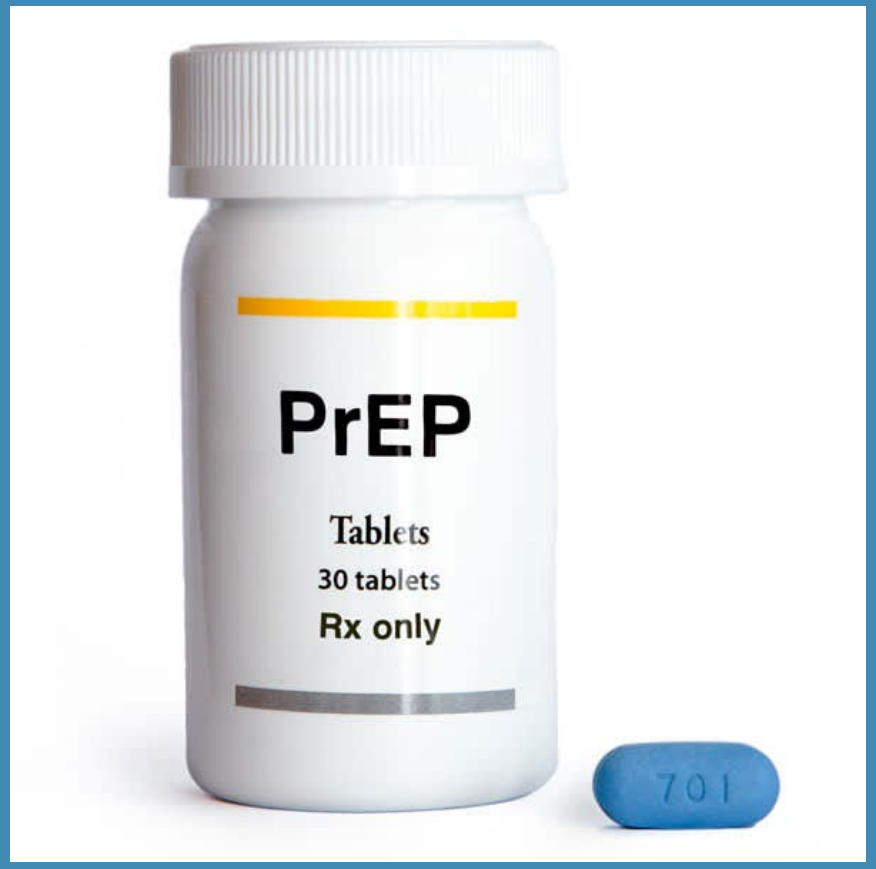
HIV NAAT TESTING IN THE MANAGEMENT OF HIV PREP



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Speaker Disclosures

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Chief Medical Officer, Q Care Plus | Avita Care Solutions

Former VP Medical Affairs, San Francisco AIDS Foundation (& Magnet Medical Director), Medical Co-Director, East Bay Advanced Care, & Clinical Medical Director, Molecular Testing Labs

does not speak for, invest in, or otherwise directly receive support from pharma

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In remembrance

Dr. Dawn K. Smith

(MD, MS, MPH)

1949-2022

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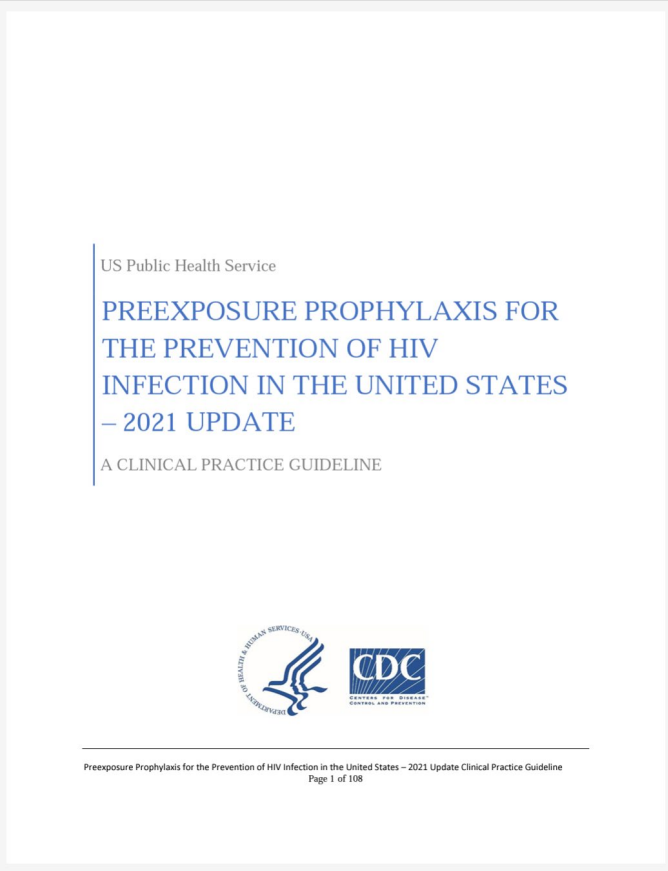
CDC HIV PREP GUIDELINES



US Public Health Service

PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES – 2021 UPDATE

A CLINICAL PRACTICE GUIDELINE

Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2021 Update Clinical Practice Guideline
Page 1 of 108

Updated December 2021
2017
2014
Interim guidance
First oral PrEP agent FDA-approved in 2012

Centers for Disease Control and Prevention: US Public Health Service: Preexposure prophylaxis for the prevention of HIV infection in the United States—2021 Update: a clinical practice guideline. https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf. Published December 2021

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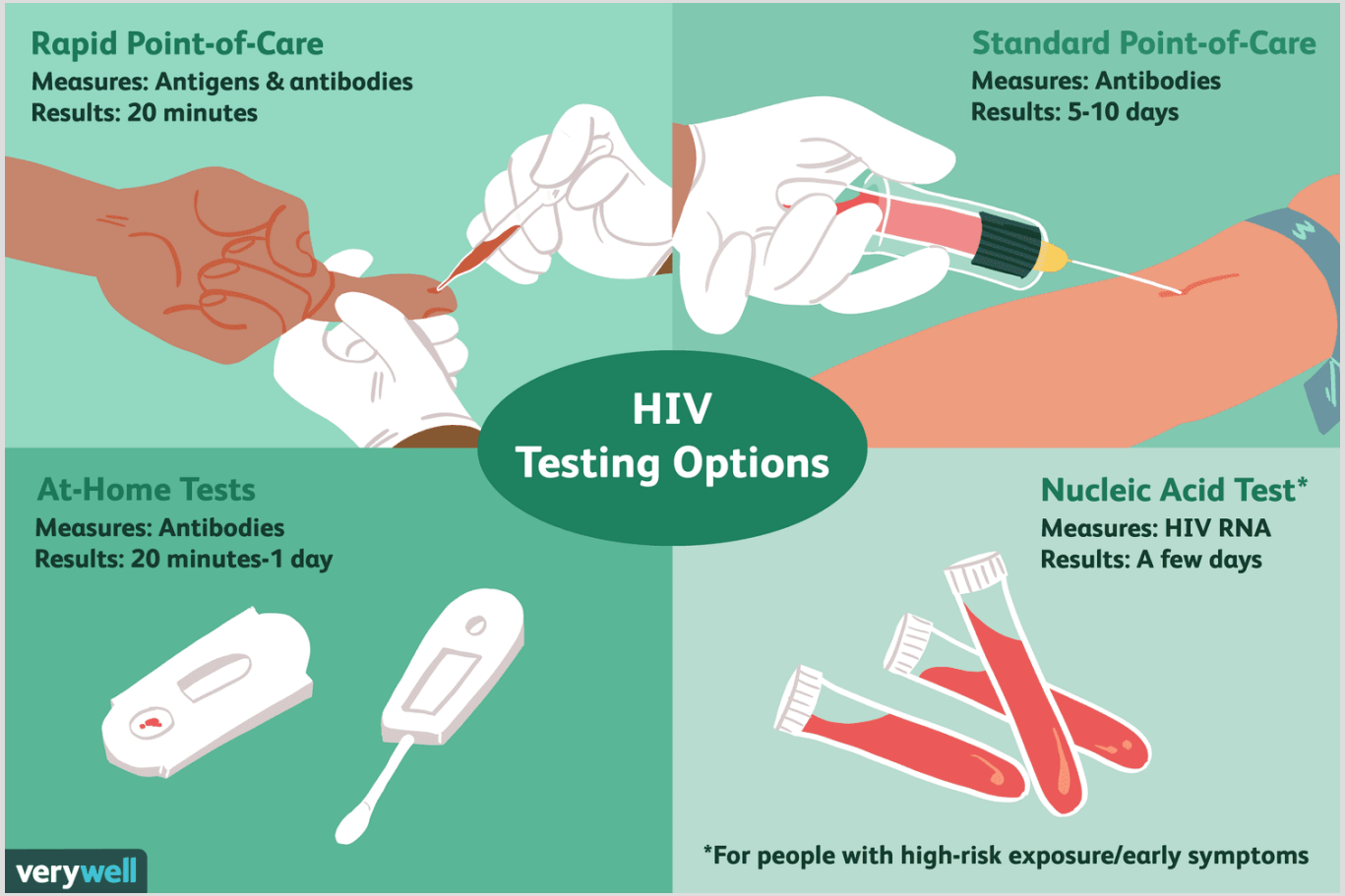
HIV TESTING MODALITIES



FACTORS
Specimen type
Assay Target
Collection Setting
Turn around time
Logistics of collection
Regulatory considerations

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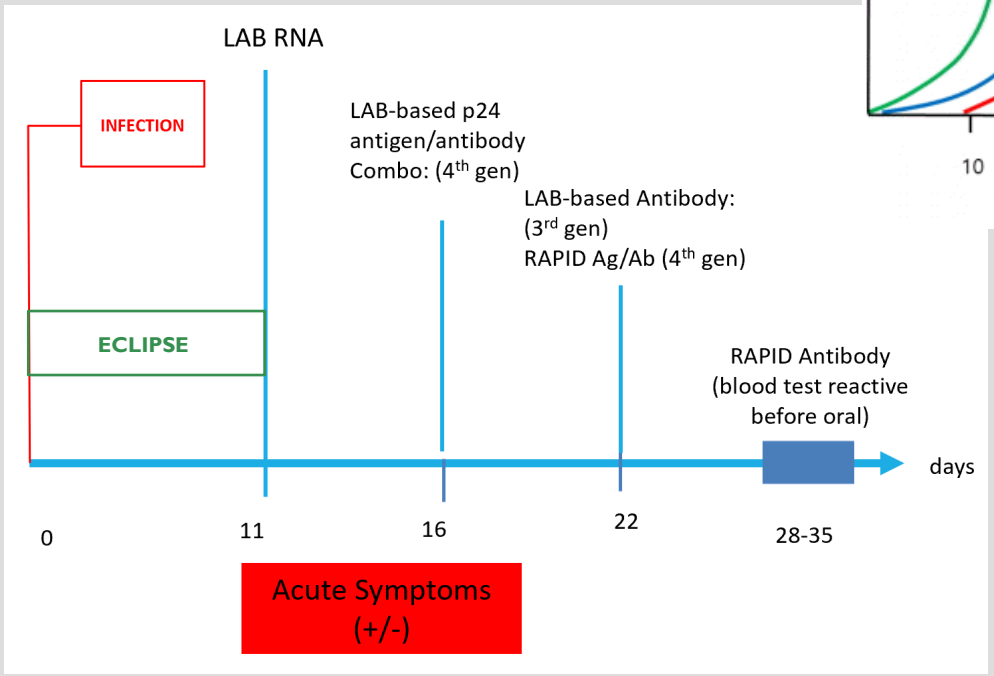
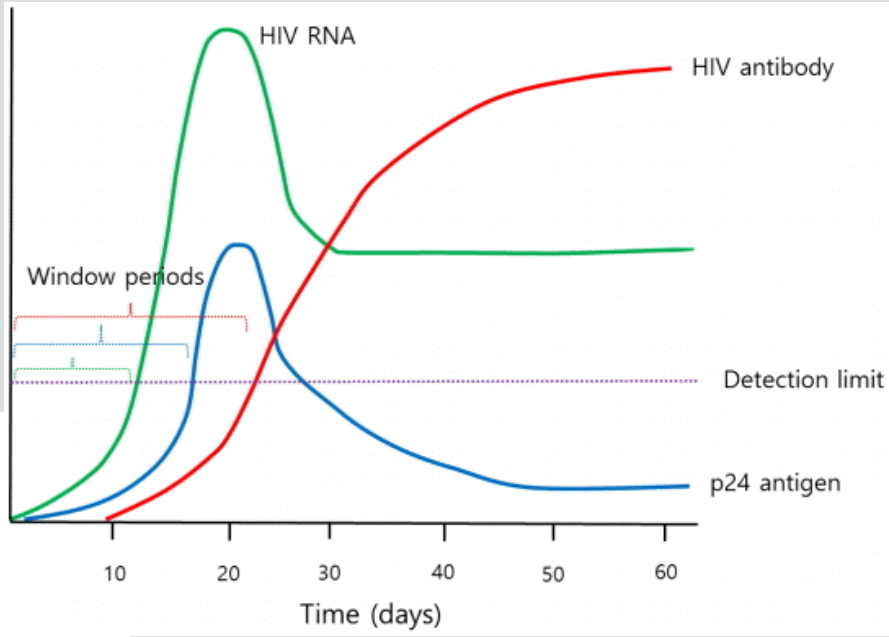
Predictability of Negative Status by HIV Tests

Approximate Sensitivity of HIV Tests for Acute/Recent Infection



HIV Infection Markers: "Window Periods"



Eclipse Phase: The short interval following HIV acquisition in which no diagnostic test is capable of detecting HIV.

Adapted from Bacon, SFCC, SFDPH

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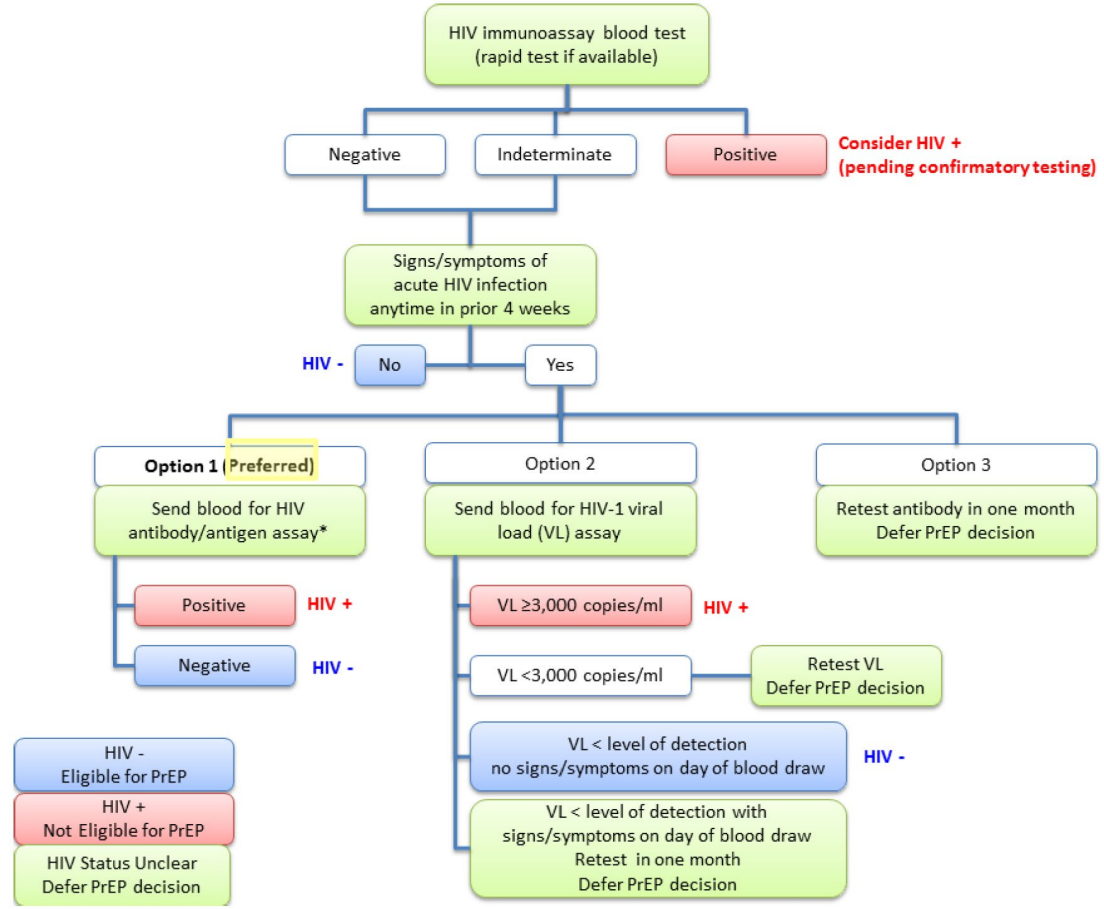
CDC GUIDANCE – 3/2018 TO 12/2021

Figure Clinician Determination of HIV Status for PrEP Provision



Centers for Disease Control and Prevention: US Public Health Service: Preexposure prophylaxis for the prevention of HIV infection in the United States—2017 Update: a clinical practice guideline. https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf. Published March 2018.

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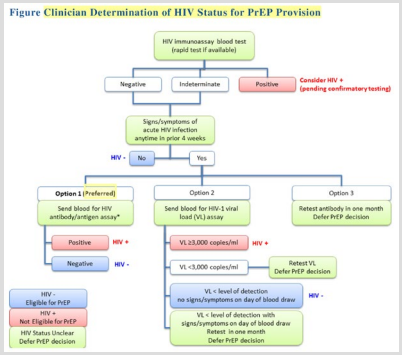
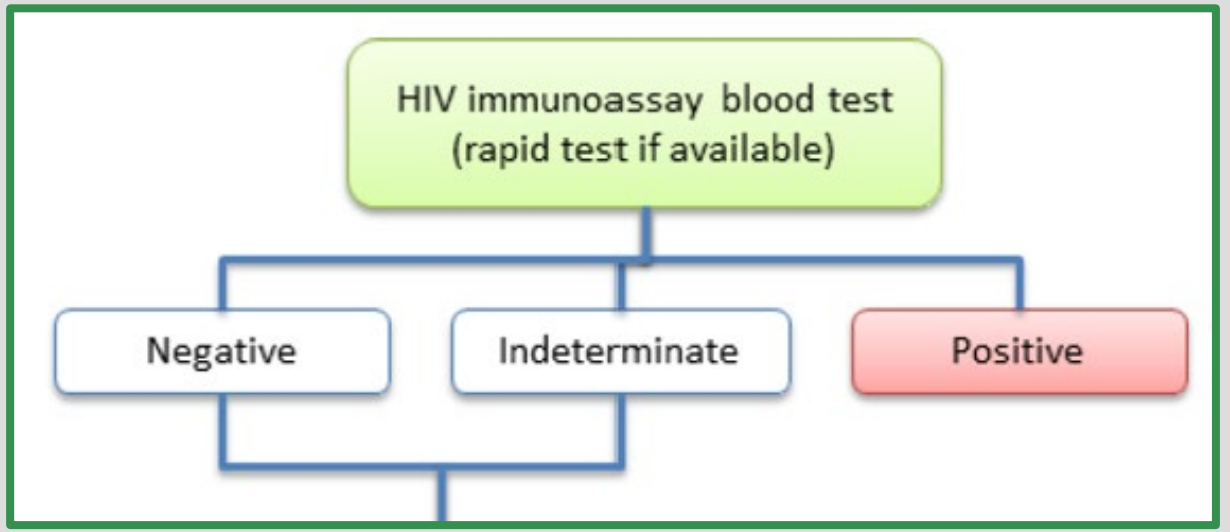
CDC GUIDANCE – 3/2018 TO 12/2021 PART 2





***Only* an immunoassay (i.e., antibody and/or antigen) test recommended**

Centers for Disease Control and Prevention: US Public Health Service: Preexposure prophylaxis for the prevention of HIV infection in the United States—2017 Update: a clinical practice guideline. https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf. Published March 2018.

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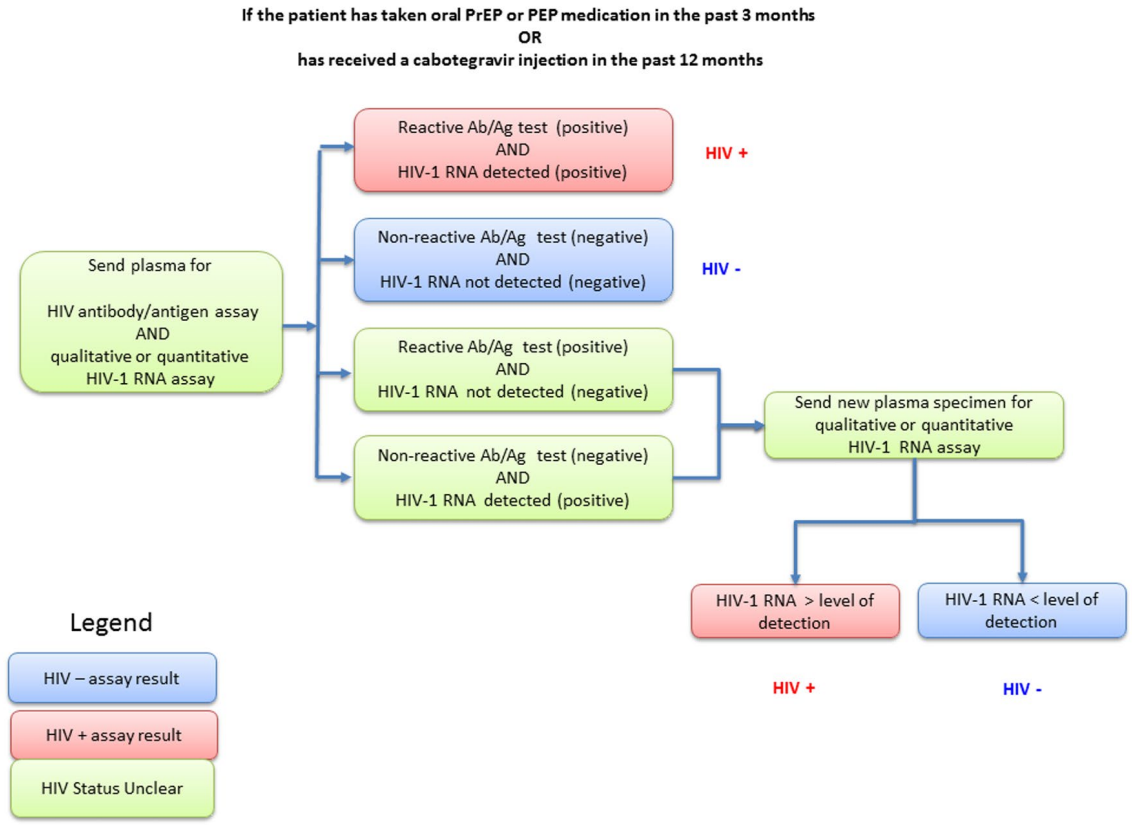
CDC GUIDANCE AS OF DECEMBER 2021

Figure 4b Clinician Determination of HIV Status for PrEP Provision to Persons with Recent or Ongoing Antiretroviral Prophylaxis Use



Centers for Disease Control and Prevention: US Public Health Service: Preexposure prophylaxis for the prevention of HIV infection in the United States—2021 Update: a clinical practice guideline. www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf. Published December 8, 2021

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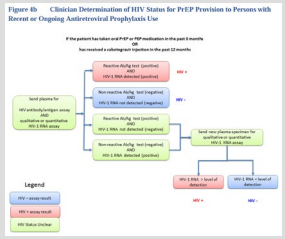
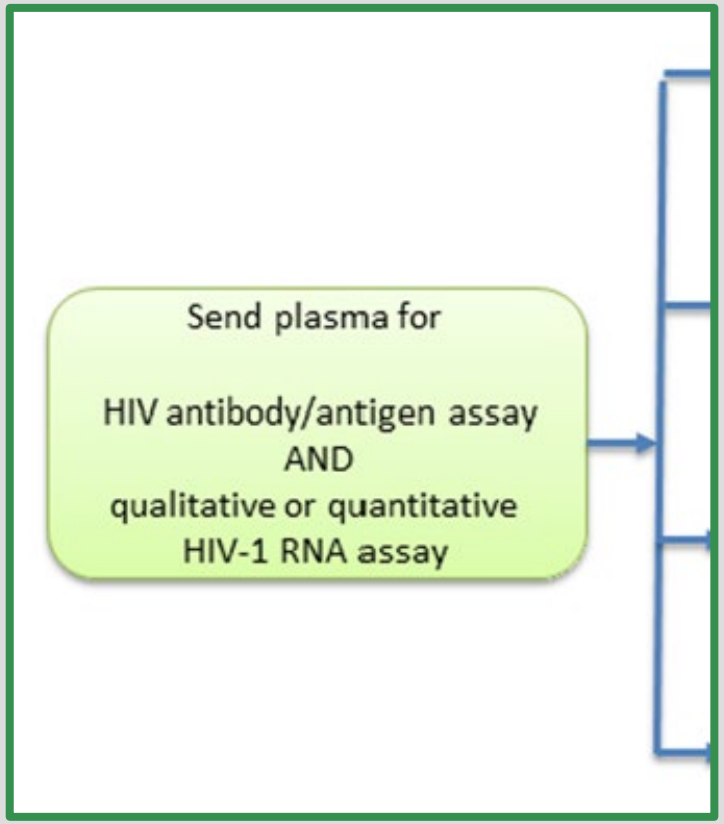
CDC GUIDANCE AS OF DECEMBER 2021

PART 2





<u>Both</u> Ag/Ab test <u>and</u> a qualitative or quantitative HIV RNA assay are recommended

Centers for Disease Control and Prevention: US Public Health Service: Preexposure prophylaxis for the prevention of HIV infection in the United States—2021 Update: a clinical practice guideline. www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf. Published December 8, 2021

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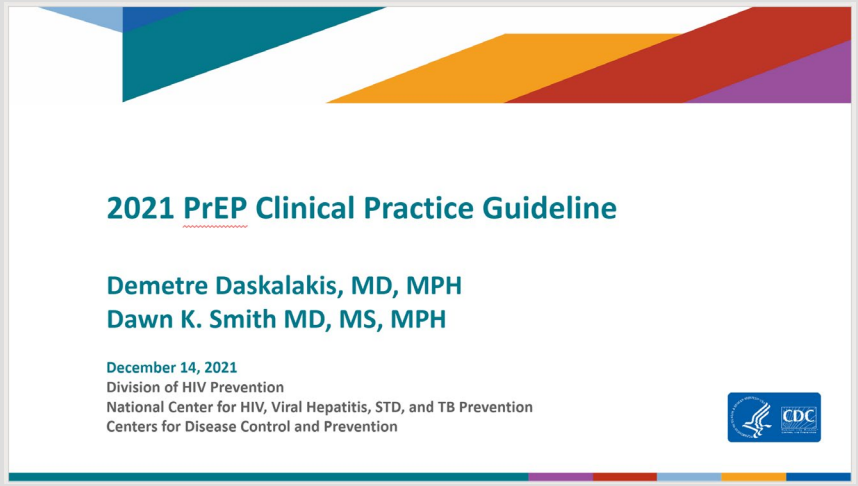
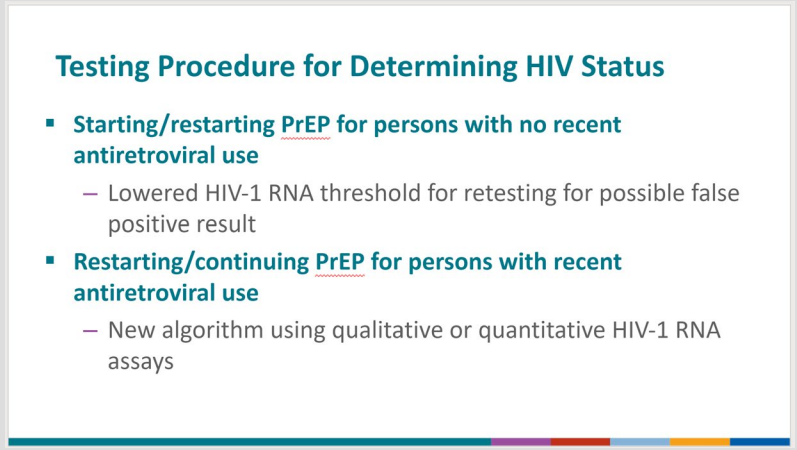
DELAYED HIV AG/AB DETECTION IN HPTN 083 (CABOTEGRAVIR-LA)





Delay between 1st reactive qualitative HIV-1 RNA test and 1st reactive Ag/Ab test (HPTN 083)

	Cabotegravir Arm			F/TDF Arm	
	Baseline n=4	Incident No CAB n=5	Incident ON CAB n=7	Baseline n=3	Incident n=30
Participant number (%)	3(75)	0	**7(100)**	3(100)	**8(21)**
Duration of delay, range, days (amongst those with delayed Ag/Ab test result)	**14-60**	**NA**	**35-185**	**14-36**	**7-68**

Extract from: Marzinke MA et al. JID, 2021:224(9):1581-1592

Daskalakis and Smith, DHP / CDC. "2021 PrEP Clinical Guideline" webinar, December 14, 2021

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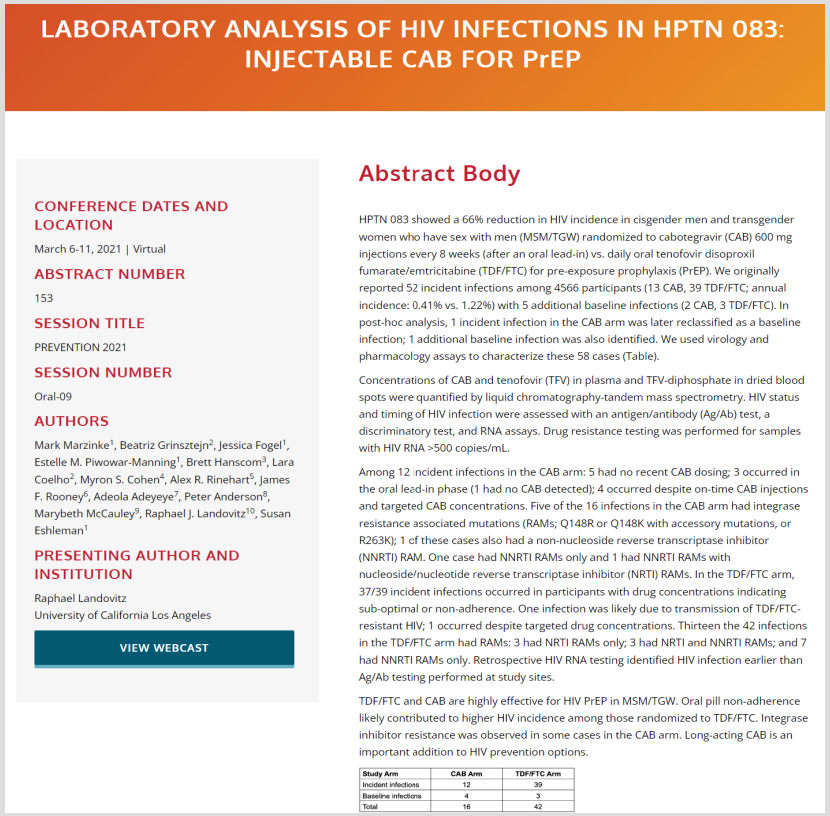
DELAYED HIV AG/AB DETECTION IN HPTN 083 (CABOTEGRAVIR-LA) PART 2



LABORATORY ANALYSIS OF HIV INFECTIONS IN HPTN 083: INJECTABLE CAB FOR PrEP

CONFERENCE DATES AND LOCATION

March 6-11, 2021 | Virtual

ABSTRACT NUMBER

153

SESSION TITLE

PREVENTION 2021

SESSION NUMBER

Oral-09

AUTHORS

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VIEW WEBCAST

Abstract Body

HPTN 083 showed a 66% reduction in HIV incidence in cisgender men and transgender women who have sex with men (MSM/TGW) randomized to cabotegravir (CAB) 600 mg injections every 8 weeks (after an oral lead-in) vs. daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for pre-exposure prophylaxis (PrEP). We originally reported 52 incident infections among 4566 participants (13 CAB, 39 TDF/FTC; annual incidence: 0.41% vs. 1.22%) with 5 additional baseline infections (2 CAB, 3 TDF/FTC). In post-hoc analysis, 1 incident infection in the CAB arm was later reclassified as a baseline infection; 1 additional baseline infection was also identified. We used virology and pharmacology assays to characterize these 58 cases (Table).

Concentrations of CAB and tenofovir (TFV) in plasma and TFV-diphosphate in dried blood spots were quantified by liquid chromatography-tandem mass spectrometry. HIV status and timing of HIV infection were assessed with an antigen/antibody (Ag/Ab) test, a discriminatory test, and RNA assays. Drug resistance testing was performed for samples with HIV RNA >500 copies/mL.

Among 12 incident infections in the CAB arm: 5 had no recent CAB dosing; 3 occurred in the oral lead-in phase (1 had no CAB detected); 4 occurred despite on-time CAB injections and targeted CAB concentrations. Five of the 16 infections in the CAB arm had integrase resistance associated mutations (RAMs; Q148R or Q148K with accessory mutations, or R263K); 1 of these cases also had a non-nucleoside reverse transcriptase inhibitor (NNRTI) RAM. One case had NNRTI RAMs only and 1 had NNRTI RAMs with nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) RAMs. In the TDF/FTC arm, 37/39 incident infections occurred in participants with drug concentrations indicating sub-optimal or non-adherence. One infection was likely due to transmission of TDF/FTC-resistant HIV; 1 occurred despite targeted drug concentrations. Thirteen the 42 infections in the TDF/FTC arm had RAMs: 3 had NRTI RAMs only; 3 had NRTI and NNRTI RAMs; and 7 had NNRTI RAMs only. Retrospective HIV RNA testing identified HIV infection earlier than Ag/Ab testing performed at study sites.

TDF/FTC and CAB are highly effective for HIV PrEP in MSM/TGW. Oral pill non-adherence likely contributed to higher HIV incidence among those randomized to TDF/FTC. Integrase inhibitor resistance was observed in some cases in the CAB arm. Long-acting CAB is an important addition to HIV prevention options.

Study Arm	CAB Arm	TDF/FTC Arm
Incident infections	12	39
Baseline infections	4	3
Total	16	42

Laboratory Analysis of HIV Infections in HPTN 083: Injectable CAB for PrEP

"Among the small number of HIV infections that occurred, the capacity of CAB LA to suppress viral replication masked the presence of the virus by reducing viral load and preventing seroconversion to HIV antibody positive (delaying HIV diagnosis)."*

* Richard Jefferys, "The Challenge of Diagnosing HIV Infection in LA PrEP Users," TAGLine, October 2021

Mark Marzinke, Beatriz Grinsztejn, Jessica Fogel, Estelle M. Piwowar-Manning, Brett Hanscom, Lara Coelho, Myron S. Cohen, Alex R. Rinehart, James F. Rooney, Adeola Adeyeye, Peter Anderson, Marybeth McCauley, Raphael J. Landovitz, Susan Eshleman, "Laboratory Analysis of HIV Infections in HPTN 083: Injectable CAB for PrEP," CROI 2021, Abstract 153, March 6-11, 2021

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(B1-B5)	No recent CAB exposure [c]
(C1-C3)	Infected during the CAB oral lead-in period
(D1-D4)	Infected in the setting of on-time CAB-LA injections

DELAYED HIV AG/AB DETECTION IN HPTN 083 (CABOTEGRAVIR-LA) PART 3

Volume 224, Issue 9
1 November 2021

Table 2. Human Immunodeficiency Virus (HIV) Test Results Associated with Delays in Detection of HIV Infection [a]

	CAB Arm			TDF/FTC Arm	
	Baseline: Group A (n=4)	Incident: Group B (n=5)	Incident: Groups C and D (n=7)	Baseline (n=3)	Incident (n=39)
Delay between 1st reactive qualitative RNA test and 1st reactive Ag/Ab test					
Participants, no. (%)	3(75)	0	7(100)	3(100)	8(21)
Duration of delay, range, d (among those with delayed Ag/Ab test result)	14-60[b]	NA	35-185	14-36	7-68[c]

"HIV testing was performed at study sites using locally available tests."

"Retrospective testing was performed at the HPTN Laboratory Center and other laboratories in the United States."

"In the CAB arm, detection of infection was delayed at study sites in all 4 baseline cases and 7 (58.3%) of 12 incident cases (median delay [range], 62 [28–72] days for baseline cases and 98 [35–185] days for incident cases)."

"In the TDF/FTC arm, detection of infection was delayed at study sites in all 3 baseline cases and 7 of 39 incident infections (17.9%) (median delay [range], 34 [14–36] days for baseline cases and 31 [7–68] days for incident cases."

Marzinke et al, Characterization of Human Immunodeficiency Virus (HIV) Infection in Cisgender Men and Transgender Women Who Have Sex With Men Receiving Injectable Cabotegravir for HIV Prevention: HPTN 083 *Journal of Infectious Diseases*, Volume 224, Issue 9, 1 November 2021, Pages 1581–1592, https://doi.org/10.1093/infdis/jiab152

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HIV RNA UTILIZATION IN ORAL PREP MANAGEMENT: ADVANTAGES & DISADVANTAGES

Advantages	Disadvantages
More sensitive test minimizes false-negatives	Higher cost of RNA vs. other; Ex: HIV Ag/Ab (no reflex) $27 vs. $329 for quant RNA vs. $389 for qual)
Identifies **acute seroconverters earlier** in HIV infection	RNA testing may entail additional logistical challenges (phlebotomy, etc.)
Further minimizes the already small chance of a PrEP patient developing **ARV-resistant HIV infection**	Significant programmatic change for programs managing oral PrEP users since 2012
Compensates for the risk of partial adherence (gaps in dosing) leading to HIV infection	Third party payors may not reimburse multiple HIV screening tests obtained on the same day
	Unclear evidence level establishing a safety signal in oral PrEP users
	No commercially available self-collected LDT with LLOD below approx. 600 IU
	Use of a second test raises concern in patients that "PrEP doesn't work"

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HIV RNA UTILIZATION IN ORAL PREP MANAGEMENT: OBSERVATIONS & IMPLICATIONS

Observations & Implications
Increasing participation in (scaling) PrEP is critical to diminishing forward HIV transmission, in an effort to achieve EHE objectives
Barriers that limit programs' ability to scale PrEP may be counterproductive
Widespread adoption of a more sensitive HIV testing approach **has been limited** by cost, logistics, longstanding patterns of practice, and other factors
Understanding the benefit of enhanced sensitivity testing since 12/2021 Guideline recommendations will be important
Contribution of **cost effectiveness analyses** will be helpful
Tension between a **population health vs. medical care model** informs local adoption of this clinical policy

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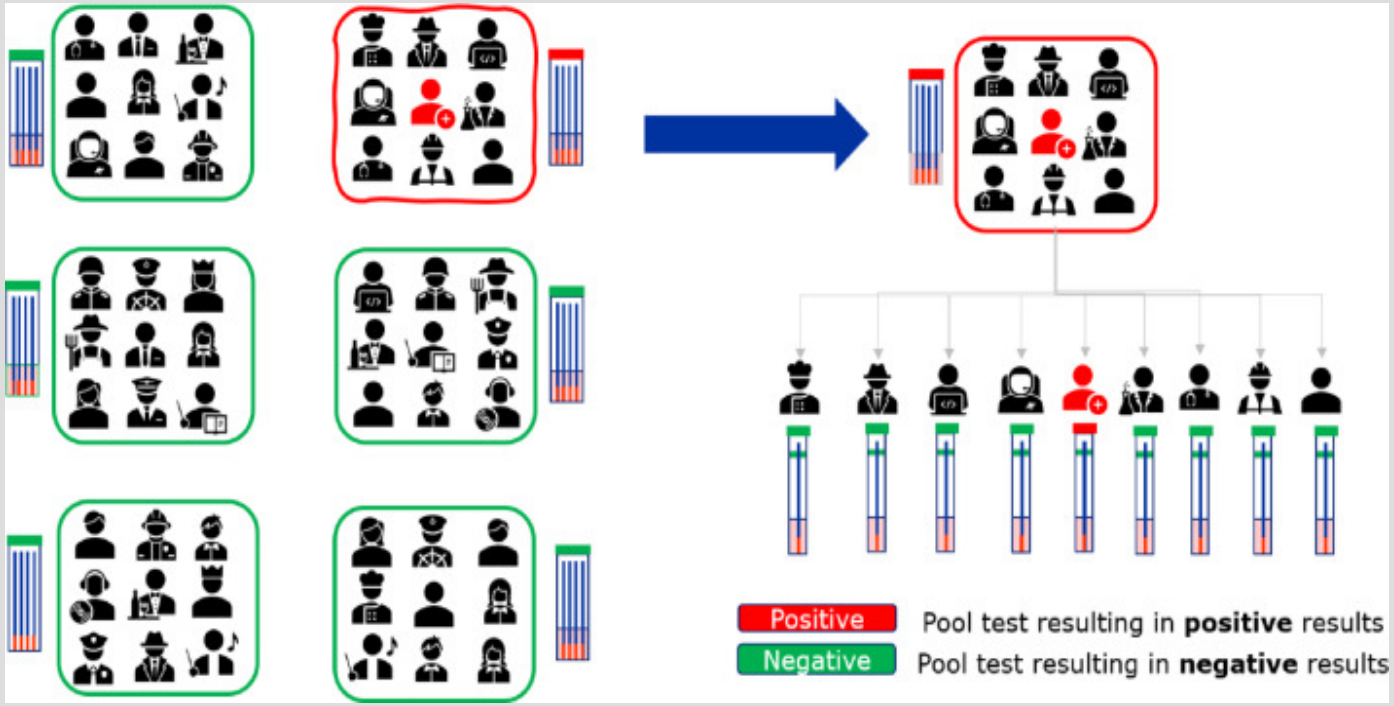
ACUTE HIV DIAGNOSIS BY SPECIMEN POOLING

Only one of the pools requires further RNA testing to identify the reactive specimen
Once a reactive pool is identified, original specimens that contributed to that pool are then tested individually to identify reactive specimen
In this example, 15 HIV RNA tests substituted for 48 such tests, were the individuals each tested separately
Limitations: increase laboratory tech effort, lengthened turn-around time
Population characteristics and pool size must be taken into consideration to identify a cost-effective specimen pooling approach.



In some settings, lab-based RNA pooling of persons testing Ab-negative is an alternative means of identifying acute HIV seroconverters without RNA testing each individual

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For More Information

This presentation and underlying evaluation was conducted by the California Prevention Training Center at UCSF

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