HIV Incidence Determination in the United States: A Multiassay Approach

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(See the major article by Eshleman et al, on pages 223–31 and the editorial commentary by Mastro, on pages 204–6.)

Background. Accurate testing algorithms are needed for estimating human immunodeficiency virus (HIV) incidence from cross-sectional surveys.

Methods. We developed a multiassay algorithm (MAA) for HIV incidence that includes the BED capture enzyme immunoassay (BED-CEIA), an antibody avidity assay, HIV load, and CD4+ T-cell count. We analyzed 1782 samples from 709 individuals in the United States who had a known duration of HIV infection (range, 0 to >8 years). Logistic regression with cubic splines was used to compare the performance of the MAA to the BED-CEIA and to determine the window period of the MAA. We compared the annual incidence estimated with the MAA to the annual incidence based on HIV seroconversion in a longitudinal cohort.

Results. The MAA had a window period of 141 days (95% confidence interval [CI], 94–150) and a very low false-recent misclassification rate (only 0.4% of 1474 samples from subjects infected for >1 year were misclassified as indicative of recent infection). In a cohort study, annual incidence based on HIV seroconversion was 1.04% (95% CI, .70%–1.55%). The incidence estimate obtained using the MAA was essentially identical: 0.97% (95% CI, .51%–1.71%).

Conclusions. The MAA is as sensitive for detecting recent HIV infection as the BED-CEIA and has a very low rate of false-recent misclassification. It provides a powerful tool for cross-sectional HIV incidence determination.

Keywords. HIV; incidence testing; United States; epidemiology.

Accurate methods to estimate the incidence of human immunodeficiency virus (HIV) infection are needed to monitor the leading edge of the epidemic [1], to identify groups at high risk of infection for targeted prevention interventions, and to evaluate the effectiveness of prevention interventions [2]. Unfortunately, after >30 years, HIV incidence and prevalence remain high in many settings [3], and practical and accurate methods for estimating HIV incidence remain elusive. Prospective cohort studies that identify HIV seroconverters are expensive and time-consuming, and they may not provide reliable estimates of HIV incidence in the relevant populations because of selection bias, changes in behavior associated with study participation, and loss to follow-up [4]. Biomarker-based methods that identify recently infected persons in cross-sectional samples are a promising alternative approach for estimating HIV incidence. However, concerns have been raised about their accuracy.
The first biomarker-based method to estimate incidence from cross-sectional samples was proposed by Brookmeyer and Quinn in 1995 [5]. In that study, HIV incidence was assessed by detecting acute HIV infections (ie, measuring the number of HIV-seronegative individuals in a population who were positive for HIV p24 antigen). Unfortunately, because the duration of seronegative HIV infection is very short, this method for determining HIV incidence is only useful for analysis of very large surveys in populations with very high annual incidence [5]. In 1998, Janssen and colleagues developed a “detuned” serologic assay [6] that differentiated between individuals with recent and those with nonrecent HIV infection, which was based on the observation that the HIV antibody titer is usually low during the first few months of infection. Other assays have since been developed for cross-sectional HIV incidence determination that measure different features of the immune response to HIV infection [7-10]. The BED capture enzyme immunoassay (BED-CEIA) is currently the most widely used commercially available assay for detecting recent HIV infection [11, 12]. Other assays measure responses such as antibody avidity and antibody isotype switching [13, 14]. Unfortunately, none of these methods provide the needed accuracy for identifying recent HIV infection in most settings.

A major limitation of serologic assays is the frequent misclassification of individuals with long-standing HIV infection as recently infected (ie, false-recent misclassification) [15]. Two factors that have been associated with false-recent misclassification by the BED-CEIA are low CD4+ T-cell count and low HIV load [16]. Some studies have suggested using a mathematical approach to adjust results obtained with these assays, to improve the precision of HIV incidence estimates [17]. However, that approach has limitations, such as requiring precise estimates of additional input adjustment factors [18-21]. Working groups have been assembled to harmonize the terminology used in this field, to facilitate collaboration among investigators, to share the findings of new research, and to focus research efforts [22].

In this report, we describe a multiassay algorithm (MAA) for identifying recent infections that can be used to determine population HIV incidence rates. This approach overcomes limitations of previous approaches developed for estimating HIV incidence that are based on cross-sectional sampling, because all individuals stop appearing to be recently infected and do not regress back to appearing to be recently infected. The MAA combines 2 serological assays with CD4+ T-cell count and HIV load. The serological assays are used to cast a wide net to identify individuals who may have recent HIV infection. HIV load and CD4+ T-cell count are used to exclude individuals who, because of advanced HIV disease (indicated by low CD4+ T-cell count) or natural- or antiretroviral-induced viral suppression (indicated by low HIV load), may be misclassified by serologic assays as recently infected.

We evaluated the performance of the MAA for estimating cross-sectional HIV incidence by using the following approach. First, we tested samples from HIV-infected individuals whose duration of HIV infection was known at the time of sample collection. Then, we determined the probabilities of whether the MAA classifies a person as recently infected and how those probabilities depend on the actual durations of infection. We used those probabilities to calculate the mean duration during which the MAA classifies a person as recently infected, an interval known as the “window period.” We then determined whether the MAA could estimate HIV incidence within 1 year preceding sample collection. Finally, we compared the annual HIV incidence estimate obtained by the MAA with the annual incidence observed in a prospective cohort study (HIV Network for Prevention Trials study 001 [HIVNET 001]).

**METHODS**

**Samples Used for Analysis**

Data analyzed in this report were obtained from testing stored plasma or serum from HIV-infected US participants in the AIDS Linked to the Intravenous Experience (ALIVE) study [23], the Multicenter AIDS Cohort Study (MACS) [24], and HIVNET 001 [25] (Table 1). We tested 1782 samples obtained from 709 individuals who had a documented HIV-negative test result with a subsequent documented HIV-positive test result within 18 months. In all 3 studies, samples were assayed for CD4+ T-cell count in real time.

**Characteristics of Individuals Studied**

A total of 1782 samples from 709 individuals with known duration of HIV infection were analyzed (Table 1). These samples were collected between 1987 and 2009 from individuals in HIVNET 001 (808 samples from 103 individuals), the ALIVE study (410 samples from 241 individuals), and the MACS (564 samples from 365 individuals) who acquired HIV infection during study follow-up. Samples from HIVNET 001 were collected near the time of HIV seroconversion and up to 53 months later; samples from the ALIVE study and the MACS were collected between 24 and 100 months after HIV seroconversion. All subjects had provided written informed consent, and the study was approved by the Institutional Review Board of the Johns Hopkins University. Most of the samples (89%) were from men. Overall, 60.1% of the individuals studied had, on the basis of self-report, been exposed to antiretroviral therapy when 1 or more of the samples was collected (44.5% of the samples included in the analysis were collected from individuals exposed to antiretroviral therapy).

**Laboratory Methods**

The BED-CEIA was performed according to the manufacturer’s instructions (Calypte Biomedical, Lake Oswego, OR) [8],...
with the following modification. All samples were run in duplicate, and the average normalized optical density (OD-n) was used for analysis. Antibody avidity was measured using a modified version of the Genetic Systems 1/2 + O enzyme-linked immunosorbent assay (Bio-Rad, Hercules, CA) [26]. Briefly, samples were diluted 1:10 in duplicate and were incubated at 4°C for 30 minutes (initial antibody-binding step). Samples were then incubated for 30 minutes at 37°C with or without the chaotropic agent diethylamine (antibody-disassociation step). For each sample, the avidity index was calculated as follows: [(optical density of the diethylamine-treated well)/(optical density of the nontreated well)] × 100.

In the MAA, a cutoff OD-n of 1.0 (rather than the standard assay cutoff of 0.8 OD-n) was used for the BED-CEIA, and a cutoff of 80% (rather than the standard assay cutoff of 40%) was used for the avidity assay; these higher assay cutoffs were used to increase the sensitivity for identifying individuals who were likely to have been recently infected at the time of sample collection; viral load and CD4+ T-cell count were used to exclude samples that falsely categorized infection as recent from that enlarged pool. Samples with the following test results yielded by the MAA were considered to be from recently infected individuals: a CD4+ T-cell count of >200 cells/mm3, a BED-CEIA of <1.0 OD-n, an avidity index of <80%, and an HIV load of

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HIVNET 001</th>
<th>ALIVE Study</th>
<th>MACS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of samples</td>
<td>808</td>
<td>410</td>
<td>564</td>
</tr>
<tr>
<td>No. of unique individuals</td>
<td>103</td>
<td>241</td>
<td>365</td>
</tr>
<tr>
<td>Risk factor(s) for HIV acquisition</td>
<td>Various*</td>
<td>Injection drug use</td>
<td>MSM</td>
</tr>
<tr>
<td>Time between last negative and first positive HIV test result, d, median (range)b</td>
<td>180 (0–376)</td>
<td>187 (0–539)</td>
<td>182 (0–547)</td>
</tr>
<tr>
<td>Duration of HIV infection, mo5</td>
<td>1–53</td>
<td>25–71</td>
<td>33–100</td>
</tr>
<tr>
<td>No. of samples per subject</td>
<td>1–13</td>
<td>1–2</td>
<td>1–2</td>
</tr>
<tr>
<td>Age, y, mean±SD</td>
<td>36.2±7.6</td>
<td>40.1±6.8</td>
<td>41.3±8.6</td>
</tr>
<tr>
<td>Male sex, % of subjects</td>
<td>88.5</td>
<td>75.6</td>
<td>100.0</td>
</tr>
<tr>
<td>Collection date, no. (%) of samples</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987–1989</td>
<td>0</td>
<td>0</td>
<td>110 (19.5)</td>
</tr>
<tr>
<td>1990–1994</td>
<td>0</td>
<td>155 (37.8)</td>
<td>208 (36.9)</td>
</tr>
<tr>
<td>1995–1999</td>
<td>808 (100.0)</td>
<td>188 (45.9)</td>
<td>145 (25.7)</td>
</tr>
<tr>
<td>2000–2004</td>
<td>0</td>
<td>58 (14.1)</td>
<td>60 (10.6)</td>
</tr>
<tr>
<td>2005–2009</td>
<td>0</td>
<td>9 (2.2)</td>
<td>41 (7.3)</td>
</tr>
<tr>
<td>CD4+ T-cell count in cells/mm³, no. (%) of samples</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;500</td>
<td>490 (60.6)</td>
<td>108 (26.3)</td>
<td>236 (41.8)</td>
</tr>
<tr>
<td>201–500</td>
<td>295 (36.5)</td>
<td>199 (48.5)</td>
<td>233 (41.3)</td>
</tr>
<tr>
<td>51–200</td>
<td>22 (2.7)</td>
<td>79 (19.3)</td>
<td>65 (11.5)</td>
</tr>
<tr>
<td>≤50</td>
<td>1 (0.1)</td>
<td>24 (5.9)</td>
<td>30 (5.3)</td>
</tr>
<tr>
<td>HIV load in copies/mL, no. (%) of samples</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50 000</td>
<td>160 (19.8)</td>
<td>114 (27.8)</td>
<td>162 (28.9)</td>
</tr>
<tr>
<td>10 001–50 000</td>
<td>204 (25.3)</td>
<td>135 (32.9)</td>
<td>147 (26.1)</td>
</tr>
<tr>
<td>401–10 000</td>
<td>214 (26.5)</td>
<td>116 (28.3)</td>
<td>140 (24.8)</td>
</tr>
<tr>
<td>≤400</td>
<td>230 (28.5)</td>
<td>45 (11.0)</td>
<td>114 (20.2)</td>
</tr>
<tr>
<td>No. (%) of samples from individuals receiving ARTd</td>
<td>343 (42.5)</td>
<td>166 (40.5)</td>
<td>284 (50.4)</td>
</tr>
</tbody>
</table>

Abbreviations: ALIVE, AIDS Linked to the Intravenous Experience (1987–2009); ART, antiretroviral therapy; HIVNET 001, HIV Network for Prevention Trials study 001 (1995–1999); MACS, Multicenter AIDS Cohort Study (1990–2009); MSM, men who have sex with men.

* MSM, 78% (80 of 103); men who use injection drugs, 4% (4 of 103), women who use injection drugs, 6% (6 of 103); women who have sex with men and use injection drugs, 7% (7 of 103).

b If participants were HIV RNA positive at their last seronegative visit (documented acute infection), the value 0 was used; the number of such participants in HIVNET 001, the ALIVE study, and MACS were 4, 18, and 50, respectively.

c Calculated as the time between the estimated date of HIV seroconversion and the date of sample collection.

d Samples collected in the era before highly active antiretroviral therapy were from individuals who were receiving less potent antiretroviral drug regimens; many of those individuals did not have viral suppression at the time of sample collection.
When the BED-CEIA was used alone, a cutoff of <0.8 OD-n was used to indicate recent infection.

Statistical Methods

All samples were evaluated using both the MAA (Figure 1) and the BED-CEIA alone (see the Laboratory Methods subsection). The proportion of individuals classified as recently infected with each method was calculated by duration of infection (stratified into intervals, Table 2). The date of HIV seroconversion was estimated for each individual as the midpoint between the last HIV-negative test result and the first HIV-positive test result except if acute infection was documented (ie, a sample was HIV RNA positive and HIV antibody negative), in which case the date of HIV seroconversion was estimated as 2 weeks after the study visit in which acute infection was documented. Uncertainty in seroconversion dates was accounted for as described further below. The logit of the probability of samples being classified as recent was modeled as a function of the duration of infection, using cubic splines (with a knot at 2 years). The cubic spline allows the probability curves to be flexible and imposes minimal assumptions on the shape of the curves. The approach does not assume that the probabilities must decrease with the duration of infection or that the probabilities are initially 1 at the time of occurrence of infection. We calculated the mean window period by computing the area under the modeled probability curves, using numerical integration [27, 28]. We also calculated the shadow, which is a statistical measure of how far back into the past (from the point that the samples were collected) HIV incidence can be estimated by the MAA (eg, a shadow of 1 year means that the MAA has the potential to measure HIV incidence up to 1 year prior to the time the samples were collected) [27, 28]. Another way of interpreting the shadow is that it is the expected duration that a person who is classified by the MAA as recently infected has actually been living with HIV infection. The shadow can be calculated directly from the probability curves modeled by the cubic splines, as described above [27]. We used bootstrapping (blocked on individual and stratified by study) to calculate confidence intervals (CIs) for the proportions classified as indicative of recent infection, the mean window duration, and the shadow [29]. We bootstrapped by resampling with replacement individuals (to

Table 2. Proportion of Samples Classified by the BED Capture Enzyme Immunoassay (BED-CEIA) Alone and the Multiassay Algorithm (MAA) as Indicative of Recent Human Immunodeficiency Virus Infection, by Estimated Infection Duration

<table>
<thead>
<tr>
<th>Infection Duration (y)</th>
<th>Samples Tested (no.)</th>
<th>Samples Classified as Recent (no.)</th>
<th>Samples Classified as Recent (%) (95% CI)</th>
<th>Samples Classified as Recent (no.)</th>
<th>Samples Classified as Recent (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0 to 0.49a</td>
<td>142</td>
<td>80</td>
<td>56.3 (43.7–65.9)</td>
<td>68</td>
<td>47.9 (34.5–57.3)</td>
</tr>
<tr>
<td>0.50 to 0.99a</td>
<td>166</td>
<td>61</td>
<td>36.7 (27.4–48.1)</td>
<td>15</td>
<td>9.0 (6.3–19.3)</td>
</tr>
<tr>
<td>1.00 to 1.99a</td>
<td>263</td>
<td>65</td>
<td>24.7 (17.0–34.1)</td>
<td>2</td>
<td>0.8 (0–2.4)</td>
</tr>
<tr>
<td>2.00 to 2.99</td>
<td>301</td>
<td>62</td>
<td>20.6 (14.0–28.3)</td>
<td>2</td>
<td>0.7 (0–1.9)</td>
</tr>
<tr>
<td>3.00 to 3.99</td>
<td>440</td>
<td>64</td>
<td>14.5 (10.4–18.4)</td>
<td>2</td>
<td>0.5 (0–1.5)</td>
</tr>
<tr>
<td>4.00 to 4.99</td>
<td>125</td>
<td>15</td>
<td>12.0 (7.5–20.2)</td>
<td>0</td>
<td>0.0 (0–1.4)</td>
</tr>
<tr>
<td>≥5.00</td>
<td>345</td>
<td>47</td>
<td>13.6 (10.2–17.2)</td>
<td>0</td>
<td>0.0 (0–1.1)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

*All samples from individuals infected for <2 years were from the HIV Network for Prevention Trials study 001 cohort.
account for multiple samples per individual) from each of the 3 studies (the MACS, the ALIVE study, and HIVNET 001). Seroconversion dates were sampled uniformly from the intervals in which seroconversion occurred within the bootstrap, to account for uncertainty in those dates. All calculations were done using the R statistical programming language.

We used the MAA to derive a cross-sectional annual HIV incidence estimate for the HIVNET 001 clinical cohort, using the following equation: \[
\text{incidence estimate} = \frac{\text{number of samples classified as recent infection} \times 100}{\text{total number of samples}} \times \text{mean window period in years}.
\]

The probability curves of samples being classified as recent infections as a function of duration of infection. Figure 2 shows the modeled probability curves of samples being classified as recent using the BED-CEIA alone and the multiassay algorithm from fitting a cubic spline to the logit of the probability. Circles and squares show observed proportions by the BED-CEIA alone and the multiasay algorithm, respectively, when samples are stratified into intervals (Table 1).

Figure 2. Modeled probabilities of an individual being classified as recently infected as a function of duration of infection. Figure shows modeled probability curves of samples being classified as recent using the BED capture enzyme immunoassay (BED-CEIA) alone and the multiassay algorithm from fitting a cubic spline to the logit of the probability. Circles and squares show observed proportions by the BED-CEIA alone and the multiasay algorithm, respectively, when samples are stratified into intervals (Table 1).
previously published mean window period [32]. While we recognize that the cross-sectional sample set that was used to estimate incidence with the MAA did not include individuals with long-term, chronic HIV infection (ie, infection of >18 months duration), only 0.3% (1 of 361) of all HIVNET 001 samples from individuals who were infected for >18 months and none of the samples from individuals who were infected for >3 years were classified by the MAA as indicative of recent infection.

**DISCUSSION**

In this report, we describe the performance of a MAA for identifying recent HIV infections that can be used to estimate HIV incidence. We found that none of the samples collected >5 years after HIV seroconversion were classified as recent by the MAA. This corrects a significant source of error with the BED-CEIA, which is currently in widespread use. Furthermore, the shadow of the MAA indicates that those samples classified as recent by the MAA were from individuals who, on average, had actually been infected for <1 year. The concordance between the MAA estimate of incidence and the observed incidence based on direct longitudinal follow-up for HIV seroconversion provides further validation of the MAA. Our analyses indicate that the MAA has the potential to estimate accurately HIV incidence levels within 1 year of sample collection. This study included samples from both men and women from across the United States, with different races and ethnic backgrounds and with different risk factors for HIV acquisition (eg, heterosexual sex, male-male sex, and injection drug use). This increases the relevance of the study findings.

An advantage of the MAA is that it uses a hierarchical approach for sample testing. Many of the samples from individuals with long-standing infection will be identified using the BED-CEIA. This assay is commercially available and is relatively inexpensive. The next step of sample testing uses the avidity assay. This assay requires a minor modification of a commercially available EIA used for HIV diagnosis and is also relatively inexpensive. Relatively few samples require HIV load testing (ie, only those with CD4+ T-cell counts of >200 cells/mm3, BED-CEIA results of <1.0 OD-n, and an avidity index of <80%); in this study, only 169 (9.5%) of 1782 samples required viral load testing. Furthermore, the order in which the BED-CEIA and avidity assays are performed can be interchanged, which may increase the cost-effectiveness of the algorithm in some settings.

It is important to note that the MAA described in this report does not require exclusion of individuals who are receiving antiretroviral therapy. The World Health Organization Working Group on HIV Incidence Assays does note that the presence of antiretroviral drugs in specimens can be used as a biomarker of long-term infection [33], and this approach has been used for cross-sectional incidence estimation in South Africa [34]. This is based on the assumption that individuals who have been infected for <1 year are unlikely to be receiving antiretroviral treatment. However, self-report of antiretroviral use may be unreliable, and laboratory tests may fail to detect antiretroviral drugs if sample collection was not timed to drug dosing. Furthermore, some recently infected individuals may be exposed to antiretroviral drugs (eg, women who receive antiretroviral drugs for prevention of mother-to-child transmission) [35]. Our previous studies show an association between antiretroviral use and misclassification by the BED-CEIA [16, 36]. However, in multivariate logistic regression models, this association is fully attenuated when HIV load is included in the model [36]. In contrast, low HIV load remains strongly associated with misclassification. Furthermore, low HIV load is associated with misclassification by the BED-CEIA and other cross-sectional incidence assays in the absence of antiretroviral drug use (eg, in elite suppressors) [37, 38]. These data fit with a conceptual model in which the anti-HIV antibody response is downregulated when the amount of replicating virus is low, regardless of the cause of viral suppression [39]. This is addressed in our MAA by excluding individuals who have a low viral load.

One limitation of the MAA is that it requires CD4+ T-cell count data. The other components of the MAA (BED-CEIA, avidity, and HIV load) can be obtained using stored plasma or serum samples; we have previously shown that BED-CEIA and avidity assay results are not significantly affected by sample storage conditions or freeze-thaw cycles [40]. In contrast, CD4+ T-cell counts must be obtained either in real time from all HIV-infected individuals or retrospectively by using cryopreserved viable samples, both of which are costly. We are exploring whether CD4+ T-cell count and HIV load testing can be replaced in the MAA with a high-resolution melting (HRM) assay that measures the level of genetic diversity of HIV in a plasma or serum sample [41]. An advantage of the HRM diversity assay over CD4+ T-cell count testing is that the HRM assay can be performed retrospectively on stored serum or plasma samples; with this approach, testing with the HRM assay would be limited to the subset of samples that are classified by the less expensive BED-CEIA and avidity tests as recent infections.

HIV surveillance by the BED-CEIA was the basis for recent estimates of HIV incidence in the United States that were prepared by the Centers for Disease Control and Prevention (CDC) [11, 12]. To address the issue of false-recent misclassification, the CDC recommended excluding persons with AIDS and persons receiving antiretroviral treatment from being counted as having recent infection, regardless of their BED-CEIA test results. The proposed MAA is consistent with that recommendation, in that it uses HIV load and CD4+ T-cell count to classify individuals with advanced HIV disease or
viral suppression as not recently infected. Previous studies have shown that HIV subtype influences the results obtained using BED-CEIA and avidity assays [32, 42]. The results presented in this report are based on analysis of samples collected in the United States, which are assumed to be predominantly from individuals with subtype B HIV infection [43]. All of the HIV strains from the cohorts studied in the report that have been sequenced are subtype B [25, 44–46]. Further work is needed to evaluate the performance of the MAA in other populations with clade B epidemics and in populations with non–clade B epidemics. Further studies are also needed to compare HIV incidence estimates obtained with the MAA to those obtained from longitudinal follow-up in other cohorts. In summary, our results indicate that the MAA can be an accurate and practical approach to estimating HIV incidence in the United States, provided that CD4+ T-cell counts are available and that the surveys are representative of the population studied.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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