A generalizable method with improved accuracy for estimation of HIV infection duration using clinical HIV testing histories

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Estimating Infection Time

• Precision (clinical diagnosis, research and epidemiological purposes)
• Classification accuracy (e.g., surveillance staging, prioritization of interventions)
• “Time since first detectable infection”
  – Hypothetical date of single copy viremia during the “ramp-up” phase
Fiebig staging (acute HIV-discrepant tests)

- “Fiebig staging” requires testing by multiple obsolete assays
- All results/testing on same (diagnostic) specimen, same day
  Creativity required to estimate infection time from an actual test history (e.g.: “RNA+/rapid test-” = “F1-4”)

McMichael et al Nature Reviews Immunology 10, 11-23 (2010)
adapted to use viral ramp-up dynamics

- However, **viral load data is typically available** as part of the testing history in all cases of antibody-negative acute HIV infection
- Hypothesis: VL alone can be used to estimate first detectable infection

McMichael et al Nature Reviews Immunology 10, 11-23 (2010)
Objectives

1. Validate and quantify precision of Fiebig stage based estimation of infection time
2. Develop and assess a simplified method using HIV viral load to estimate infection time in Ab negative acute HIV
Data: plasma donor panels with precisely observed date of first detectable infection

- Data only considered from panels in which there were consecutive measurements <7 days apart going from below 100 copies to above 100 copies HIV RNA
- DDI at 100 RNA copies (DDI$_{100}$) imputed within 1-6 day window
- 53 plasma donor panels, 468 specimens with mean RNA interval 3.5 days
- 174 WB negative specimens (147 F1-2, 27 F3)
- 60 specimens from 17 panels in original Fiebig publication
Validation of Fiebig-based Estimation
N=119 specimens (non-UCSF/BSRI specimens only)

- Modest but statistically significant correlation of estimated vs. observed DDI
- $R^2=0.34$
- Precision of Fiebig-derived EDDI roughly +/- 10 days

Observed time from first detected infection to sample
VL ramp-up model development
UCSF-BSRI specimens only

Slope=0.33 log/day
Improved Estimation using VL Ramp-up Model
N=119 specimens (non-UCSF/BSRI specimens only)

Observed time from first detected infection to sample
Acute HIV Staging: Conclusions

- Fiebig staging for stage 1-3 specimens (gold standard) estimates within about 10 days of the true DDI in majority of cases

- For patients with acute HIV and a same-day, quantitative viral load, estimation by viral load greatly improves this precision over the Fiebig-derived method (closer to 5 days)
Objectives

1. Validate and quantify precision of Fiebig stage based estimation of infection time
2. Develop and assess a simplified method using HIV viral load to estimate infection time in Ab negative acute HIV
3. Develop and assess a generalizable method for estimating infection time from clinical testing histories
A Generalizable Method

- Based on testing history that is available
- Accommodate tests performed on different days
- Accommodate data from past, present and future assays
- Accommodate incomplete data ("viral load positive", "rapid test negative")
- For a given patient, give both a best estimate of infection timing and information on plausible bounds on that estimate
Sequence of HIV Assay Reactivity During Early HIV Infection relative to Western Blot*

*Assay sensitivity above is based on frozen plasma from 17 seroconverters. Whole-blood and oral fluid have not been characterized for early infection.

Deriving an estimated date of detectable infection (EDDI) from real-world testing history: “WB midpoint method”

HIV – test date

Assumed WB conversion

HIV+ test date
Deriving an estimated date of detectable infection (EDDI) from real-world testing history: “WB midpoint method”

HIV – test date

Assumed WB conversion

HIV+ test date

EDDI = midpoint -30 days?
adapted to incorporate knowledge about specific tests’ conversion dynamics

HIV – test: Aptima

earliest plausible DI

latest plausible DI

HIV+ test date: MS+
→ incorporating knowledge about specific tests’ conversion dynamics

HIV – test: Aptima

HIV+ test date: MS+

plausible interval

EP-DI

LP-DI
incorporating knowledge about specific tests’ conversion dynamics

HIV – test: Aptima

HIV+ test date: MS+

EDDI

EP-DI

LP-DI
Diagnostic Test History – Example 1

<table>
<thead>
<tr>
<th>Test Date</th>
<th>Adjusted Date</th>
<th>Test Name</th>
<th>Test Estimate</th>
<th>Test Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>April 23, 2015</td>
<td>March 31, 2015</td>
<td>Determine RT</td>
<td>Masciotra calc adjusted</td>
<td>Negative</td>
</tr>
<tr>
<td>April 23, 2015</td>
<td>April 18, 2015</td>
<td>Liat Quant</td>
<td>DT formula</td>
<td>Negative</td>
</tr>
<tr>
<td>June 9, 2015</td>
<td>May 17, 2015</td>
<td>Determine RT</td>
<td>Masciotra calc adjusted</td>
<td>Positive</td>
</tr>
<tr>
<td>June 9, 2015</td>
<td>May 12, 2015</td>
<td>WB Full</td>
<td>CDC calc adjusted</td>
<td>Positive</td>
</tr>
</tbody>
</table>
Visual Representation of Test History Indicating DDI Interval – Example 1

EP-DDI = April 18, 2015
DDI interval = 24 days
LP-DDI = May 12, 2015
EDDI = April 30, 2015
Visual Representation of Test History Indicating DDI Interval – Example 1

EP-DDI = April 18, 2015
DDI interval = 24 days
LP-DDI = May 12, 2015
EDDI = April 30, 2015
Visual Representation of Test History Indicating DDI Interval – Example 1

EP-DDI = April 18, 2015
DDI interval = 24 days
LP-DDI = May 12, 2015
EDDI = April 30, 2015
Visual Representation of Test History Indicating DDI Interval – Example 1

EP-DDI = April 18, 2015
DDI interval = 24 days
LP-DDI = May 12, 2015
EDDI = April 30, 2015
Visual Representation of Test History Indicating DDI Interval – Example 1

Ep-DDI = April 18, 2015
DDI interval = 24 days
LP-DDI = May 12, 2015
EDDI = April 30, 2015
## Diagnostic Test History – Example 2

<table>
<thead>
<tr>
<th>Test Date</th>
<th>Adjusted Date</th>
<th>Test Name</th>
<th>Test Estimate</th>
<th>Test Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dec. 10, 2012</td>
<td>Nov. 30, 2012</td>
<td>ARCHITECT</td>
<td>CDC calc adjusted</td>
<td>Negative</td>
</tr>
<tr>
<td>Dec. 12, 2012</td>
<td>Dec. 5, 2012</td>
<td>AptimaPool10</td>
<td>DT formula</td>
<td>Negative</td>
</tr>
<tr>
<td>Jan. 15, 2013</td>
<td>Jan. 5, 2013</td>
<td>ARCHITECT</td>
<td>CDC calc adjusted</td>
<td>Positive</td>
</tr>
<tr>
<td>Jan. 24, 2013</td>
<td>Jan. 16, 2013</td>
<td>bDNA</td>
<td>DT formula</td>
<td>Positive</td>
</tr>
<tr>
<td>March 26, 2013</td>
<td>March 18, 2013</td>
<td>bDNA</td>
<td>DT formula</td>
<td>Positive</td>
</tr>
<tr>
<td>April 23, 2013</td>
<td>April 15, 2013</td>
<td>bDNA</td>
<td>DT formula</td>
<td>Positive</td>
</tr>
</tbody>
</table>
Visual Representation of Test History Indicating DDI Interval – Example 2

EP-DDI = December 5, 2012
DDI interval = 22 days
LP-DDI = December 27, 2012
EDDI = December 16, 2012
EP-DDI = December 5, 2012
DDI interval = 22 days
LP-DDI = December 27, 2012
EDDI = December 16, 2012
Visual Representation of Test History Indicating DDI Interval – Example 2

EP-DDI = December 5, 2012
DDI interval = 22 days
LP-DDI = December 27, 2012
EDDI = December 16, 2012
Visual Representation of Test History Indicating DDI Interval – Example 2

EP-DDI = December 5, 2012
DDI interval = 22 days
LP-DDI = December 27, 2012
EDDI = December 16, 2012
Validation of Testing History Method (1)
n=20 panels, 81 specimens: non-CDC panels only

<table>
<thead>
<tr>
<th>Method</th>
<th>Estimated DDI</th>
<th>(ICC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiebig stage-based</td>
<td></td>
<td>0.95</td>
</tr>
<tr>
<td>Offset-based</td>
<td></td>
<td>0.95</td>
</tr>
</tbody>
</table>

(ICC) = 0.95 (0.93, 0.97)

Time since observed DDI (days)
Validation of Testing History Method (2) 3-point series

Test 1
RNA+3G-

Test 2
3G+WB-

Test 3
3G+WBind

Observed DDI

Fiebig EDDI

Testing History Method EDDI
Validation of Testing History Method

n=35 panels, 118 specimens: 3-point series only

Same day results (Fiebig)

- ICC=0.33 (0.18, 0.76)

Separated bleeds (offset based)

- ICC=0.47 (0.36, 0.69)
Conclusions

• The performance of a new, generalizable method for estimating infection time from routine clinical history compares favorably with less flexible methods that have been previously used.

• For patients with discrepant results in acute HIV and a quantitative viral load, the viral ramp-up method substantially improves precision of infection timing estimates compared to Fiebig staging.

• For patients with discrepant acute results but no quantitative VL, the testing history method gives infection timing estimates similar to previously used methods regardless of the tests used.

• Precision of estimates derived from the testing history method is robust to separation of testing dates.
Immediate next steps

• Public data conversion tool (housed by CEPHIA)
• Creation of clinician tool
• Update offsets as available
• Assess use of supplemental assays for improving estimates and diagnosing early infection