

Multi-Assay Algorithm for Monitoring the HIV Pandemic's Leading Edge

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The HIV pandemic continues to evolve in a spatially and socially dynamic manner. After peaking in 1997, the average global incidence of HIV infections has dropped and stabilized to a certain degree (see figure). Nevertheless, national epidemics continue to grow in many parts of the world. For example, from 2001 to 2011 the rate of new HIV infections rose in Eastern Europe and Central Asia, and there was a concomitant shift in the primary route of infection in these regions from intravenous drug use to sexual transmission. Ongoing outbreaks of HIV are also occurring in the Middle East and North Africa (UNAIDS, 2012). Reliable methods for quantifying HIV incidence are needed to monitor the dynamic leading edge of the global pandemic. This, in turn, will facilitate the optimal allocation of key resources, such as prevention interventions and antiretroviral treatments, to populations at greatest risk.

Simply put, 'incidence' is the rate at which new cases of a disease occur in a population over a given time period. Though this valuable measure of risk sounds straightforward enough, its assessment is far from trivial, particularly in the case of HIV. In one approach for estimating incidence, a large HIV-uninfected cohort is monitored over a long period of time for HIV seroconversion, requiring large investments of time and money. However, the individuals at highest risk of infection are often the most difficult to follow. An alternative approach for estimating incidence measures the prevalence of acute HIV infections at essentially a single time point in a random cross-section of a focal population. The 'acute' period of HIV infection typically occurs 2-4 weeks after infection, and infections are classified as 'recent' for 5-6 months following infection. Though cross-sectional studies can be carried out more widely and rapidly than cohort studies, their limitations include brevity of the acute stage of HIV infection and the imprecision of any one serological method for detecting acute HIV infection.

Recently, Oliver Laeyendecker of the National Institute of Allergy and Infectious Diseases and Dr. Susan Eshleman of the Johns Hopkins University School of Medicine led a collaborative effort to develop a promising new algorithm for accurately detecting recent HIV infections in cross-sectional studies. A number of other scientists at different institutes contributed to this research, which is described in two papers jointly published in the *Journal of Infectious Diseases*, including Drs.

Deborah Donnell, James Hughes and Jing Wang of the Vaccine and Infectious Disease Division at the Fred Hutchinson Cancer Research Center.

The most widely used serological assay for detecting recent HIV infection is the BEDTM capture enzyme immunoassay (BED-CEIA). This assay measures the ratio of anti-HIV IgG to total IgG and estimates recent infection based on assumptions regarding a monotonic increase in this ratio following HIV infection. However, it is now known that the BED-CEIA frequently misclassifies individuals with long-standing HIV infection as being recently infected. Laeyendecker *et al.* describe a hierarchical, multi-assay algorithm (MAA) for identifying recent HIV infections that builds upon the BED-CEIA assay. In the MAA, two serological tests help cast a broad net for recent infections: the BED-CEIA, which tests the proportion of antibodies that are HIV specific, and an assay that measures the avidity, or binding strength, of HIV antibodies to certain HIV antigens. These assays are combined with measurements of HIV viral loads and CD4 cell counts, which help to exclude false positives. By re-analyzing stored plasma and serum from HIV infected individuals who participated in three cohort studies in the United States, Laeyendecker *et al.* found that the MAA is as sensitive as the BED-CEIA for detecting recent HIV infection. However, unlike the BED-CEIA, which can cause false-recent misclassification for up to several years after infection, the probability of appearing recently infected on the basis of the MAA converges to zero within one year.

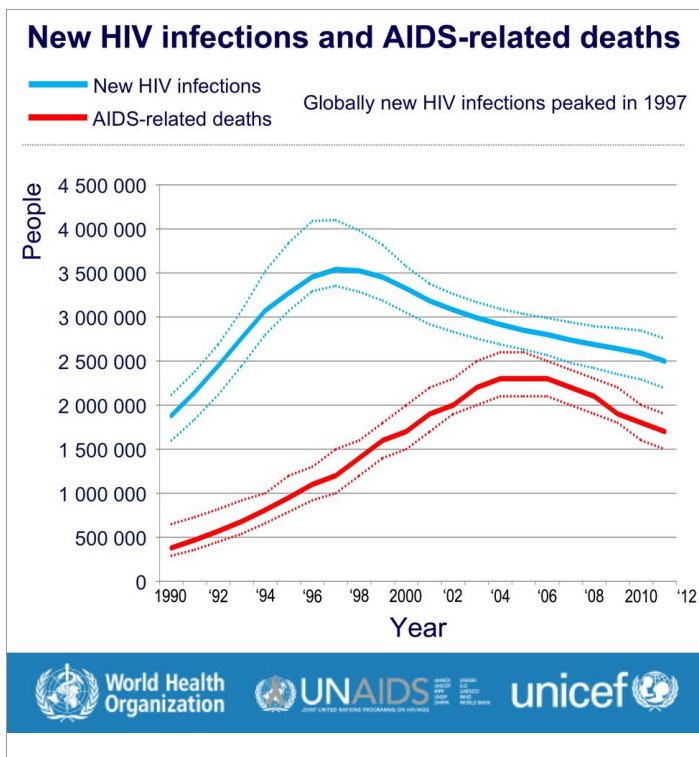
In the companion paper, Eshleman *et al.* validated the performance of the MAA in detecting recent HIV infection using data and samples from the HIV Prevention Trials Network (HPTN) 064 Study – a cohort study enrolling 2,099 women at high risk for HIV acquisition in the United States. This allowed for a direct comparison of HIV incidence observed longitudinally to that estimated cross-sectionally. Once again, the researchers found that the MAA did not suffer from a propensity to overestimate recent infections, which characterized other serological measures applied to samples from the HPTN 064 cohort. Moreover, HIV incidence estimated on the basis of a cross-sectional application of the MAA to these data closely matched the direct measurement of incidence on the basis of longitudinal seroconversion, although the number of seroconverters in this cohort was rather small.

While AIDS-related illnesses are still among the leading causes of death worldwide, there are reasons to be optimistic about many trends in the HIV pandemic. According to the 2012 UNAIDS World AIDS Day Report, between 2001 and 2011 the rate of new HIV infections dropped by more than 50% in the adult populations of 25 countries. Fortunately, the work by Laeyendecker *et al.* and Eshleman *et al.* now equips the epidemiologist's toolkit with a new monitoring instrument that will likely contribute to furthering these trends in the years to come.

[Laeyendecker O, Brookmeyer R, Cousins MM, Mullis CE, Konikoff J, Donnell D, Celum C, Buchbinder SP, Seage GR, Kirk GD, Mehta SH, Astemborski J, Jacobson LP, Margolick JB, Brown J, Quinn TC, Eshleman SH](#). 2012. HIV incidence determination in the United States: a multi-assay approach. *Journal of Infectious Diseases*, Epub ahead of print, doi:10.1093/infdis/jis659.

[Eshleman SH, Hughes JP, Laeyendecker O, Wang J, Brookmeyer R, Johnson-Lewis L, Mullis CE, Hackett J Jr, Vallari AS, Justman J, Hodder S](#). 2012. Use of a multi-faceted approach to analyze HIV incidence in a cohort study of women in the United States: HIV Prevention Trials Network 064 Study. *Journal of Infectious Diseases*, Epub ahead of print, doi:10.1093/infdis/jis658.

Also see: [UNAIDS](#). 2012. World Aids Day Report. Geneva, Switzerland: UNAIDS.



World Health Organization

Global annual incidence of new HIV infections (blue) and occurrence of AIDS-related deaths (red). The global peak in new HIV infections occurred in 1997, with the peak in AIDS-related deaths following eight years later.