiang cohort (unpublished data) by dividing the number of seroconversions (n = 29) by person-years. A 95% confidence interval was calculated for the observed incidence, assuming a Poisson distribution. In addition, a cross-sectional study randomly recruited 1,170 participants concurrently with the HPTN033 Xinjiang cohort amid the same IDU population; HIV positivity was determined by EIA screening test and confirmed by Western blotting. The BED-CEIA HIV-1 incidence was calculated as follows: \( I = \frac{(365/W)\text{Ninc}}{\text{Nneg} + (365/W)\text{Ninc}/2}) \times 100, \) where Ninc is the number of recent infections as determined by BED-CEIA, Nneg is the total number of HIV-seronegative subjects, and W is the mean window period of the assay, assumed to be 153 days (6, 16, 17, 20).
misclassification in our incidence estimate, because we did not know the proportion of the persons infected for ≥2 years in the pool of cross-sectionally obtained serospecimens. Limitations of our study also include our inability to characterize the specificity of results for those infected for 1 to 2 years. Thus, modeling is needed to adjust for the misclassification of individuals with long-term infection falsely identified as recent infections. Further validation of this assay with additional Chinese and other populations with divergent subtypes is needed.

We have presented the first step in validating the use of the BED-CEIA in China to identify recent infections. Definitive validation of the BED-CEIA should use larger panels of seroconverters from geographic areas where different subtypes are circulating. Cohorts should include persons with both early and late HIV infections and should be accompanied by epidemiological data to permit the exploration of reasons for false positives (e.g., low CD4+ cell counts, HIV antiretroviral therapy, and treatment of hepatitis B). The BED-CEIA shows promise for measurement of HIV-1 incidence by cross-sectional surveys in China, where the vastness of the country and the wide diversity of HIV transmission make targeted interventions for the areas and subpopulations of greatest need a more cost-efficient disease control strategy.

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REFERENCES
1. Bishop, Y. M. M., S. E. Fienberg, and P. W. Holland. 1975. Discrete multivariate analysis: theory and practice, section 14.6. MIT Press, Cambridge, MA.
2. Brookmeyer, R., and T. Quinn. 1995. Estimation of current human immunodeficiency virus incidence rates from a cross-sectional survey using early diagnostic tests. Am. J. Epidemiol. 141:166–172.
3. Bulterys, M., A. Chao, A. Dushimimana, and B. Parekh. 2004. Unsafe injections and transmission of HIV-1 in sub-Saharan Africa. Lancet. 363:1650.
4. Carr, J., M. Salminen, C. Koch, D. Gottle, A. Artenstein, P. Hegeirch, D. St Louis, D. Burke, and F. McGettigan, 1996. Full-length sequence and mosaic structure of a human immunodeficiency virus type 1 isolate from Thailand. J. Virol. 70:5935–5943.
5. CDC. 1997. Revised guidelines for performing CD4+ T-cell determinations in persons infected with human immunodeficiency virus (HIV). Morb. Mortal. Wkly. Rep. Recomm. Rep. 46:1–29.
6. CDC. 2005. HIV-1 BED incidence EIA laboratory training manual. CDC, Atlanta, GA.
7. Reference deleted.
8. China Center for Disease Control and Prevention. 2004. National Guideline for Detection of HIV/AIDS. China Center for Disease Control and Prevention, Beijing, China.
9. Cleghorn, F., N. Jack, J. Murphy, J. Edwards, B. Mahabir, R. Paul, T. O’Brien, M. Greenberg, K. Weinhold, C. Bartholomew, R. Brookmeyer, and W. Blattner. 1998. Direct and indirect estimates of HIV-1 incidence in a high-prevalence population. Am. J. Epidemiol. 147:834–839.
10. de Freitas Oliveira, C., M. Ueda, R. Yamashiro, R. Rodrigues, H. Sheppard, and L. de Macedo Brigido. 2005. Rate and incidence estimates of recent human immunodeficiency virus type 1 infections among pregnant women in Sao Paulo, Brazil, from 1991 to 2002. J. Clin. Microbiol. 43:1439–1442.
11. Dobbs, T., S. Kennedy, C. Pau, J. McDougal, and B. Parekh. 2004. Performance characteristics of the immunoglobulin G-capture BED-enzyme immunoassay, an assay to detect recent human immunodeficiency virus type 1 seroconversion. J. Clin. Microbiol. 42:2623–2628.
12. Gao, F., D. Robertson, S. Morrison, H. Hui, S. Craig, J. Decker, P. Fultz, M. Ackers, and M. Gurwith. 1996. The heterosexual human immunodeficiency virus type 1 epidemic in Thailand is caused by an inter-subtype (A/E) recombinant of African origin. J. Virol. 70:7013–7029.
13. Gupta, P., L. Kingsley, H. Sheppard, L. Harrison, R. Chatterjee, A. Ghosh, P. Roy, and D. Neogi. 2003. High incidence and prevalence of HIV-1 infection in high risk population in Calcutta, India. Int. J. STD AIDS 14:463–466.
14. Hu, D., S. Vanichseni, P. Mock, N. Young, T. Dobbs, and R. Byers. 2003. HIV-1 incidence estimates by detection of recent infection from a cross-sectional sampling of injection drug users in Bangkok: use of the IgG capture BED enzyme immunoassay. AIDS Res. Hum. Retrov. 19:727–730.
15. Janssen, R., G. Satten, S. Trister-Greenval, B. Parekh, T. O’Brien, B. Weihlen, F. Hecht, N. Jack, F. Cleghorn, J. Kahn, M. Chesney, and M. Busch. 1998. New testing strategy to detect early HIV-1 infection for use in incidence estimates and for clinical and prevention purposes. JAMA 280:42–48.
15a. Lee, L. M., and M. T. McKenna. 2007. Monitoring the incidence of HIV infection in the United States. Public Health Rep. 122(Suppl. 1):72–79.
16. McDougal, J. S., B. S. Parekh, M. L. Peterson, B. M. Branson, T. Dobbs, M. Ackers, and M. Gurwith. 2006. 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. Retrov. 22:455–458.
17. McDougal, J., C. Pilcher, B. Parekh, G. Gershy-Damet, B. Branson, K. Marsh, and S. Wiktor. 2005. Surveillance for HIV-1 incidence using tests for recent infection in resource-constrained countries. AIDS Res. Hum. Retrov. 21:525–530.
18. McFarland, W., M. Busch, T. Kellogg, B. Rawal, G. Satten, M. Katz, J. DiLely, and R. Janssen. 1999. Detection of early HIV infection and estimation of incidence using a sensitive/less sensitive enzyme immunoassay testing strategy at anonymous counseling and testing sites in San Francisco. J. Acquir. Immune. Defic. Syndr. 22:484–489.
19. Nesheim, S., B. Parekh, K. Sullivan, M. Bulterys, T. Dobbs, M. Lindsay, S. Cashat-Cruz, B. Byers, and F. Lee. 2005. Temporal trends in HIV type 1 incidence among inner-city childbearing women in Atlanta: use of the IgG-capture BED-enzyme immunoassay. AIDS Res. Hum. Retrov. 21:537–544.
20. Nokosesorn, T., P. Mock, T. Mastro, S. Sangkharamya, M. Sweat, K. Limpakarnjanarat, J. Laosakkithiboran, N. Young, S. Morse, S. Schmid, and B. Wenyiger. 1998. HIV-1 subtype E incidence and sexually transmitted diseases in a cohort of military conscripts in northern Thailand. J. Acquir. Immune. Defic. Syndr. Hum. Retroviroi. 18:372–379.
21. Parekh, B., D. Hu, S. Vanichseni, G. Satten, D. Candal, N. Young, D. Kitayaporn, L. Srisuwanvilai, S. Rakhtam, R. Janssen, K. Choopanya, and T. Mastro. 2001. Evaluation of a sensitive/less sensitive testing algorithm using the 3A11-LS assay for detecting recent HIV-1 seroconversion among individuals with HIV-1 subtype B or E infection in Thailand. AIDS Res. Hum. Retroviroi. 17:453–458.
22. Parekh, B., M. Kennedy, T. Dobbs, C. Pau, R. Byers, T. Green, D. Hu, S. Vanichseni, N. Young, K. Choopanya, T. Mastro, and J. McDougal. 2002. Quantitative detection of increasing HIV type 1 antibodies after seroconversion: a simple assay for detecting recent HIV infection and estimating incidence. AIDS Res. Hum. Retroviroi. 18:295–307.
23. Parekh, B., and J. McDougal. 2001. New approaches for detecting recent HIV-1 infection. AIDS Rev. 3:183–193.
24. Vanichseni, S., D. Kitayaporn, T. Mastro, P. Mock, S. Rakhtam, D. Des Jarlais, S. Sujarita, L. Srisuwanvilai, N. Young, C. Wasi, S. Subbarao, W. Heyward, L. Esparza, and K. Choopanya. 2001. Continued high HIV-1 incidence in a vaccine trial preparatory cohort of injection drug users in Bangkok, Thailand. AIDS 15:497–405.
25. Vonhnanak, S., B. Parekh, T. Dobbs, C. Mean, H. Leng, and R. Detels. 2005. Trends of HIV seroincidence among HIV sentinel surveillance groups in Cambodia. J. Acquir. Immune. Defic. Syndr. 39:587–592.
26. Young, C., D. Hu, R. Byers, S. Vanichseni, N. Young, R. Nelson, P. Mock, K. Choopanya, R. Janssen, T. Mastro, and J. Mei. 2003. Evaluation of a sensitive/less sensitive testing algorithm using the bioMerieux Vironostika-LS assay for detecting recent HIV-1 subtype B’ or E infection in Thailand. AIDS Res. Hum. Retroviroi. 19:481–486.
27. Zheng, G., and Y. Jia. 2007. The feasibility of measuring HIV-1 incidence using BED-capture enzyme immunoassay (BED-CEIA) in China. Chin. J. Nat. Med. 9:262–265.