Positive Predictive Value of HIV Serological Tests in HPTN 084 Trial

Session title: HIV prevention: novel approaches and promising findings
IAS 2023, Brisbane Australia, Abstract 5788

- Mina Hosseinipour, University of North Carolina at Chapel Hill
• What is your main question?
  • What is the positive predictive value of the HPTN on-site HIV testing algorithm?

• What did you find?
  • Two reactive HIV serology tests had high positive predictive value. The Ag/Ab test resulted in a high number of false positive results and had low positive predictive value, particularly for those on Cabotegravir LA.

• Why is it important?
  • As programs roll-out CAB LA, interpreting HIV status based on currently available serology testing will require strategies for confirmatory testing, counselling and transition planning to ART or resumption of PrEP.
• HPTN 084 showed that injectable cabotegravir (CAB) is effective for PrEP in women and superior to oral TDF/FTC \(^1\).

• HIV diagnosis in the context of PrEP use may be complicated by both false negative and false positive tests results.
  
  • False positive due to non-biologic reasons
  
  • False positive due to biologic causes (cross-reacting pathogens)
  
  • “LEVI” syndrome\(^2\)- Delayed Detection of Antibodies or Viral suppression secondary to Long Acting antiretrovirals

• False Negative- Delayed ART initiation, Emergence of Resistance

• False Positives- Incorrect Initiation of ART, Implication for PrEP gaps, and Complex Counseling

\(^1\) Delaney Moretiwe, Lancet 2022,
\(^2\) Eshleman, CROI 2023
Serial Testing

• First Test- High Sensitivity
• Second- High Specificity
• Third- High Specificity

Goal: 99% PPV
Optimal Tests should have
≥99% sensitivity
≥98% specificity
HPTN 084 Timeline & Primary Result

Blinded Period
2017-Nov 2020

Unblinded Period
Nov 2020-Jan/Jul 2022

Open Label Extension
Jan/Jul 2022-Present

HIV incidence

6 infections
3334 person years

HR 0.11; 95% CI 0.05 - 0.24

56 infections
3292 person years

1.70

0.18

CAB n=1613*

TDF/FTC n=1610

AIDS 2022, Montreal, abstract #OALBX0108
Objective

We evaluated the positive predictive value (PPV) of the HPTN 084 Site testing algorithm to guide HIV treatment initiation decisions in women on PrEP.
Any Reactive Test Prompts Product Hold and Site Confirmatory Testing and Central Lab assessment

Further testing was conducted by the HPTN Laboratory Center

- Back Testing of Previous Visits
- Additional Ag/Ab testing (Architect HIV Ag/Ab Combo test)
- Additional Ab testing (Geenius HIV 1/2 Confirmatory Assay)
- Additional qualitative RNA testing (Aptima HIV RNA Qualitative assay; LOD 30 copies/ml)
- Viral load testing (RealTime HIV Viral Load Assay; LOQ 400 copies/ml)
- Single copy RNA testing (as needed) (University of Pittsburgh)
Methods

Approach

• Testing Records for all visits from the blinded and unblinded periods through May 2022 with adjudication through Nov 2022 (Additional Testing data since last report)
  • Excludes the Open Label Extension
  • Excludes Screening and Enrollment visit
  • Excludes those with no Testing records after Enrollment

• Focused on 1st reactive testing visit

Outcomes

• Positive Predictive Value (95% CI)= Centrally Adjudicated result (True Positive) vs. Initial Site based reactive (Test Positive)

• Difference in PPV by arm (CAB-LA vs TDF/FTC)
3224 Participants in HPTN 084

44 excluded
3 Reactive at enrollment
41 no additional HIV testing

3180 Participants
67314 visits

159 (5%) Participants with any reactive tests (162 initial reactive visits)

3018 (95%) No Reactive Testing
3 (<1%) Reactive testing but unknown HIV status

88 False Reactive visits
47 CAB
41 TDF/FTC

74 True Reactive visits
8 CAB
66 TDF/FTC
### Results: Testing Patterns

<table>
<thead>
<tr>
<th>Site Testing Algorithm</th>
<th>Rapid Test 1</th>
<th>Rapid Test 2</th>
<th>Antigen/Antibody</th>
<th>Number of initial reactive visits with this pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 rapid tests per visit</td>
<td>Nonreactive</td>
<td>Nonreactive</td>
<td>Nonreactive</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Nonreactive</td>
<td>Nonreactive</td>
<td>Reactive</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>Reactive</td>
<td>Nonreactive</td>
<td>Reactive</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Reactive</td>
<td>Nonreactive</td>
<td>Nonreactive</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Reactive</td>
<td>Reactive</td>
<td>Reactive</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Reactive</td>
<td>Reactive</td>
<td>Nonreactive</td>
<td>0</td>
</tr>
<tr>
<td>1 rapid test per visit</td>
<td>Nonreactive</td>
<td>N/A</td>
<td>Nonreactive</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Nonreactive</td>
<td>N/A</td>
<td>Reactive</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Reactive</td>
<td>N/A</td>
<td>Nonreactive</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Reactive</td>
<td>N/A</td>
<td>Reactive</td>
<td>5</td>
</tr>
</tbody>
</table>
### Results (Overall)

**PPV for any reactive test: 74/162 (46%, CI:38%, 54%)**

<table>
<thead>
<tr>
<th>Test</th>
<th># Reactive Tests</th>
<th>Confirmed Positive</th>
<th>PPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid Tests (all types)*</td>
<td>114</td>
<td>89/114</td>
<td>78% (69%,85%)</td>
</tr>
<tr>
<td>Alere Determine</td>
<td>56</td>
<td>40/56</td>
<td>71% (58%, 83%)</td>
</tr>
<tr>
<td>Oraquick Advance</td>
<td>49</td>
<td>44/49</td>
<td>90% (78%, 97%)</td>
</tr>
<tr>
<td>2 Rapid Tests Reactive</td>
<td>40</td>
<td>40/40</td>
<td>100% (91%, 100%)</td>
</tr>
<tr>
<td>Ag/Ab Test (All types)</td>
<td>136</td>
<td>73/136</td>
<td>54% (45%, 62%)</td>
</tr>
<tr>
<td>Any Rapid Reactive and Ag/Ab Reactive</td>
<td>48</td>
<td>48/48</td>
<td>100% (93%, 100%)</td>
</tr>
</tbody>
</table>

*Some rapid tests were used too infrequently to calculate an accurate PPV*
## Results (by ARM)

<table>
<thead>
<tr>
<th>Test Type</th>
<th>HIV-positive/ total reactive (CAB)</th>
<th>HIV-positive/ total reactive (TDF/FTC)</th>
<th>PPV (95% CI) (CAB)</th>
<th>PPV (95% CI) (TDF/FTC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid test¹ (all types)</td>
<td>8/20</td>
<td>81/94</td>
<td>40% (19%, 64%)</td>
<td>86% (78%, 92%)</td>
</tr>
<tr>
<td>Alere Determine²</td>
<td>4/12</td>
<td>36/44</td>
<td>33% (10%, 65%)</td>
<td>82% (67%, 92%)</td>
</tr>
<tr>
<td>OraQuick ADVANCE</td>
<td>4/5</td>
<td>40/44</td>
<td>Insufficient sample size</td>
<td>91% (78%, 97%)</td>
</tr>
<tr>
<td>Two reactive rapid tests</td>
<td>4/4</td>
<td>36/36</td>
<td>Insufficient sample size</td>
<td>100% (90%, 100%)</td>
</tr>
<tr>
<td>Ag/Ab test³</td>
<td>7/42</td>
<td>66/94</td>
<td>17% (7%, 31%)</td>
<td>70% (60%, 79%)</td>
</tr>
<tr>
<td>Any reactive rapid or Ag/Ab test⁴</td>
<td>8/55</td>
<td>66/107</td>
<td>15% (6%, 27%)</td>
<td>62% (52%, 71%)</td>
</tr>
</tbody>
</table>

Difference in PPV (CAB vs. TDF/FTC): ¹-46% (-72%, -21%), ²-48% (-83%, -14%), ³-54% (-70%, -37%), ⁴-47% (-62%, -33%)
Conclusions

Two reactive Rapid Tests correctly confirmed HIV diagnosis to recommend treatment initiation in this study.

PPV is lower when using CAB-LA due to its High Prevention efficacy resulting in Lower HIV incidence.

With a single reactive HIV test and high frequency of false positive testing, PrEP programs should anticipate the need for further testing, counseling about false positivity, and plans to resume PrEP after excluding HIV.

More data is needed to determine if additional testing may be required in the setting of CAB.
HPTN 083 and HPTN 084 studies added HIV-RNA testing in their Open Label Extensions to explore the role of HIV-RNA for diagnosis as programs consider their testing strategies to minimize false negatives and interpret on site serological testing.

Next Steps

HIV Testing Algorithms will be evaluated further in the Open Label Extensions of HPTN 083 and HPTN 084
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