HPTN 084: HIV testing and implications for starting ART

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24 January 2023

HPTN
HIV Prevention
Trials Network

V1.0

HIV testing during the OLE

	Blinded	Unblinded	Open Label Extension 1	Open Label Extension 2
Population	Women at Substantial Risk	Same	HPTN 084 + HPTN 084-1 participants	Those who received CAB in OLE 1
Site HIV Testing	**Rapid Antibody (1 or 2) plus Ag/Ab**	**Rapid Antibody (1 or 2) plus Ag/Ab**	**Added VL**	**Same**
Family Planning Requirement	Yes	Yes	No	No
Pregnancy	Stopped CAB, Used TDF/FTC	Stopped CAB, Used TDF/FTC	Pregnancy Study for CAB dosing	Pregnancy Study for CAB dosing
Oral Lead in	Oral Lead in required	Not applicable	Not required	Not applicable

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 negtive, Ag/Ab negative, HIV RNA <40 copies

Example 4

- Participant on CAB
- Initial visit
  - RDT negtive, 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

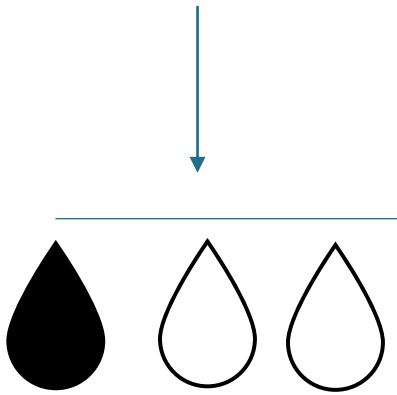
Summary experience in OLE1

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

	N=85
All 3 tests positive at index	4
2 tests positive at index	4
RDT only positive at index	19
Ag/Ab positive at index	43
HIV RNA positive at index ≤51	13
HIV RNA positive at index > 40	2

Considerations for interpretation of test results

Visit



Ag/Ab, RNA results available Product hold initiated at <u>next visit</u> if positive

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

If RDT negative, proceed to injection
<u>If positive product hold</u>

…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

Annals of Internal Medicine®

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Brief Communications | 5 January 1999

Misdiagnosis of HIV Infection by HIV-1 Plasma Viral Load Testing: A Case Series

Josiah D. Rich, MD, MPH, Nathan A. Merriman, ScB, Eleftherios Mylonakis, M

Author, Article, and Disclosure Information

https://doi.org/10.7326/0003-4819-130-1-199901050-00007

Use of an Indeterminate Range in HIV Early Infant Diagnosis: A Systematic Review and Meta-Analysis

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Challenge: interpretation of low viral loads, particularly with low pre-test probability of infection

… more data needed

HPTN 084 Long-acting Injectable For the Epidemic

Management of reactive HIV RNA

Index	Confirmatory	Recommendation
<200 copies, includes <LLOD	Not detected	Isolated positive; continue PrEP
<200 copies	<200 copies	Stop CAB, start ART
>200 copies	RNA detected	Stop CAB, start ART
>200 copies	RNA Not detected	Stop CAB, start ART

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: ?

HIV RNA and ART initiation

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

Potential referral to A5321

HPTN HIV Prevention Trials Network

Your CTU may have received an invitation to participate in this study

Date: January 11, 2023

To: ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators

From: Protocol Team A5321

Subject: Site Query for Protocol A5321

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

HPTN 084 Long-acting Injectable For the Epidemic

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 interuption 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

- Overall support for the HIV Prevention Trials Network (HPTN) is provided by the National Institute of Allergy and Infectious Diseases (NIAID), Office of the Director (OD), National Institutes of Health (NIH), National Institute on Drug Abuse (NIDA), the National Institute of Mental Health (NIMH), and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) under Award Numbers UM1AI068619-15 (HPTN Leadership and Operations Center), UM1AI068617-15 (HPTN Statistical and Data Management Center), and UM1AI068613-15 (HPTN Laboratory Center).

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