Impact of HIV-1 subtype and Sex on Sedia Limiting Antigen Avidity Assay Performance

Eduard Grebe,1,2 Gary Murphy,3 Sheila M. Keating,1,4 Dylan Hampton,1 Shelley N. Facente,1,5 Kara Marson,4 Andrew Longosz,6 Susan H. Eshleman,6 Alex Welte,2 Neil Parkin,7 Michael P. Busch,1,4 Thomas C. Quinn,6,8 Oliver Laeyendecker4,5

1Vitalant Research Institute, San Francisco, CA; 2DIST-NRF Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA), Stellenbosch University, Stellenbosch, South Africa; 3Public Health England, London, UK; 4University of California, San Francisco, San Francisco, CA; 5Facente Consulting, Richmond, CA; 6Johs Hopkins University School of Medicine, Baltimore, MD; 7Data First Consulting, Belmont, CA; 8Laboratory of Immunoregulation, Division of Intramural Research, National Institute of Allergy and Infectious Diseases, NIH, Baltimore, MD

Background

- The Sedia® Limiting Antigen Avidity ELISA (LAg-Avidity Assay) is the most widely-used immunoassay used in recent infection testing algorithms (RTAs) for population-level HIV incidence surveillance.
- We combined data from two groups (JHU/NIAD and CEPHIA) to assemble the largest single dataset of Sedia LAg-Avidity results from seroconverter cohorts, consisting of 2,397 subjects and 10,322 specimens.
- We evaluated a wide range of RTAs combining LAg-Avidity normalized optical density (ODn) thresholds with viral load thresholds for incidence surveillance performance.
- Performance is defined as the precision of incidence estimates achievable in surveillance scenarios.
- We investigated the impact of HIV-1 subtype and sex on critical performance characteristics of the assay/RTA.

Methods

- Harmonized estimated dates of detectable infection (EDDIs) were produced for all subjects with full diagnostic testing histories (see Grebe et al. doi:10.1101/325888).
- Two key performance characteristics of a test for recent infection were estimated for each threshold combination:
  - The mean duration of recent infection (MDRI): the average time post-EDDI that a subject exhibits the recent marker.
  - The false-recent rate (FRR): the proportion of subjects infected for longer than a specified cut-off time (2 years) that nevertheless test recent.
- We tested for differences in MDRI by subtype and sex using two-sample Z-tests.
- To evaluate surveillance performance, we defined epidemiological scenarios (subtype distribution, incidence, prevalence, treatment coverage) and estimated context-adapted MDRI (weighted average of subtype-specific MDRIs, adjusted for screening test) and context-specific FRR (weighted according to density of the times-since-infection and subtype-specific MDRIs, adjusted for screening test) and context-specific FRR (weighted according to density of the times-since-infection and subtype-specific MDRIs, adjusted for screening test) for population-level HIV incidence surveillance.

Results

• Females show consistently higher ODn measurements on the LAg-Avidity assay than males with similar durations of infection (Figure 1) and significantly shorter MDRI than males (Table 1).

Table 1: Mean duration of recent infection (MDRI) by sex and pregnancy status

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Male</th>
<th>Female</th>
<th>Pregnancy Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>34.6</td>
<td>20.6</td>
<td>N/A</td>
</tr>
<tr>
<td>B</td>
<td>34.6</td>
<td>20.6</td>
<td>N/A</td>
</tr>
<tr>
<td>C</td>
<td>34.6</td>
<td>20.6</td>
<td>N/A</td>
</tr>
<tr>
<td>D</td>
<td>34.6</td>
<td>20.6</td>
<td>N/A</td>
</tr>
</tbody>
</table>

• No statistically significant difference in MDRI by pregnancy status (Table 1).

• MDRI point estimates differed substantially between subtypes, and the differences between subtypes A and C as well as C and D were statistically significant (Figure 2).

Conclusions

• MDRI and FRR vary substantially by sex and HIV-1 subtype (FRR data not shown).

Table 2: MDRI and FRR estimates by threshold and HIV-1 subtype

<table>
<thead>
<tr>
<th>Threshold</th>
<th>MDRI</th>
<th>FRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>0.05</td>
<td>0.03</td>
</tr>
<tr>
<td>2.0</td>
<td>0.36</td>
<td>0.12</td>
</tr>
<tr>
<td>2.5</td>
<td>0.69</td>
<td>0.20</td>
</tr>
</tbody>
</table>

• MDRI and FRR differ on the order of 40 days at the standard (ODn) thresholds and differences were statistically significant. Our results do not show a significant pregnancy effect, although data were limited.

• We observed statistically significant MDRI differences between clades A and C and between A and B.

• Optimal precision in surveillance scenarios was achieved using ODn thresholds of approximately 1.0 to 2.5.

• Context-adapted MDRI and FRR estimates are required to obtain accurate incidence estimates.

A table with MDRI and FRR estimates by threshold and HIV-1 subtype available at: tools.incidence-estimation.org/hiv-avidin-test/

References


Acknowledgements

The authors acknowledge the support of the HIV Prevention Trials Network (HPTN), which provided computational resources for this study. HPTN was supported by the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), and Department of Defense (DoD). Additional support was provided by Centers for Disease Control and Prevention (CDC), National Heart, Lung, and Blood Institute (NHLBI), National Institute of Mental Health (NIMH), National Institute of Child Health and Human Development (NICHD), National Cancer Institute (NCI), and the Bill & Melinda Gates Foundation. The content is solely the responsibility of the authors and does not necessarily represent the official views of any of the funders.

Contact: EGrebe@vitalant.org

Consortium for the Evaluation and Prevention of HIV Incidence Assay Validity