HPTN 084: HIV testing and implications for starting ART

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24 January 2023
### HIV testing during the OLE

<table>
<thead>
<tr>
<th></th>
<th>Blinded</th>
<th>Unblinded</th>
<th>Open Label Extension 1</th>
<th>Open Label Extension 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Women at Substantial Risk</td>
<td>Same</td>
<td>HPTN 084 + HPTN 084-1 participants</td>
<td>Those who received CAB in OLE 1</td>
</tr>
<tr>
<td><strong>Site HIV Testing</strong></td>
<td>Rapid Antibody (1 or 2) plus Ag/Ab</td>
<td>Rapid Antibody (1 or 2) plus Ag/Ab</td>
<td>Added VL</td>
<td>Same</td>
</tr>
<tr>
<td><strong>Family Planning Requirement</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>Stopped CAB, Used TDF/FTC</td>
<td>Stopped CAB, Used TDF/FTC</td>
<td>Pregnancy Study for CAB dosing</td>
<td>Pregnancy Study for CAB dosing</td>
</tr>
<tr>
<td><strong>Oral Lead in</strong></td>
<td>Oral Lead in required</td>
<td>Not applicable</td>
<td>Not required</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
HIV testing in the context of ART

• False negative
  • Suppression of viremia with low VL and delays in seroconversion
  • Conventional diagnostics may not detect early infection
  • Delays in detection have the potential to lead to resistance d/t monotherapy in the context of HIV infection

• Response
  • Add more sensitive tests e.g. HIV RNA
  • Rapid ART initiation
HIV testing in the context of ART

• False reactive
  • Large numbers of tests performed
  • Even with highly sensitive tests (99%), may observe false reactives
    • Positive predictive value influenced by prevalence/prior probability of test positive
  • False reactives may be more common in presence of other infections e.g. syphilis, malaria; pregnancy; steroid use
  • Limitations even with HIV RNA
    • E.g. In PMTCT setting in South Africa,
      • 16% of all non-negative results are indeterminate, 76% were negative on repeat testing
      • Possible reasons include low PPV due to low prevalence and samples near or at limit of detection

• Response
  • Risk of starting ART in someone who is not HIV positive

Luo, JAIDS 2019
Challenge

• Is this a participant who needs ART?

• Is this a participant who needs PrEP?

• For participants with prior CAB exposure, delays in decision-making either way have consequences
  • Possible resistance vs. possible infection
• The data presented here are preliminary
• Please do not share or distribute publicly
Example 1

• Participant on TDF/FTC
• Initial visit
  • RDT reactive, Ag/Ab negative, HIV RNA negative
• Product hold
• Confirmatory visit
  • All tests non-reactive
Example 1

- Participant on TDF/FTC
- Initial visit
  - RDT reactive, Ag/Ab negative, HIV RNA negative
- Product hold
- Confirmatory visit
  - All tests non-reactive

- Final outcome: Participant uninfected, resume product
Example 2

- Participant on TDF/FTC
- Initial visit
  - RDT reactive, Ag/Ab reactive, HIV RNA negative
- Confirmatory visit
  - Ag/Ab reactive, HIV RNA 1144 copies/ml
- Final outcome: Participant infected, start ART
Example 3

- Participant on CAB
- Initial visit
  - RDT negative, Ag/Ab reactive, HIV RNA negative
- Confirmatory visit
  - HIV RNA detectable

- Final outcome: Participant infected, start ART
Example 4

- Participant on CAB
- Initial visit
  - RDT negative, Ag/Ab negative, HIV RNA <40 copies
Example 4

- Participant on CAB
- Initial visit
  - RDT negative, Ag/Ab negative, HIV RNA <40 copies
- Product hold
- Confirmatory visit
  - HIV RNA detectable, Ag/Ab positive, Genius indeterminate
  - HIV RNA >140,000 copies

- Final outcome: Participant infected, start ART
Summary experience in OLE1

- Interpretation of testing more complex
  - More participants on CAB
  - More CAB starts/re-starts
  - Addition of RNA

<table>
<thead>
<tr>
<th>Test</th>
<th>N=85</th>
</tr>
</thead>
<tbody>
<tr>
<td>All 3 tests positive at index</td>
<td>4</td>
</tr>
<tr>
<td>2 tests positive at index</td>
<td>4</td>
</tr>
<tr>
<td>RDT only positive at index</td>
<td>19</td>
</tr>
<tr>
<td>Ag/Ab positive at index</td>
<td>43</td>
</tr>
<tr>
<td>HIV RNA positive at index ≤51</td>
<td>13</td>
</tr>
<tr>
<td>HIV RNA positive at index &gt; 40</td>
<td>2</td>
</tr>
</tbody>
</table>
Considerations for interpretation of test results

- If RDT negative, proceed to injection
- If positive, product hold

Ag/Ab, RNA results available. Product hold initiated at next visit if positive.

Confirmatory tests may be influenced by whether or not injection received recently.

…Not the same issue for TDF/FTC
Lessons learned

• Don’t retest samples from same day
• Don’t use discriminatory test if Ag/Ab not reactive
• HIV DNA no longer will be routine
  • Will require consultation with chairs
• Manage the participant not the test!
New guidance forthcoming

• Index test

• Confirmatory testing visit
  • Excludes lab mix up
  • May be influenced by whether or not injection provided
  • Consider interval between visits

• Guidance based on whether or not participants have ever received CAB injection
  • Please provide information on prior CAB exposure and date of last injection
Challenge: interpretation of low viral loads, particularly with low pre-test probability of infection

… more data needed
## Management of reactive HIV RNA

<table>
<thead>
<tr>
<th>Index</th>
<th>Confirmatory</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200 copies, includes &lt;LLOD</td>
<td>Not detected</td>
<td>Isolated positive, continue PrEP</td>
</tr>
<tr>
<td>&lt;200 copies</td>
<td>&lt;200 copies</td>
<td>Stop CAB, start ART</td>
</tr>
<tr>
<td>&gt;200 copies</td>
<td>RNA detected</td>
<td>Stop CAB, start ART</td>
</tr>
<tr>
<td>&gt;200 copies</td>
<td>RNA Not detected</td>
<td>Stop CAB, start ART</td>
</tr>
</tbody>
</table>

### Diagnostic uncertainty
- Could be emergent infection
- Could be false positive
- Referral for treatment will become a nuanced discussion with the potential for an ATI after 12-18 mos
Example 6

- Participant on CAB
- Initial visit
  - RDT negative, Ag/Ab negative, HIV RNA 452 copies
  - Repeat RNA undetectable
- Confirmatory visit
  - All tests non reactive
- Additional tests
  - DNA undetectable
- Final outcome: ?
Options

1. Hold PrEP and wait for emergence additional positive tests?
   - Risk of HIV infection if uninfected
   - Risk of HIV resistance if infected

2. Initiate ART
   - Strong possibility of infection
   - Test profile may be unfamiliar to routine treatment services
   - Could start ART but explore a treatment interruption in 12-18 mos
Sending queries to alias
Your CTU may have received an invitation to participate in this study

The protocol team for A5321, "Decay of HIV-1 Reservoirs in Subjects on Long-Term Antiretroviral Therapy: the ACTG HIV Reservoirs Cohort (AHRC) Study", is writing to request your site's interest in enrolling in a new, additional cohort in the existing ACTG Protocol A5321: The ACTG HIV Reservoirs Cohort (AHRC) Study. A5321 will be adding Group 6, for persons with confirmed or suspected HIV-1 infection acquired while taking long-acting injectable cabotegravir (CAB-LA) for HIV pre-exposure prophylaxis (PrEP). Such individuals may come from clinical trials, demonstration projects, or clinical programs, including routine care. There is great interest in understanding whether CAB-LA PrEP apparent "failures" may have more limited seeding of the HIV-1 reservoir when screening assays detect such failures at very low levels of viremia. However, such failures are rare. The other Groups of ACTG A5321 will not be open to non-US sites.

You are being asked about your interest in opening ACTG A5321 Group 6 because of your co-location or proximity to a site conducting HPTN 083 or HPTN 084, another demonstration project, or pilot PrEP program using CAB-LA.

CRS Leaders/CTU PI’s with ACTG core- or protocol-specific site designation, please confer with HPTN sites or clinics that provide CAB-LA pre-exposure prophylaxis that are local, overlapping, or geographically proximate (such that referral would be appropriate/feasible) regarding the feasibility of enrolling participants with HIV-1 infection acquired while taking CAB-LA for PrEP. This survey should be filled out by the ACTG core- or protocol-specific site after those discussions and with input from colleagues at HPTN or other PrEP delivery sites.

Please submit your responses in SurveyMonkey using the following link: https://www.surveymonkey.com/r/A5321SiteSurvey

Information that you provide in response to this query will greatly assist the A5321 team in determining whether any changes to the protocol should be considered.

Please complete the survey by January 25, 2023.

Have mapped most 084 sites to a CTU that may be included
Responding to updated guidance

- Balance potential for false negative vs false positive
- Balance need for PrEP vs need for ART
- Communicate diagnostic uncertainty and the trade offs of any decision
  - In these rare cases, there is no “right answer”
- Counselling and shared decision-making important
- Will need to also build effective partnerships with treatment partners esp treatment interruption is an option
- Community education
Next steps

- Reactions from sites
- Counselling discussion
- Provide information re potential A5321 sites
- Release revised HIV testing guidance
- Update SSP to provide additional guidance on these options
- Community conversations
- Anything else?
  - E.g. participant-facing materials regarding discordant results, purpose of the different tests, etc
Acknowledgments

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• The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.