Surveillance for Incident HIV Infection: New Technology and New Opportunities

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Summary: Although surveillance for HIV infection has traditionally focused on the incidence of AIDS and the prevalence of HIV, new diagnostic technologies that allow the estimation of incident HIV infection have become available. Number and distribution of new cases of HIV infection, rather than old cases, are the data most relevant to guide rational application of HIV prevention programs. Historically, incident HIV infection has been measured in longitudinal cohort studies, diagnosed clinically or since 1993 by detection of seroconverting patients (during the window period before appearance of HIV antibody) who are viremic as measured by p24 antigen or RNA-PCR. The sensitive-less sensitive EIA test (or serologic testing algorithm for recent HIV seroconversion [STAHRS]) has now made the serologic diagnosis of incident HIV infection in individual patients as well as the estimation of HIV incidence in populations possible. Examples of the public health application of this are studies of HIV incidence in anonymous test site attendees, sexually transmitted disease clinic patients, and in-treatment injection drug users in San Francisco. These sorts of studies allow us not only to measure incidence cross-sectionally but also facilitate surveillance for HIV subtypes and primary antiretroviral resistance, targeting early antiretroviral therapy and partner notification, and understanding who is “failing” prevention. Having an HIV surveillance system that focuses on incident rather than prevalent infection should be our long-term goal.


Surveillance is the traditional public health practice of determining the distribution of disease in human populations. Langmuir (1) defined surveillance as “the continuous observation of the distribution of and trends in the incidence of diseases through the systematic collection, consolidation and evaluation of reports of morbidity and mortality and other data” [emphasis added]. The most commonly cited purposes of surveillance are five-fold: to establish the epidemiology of a disease, to initiate public health control programs, to target prevention programs and resources, to evaluate the effectiveness of prevention and control programs, and to project the future numbers of cases of a disease (2). Thus, surveillance provides the strategic intelligence needed to guide public health programs rationally.

SURVEILLANCE FOR PREVALENT HIV INFECTION

Surveillance for HIV infection and AIDS has historically focused on surveillance for incident AIDS cases. The earliest surveillance system designed by the Centers for Disease Control and Prevention (CDC) (3) was designed to provide an accurate account of the numbers of new AIDS cases and, through the collection of AIDS-related mortality data, the prevalence of AIDS (often referred to as the number of persons living with AIDS).
Subsequently, the CDC encouraged states to begin surveillance for prevalent HIV infection (4), which in many states forms the backbone of the HIV/AIDS surveillance system. Although surveillance for prevalent HIV infection, in CDC’s words, “provide[s] a more timely measure to detect emerging patterns of HIV transmission, a more complete measure of the number of persons with HIV infection and disease, and a better mechanism to evaluate access to HIV testing and medical and prevention services than AIDS surveillance alone” (4), problems with underdiagnosis of asymptomatic HIV infection and underreporting of diagnosed HIV infection likely make this surveillance system inaccurate.

To illustrate this point, the CDC reported that at the end of 1998 of the 274,624 people living with AIDS in the United States 97,962 were from the 33 states plus the United States Virgin Islands that have surveillance systems for prevalent HIV infection (5). In the same 34 reporting areas 98,136 people were reported to be alive with HIV infection that had not yet progressed to AIDS at the end of 1998 (5). Assuming that the distribution of HIV infections is approximately the same as the distribution of AIDS cases in the United States (97,962/274,624), 35.7 percent of non-AIDS HIV infections in the United States should be coming from these 34 states and territory, and the national estimate of non-AIDS HIV infection would be 275,112. Thus, the total number of HIV infections, including AIDS, would be 275,112 non-AIDS HIV infections plus 274,624 AIDS cases or 549,736 total HIV infections. If there are, as Holmberg estimated in 1996, 700,000 prevalent HIV infections (including AIDS) in the United States (6), the completeness of reporting of HIV infection nationally would be about 79 percent.

New diagnostic technologies, epidemiologic methods, and public health programs have become available over the last decade, and they provide approaches to more accurate surveillance for prevalent HIV infection. These include increased availability of HIV counseling and testing, laboratory-based reporting of HIV infection (7), rapid diagnostic methods that preclude the need for patients to return for test results such as the single-use diagnostic system (SUDS) (8), sentinel HIV surveillance (9,10), and the use of capture-recapture methods for estimating HIV prevalence (11). Sentinel HIV surveillance especially has been extensively used. This system comprises repeated cross-sectional serologic surveys that serially measure the prevalence of HIV in reproducible populations at risk. The study populations are usually convenience or opportunistic samples, such newborn infants or clinic patients, whose serum was originally drawn for other purposes but tested for HIV for purposes of surveillance. To improve validity, participation bias is often minimized by “blinding.” That is, specimens and records are stripped of identifying information and tested for HIV antibody without the subjects’ knowledge or consent. Trends in HIV prevalence in sentinel populations over time are thought to act as an early warning system for infection in the wider population at risk.

**SURVEILLANCE FOR INCIDENT HIV INFECTION**

However, quite apart from questions of how to improve surveillance for prevalent HIV infection and the debate over the sagacity of HIV reporting (12) is the fact that the datum that is most important in rationally guiding HIV prevention programs is HIV incidence, the number and distribution of new HIV infections in a population. New cases of HIV infection, rather than old cases of HIV infection, represent failures of current public health programs and signal a need for refining approaches to preventing HIV transmission.

The validity of the assumption that prevalent infection mirrors recent infection is made tenuous by the long period of time from initial HIV infection to diagnosis of infection and development of symptoms. Temporal trends in prevalent HIV infection are affected by knowledge of serostatus, willingness of HIV-infected individuals to participate in voluntary studies, and, in clinic-based blinded sentinel surveillance systems, the care-seeking behaviors of people with HIV infection. That HIV prevalence does not correlate with HIV incidence has been empirically demonstrated in several studies (13–19). At best, prevalent HIV infection, especially in areas with established HIV epidemics, is a poor proxy for incident HIV infection, and surveillance systems that directly measure HIV incidence are far more central to monitoring current trends in HIV transmission.

Historically, incident HIV infection has been measured directly in longitudinal cohort studies. For a variety of reasons these have proven to be overly expensive, logistically complicated, or inaccurate (19). Retrospective longitudinal studies using records of persons repeatedly tested for HIV have also been used to estimate HIV incidence (18,20–24), and HIV incidence has been modeled indirectly in serial cross-sectional surveys (25). Incident HIV infection can also be diagnosed clinically as the acute retroviral syndrome (26) and beginning with studies in 1993 diagnosed serologically in patients with HIV antigen-positive (e.g., p24 or RNA-PCR-positive) and HIV antibody-negative serum specimens. Patients with this antigen-antibody combination are in the initial “window period” of HIV infection, a narrow period of
between 6 and 11 days preceding seroconversion (27). Given the narrowness of this time period, however, this diagnostic method has been impractical clinically and reserved for only the largest epidemiologic studies (17).

**USE OF THE SENSITIVE—MORE SENSITIVE EIA IN INCIDENT HIV SURVEILLANCE**

A new technology that employs two enzyme-linked immunosorbent assays (EIA) with greater and lesser sensitivity (the sensitive-less sensitive EIA, “detuned” EIA or serologic testing algorithm for recent HIV seroconversion [STARHS]), introduced as a research tool in 1997, has the potential to revolutionize the measurement of HIV infection and, for the first time, make the serologic diagnosis of incident HIV infection in individual patients practical (28). The sensitive-less sensitive EIA method combines two separate EIA tests, one more sensitive to low levels of HIV antibody (3A11) and one less sensitive to low levels of HIV antibody (3A11-DT) (28). Patients who are positive for the 3A11 EIA and negative for the 3A11-DT EIA are estimated to have become infected within the last 129 days (95% CI, 109–149 days). Patients who are positive by both tests became infected more than 129 days earlier, and patients negative by both tests are uninfected. Incidence is calculated by dividing the number of incident cases by the number of patients 3A11-positive/3A11-DT-negative plus the number of patients 3A11-negative (i.e., all those at risk of becoming infected) and by multiplying the resulting quotient by 365/129 (to annualize the rate). This method is so far limited to type B clades; ongoing studies are examining its use for non-type B clades.

The San Francisco Department of Public Health has employed this new testing technology to test stored HIV-positive sera from publicly funded anonymous HIV counseling and testing sites to test stored HIV-positive sera collected as part of blinded sentinel surveillance studies of HIV prevalence among patients at a San Francisco drug treatment clinic and at the municipal sexually transmitted disease clinic (19,29,30).

Among the 21,292 sera tested for HIV at anonymous testing sites in San Francisco from 1996 through 1998, 452 (2.1%) were positive for HIV (19). Of these 452 stored seropositive specimens, 79 (17.5%) were identified as recent seroconversions by the sensitive/less sensitive EIA. This corresponds to an HIV incidence rate among the population anonymously tested for HIV infection of 1.1 per 100 person years (py). Of the 79 early infections, 66 (84%) occurred in men who have sex with men (MSM). Among MSM, HIV incidence remained relatively stable over the 6 half-years of observation, ranging from a low of 1.1 per 100 py in July–December 1997 to a high of 2.4 per 100 py in both January–June 1998 and July–December 1998. By transmission category incidence rates were highest among MSM who injected drugs (6.3 per 100 py), those whose sex and transmission category were unknown (3.7 per 100 py), and MSM without histories of injection drug use (1.6 per 100 py) (Table 1). By race and ethnicity, incidence rates were highest among Latinos (3.1 per 100 py) and Asians and Pacific Islanders (2.0 per 100 py), followed by whites (1.9 per 100 py) and blacks (1.1 per 100 py). Incidence was also elevated in certain age groups, with 21-to-25-year-olds and 26-to-30-year-olds having the highest incidence at 2.6 per 100 py. After adjustment, risk factors in the prior year that were significantly associated with recent HIV infection among MSMs were unprotected anal intercourse (adjusted odds ratio [AOR], 2.7; 95% CI, 1.6–4.4), injection drug use (AOR, 3.2, 95% CI 1.7–6.0), and more than 10 sexual partners (AOR, 2.0; 95% CI, 1.2–3.2) (19).

Similarly, among 688 injection drug users attending a drug treatment clinic in San Francisco from 1995 through 1998, 19 (4.2%) of 436 patients who had a single specimen available for testing were HIV-infected and 13 (5.6%) of 220 who had more than one specimen available for testing were infected (29). Among patients with

**TABLE 1. Incident HIV infection among anonymous test site clients by transmission category, San Francisco, 1996–1998**

<table>
<thead>
<tr>
<th>Transmission category</th>
<th>n</th>
<th>HIV-positive (%)</th>
<th>Early infections (%)</th>
<th>HIV incidence per 100 person years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>21,292</td>
<td>452 (2.1)</td>
<td>79 (17)</td>
<td>1.1 (0.68–1.6)</td>
</tr>
<tr>
<td>MSM</td>
<td>9,380</td>
<td>310 (3.3)</td>
<td>53 (17)</td>
<td>1.6 (0.99–2.7)</td>
</tr>
<tr>
<td>MSM-IDU</td>
<td>626</td>
<td>58 (9.3)</td>
<td>13 (22)</td>
<td>6.3 (2.6–13.8)</td>
</tr>
<tr>
<td>Male, risk unknown</td>
<td>446</td>
<td>13 (2.9)</td>
<td>2 (15)</td>
<td>1.3 (0.09–6.3)</td>
</tr>
<tr>
<td>Gender and risk unknown</td>
<td>889</td>
<td>55 (6.2)</td>
<td>11 (20)</td>
<td>3.7 (1.4–8.5)</td>
</tr>
</tbody>
</table>

MSM, men who have sex with men; IDU, injection drug use. Data from McFarland et al. (18).
more than one specimen available, there were no observed seroconversions by conventional serial testing (95% CI, 0–1.02 per 100 py). No early infections were detected among all 656 clients by the sensitive/less sensitive EIA method (95% CI, 0–1.9 per 100 py); the upper 95% confidence bound was 5.7 per 100 py among those with serial specimens and 2.9 per 100 py among those with single specimens available.

The sensitive/less sensitive EIA has great epidemiologic and possible clinical utility because it makes the detection of incident HIV infection practical. It can be used to estimate the incidence of HIV infection in various cross-sectional population-based studies, to conduct surveillance for HIV subtypes and primary antiretroviral resistance among newly infected individuals, to target early antiretroviral therapy if this proves clinically useful, and to target partner notification systems much more narrowly than with prevalent HIV infection in index patients, and to understand individuals who “fail” prevention. This last use of the more sensitive-less sensitive EIA, especially in low incidence settings where the numbers of newly infected individuals will be small, offers the opportunity to understand in much greater detail why individuals are becoming infected, a strategy more akin to the individual case investigations conducted for low incidence diseases of public health importance such as botulism and vaccine-preventable diseases.

But can surveillance for incident HIV infection become a core component of our surveillance for HIV infection? A case definition for incident HIV infection might include, for instance, individuals with the acute retroviral syndrome, those who are antigen-positive and antibody-negative, those who are documented to have seroconverted, and those who are positive by the more sensitive/less sensitive EIA (Table 2). However, having a laboratory test, even if it eventually moves from the research setting to clinical practice, does not guarantee a sensitive surveillance system. Patients would still need to present for medical care, their physicians would still have to order the correct tests or make the diagnosis of the acute retroviral syndrome clinically, and finally either their physicians or the laboratory (in a laboratory-based reporting system) would have to report the results. Likely the first step (having patients present during the seroconversion period) and the second step (having the physician suspect acute retroviral syndrome and either order the test or make a clinical diagnosis) will be the weakest links in this chain. However, the advantages of understanding who is becoming infected and why will even in the short term offer significantly more insight into the most crucial issues in HIV prevention than surveillance for prevalent HIV infection. Should surveillance for incident infection supplant surveillance for prevalent infection? Given the limitations of underdiagnosis and underrecognition, this will likely be impractical in the near future, and surveillance for incident infection will be used more extensively to supplement surveillance for prevalent infection. However, having an HIV surveillance system that focuses on incident rather than prevalent infection should become our long-term goal, and with further improvements in diagnostic technology and improved recognition by physicians this goal may be achievable.

**REFERENCES**


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**TABLE 2. A possible case definition for incident HIV infection**

<table>
<thead>
<tr>
<th>Acute retroviral syndrome diagnosed by a physician following a high-risk exposure, or laboratory evidence of acute HIV infection as evidenced by:</th>
</tr>
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<tbody>
<tr>
<td>Positive by the sensitive EIA and negative by the less sensitive EIA</td>
</tr>
<tr>
<td>Seroconversion in two specimens at least 1 month apart</td>
</tr>
<tr>
<td>Antigen (p24 or PCR) positive and HIV antibody negative</td>
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</tbody>
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