

Impact of PrEP on HIV Detection

Brian Custer

Vitalant Research Institute

&

University of California San Francisco

11 May 2023



IPFA/PEI 29th International Workshop on Surveillance and Screening of Blood-borne Pathogens

10 - 11 May, 2023 | Bologna, Italy



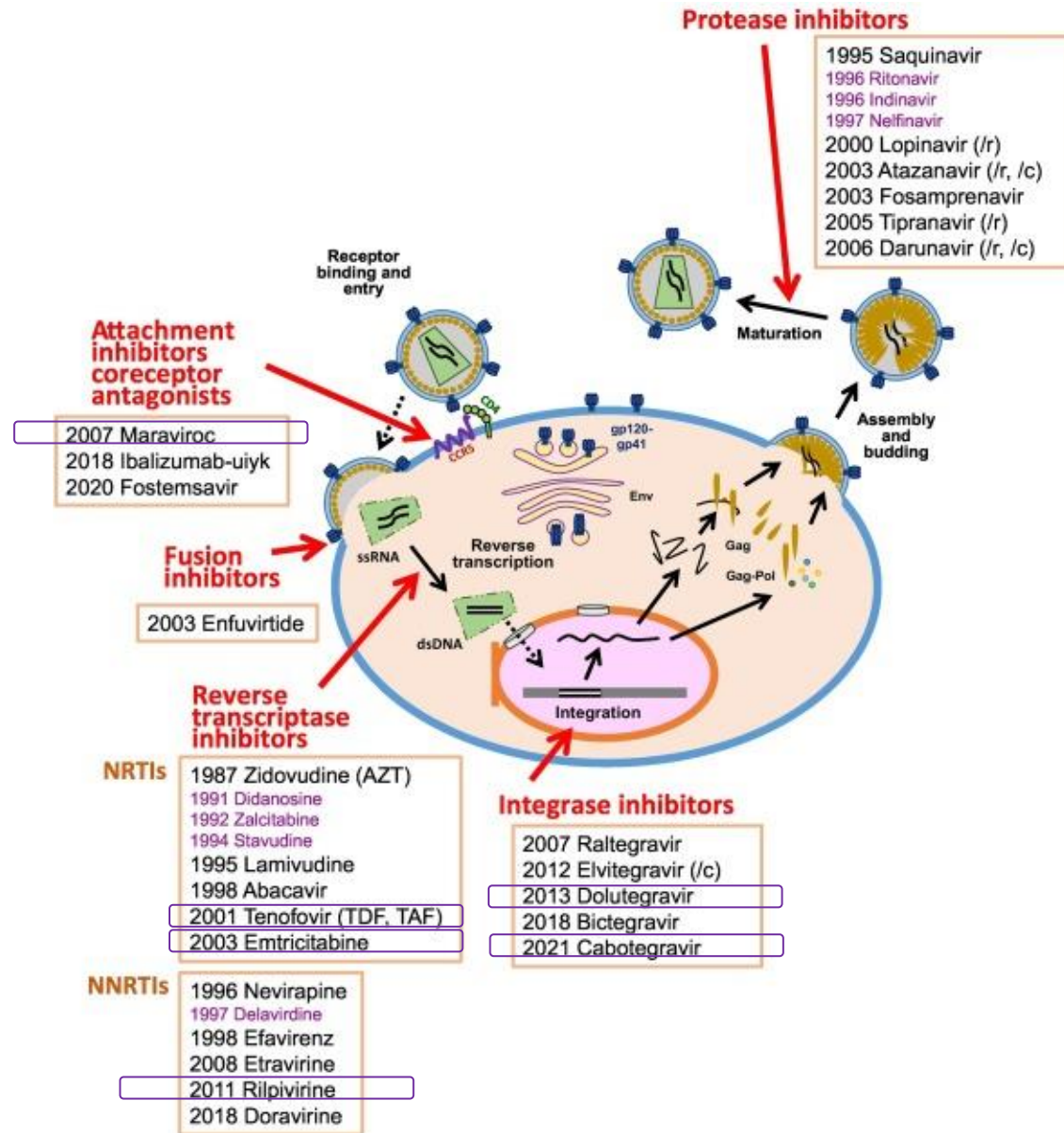
Disclosures

Grifols Diagnostics Solutions

Abbott Speakers Bureau

Pre-Exposure Prophylaxis (PrEP) Clinical Trials of Long-Acting Methods

Internal use



NIAID is funding research on 4 types of long-acting HIV prevention.

INTRAVAGINAL RING (IVR)



Polymer ring inserted into the vagina releases antiretroviral drug over time.

IMPLANT



Device implanted in the body releases antiretroviral drug over time.

INJECTABLE



Long-acting antiretroviral drug is injected into the body.

ANTIBODY



Antibody is infused or injected into the body.

How many products are under investigation?



dapivirine IVR

(MTN 034/REACH clinical trials)

tenofovir IVR (CONRAD)

Truvada IVR (Oak Crest Institute of Science)



cabotegravir (SLAP-HIV project)

dolutegravir (University of North Carolina)

tenofovir alafenamide (Oak Crest Institute of Science)

tenofovir alafenamide & emtricitabine

(Houston Methodist Research Institute)



cabotegravir (HPTN 077, 083 & 084 clinical trials)



CAP256V2LS (NIAID VRC & CAPRISA)

N6LS (VRC 609 clinical trial)

PGT121.414.LS (NIAID)

Sanofi trispecific antibody (NIAID VRC & Sanofi)

VRC01

(AMP Studies, HVTN 116 & IMPAACT P1112 clinical trials)

VRC01LS (HVTN 116 & IMPAACT P1112 clinical trials)

VRC07-523LS

(VRC 610, HVTN 127/HPTN 087 & IMPAACT P1112 clinical trials)

REVIEW

Challenges of HIV diagnosis and management in the context of pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP), test and start and acute HIV infection: a scoping review

Tamara Elliott^{1,2} , Eduard J Sanders^{3,4}, Meg Doherty⁵, Thumbi Ndung'u^{6,7,8,9}, Myron Cohen¹⁰ , Pragna Patel¹¹, Gus Cairns^{12,13}, Sarah E Rutstein¹⁰, Jintanat Ananworanich^{14,15} , Colin Brown^{16,17} and Sarah Fidler^{1,18,S} 

Discussion: Missed acute HIV infection prevents people living with HIV (PLHIV) from accessing early treatment, increases likelihood of onward transmission, and allows for inappropriate initiation or continuation of PrEP, which may result in HIV drug resistance. While immediate ART is recommended for all PLHIV, studies have shown that starting ART in the setting of acute HIV infection may result in a delayed or complete absence of development of HIV-specific antibodies, posing a diagnostic challenge that is particularly pertinent to resource-limited, high HIV burden settings where HIV-antibody POCTs are standard of care. Similarly, ART used as PrEP or PEP may suppress HIV RNA viral load, complicating current HIV testing algorithms in resource-wealthy settings where viral detection is included. As rollout of PrEP continues, HIV testing algorithms may need to be modified.

Conclusions: With increasing use of PrEP and ART in acute infection we anticipate diagnostic challenges using currently available HIV testing strategies. Research and surveillance are needed to determine the most appropriate assays and optimal testing algorithms that are accurate, affordable and sustainable.

Impact of early ART on HIV test performance

Incomplete HIV Type 1 Antibody Evolution and Seroreversion in Acutely Infected Individuals Treated with Early Antiretroviral Therapy

Sigall Kassutto,^{1,2} Mary N. Johnston,² and Eric S. Rosenberg²

Clinical Infectious Diseases 2005;40:868–73

- 3/150 patients did not develop fully evolved Ab pattern (2%)
- Ab testing performed using HIV-1/2 ELISA (Abbott) and HIV-1 Western blot (BioRad)
- VL measured using Roche Amplicor and Chiron branched DNA

Generation	Capture reagent	Detects
1st	Whole viral lysate	IgG antibody
2nd	Recombinant proteins or synthetic peptides	IgG antibody
3rd	Recombinant proteins or synthetic peptides	IgM and IgG
4th	Recombinant proteins or synthetic peptides; anti-p24 antibody	IgM, IgG and p24
5th	Recombinant proteins or synthetic peptides; anti-p24 antibody	Distinguishes between p24 and antibodies

Seroreversion in Subjects Receiving Antiretroviral Therapy during Acute/Early HIV Infection

C. Bradley Hare,¹ Brandee L. Pappalardo,^{4,a} Michael P. Busch,⁴ Annika C. Karlsson,^{2,a} Bruce H. Phelps,⁵ Steven S. Alexander,⁶ Christopher Bentsen,⁷ Clarissa A. Ramstead,¹ Douglas F. Nixon,² Jay A. Levy,³ and Frederick M. Hecht¹

Clinical Infectious Diseases 2006;42:700–8

- 6/87 subjects developed seroreversion (7%)
- Ab testing performed using 2nd-gen EIAs (BioMérieux, Bio-Rad), 3rd-gen EIA (Bio-Rad), strip immunoblot assay (Chiron), and Western blot assays (Ortho, Bio-Rad)

Early ART: REDS-III MATHS cohort

- SANBS-led study (Vermeulen and colleagues)
- 925 total samples tested (19 elite, 52 acute, 40 recent; ~7-11 samples per participant spanning 1.2-1.5 years)
 - Ab reactivity comparing ART within 30 days vs 30-90 days vs >90 days of EDDI
 - Rapid assays

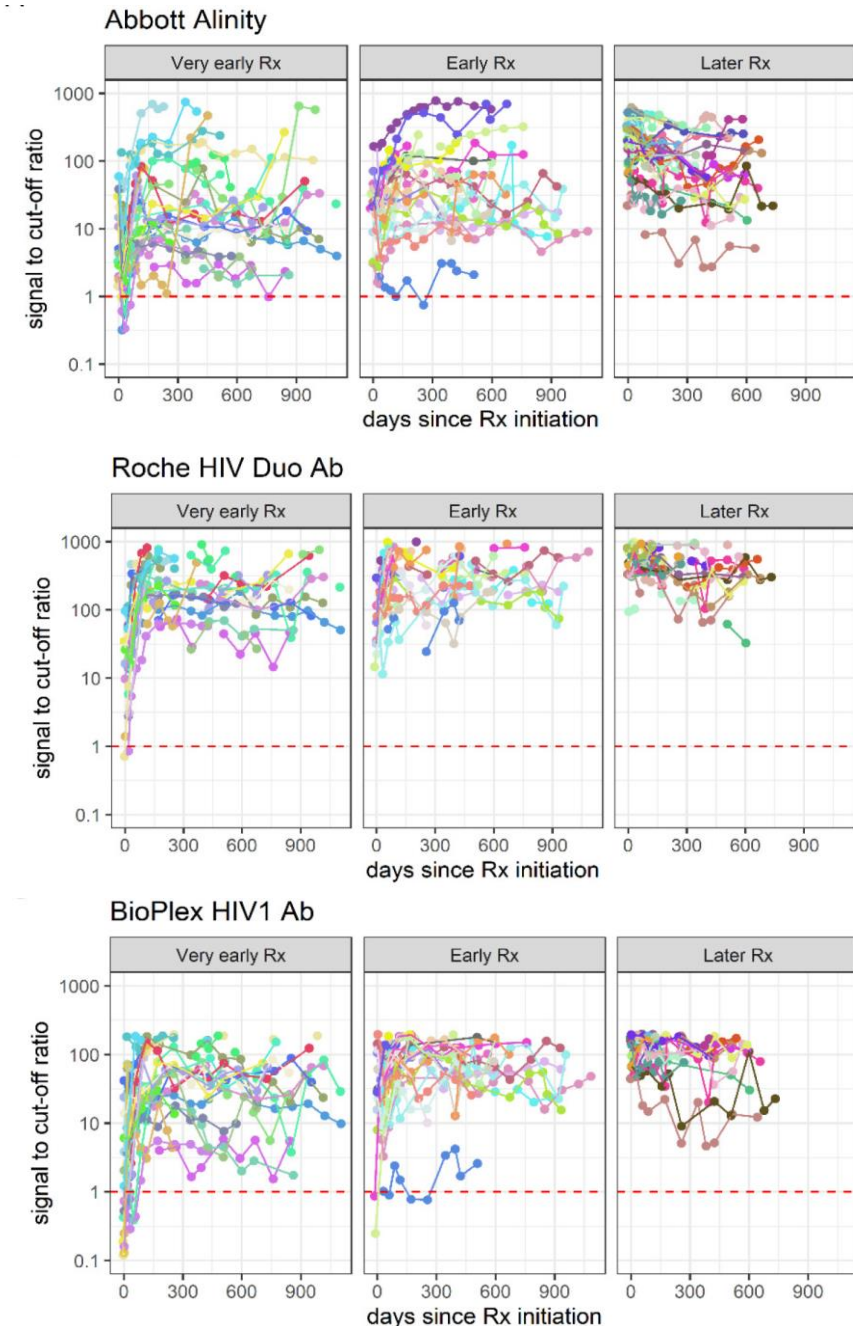
“4 th generation” instrumented Ag/Ab combo test	
Abbott Alinity s HIV Ag/Ab Combo	Chemiluminescent
“5 th generation” instrumented Ag/Ab combo tests	
Bio-Rad Bioplex HIV Ag-Ab assay	Fluorescent
Roche Elecsys HIV Duo	Electrochemiluminescent

Completed blood screening studies: ART not PrEP

The Impact of Early Antiretroviral Treatment (ART) for HIV on the Sensitivity of the Latest Generation of Blood Screening and Point of Care Assays

Marion Vermeulen^{1,2,*} , Cari van Schalkwyk³, Genevieve Jacobs¹, Karin van den Berg^{1,2,4} , Mars Stone^{5,6}, Sonia Bakkour^{5,6}, Brian Custer^{5,6} , Ute Jentsch¹, Michael P. Busch^{5,6}, Edward Murphy^{5,6} and Eduard Grebe^{3,5,6}

The absence of a pattern of declining reactivity on high-throughput screening assays, even in the very early treatment group, and 100% detection using these assays in all treatment groups, are reassuring.



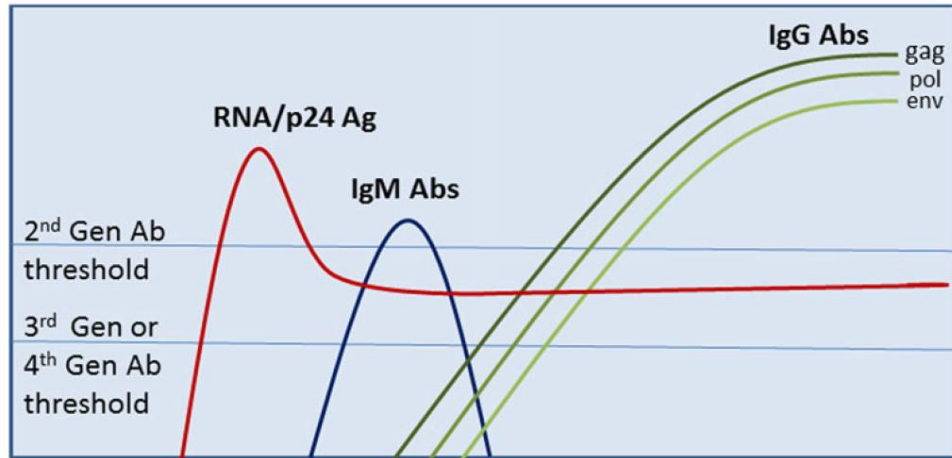
HIV infection progression

Timing Is Everything: Shortcomings of Current HIV Diagnostics in the Early Treatment Era

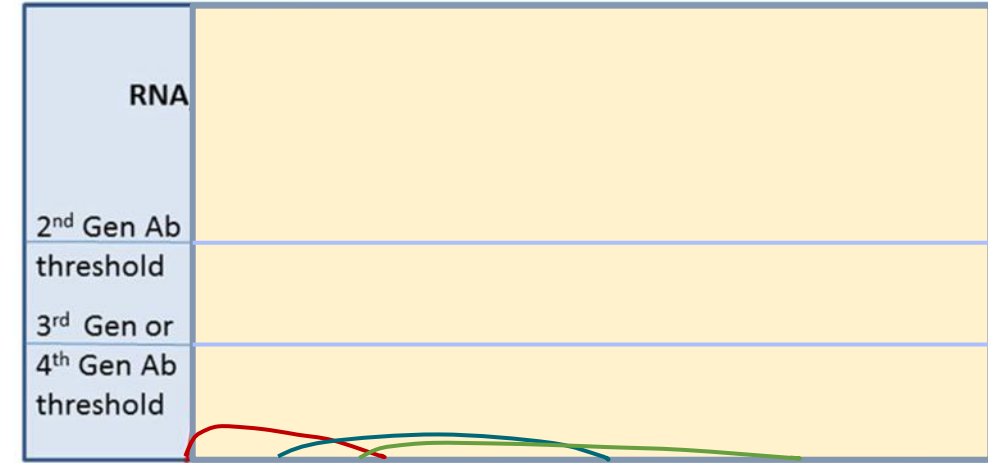
Sheila M. Keating, Christopher D. Pilcher, and Michael P. Busch

Blood Systems Research Institute and Departments of Medicine and Laboratory Medicine, University of California, San Francisco

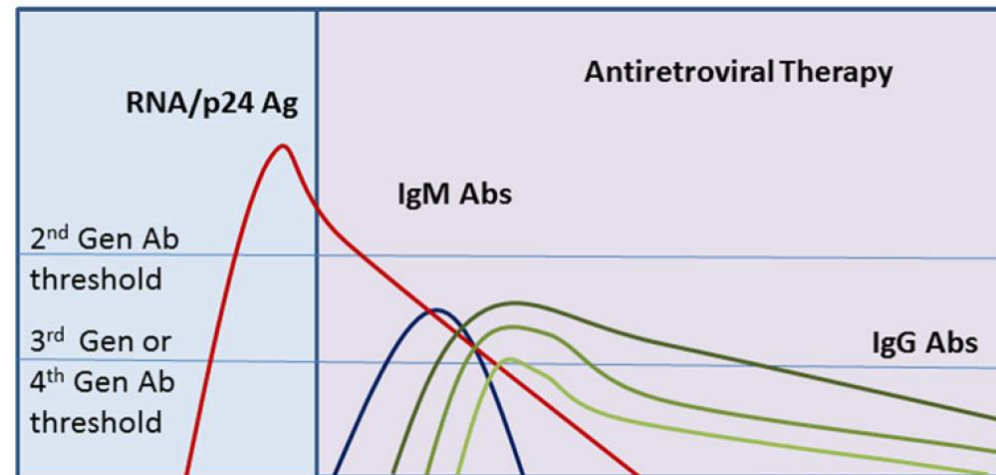
Without ART



PrEP Breakthrough?



With Early ART



- What happens to HIV progression and detection for someone taking PrEP or PEP if there is a breakthrough rather than aborted infection?
- How will the biomarkers of infection be altered?
- Can we detect those markers using blood screening assays?

The context is important – Many options for PrEP and direct to consumer marketing of pharmaceuticals in the US

Internal use



teva | emtricitabine and tenofovir
disoproxil fumarate
tablets 200mg/300mg

Are Emtricitabine and Tenofovir
Disoproxil Fumarate Tablets for PrEP
Right for Me?

Getting
Started

**A Single Pill Taken
Once Daily Can Help
Reduce the Risk of
HIV-1 Infection**

Teva's FDA-approved generic
version of Truvada®
(emtricitabine 200
mg/tenofovir disoproxil
fumarate 300 mg) tablets



PrEP and Blood Donation in the U.S.

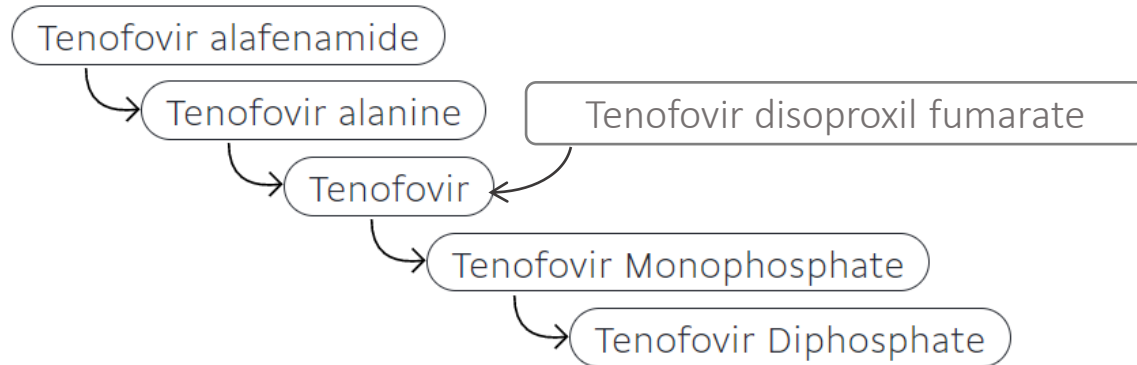
- Use has steadily increased among populations targeted for public health interventions (MSM, higher risk heterosexuals, persons who inject drugs)
- **Truvada®** consists of dual therapy of emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF)
 - Approved for use as PrEP in 2012 (approved as ART in 2004)
 - Generic version first approved for use in 2017, not available until 2020
 - Prescribed as pills taken daily by mouth
- **Descovy®** consists of dual therapy of emtricitabine (FTC) and tenofovir alafenamide (TAF)
 - Approved for use as PrEP in 2016 (approved as ART in 2015)
 - Prescribed as pills taken daily by mouth

For blood donation, use of oral PrEP is asked on the donor history questionnaire (DHQ) and is a 3-month deferral since last use

- **Apretude®** is monotherapy of injected cabotegravir (CAB)
 - Approved for use as PrEP in 2021
 - Long-acting antiretroviral shown to be highly effective in preventing HIV infection
 - Prescribed as IM injections every 2 months

Next version of DHQ: For blood donation, use of injected PrEP is a 2-year deferral since last injection (until more data are available)

Tenofovir: TAF and TDF in PBMCs



Tenofovir Diphosphate (TFV-DP) is a competitive inhibitor of HIV-1 reverse transcriptase

PBMC TFV-DP concentrations have been a strong correlate of PrEP efficacy in clinical trials, with concentrations of 40 and 83 fmol/10⁶ cells being associated with 90 and 99% efficacy in the iPrEx study, respectively.

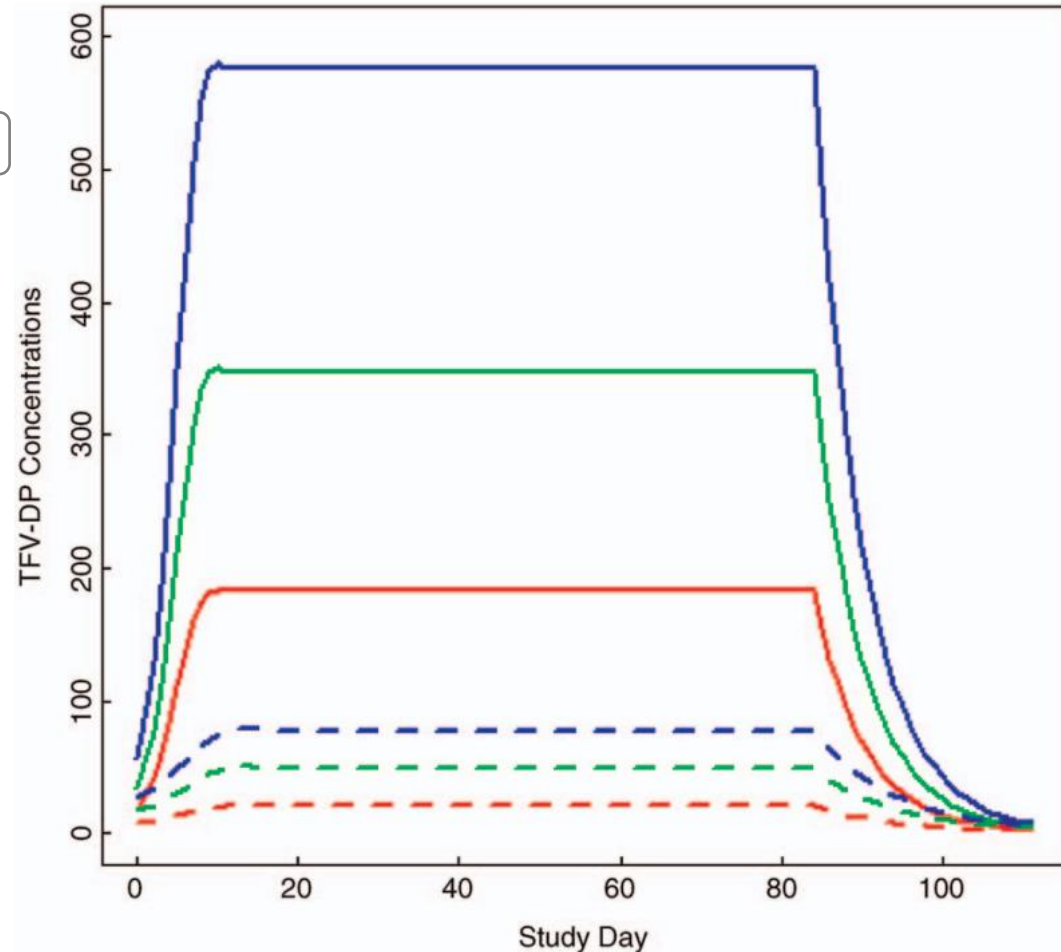
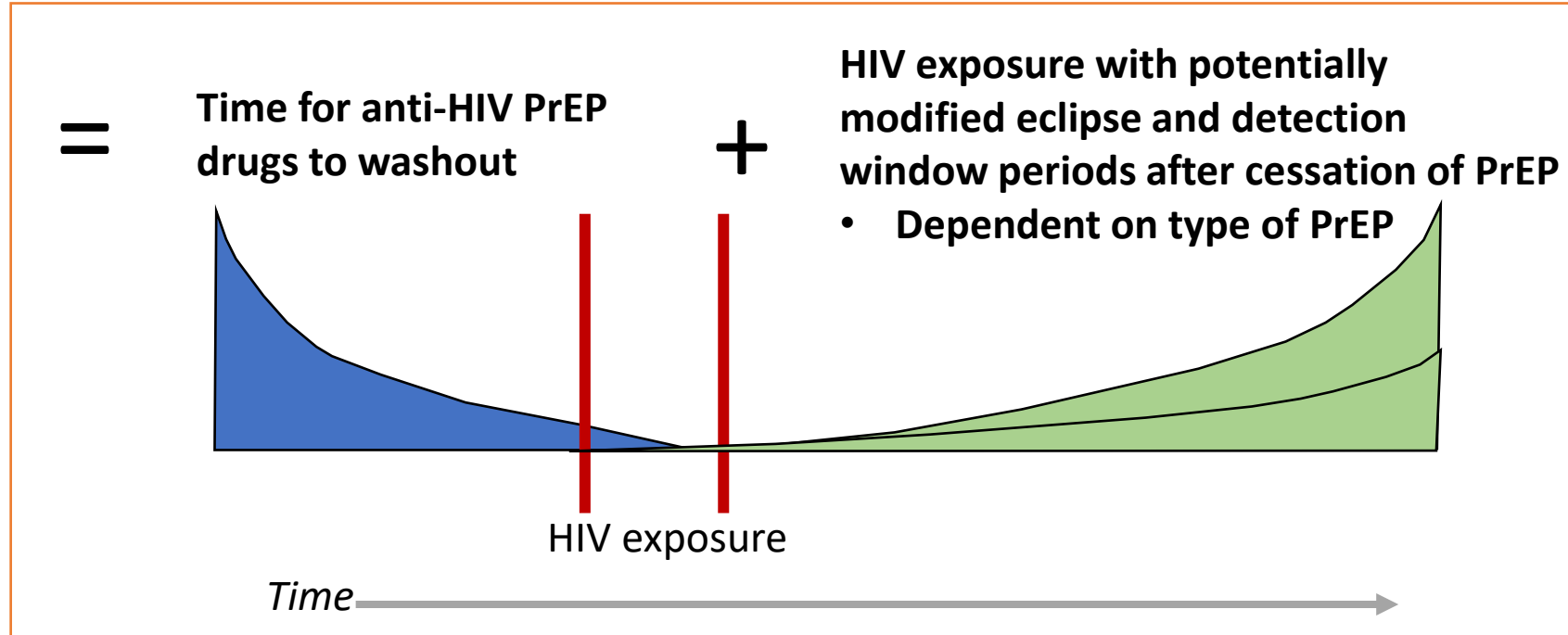


Fig. 1. Predicted TFV-DP concentrations in peripheral blood mononuclear cell following F/TDF and F/TAF. Model-fitted TFV-DP in PBMC (fmol/10⁶ cells) by study day for 33% dosing (red), 67% dosing (green) and 100% dosing (blue). Solid lines are concentrations following F/TAF dosing; dashed lines are concentrations following F/TDF dosing.

Why defer donors for 3 or 4 months or longer after discontinuation of PrEP? – Two complex time varying considerations

Impaired laboratory test detection of HIV

- Serology window period on PrEP
- NAT window period on PrEP



- TDF and FTC each have a plasma half-life of less than 1 day
- FTC Intracellular half-life > 20 hrs
- TDF Intracellular half-life > 60 hrs
- TAF Intracellular half-life > 150 hrs
- CAB plasma half-life
 - 45.3 days (95% CI 37.6–54.5) for males
 - 60.4 days (95% CI 52.9–69.0) for female

Adapted from S. Drewes, Canadian Blood Services

HIV antiretroviral therapy and prevention use in US blood donors: a new blood safety concern



American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Copyright © 2020 American Society of Hematology

Brian Custer,^{1,2} Claire Quiner,^{1,3} Richard Haaland,⁴ Amy Martin,⁴ Mars Stone,^{1,2} Rita Reik,⁵ Whitney R. Steele,⁶ Debra Kessler,⁷ Phillip C. Williamson,⁸ Steven A. Anderson,⁹ Alan E. Williams,⁹ Henry F. Raymond,¹⁰ Willi McFarland,¹¹ William T. Robinson,^{12,13} Sara Glick,¹⁴ Kwa Sey,¹⁵ C. David Melton,¹⁶ Simone A. Glynn,¹⁷ Susan L. Stramer,¹⁸ and Michael P. Busch,^{1,2} for the Transfusion-Transmissible Infections Monitoring System

Samples for PrEP testing collected during period of 9/2018 – 5/2019

Antiretroviral therapy (ART) to treat infection and pre-exposure prophylaxis (PrEP) to prevent HIV infection modify detectability of biomarkers of HIV infection in blood and could change the safety of the blood supply.
Are people on ART and PrEP donating blood?

Transfusion Transmissible Infections Monitoring System (TTIMS)



Accepted Male and Female Donors

Laboratory assessment of ART use in accepted blood donors



HIV+ Donations
n=299



HIV- Donations
n=300

15% had ART Drugs in Donation 85% had No ART Drugs in Donation 100% had No ART Drugs in Donation



Accepted First-Time, Male Donors

Laboratory assessment of PrEP use in accepted blood donors



HIV-/Other infections - Donations
n=1494

0.6% had PrEP Drugs in Donation 99.4% had No PrEP Drugs in Donation

National HIV Behavior Surveillance (NHBS) Survey



Male NHBS survey participants

Self-reported PrEP & blood donation in men who have sex with men



+



HIV- Respondents
n=591

4.8% PrEP Use and Donation Proximate in Time 94.2% No Donation Proximate to PrEP

The implications for our ability to detect HIV infection in donated blood in persons using ART or PrEP needs further investigation



Transfusion
Transmissible
Infections
Monitoring
System

PrEP Use in Infection Negative Donors: Sampling 9/2018 – 5/2019

Geographic Location	Samples	PrEP Drugs Detected n (% & 95%CI)
Boston, MA	176	0 (0)
Los Angeles, CA	344	2 (0.6)
Miami, FL	243	1 (0.4)
New York City, NY	350	2 (0.6)
San Francisco, CA	211	2 (1.0)
Washington, DC	170	2 (1.2)
Total	1494	9 (0.6%; 0.03 – 1.1%)

Approximate days since last dose	Number of Donors n (%)
1	3 (33.3%)
2	2 (22.2%)
3	4 (44.4%)
Total	9

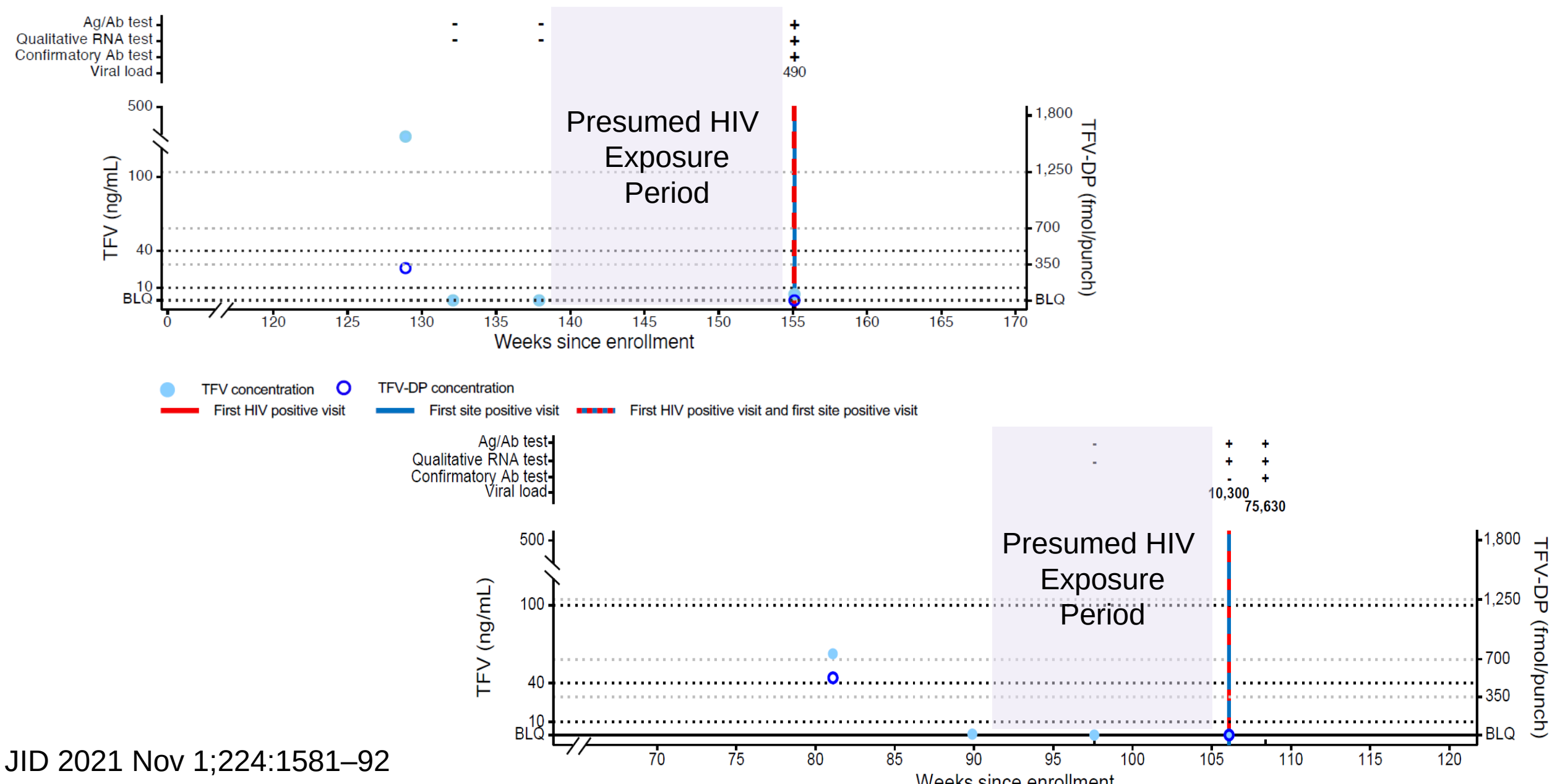
Nota Bene

The slides on PrEP breakthrough infections are data from clinical trials and other sources.

These data are from persons with higher risk of HIV acquisition and may not be reflective of accepted blood donors under individual risk assessment or other donor selection strategies.

HIV Detection with oral PrEP (TDF/FTC) Use: HPTN 083

Case E1

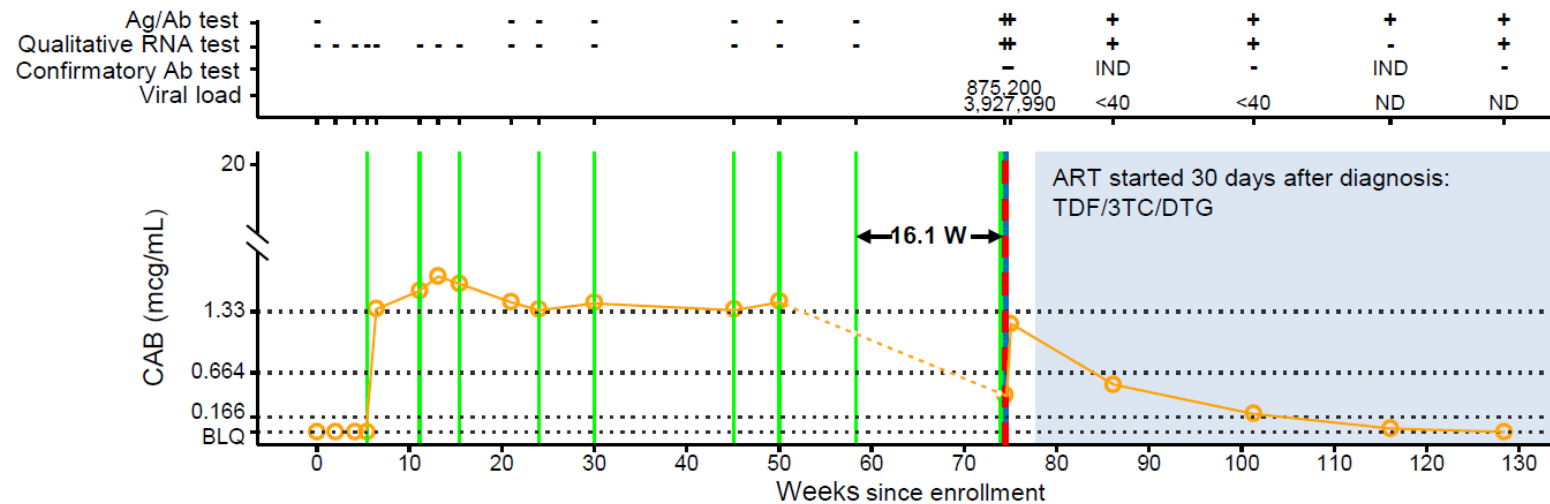


HIV Detection with injected PrEP (CAB) use: HPTN 084

(D) Case DX

Visit type	Diagnosis visit type	Site Testing					HPTN LC Testing				
		Rapid 1 test	Rapid 2 test	Ag/Ab test	Viral load	Confirmatory Ab test	Ag/Ab test	Qualitative RNA test	Confirmatory Ab test	Viral load	Resistance
Enrollment		NR	NR	NR			NR	NR			
Week 2		NR	NR	NR				NR			
Week 4		NR	NR	NR				NR			
Week 5 (Inj 1)		NR	NR	NR				NR			
Week 6		NR	NR	NR				NR			
Week 9 (Inj 2)		NR	NR	NR				NR			
Week 13		NR	NR	NR				NR			
Week 17 (Inj 3)		NR	NR	NR				NR			
Week 21		NR	NR	NR			NR	NR			
Week 25 (Inj 4)		NR	NR	NR			NR	NR			
Week 33 (Inj 5)		NR	NR	NR			NR	NR			
Week 42 (Inj 6)		NR	NR	NR			NR	NR			
Week 49 (Inj 7)		NR	NR	NR			NR	NR			
Week 57 (Inj 8)		NR	NR	NR			NR	NR			
Week 73 (Inj 9)	1 st HIV POS 1 st SITE POS	NR	NR	R	1,000,879	NEG	R	R	NEG	875,200	WT
Week 73.1		NR	NR	R	2,709,014	NEG	R	R	NEG	3,927,990	WT
Week 89							R	R	IND	<40	
Week 97							R	R	NEG	<40	
Week 113							R	NR	IND	ND	
Week 129							R	R	NEG	ND	

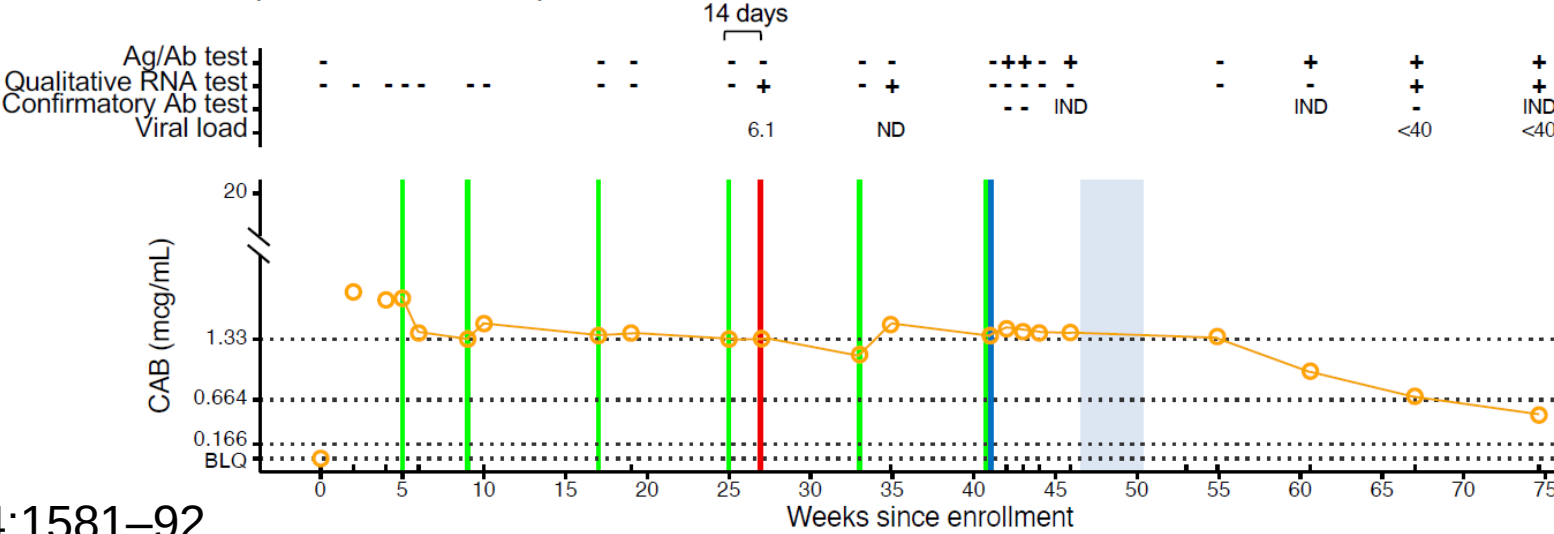
Subtype C



HIV Detection with injected PrEP (CAB) use: HPTN 083

		Site Testing					HPTN LC Testing			
Visit type	Diagnosis visit type	Rapid 1 test	Ag/Ab test	DNA test	Viral load	Confirmatory Ab test	Ag/Ab test	Qualitative RNA test	Confirmatory Ab test	Viral load
Enrollment		NR	NR				NR	NR		
Week 2		NR	NR					NR		
Week 4		NR	NR					NR		
Week 5*		NR	NR					NR		
Week 6		NR	NR					NR		
Week 9*		NR	NR					NR		
Week 10		NR	NR					NR		
Week 17*		NR	NR				NR	NR		
Week 19		NR	NR				NR	NR		
Week 25*		NR	NR				NR	NR		
Week 27	1st HIV POS	NR	NR				NR	R		SCA 6.1
Week 33*		NR	NR				NR	NR		
Week 35		NR	NR				NR	R		ND
Week 41*	1st SITE POS	NR	R		ND		NR	NR		
Interim visit		R	R	Detect, <LOD	ND		R	NR	NEG	
Interim visit		NR	R				R	NR	NEG	
Week 43		NR	R				NR	NR		
Interim		NR	R	ND	ND		R	NR	INDET	
Interim**		R	R	Detect, <LOD	ND		NR	NR		
Interim		NR	R				R	NR	INDET	
Interim		NR	R	Detect, 5.8	23	POS	R	R	NEG	<40
Interim		R	R		23		R	R	INDET	<40

**Started a 30-day course of TDF/3TC/DRVr 7 days later for PEP; later started ART with TDF/3TC/DRVr with a viral load of 1700



PrEP-Breakthrough Infections during HPTN 083, cis-gender MSM and transwomen: ^{Internal use}

Table 2. Human Immunodeficiency Virus (HIV) Test Results Associated With Delays in Detection of HIV Infection^a

PrEP breakthrough infections were evident for both oral and injected PrEP formulations

	CAB Arm	TDF/FTC Arm
	Incident: Groups C and D (n = 7)	Incident (n = 39)
Delay between 1st reactive qualitative RNA test and 1st reactive Ag/Ab test		
Participants, no. (%)	7 (100)	8 (21)
Duration of delay, range, d (among those with delayed Ag/Ab test result)	35–185	7–68 ^c
Delay between 1st reactive qualitative RNA test and 1st positive confirmatory Ab test		
Participants, no. (%)	7 (100) ^e	18 (46) ^f
Duration of delay, d (among those with delayed confirmatory Ab test result)	36–185 ^e	4–68 ^{c,f}
Participants with assay reversion, no. (%)		
Ag/Ab test (from reactive to nonreactive)	2 (29)	0
Confirmatory Ab test (from indeterminate to negative)	1 (14) ^g	0
Qualitative RNA test (from reactive to nonreactive)	2 (29)	0

Abbreviations: Ab, antibody; Ag, antigen; CAB, cabotegravir; NA, not applicable; TDF/FTC, tenofovir disoproxil fumarate–emtricitabine.

^aTable 2 shows the delays observed for different human immunodeficiency virus (HIV) test outcomes at the HIV Prevention Trials Network (HPTN) Laboratory Center for the participant groups described in Table 1. The table also shows the number of cases in which reversion of test results was observed for the Ag/Ab test, the confirmatory Ab test, and the qualitative RNA test. Data are shown for visits before initiation of antiretroviral therapy (ART).

^bOne case did not have a reactive Ag/Ab test after 41 days of follow-up.

^cExcludes 1 case with a 372-day visit window.

Blood safety implications and advancing testing for screening donors with HIV infections taking ART and PrEP therapies



1. Characterization of the altered dynamics of viremia and seroconversion and performance of blood donor screening assays.
2. Seek to assess whether testing of whole blood (WB) using simple WB processing methods by donor screening NAT and viral load (VL) assays/platforms enables detection of HIV infections not detectable by current blood screening plasma-based testing algorithms.
3. Evaluation of whether sensitive multiplexed HIV antigen assays could detect low level humoral immune responses not detectable by current commercially available donor screening and diagnostic serological assays, which will lead to enhancement of those assays.

Blood screening tests

Abbott Alinity s HIV Ag/Ab Combo

Ortho Vitros HIV Combo

Roche Elecsys HIV Duo

Grifols Procleix Ultrio Elite dHIV

Roche cobas MPX

Studies focused on oral PrEP and detection of breakthrough infections using blood screening assays are currently in the data analysis phase

The results are preliminary

PrEP studies – iPrEx & Partners PrEP

- 374 participants; 180 from iPrEx and 194 from Partners – monthly visits with 2 RT
- Median age 27yo; IQR 23-34, range 18-62
- **261 HIV seroconverters; 113 highly exposed seronegatives (HESN)**
- **162 assigned to placebo; 140 assigned to FTC/TDF; 72 assigned to TDF**
- **152 seroconversions in placebo group; 72 among FTC/TDF group; 37 in tenofovir group**
- Tests performed using **3 samples prior to the date of first positive rapid test from seroconverters**, and **2 samples from HESN** (end of study and 8 weeks post-study)
 - Roche Cobas MPX
 - Abbott Alinity s HIV Ag/Ab Combo
 - Roche Elecsys HIV Duo
 - **Ortho VITROS HIV Combo (pending results)**

PrEP studies – iPrEx & Partners PrEP

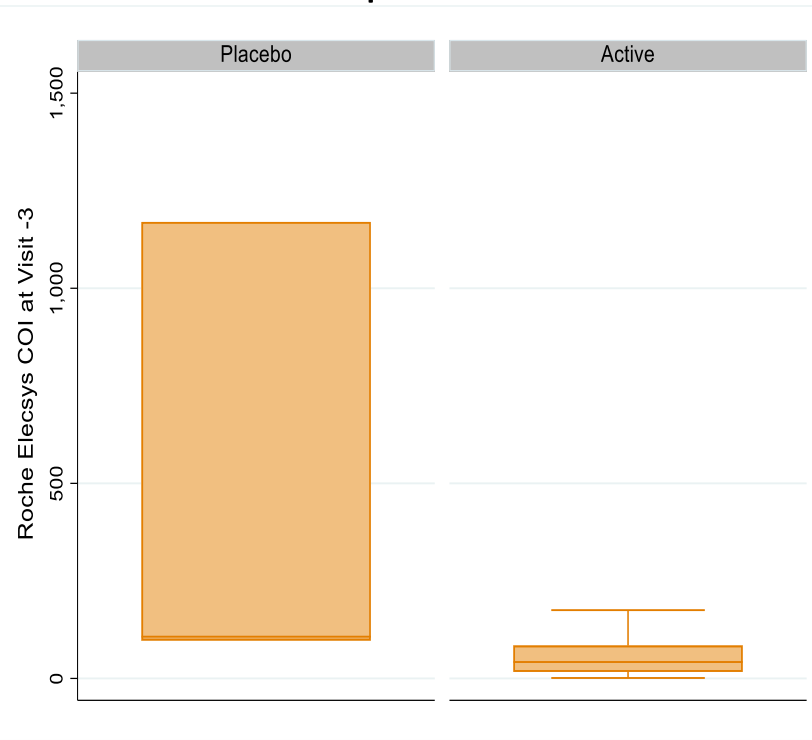
Samples from 261 seroconverters

- Median time between visit and SC slightly higher for participants assigned to active intervention ($p < 0.05$ for visit -3 only)

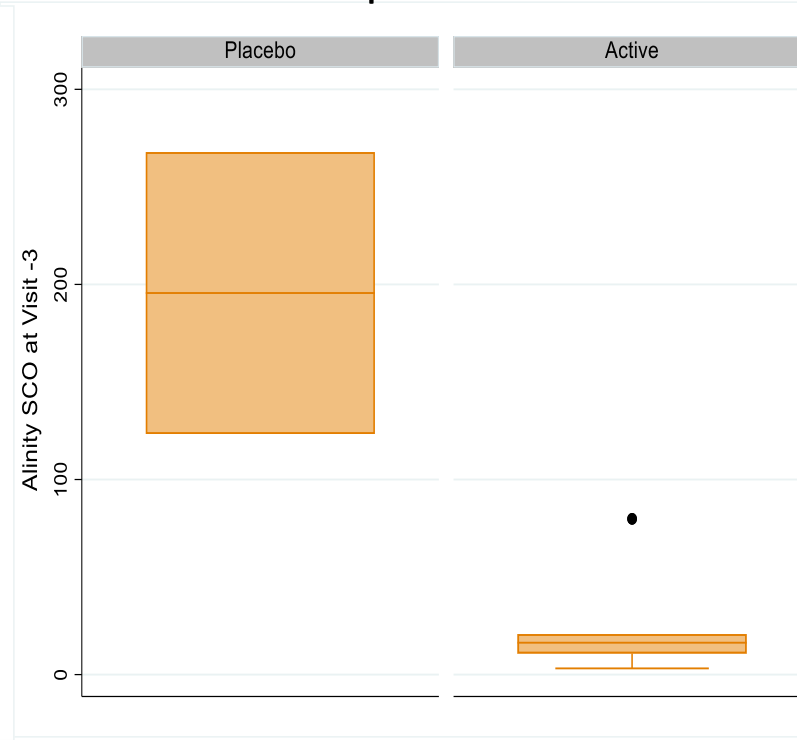
Median days to first positive Rapid Test	Visit -3	Visit -2	Visit -1
All participants	229 (197-255)	148 (119-173)	69 (42-88)
Placebo	225 (196-252)	145 (117-169)	63 (42-85)
Active	251 (199-282)	165 (133-198)	80 (45-114)
FTC/TDF	250 (209-282)	165 (139-201)	82 (56-130)
TDF	251 (196-284)	157 (114-177)	56 (32-86)

PrEP studies – iPrEx & Partners PrEP – Samples from 261 seroconverters*

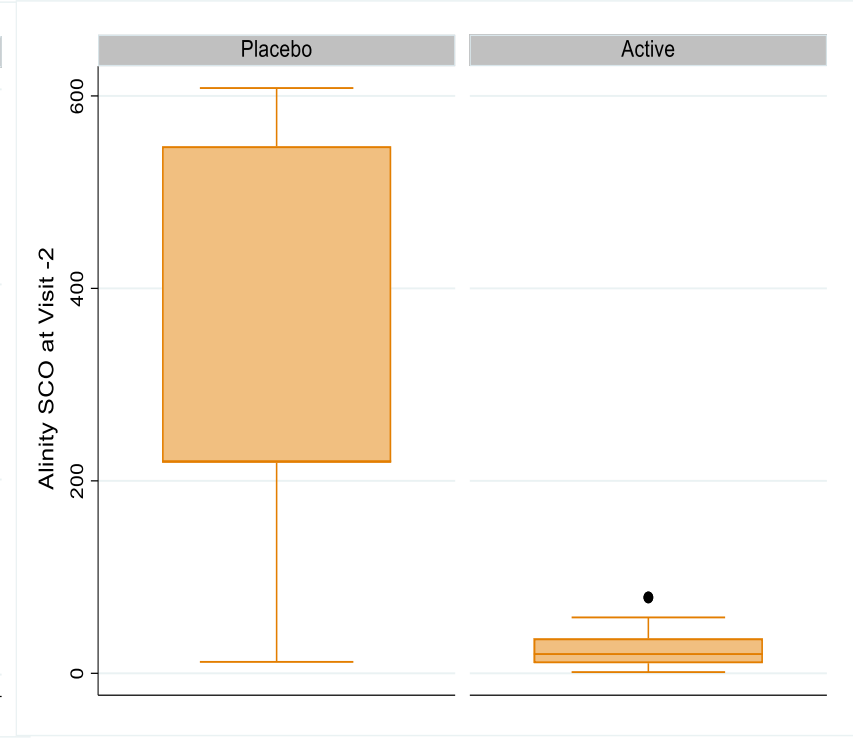
p=0.041



p=0.046



p=0.020



*restricted to samples with reactive results

Summary

- PrEP changes the ability to detect HIV RNA and Abs
 - Both are dramatically modified, but dependent on as yet inadequately defined factors
 - Different formulations have different effects making the situation increasingly challenging
- Non-adherence to dosing drives the risk of low level (masked) HIV infection
- Detection of PrEP use through biomarker testing is not yet developed
 - No high throughput assays
 - ARV detection in plasma $\neq$ intracellular ARV concentration and can therefore be misleading
- More insights to come as REDS-IV-P completes 2nd and 3rd Aims

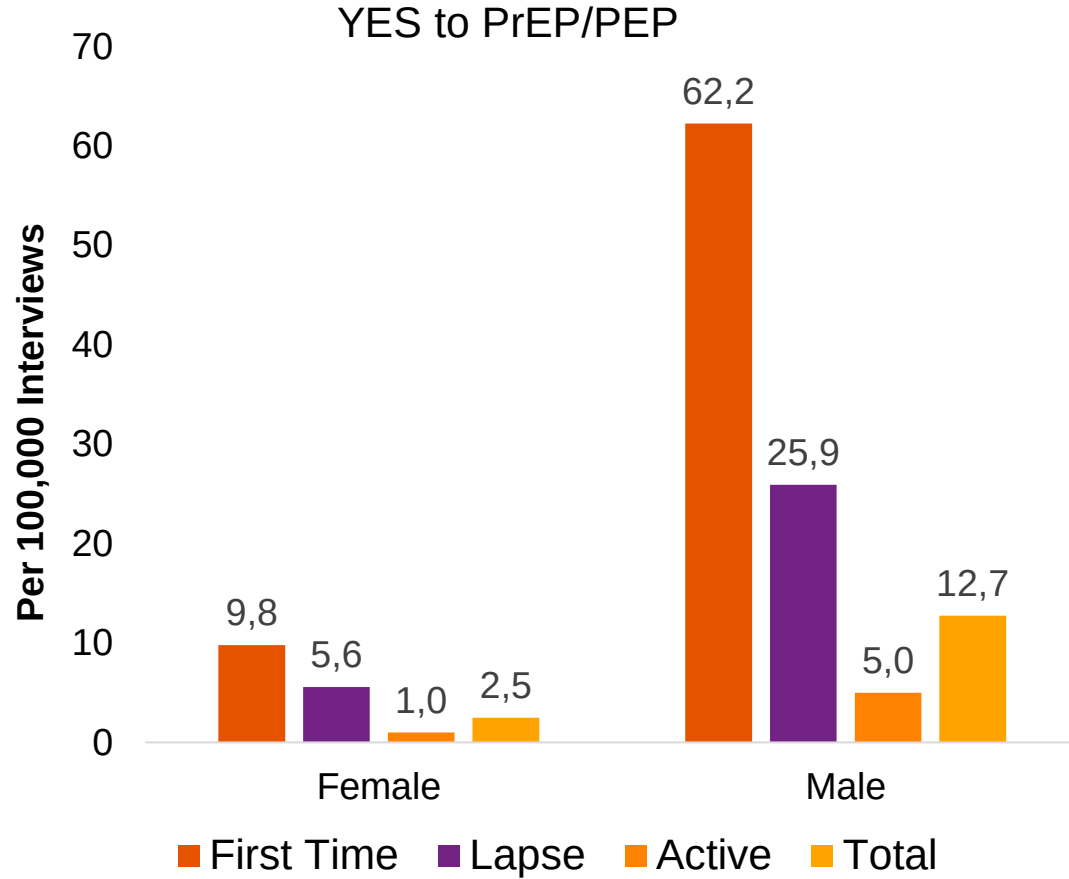
Thank You

Additional Slides

Donor History Questionnaire changed in mid-2020: Donors Are Disclosing PrEP/PEP Use in the U.S.

In the past 3 months, have you taken any medication to prevent an HIV infection?

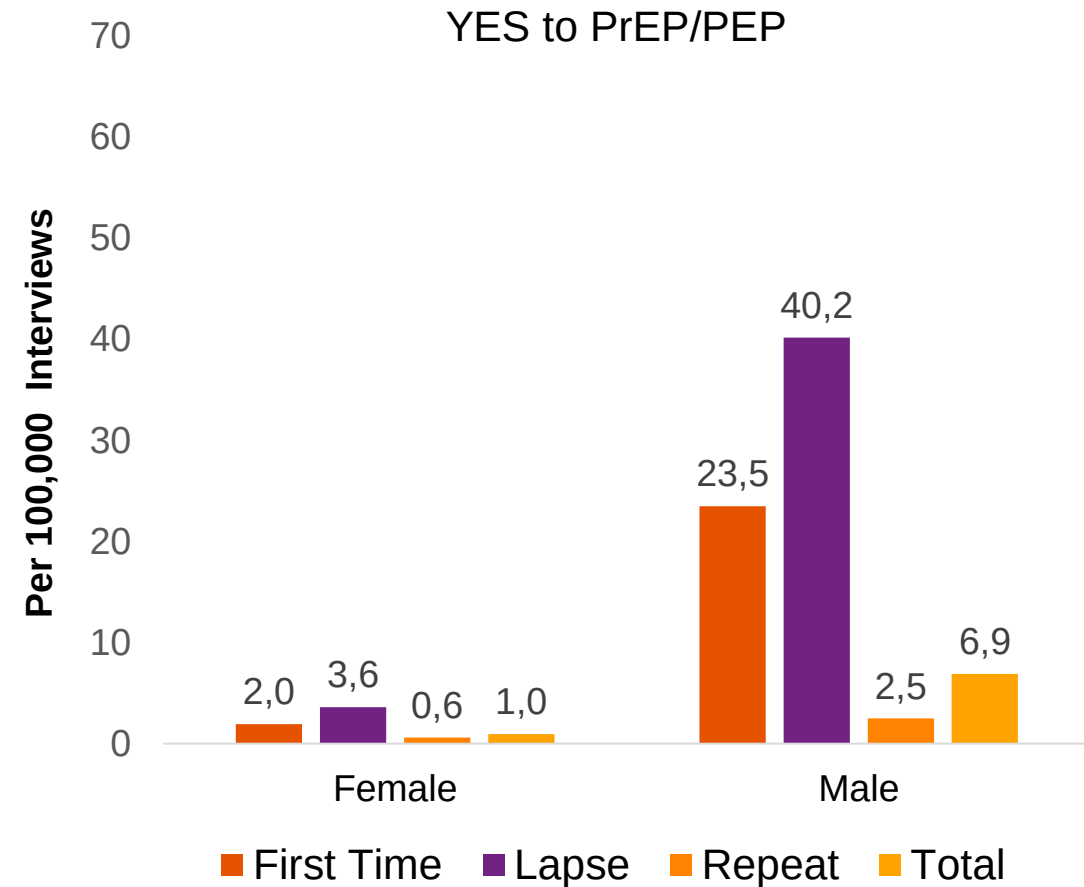
Vitalant Results



Reengaged/Lapse = prior registration to donate >730 days.

Active/Repeat = prior registration to donate ≤730 days.

ARC Results



†Responses collected between 6/8/2020 and 08/31/2022

Evidence of HIV pre-exposure or post-exposure prophylaxis (PrEP/PEP) among blood donors: a pilot study, England June 2018 to July 2019

Heli Harvala ^{1,2} Claire Reynolds,³ Samreen Ijaz,⁴ Vicki Maddox,¹ Sujan Dilly Panchala,⁵ Alieu Amara,⁵ Laura Else,⁵ Susan Brailsford,^{1,3} Saye Khoo⁵

Male blood donors with confirmed positive syphilis who were not HIV-reactive in screening

- 3 of 46 (6.5%) samples from these donors had detectable levels of both TFV and FTC and one only TFV
 - 2 estimated to have last taken oral PrEP/PEP medication within a day of donating
 - 1 likely within 2 days
- Blood donors in England were not specifically asked about PrEP usage at the time of the study, although they would have been expected to declare this under 'use of any medication', including over-the-counter medication.

Undeclared pre-exposure or post-exposure prophylaxis (PrEP/PEP) use among syphilis-positive blood donors, England, 2020 to 2021

Victoria Maddox¹, Claire Reynolds², Alieu Amara³, Laura Else³, Susan R Brailsford^{1,2,4}, Saye Khoo³, Heli Harvala^{1,5}

177 anonymized residual plasma samples collected from syphilis-infected male blood donors in England

- 10 (5.6%) with evidence of oral PrEP use
 - 9 with past and 1 with recent syphilis

Harvala H, et al. Sex Transm Infect 2022;**98**:132–135. doi:10.1136/sextrans-2021-054981