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HIV Testing in the Era of PrEP:

When the Tests are Discordant

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HPTN Regional Meeting, Lima Peru, March 26, 2018

Scope of the Challenge

- 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 (4^{th} or 5^{th} 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

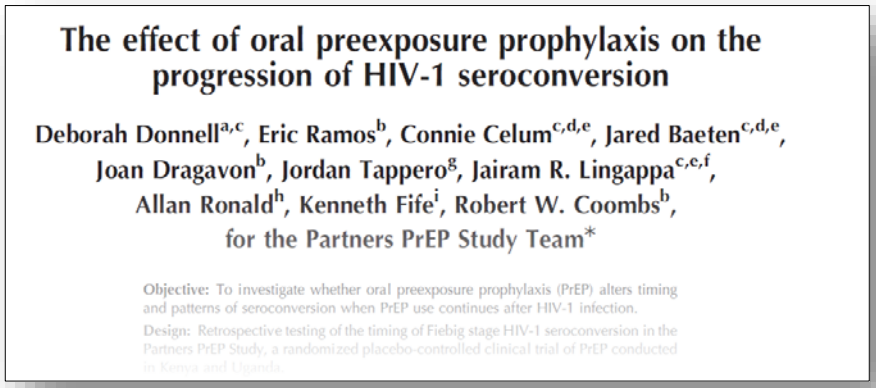
- False Positive Rate (FPR) = 1-Specificity
- Each Instrumented Ag/Ab platform has unique performance characteristics
  - Reported Specificity of Abbott Architecht Ag/Ab test is 100% with 95% CI 99.18-100%
  - FPR 0 (0-0.82%)
  - 0.82% x 256,500 = **2,103 false positive tests**

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



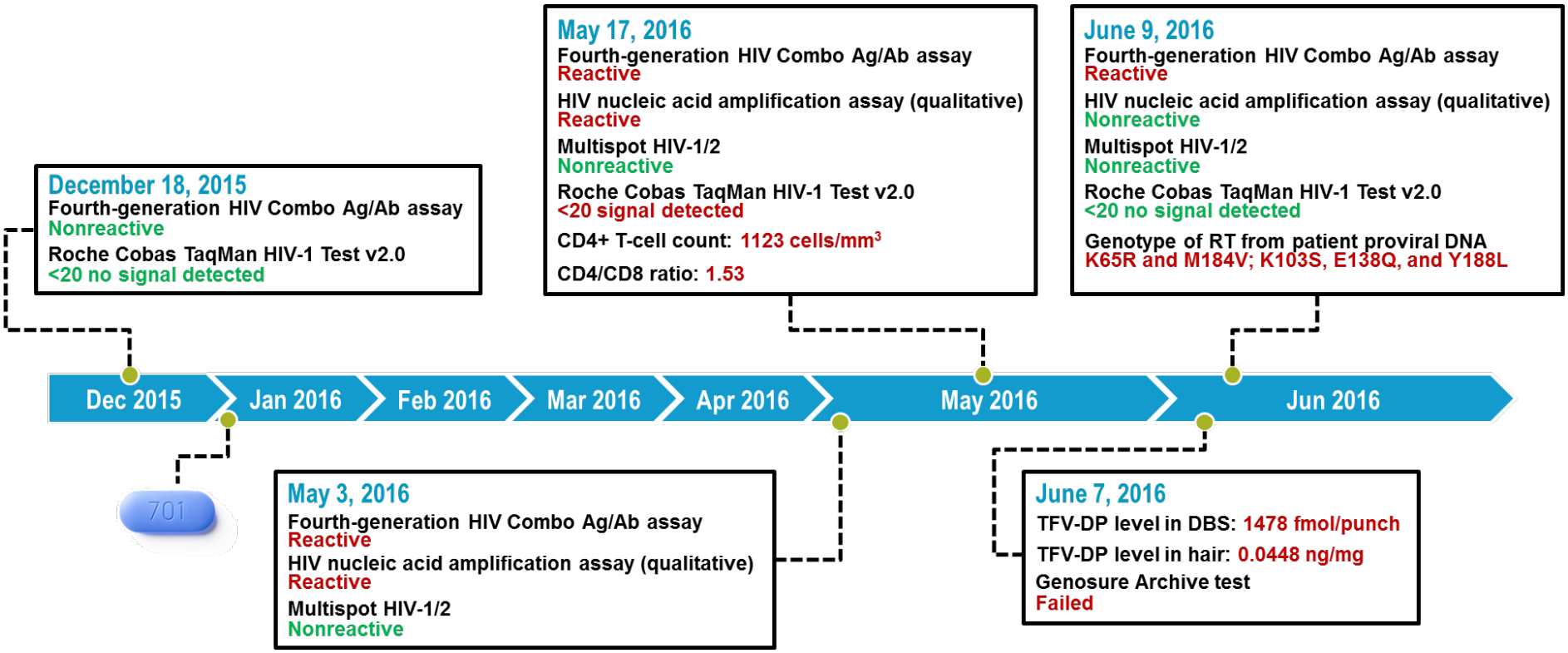
The effect of oral preexposure prophylaxis on the progression of HIV-1 seroconversion

Deborah Donnell[a,c], Eric Ramos[b], Connie Celum[c,d,e], Jared Baeten[c,d,e], Joan Dragavon[b], Jordan Tappero[g], Jairam R. Lingappa[c,e,f], Allan Ronald[h], Kenneth Fife[i], Robert W. Coombs[b], for the Partners PrEP Study Team*

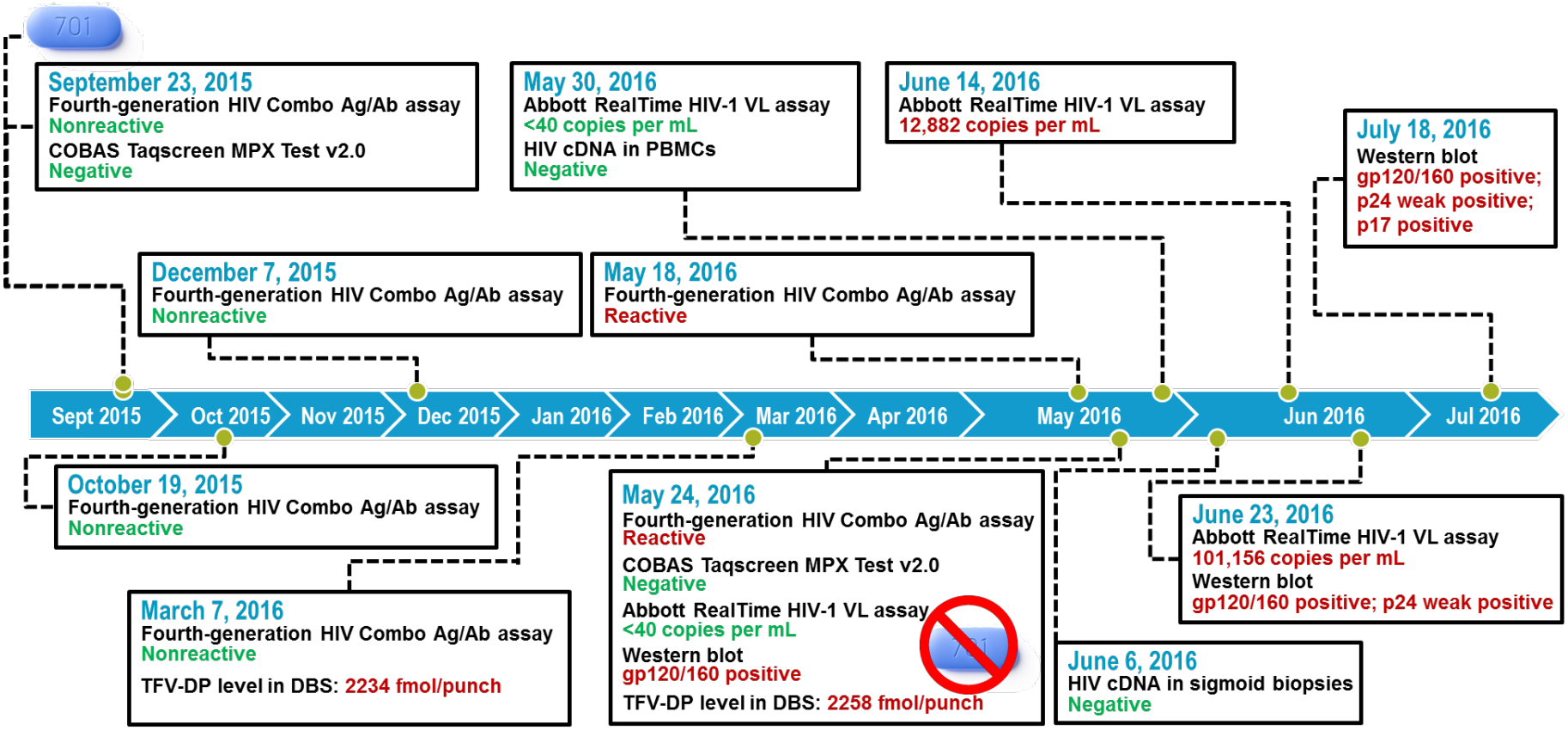
Objective: To investigate whether oral preexposure prophylaxis (PrEP) alters timing and patterns of seroconversion when PrEP use continues after HIV-1 infection.

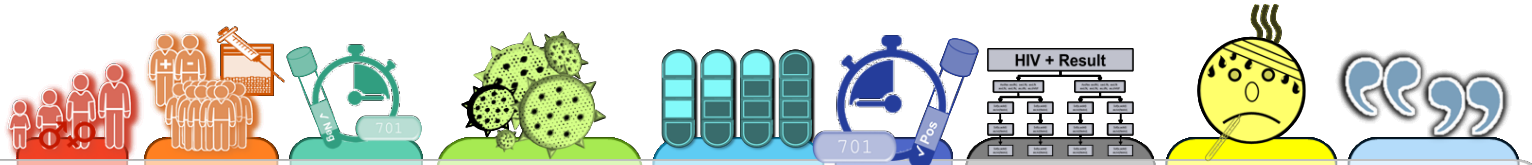
Design: Retrospective testing of the timing of Fiebig stage HIV-1 seroconversion in the Partners PrEP Study, a randomized placebo-controlled clinical trial of PrEP conducted in Kenya and Uganda.

MARKOWITZ, JAIDS, 2017



HOORNENBORG, LANCET HIV, 2017





Subject A	43♂	HSV1	2 mos	Seroconversion w/ MDR virus NRTI, NNRTI, INI	DBS, plasma	24 mos	(+) p24 ag RNA 27k (-) WB	Abd. Pain Colo: Sigmoid patches	Knox NEJM 2017
Subject B	26♂	+/-	2 wks	Proviral DNA: Seroconversion w/ MDR virus NRTI, NNRTI (not partner's)	DBS, hair	5 mos	(+) 4th gen (+) Qual. NAAT (-) RNA	None	Markowitz JAIDS 2017
Subject C	50♂	MP Chemsex LGV	Same day	Seroconversion w/ WT virus	DBS	8 mos	(+) 4th gen WB gp160 only (-) QL/QT RNA (-) PBMC DNA Interruption	Fever Dysuria	Hoornenborg Lancet HIV 2017
Subject D	34♂		2 mos, on for 3, off for 2, restart without testing	Seroconversion w/ MDR virus NRTI, NNRTI	Plasma, hair	10 mos p restart	(+) 4th gen RNA 27K	None	Thaden CROI 2018 Abstract #1041

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

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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
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Robert Grant MD PhD
Beatriz Grinsztejn MD PhD
Mina Hosseinipour MD MPH
James P. Hughes PhD
Sinead Delaney-Moretlwe
Daniel R. Kuritzkes
David A. Margolis, MD MPH
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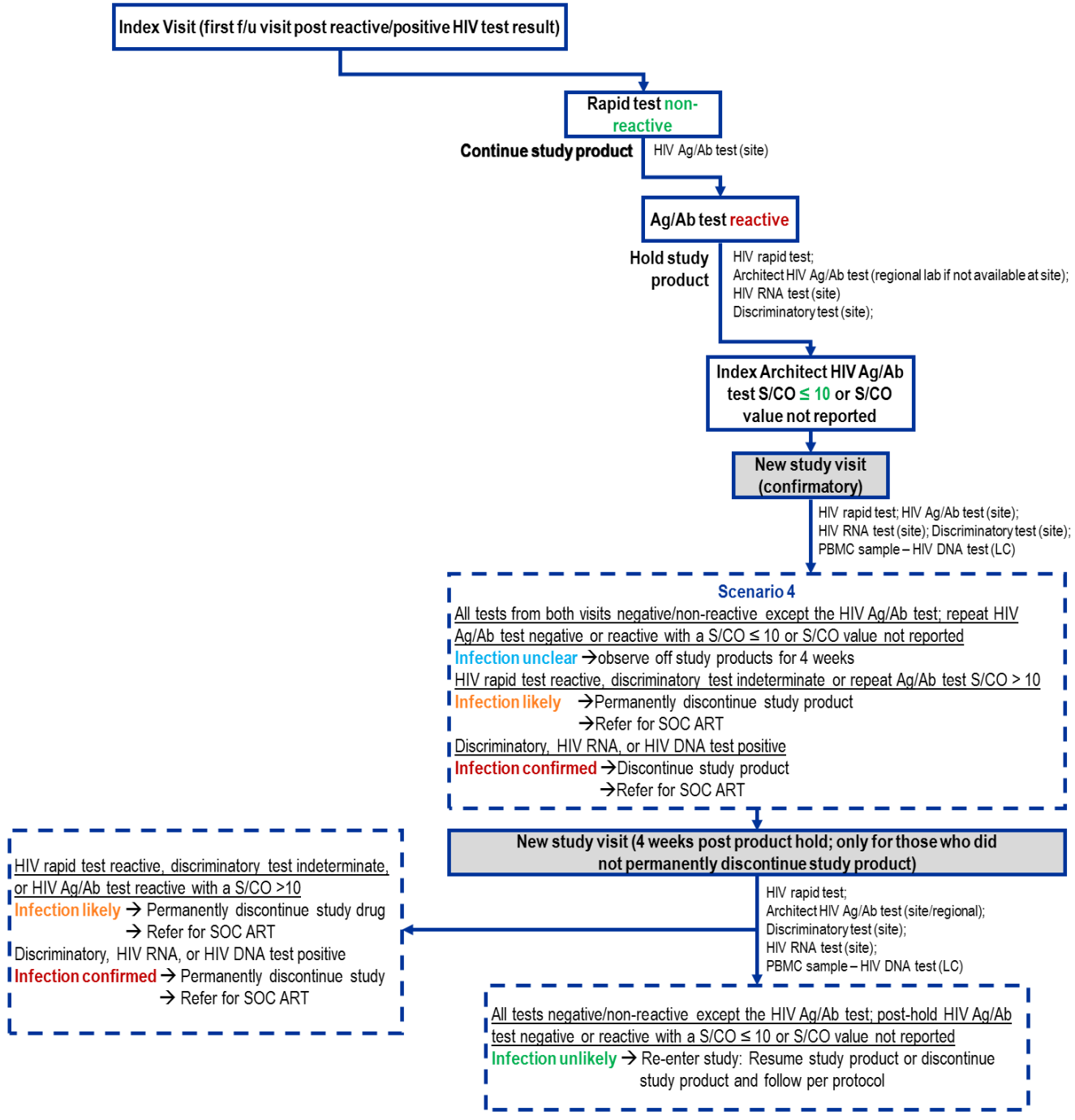
Jean-Michel Molina MD PhD
Deborah Persaud MD PhD
Estelle Piwowar-Manning
James Rooney MD
Paul E. Sax MD
Scott Rose
Nirupama Deshamane Sista PhD
Sheryl Zwerski RN PhD


Index Visit (first f/u visit post reactive/positive HIV test result)
Rapid test non-reactive
Continue study product
HIV Ag/Ab test (site)
Ag/Ab test reactive
Hold study product
HIV rapid test;
Architect HIV Ag/Ab test (regional lab if not available at site);
HIV RNA test (site)
Discriminatory test (site);
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 reactive, discriminatory test indeterminate, or HIV Ag/Ab test reactive with a S/CO >10
Infection likely → Permanently discontinue study drug
→ Refer for SOC ART
Discriminatory, HIV RNA, or HIV DNA test positive
Infection confirmed → Permanently discontinue study
→ Refer for SOC ART
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

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ACKNOWLEDGEMENTS

The HIV Prevention Trials Network is funded by the National Institute of Allergy and Infectious Diseases (UM1AI068619, UM1AI068613, UM1AI1068617), with co-funding from the National Institute of Mental Health, and the National Institute on Drug Abuse, all components of the U.S. National Institutes of Health.

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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.

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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”).