Seroconversion, seroreversion, and serowaffling among participants initiating antiretroviral therapy in Project DETECT

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Disclosures: NONE

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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC.

Background: Terminology

Seroconversion: development of antibodies in serum as result of infection or immunization.

Incomplete seroconversion: absence of complete seroconversion.

Seroreversion: decrease in antibodies to levels below the cutoff of an assay.

Serowaffling: a reactive test result followed by non-reactive then again by a reactive result.

Background

1) Incomplete HIV seroconversion and seroreversion are being identified more frequently than previously recognized, particularly in persons who initiate antiretroviral therapy (ART) during acute HIV infection (AHI).

2) There is increased recognition of false-negative tests in PrEP programs, especially with oral fluid tests and injectable PrEP.

3) Increased availability of home, self-tests has resulted in greater testing of HIV-positive persons already receiving ART.

This analysis was undertaken to describe patterns of incomplete seroconversion and seroreversion and serowaffling by specimen and test type in Project DETECT.

Methods (1)

Project DETECT

• Prospective, cross-sectional study to evaluate point-of-care (POC) HIV tests in real-time with unprocessed whole blood (WB) and oral fluid (OF) specimens.

• Participants with discordant results were enrolled into a longitudinal substudy.

• Follow-up continued until:
  • HIV-positive participants: concordant reactive results on all HIV tests or 1 year
  • Participants with false-positives: two sequential concordant nonreactive results

• DETECT visit schedule (in days):

  3 7 10 14 21 28 42 56 70 Monthly 365

• See Lauren Violette’s presentation today on the Geenius Index
  C3: Session 5: Emerging Technology, Th 230p

Methods (2)

HIV tests used in Project DETECT

<table>
<thead>
<tr>
<th>Device</th>
<th>Manufacturer</th>
<th>Specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP HIV 1/2 Assay</td>
<td>Chembio Diagnostics System</td>
<td>OF, FS, WB, VP WB</td>
</tr>
<tr>
<td>OraQuick Advance Rapid HIV 1/2 Antibody Test</td>
<td>OraSure Technologies, Inc</td>
<td>OF, FS, WB, VP WB</td>
</tr>
<tr>
<td>INSTI HIV-1/HIV-2 Rapid Antibody Test</td>
<td>bioLytical Laboratories, Inc</td>
<td>FS, WB, VP WB</td>
</tr>
<tr>
<td>Determine HIV 1/2 Ag/Ab Combo</td>
<td>Abbott Laboratories</td>
<td>FS, WB, VP WB*</td>
</tr>
<tr>
<td>Geenius HIV 1/2 Supplemental Assay</td>
<td>Bio-Rad Laboratories, Inc.</td>
<td>FS, WB, VP WB</td>
</tr>
<tr>
<td>GS HIV-1/HIV-2 Combo EIA</td>
<td>Bio-Rad Laboratories, Inc.</td>
<td>FS, WB, VP WB</td>
</tr>
<tr>
<td>RealTime HIV-1</td>
<td>Abbott Laboratories</td>
<td>Individual or pools of 10</td>
</tr>
</tbody>
</table>

OF: oral fluid; FS: fingerstick; WB: whole blood; VP: venipuncture

*Not approved for use on venipuncture whole blood

Methods (3)

Terminology

Complete seroconversion: all POC tests reactive at study censoring.

Incomplete seroreversion: at least one test remained non-reactive.

Seroreversion: sustained regression:

Serowaffling: using the same combo of specimen type and device:
### Methods (4)

#### Statistical Analysis

**Analysis Plan**
- Descriptive: frequencies of seroreversion and serowaffling by participant and specimen type.
- Primary analysis: impact of Fiebig stage at antiretroviral therapy (ART) initiation on incomplete seroconversion, seroreversion, and serowaffling by Fisher’s exact tests.
- Dichotomized at stage I-VI versus V-VI because of small numbers.

### Results (1)

#### Flow chart of DETECT enrollment and test results

- UV: venipuncture; WB: whole blood; GI: Geenius; OF: oral fluid; FS: fingerstick; S/CO: signal to cut-off ratio; ND: not done; NR: non-reactive; R: reactive; Ind: indeterminate.
- ART start = study day 1.
- An S/CO ratio ≥1 is considered reactive.
- All specimens were p31 non-reactive.

### Results (2): Example of complete seroconversion following AHI

<table>
<thead>
<tr>
<th>Day</th>
<th>Determine</th>
<th>VP</th>
<th>WB</th>
<th>OQ</th>
<th>FS</th>
<th>WB</th>
<th>Geenius VP</th>
<th>DPP</th>
<th>OF</th>
<th>OQ</th>
<th>OF</th>
<th>Geenius FS</th>
<th>DPP</th>
<th>OF</th>
<th>OQ</th>
<th>OF</th>
<th>S/CO (copies/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-10</td>
<td>Ab</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>(0.69)</td>
<td>NR</td>
<td>Ab</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>(0.72)</td>
<td>NR</td>
<td>Ab</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>-9</td>
<td>Ab</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>(0.69)</td>
<td>NR</td>
<td>Ab</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>(0.72)</td>
<td>NR</td>
<td>Ab</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>-8</td>
<td>Ab</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>(0.69)</td>
<td>NR</td>
<td>Ab</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>(0.72)</td>
<td>NR</td>
<td>Ab</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>-7</td>
<td>Ab</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>(0.69)</td>
<td>NR</td>
<td>Ab</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>(0.72)</td>
<td>NR</td>
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<td>Ab</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>(0.69)</td>
<td>NR</td>
<td>Ab</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>(0.72)</td>
<td>NR</td>
<td>Ab</td>
<td>R</td>
<td>R</td>
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<td>R</td>
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<td>R</td>
<td>R</td>
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<td>(0.69)</td>
<td>NR</td>
<td>Ab</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>(0.72)</td>
<td>NR</td>
<td>Ab</td>
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<td>Ab</td>
<td>R</td>
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<td>R</td>
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<td>(0.69)</td>
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<td>(0.72)</td>
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<td>(0.69)</td>
<td>NR</td>
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<td>(0.72)</td>
<td>NR</td>
<td>Ab</td>
<td>R</td>
<td>R</td>
</tr>
</tbody>
</table>

### Results (3): Example of incomplete seroconversion and seroreversion

- ORANGE = reactive; GREEN = indeterminate; BLUE = non-reactive.
- An S/CO ratio ≥1 is considered reactive.
- All specimens were p31 non-reactive.

### Results (4): Example of serowaffling following diagnosis in AHI

- UV: venipuncture; WB: whole blood; GI: Geenius; OF: oral fluid; S/CO: signal to cut-off ratio; ND: not done; NR: non-reactive; R: reactive.
- ART start = study day 1.
- Participant had negative Western Blot assays on these days.
- All specimens were p31 non-reactive.
Results (5): Overall outcomes of participants with discordant results

<table>
<thead>
<tr>
<th>ID</th>
<th>Days from enrollment to diagnosis</th>
<th>Fiebig stage at diagnosis</th>
<th>Days from enrollment to ART start</th>
<th>Fiebig stage at ART start</th>
<th>Complete v. incomplete seroconversion</th>
<th>Seroreversion specimen type</th>
<th>Serowaffling specimen type</th>
<th>Days from enrollment to study censoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 -7 I 110 II/III Complete</td>
<td>IV</td>
<td>18</td>
<td>IV</td>
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<td></td>
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<td>2</td>
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<td>II/III</td>
<td>15</td>
<td>IV</td>
<td>Complete</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>3</td>
<td>1442 -8 II/III 0 IV Complete</td>
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<td>10</td>
<td>IV</td>
<td>Complete</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>4</td>
<td>1785 -4 II/III 3 IV Complete</td>
<td>II/III</td>
<td>26</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>5</td>
<td>1721 -7 II/III 2 V Complete</td>
<td>IV</td>
<td>6</td>
<td>V</td>
<td>Complete</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1644 0 I 37 V Complete</td>
<td>IV</td>
<td>47</td>
<td>V</td>
<td>Complete</td>
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<tr>
<td>7</td>
<td>1507 -9 II/III 1 V Complete</td>
<td>IV</td>
<td>7</td>
<td>V</td>
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</tr>
<tr>
<td>8</td>
<td>1251 0 V 0 V Complete</td>
<td>IV</td>
<td>11</td>
<td>V</td>
<td>Complete</td>
<td></td>
<td></td>
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<tr>
<td>9</td>
<td>1582 -2 II/III 0 II/III Complete</td>
<td>IV</td>
<td>119</td>
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<td>Complete</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>10</td>
<td>1244 -17 II/III -7 V Complete</td>
<td>IV</td>
<td>33</td>
<td>V</td>
<td>Complete</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1927 -12 II/III 2 V Incomplete</td>
<td>II/III</td>
<td>8</td>
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<td></td>
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<td>12</td>
<td>1843 0 II/III n/a n/a Incomplete</td>
<td>IV</td>
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<td>V</td>
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<tr>
<td>16</td>
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<td>Complete</td>
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<td></td>
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<tr>
<td>17</td>
<td>1373 -20 I -6 V Incomplete</td>
<td>IV</td>
<td>366</td>
<td>IV</td>
<td>Complete</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>1815 -16 II/III 1 V Incomplete</td>
<td>IV</td>
<td>347</td>
<td>IV</td>
<td>Complete</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>1176 -1 V/VI 2 VI Incomplete</td>
<td>IV</td>
<td>301</td>
<td>VI</td>
<td>Complete</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

POC: point-of-care; OF: oral fluid; FS: fingerstick; WB: whole blood

Notes:
1. These are publication IDs, completely deidentified and no relationship to study ID; to be used across publications.
2. Follow-up continued until participants had concordant reactive results on all tests, completed one year of follow-up, or were lost to follow-up.
3. OF remained negative at study censoring at d8 and d9.
4. One or both OF were persistently negative throughout follow-up.

Results (6)

Statistical Analysis

19 (95%) of 20 participants started ART during follow-up
- median ART start on day 0 (IQR 0-2, range -21 to 37)

Fiebig Stage at ART start

<table>
<thead>
<tr>
<th>II/III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No associations were seen between Fiebig stage at ART start with:
- Complete seroconversion ($p=1.0$)
- Seroregression ($p=1.0$)
- Serowaffling ($p=.7$)

Limitations

- Small numbers of participants who started ART in AHI
- Assumptions about Fiebig staging at ART start
- We did not follow participants with concordant results to know if they later experienced seroreversion or serowaffling.
- Similarly, it is possible that some participants experienced seroconversion following study censoring.

Conclusions

- There is variability in test performance of different tests on different specimen types.
- Incomplete seroconversion, seroreversion, and serowaffling may represent a growing problem for PrEP programs and HIV testing programs that promote early treatment with hopes of ending the HIV epidemic in the U.S.
- PLWH, especially on ART, should not re-test or be re-tested using POC tests in case non-reactive results lead people to stop ART.
- Additional work is needed to develop and evaluate new testing technologies for HIV screening and diagnosis, particularly with new and upcoming PrEP modalities.

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Study Participants

Co-Authors
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- Hollie Clark
- Andy Cornelius-Hudson
- Kevin Delaney
- David Katz
- Sarah McDougal
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