HIV Testing
in the Era of PrEP:
When the Tests are Discordant

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In HPTN 083, a full HIV testing algorithm is used at 57 study visits

- Each includes a rapid FDA-cleared HIV EIA and an instrumented (4th or 5th generation) Ag/Ab test
- Also an HIV RNA at screening and as clinically indicated during the study
- 4,500 participants will be enrolled
- ~256,500 HIV testing events
256,500 HIV Testing Events

- False Positive Rate (FPR) = 1-Specificity
- Each Instrumented Ag/Ab platform has unique performance characteristics
  - Reported Specificity of Abbott Architect Ag/Ab test is 100% with 95% CI 99.18-100%
  - FPR 0 (0-0.82%)
  - 0.82% x 256,500 = 2,103 false positive tests
2,103 False Positive Tests

- Likely overestimate, as does not account for those screened out for “false positive” testing prior to study entry
- Multiple testing methods at each visit also provide additional opportunity for false positive results
- **Must be balanced with high probability that a newly detected reactive/positive test in high-risk population more likely to represent real infection**
TDF/FTC PrEP Delays Seroconversion

- 25 days vs. 17 days to Feibig V
- 7-fold odds of >100 day delay in site detection of seroconversion
- 0.75 log decrease in viral load
December 18, 2015
Fourth-generation HIV Combo Ag/Ab assay
Nonreactive
Roche Cobas TaqMan HIV-1 Test v2.0
<20 no signal detected

May 17, 2016
Fourth-generation HIV Combo Ag/Ab assay
Reactive
HIV nucleic acid amplification assay (qualitative)
Reactive
Multispot HIV-1/2
Nonreactive
Roche Cobas TaqMan HIV-1 Test v2.0
<20 signal detected
CD4+ T-cell count: 1123 cells/mm³
CD4/CD8 ratio: 1.53

June 9, 2016
Fourth-generation HIV Combo Ag/Ab assay
Reactive
HIV nucleic acid amplification assay (qualitative)
Nonreactive
Multispot HIV-1/2
Nonreactive
Roche Cobas TaqMan HIV-1 Test v2.0
<20 no signal detected
Genotype of RT from patient proviral DNA
K65R and M184V; K103S, E138Q, and Y188L

May 3, 2016
Fourth-generation HIV Combo Ag/Ab assay
Reactive
HIV nucleic acid amplification assay (qualitative)
Reactive
Multispot HIV-1/2
Nonreactive

June 7, 2016
TFV-DP level in DBS: 1478 fmol/punch
TFV-DP level in hair: 0.0448 ng/mg
Genosure Archive test
Failed
<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Disease</th>
<th>Duration</th>
<th>Methods</th>
<th>Duration</th>
<th>Results</th>
<th>Symptoms</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>43♂</td>
<td>HSV1</td>
<td>2 mos</td>
<td>Seroconversion w/ MDR virus NRTI, NNRTI, INI</td>
<td>24 mos</td>
<td>(+) p24 ag RNA 27k (-) WB</td>
<td>Abd. Pain Colo: Sigmoid patches</td>
<td>Knox NEJM 2017</td>
</tr>
<tr>
<td>B</td>
<td>26♂</td>
<td>+/-</td>
<td>2 wks</td>
<td>Proviral DNA: Seroconversion w/ MDR virus NRTI, NNRTI (not partner’s)</td>
<td>5 mos</td>
<td>(+) 4th gen (+) Qual. NAAT (-) RNA</td>
<td>None</td>
<td>Markowitz JAIDS 2017</td>
</tr>
<tr>
<td>C</td>
<td>50♂</td>
<td>MP Chemsex LGV</td>
<td>Same day</td>
<td>Seroconversion w/ WT virus</td>
<td>8 mos</td>
<td>(+) 4th gen WB gp160 only (-) QL/QT RNA (-) PBMC DNA Interruption</td>
<td>Fever Dysuria</td>
<td>Hoornenborg Lancet HIV 2017</td>
</tr>
<tr>
<td>D</td>
<td>34♂</td>
<td></td>
<td>2 mos, on for 3, off for 2, restart without testing</td>
<td>Seroconversion w/ MDR virus NRTI, NNRTI</td>
<td>10 mos p restart</td>
<td>(+) 4th gen RNA 27K</td>
<td>None</td>
<td>Thaden CROI 2018 Abstract #1041</td>
</tr>
</tbody>
</table>
We have no information on delay of Seroconversion process with CAB

- Oral CAB may (or may not) be similar to oral TDF/FTC
- Limited information available for “time-to-viremia” during CAB LA decay
  - Few failures thus far in CAB LA treatment studies
  - 4x PA-IC$_{90}$ may be reasonable estimate
- CAB LA, if approved, will be deployed in varying-resources areas, thus a pragmatic approach must be balanced with caution
Approaches Considered

• Maximally conservative
  – Any reactive HIV testing = No further study products
  – Impractical: Impugns primary study outcome
  – Not consistent with clinical practice

• Minimally conservative
  – Absent RNA viremia, low risk for resistant quasispecies selection, continue
Consensus Panel Convened

Grace Aldrovandi MD PhD
Jared Baeten MD PhD
Bernard Branson MD
David Burns MD
Connie Celum MD MPH
Robert Coombs, PhD
Wafaa El-Sadr MD MPH
Sue Eshleman MD PhD
Jennifer Farrior
Myron S. Cohen MD
Deborah Donnell, PhD
Joseph J. Eron MD
Kailazarid Gomez-Feliciano
Robert Grant MD PhD
Beatriz Grinsztejn MD PhD
Mina Hosseinipour MD MPH
James P. Hughes PhD
Sinead Delaney-Moretlwe
David A. Margolis, MD MPH
Marybeth McCauley
Jean-Michel Molina MD PhD
Deborah Persaud MD PhD
Estelle Piwowar-Manning
James Rooney MD
Paul E. Sax MD
Scott Rose
Nirupama Deshamane Sista PhD
Sheryl Zwerski RN PhD
Index Visit (first f/u visit post reactive/positive HIV test result)

Rapid test non-reactive
Continue study product

Ag/Ab test reactive
Hold study product

Index Architect HIV Ag/Ab test S/CO ≤ 10 or S/CO value not reported

New study visit (confirmatory)

HIV rapid test; HIV Ag/Ab test (site);
HIV RNA test (site); Discriminatory test (site);
PBMC sample – HIV DNA test (LC)

Scenario 4
All tests from both visits negative/non-reactive except the HIV Ag/Ab test; repeat HIV Ag/Ab test negative or reactive with a S/CO ≤ 10 or S/CO value not reported

Infection unclear ➔ observe off study products for 4 weeks
HIV rapid test reactive, discriminatory test indeterminate, or repeat Ag/Ab test S/CO > 10

Infection likely ➔ permanently discontinue study product
➢ Refer for SOC ART

Discriminatory, HIV RNA, or HIV DNA test positive

Infection confirmed ➔ discontinue study product
➢ Refer for SOC ART

New study visit (4 weeks post product hold; only for those who did not permanently discontinue study product)

HIV rapid test; Architect HIV Ag/Ab test (site/regional);
Discriminatory test (site);
HIV RNA test (site);
PBMC sample – HIV DNA test (LC)

All tests negative/non-reactive except the HIV Ag/Ab test; post-hold HIV Ag/Ab test negative or reactive with a S/CO ≤ 10 or S/CO value not reported

Infection unlikely ➔ Re-enter study; resume study product or discontinue study product and follow per protocol
ACKNOWLEDGEMENTS

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Clinical Scenario #1

*Index Sample:* Reactive HIV rapid test, Negative instrumented HIV Ag/Ab test

**Rationale:** This scenario is consistent with false-positive HIV rapid testing. In the absence of a positive instrumented Ag/Ab test, an indeterminate or positive discriminatory test, or a positive HIV RNA test, it is very unlikely that a reactive point-of-care HIV rapid test represents true infection. The goal of this management strategy is to minimize time off study-product in a high-risk population. The risk of selecting for drug resistant HIV by continuing PrEP with a single ARV (cabotegravir) or a dual-agent regimen (TDF/FTC) is very low. If a positive HIV DNA test result is obtained from the confirmatory visit after study product is resumed, study products will be permanently discontinued and SOC ART will be initiated. If HIV rapid tests are reactive at subsequent study visits for participants who resume study product, please refer to additional considerations below (“Persistently Positive/Reactive HIV Screening Tests”).
Clinical Scenario #2

**Index Sample:** Reactive HIV rapid test, Reactive instrumented HIV Ag/Ab test (as defined by the manufacturer)

**Rationale:** Participants are presumed to be HIV infected when reactive/positive results are obtained for two different HIV screening assays, even if discriminatory tests, HIV RNA tests, and the HIV DNA test are negative. In these cases, viral replication and anti-HIV antibody production may be suppressed by PrEP. The guiding principle for this management strategy is to minimize the time from presumptive incident infection to initiation of fully suppressive ART, to minimize establishment of an HIV and maximize the potential for future elimination/cure of HIV infection.
Clinical Scenario #3

**Index Sample:** Reactive HIV rapid test, Reactive instrumented HIV Ag/Ab test (as defined by the manufacturer)

**Rationale:** Participants are presumed to be HIV infected if the Architect HIV Ag/Ab Combo test is reactive with a S/CO ratio >10. In these cases, viral replication and anti-HIV antibody production may be suppressed by PrEP. The guiding principle for this management strategy is to minimize the time from presumptive incident infection to initiation of fully suppressive ART, to minimize establishment of an HIV and maximize the potential for future elimination/cure of HIV infection.
Clinical Scenario #4

Index Sample: **Negative** rapid HIV test, **Reactive** Architect HIV Ag/Ab test with a signal-to-cutoff ratio (S/CO) ≤10 or S/CO ratio not reported by the laboratory

**Rationale:** There is some evidence that HIV RNA should be detected 4 weeks after TDF/FTC discontinuation. Negative test results for a discriminatory test (if performed), an HIV RNA test, and an HIV DNA test, all performed 4 weeks after TDF/FTC discontinuation, provide reasonable assurance that a participant is not infected. There are no data on the amount of time required after injections stop before HIV antibody, HIV RNA or HIV DNA will be detected in individuals who become infected while receiving CAB-LA PrEP. One could argue that 4 weeks after discontinuation of CAB-LA injections would not be long enough for HIV infection to be unmasked. However, withholding of PrEP from participants at high-risk for HIV acquisition for 8 or 12 weeks (the time anticipated for CAB-LA to “decay” to 4 x PA-IC90) is not prudent. In addition, in the absence of detectable HIV RNA and HIV DNA, the risk of selecting for drug-resistant HIV in those with true infection should be very low. Further, continued use of single- or dual-drug PrEP, even in cases with low-level reservoir seeding, could theoretically lead to reservoir eradication (cure of infection). Therefore, a 4-week interval after the last CAB-LA injection seems to provide a reasonable balance of risks and benefits in this setting. If instrumented HIV Ag/Ab tests are reactive at subsequent study visits for participants who resume study product, please refer to additional considerations below (“Persistently Positive/Reactive HIV Screening Tests”).