Current Considerations on Pre-Exposure Prophylaxis (PrEP) Use in Blood Donors

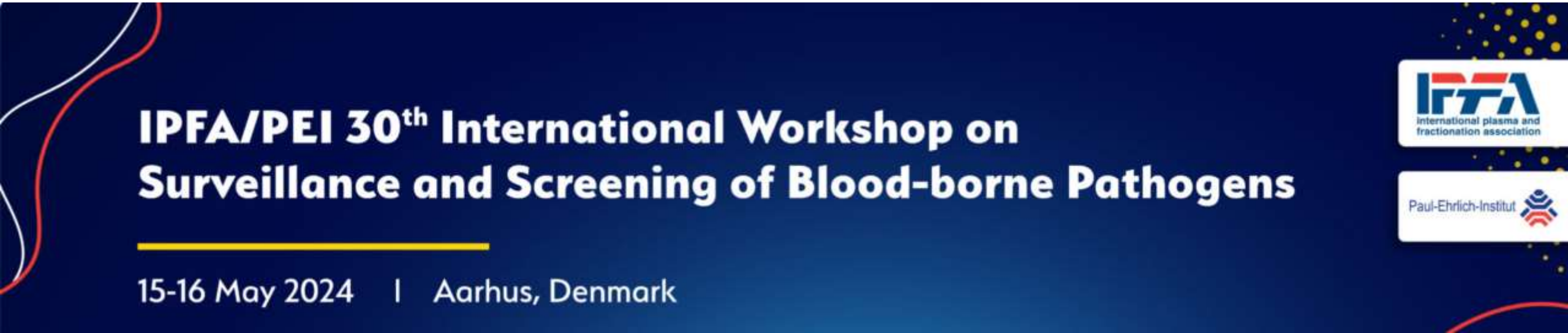
Brian Custer

Vitalant Research Institute

&

University of California San Francisco

15 May 2024



Disclosures

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Abbott Diagnostics

Grifols Diagnostics Solutions

Hologic

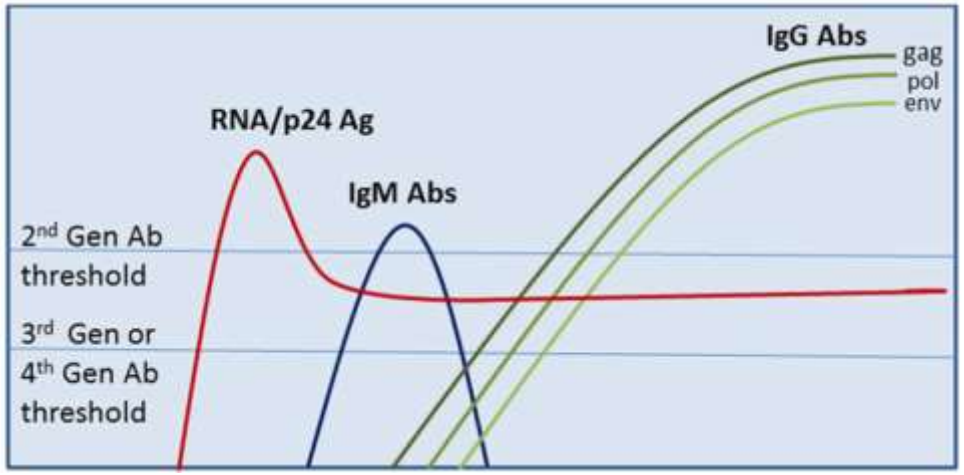
HIV infection progression

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

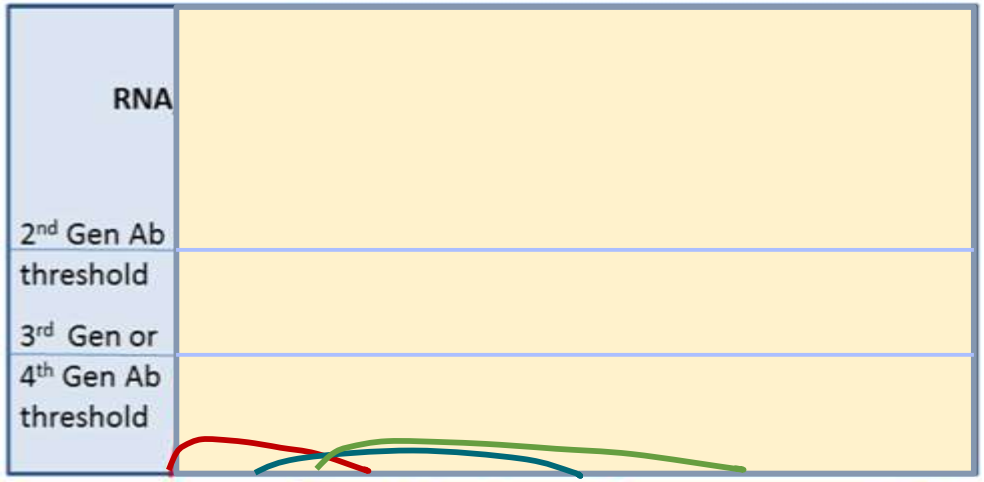
Sheila M. Keating, Christopher D. Pilcher, and Michael P. Busch

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

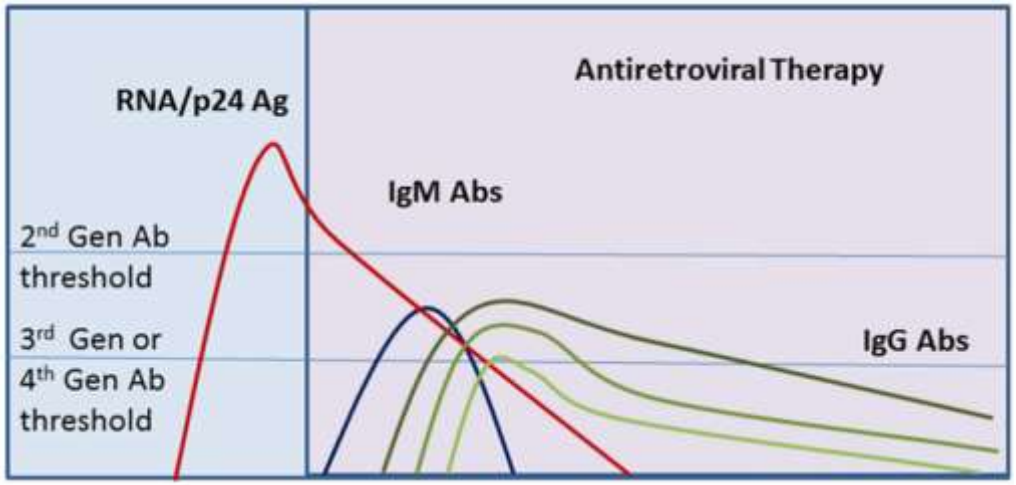
Without ART



PrEP Breakthrough HIV Infection with Intermittent PrEP Use – Not Detectable?



With Early ART following HIV Infection Diagnosis



CID 2016:63 (15 August)

PrEP Access and Blood Donor Selection in the US

➢ **Use has steadily increased among populations selected for public health interventions (men who have sex with men, higher risk heterosexuals, persons who inject drugs) – 2022 Estimates:**

Group	PrEP Eligible	Prescribed PrEP	PrEP Coverage
Males	989,200	405,189	41%
Females	227,010	32,854	14.5%
Total	1,216,210	438,043	36%

https://www.cdc.gov/hiv/library/reports/surveillance-data-tables/vol-4-no-3/index.html

- **Truvada® and generic versions** consist 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/PEP 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

➢ **For blood donation, use of injected PrEP is asked on the DHQ and is a 2-year deferral since last injection.**

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

Impaired laboratory test detection of HIV

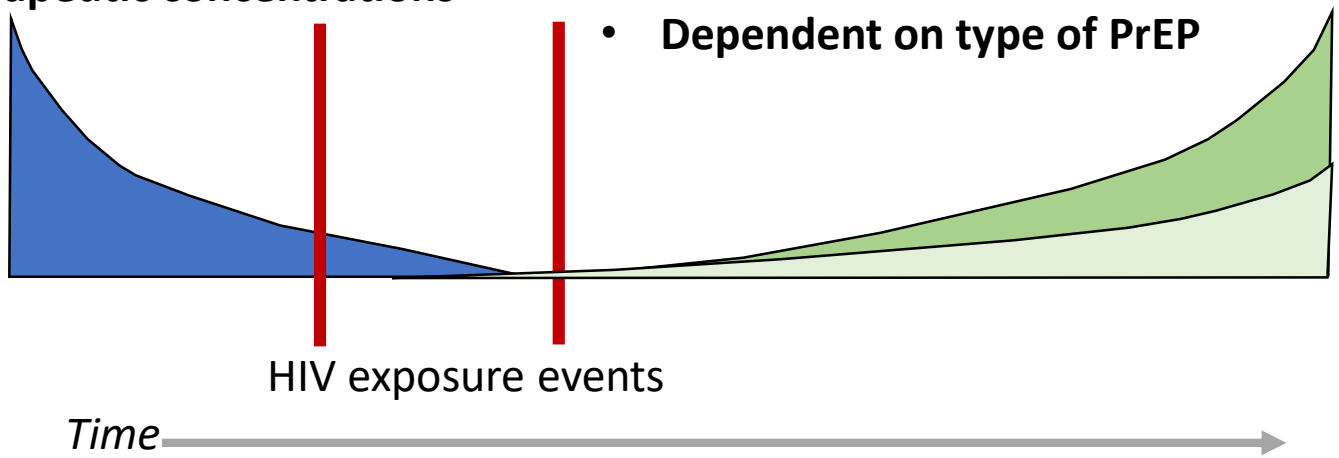
Level of PrEP adherence and time of last dose influence:

- NAT window period for persons on PrEP
- Serology window period for persons on PrEP

= **(1) Time for anti-HIV PrEP drugs to reach sub-effective therapeutic concentrations**

+ **(2) HIV exposure with potentially modified eclipse and detection window periods after use or with intermittent use**

- **Dependent on type of 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 for males
  - 60·4 days for females

Adapted from S. Drewes, Canadian Blood Services and

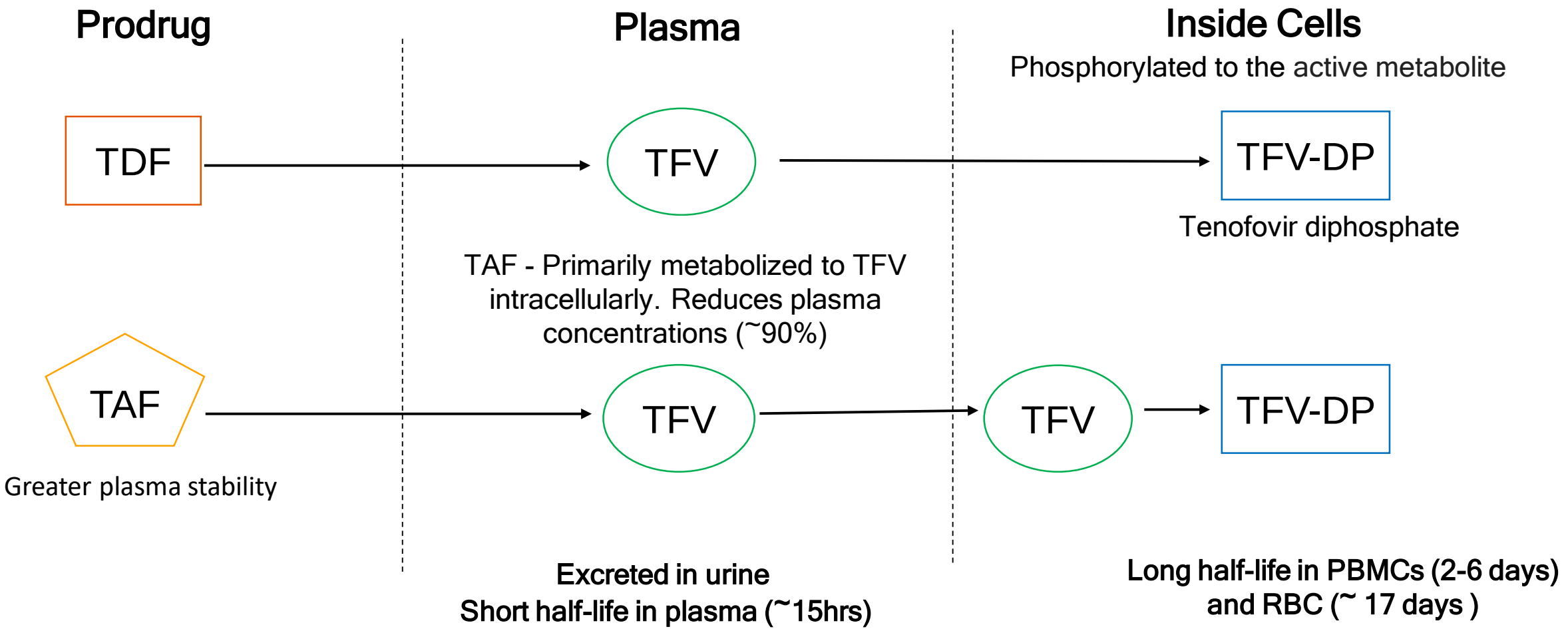
Seed CR, Styles CE, Hoad VC, Yang H, Thomas MJ, Gosbell IB. Effect of HIV pre-exposure prophylaxis (PrEP) on detection of early infection and its impact on the appropriate post-PrEP deferral period. Vox Sang. 2021 Apr;116(4):379-387. doi: 10.1111/vox.13011. Epub 2020 Sep 23. PMID: 32965051.

Existing Challenges of Measuring Adherence/Detecting PrEP (Outside of Blood Safety)

- **Traditional methods** for measuring adherence to HIV PrEP are unreliable.
  - Self-report (considered an overestimate due to multiple biases (e.g., social desirability, recall)
  - Pill counts (easily manipulated, cannot measure ingestion)
- Growing interest in **objective methods** for monitoring adherence – involves measuring drug concentrations in a biomatrix such as whole blood, plasma, RBC, PBMC, hair, or urine
  - Each biomatrix is relevant for different types of monitoring questions
- Most existing methodologies rely on **liquid chromatography-tandem mass spectrometry (LC-MS/MS)**
  - Costly and requires substantial time, equipment, and technical expertise
  - Limited routine clinical or high throughput use

Koss CA, *et al. Clin Infect Dis* 2018; **66**: 213-9.

Tenofovir Metabolism – What to target for detection?

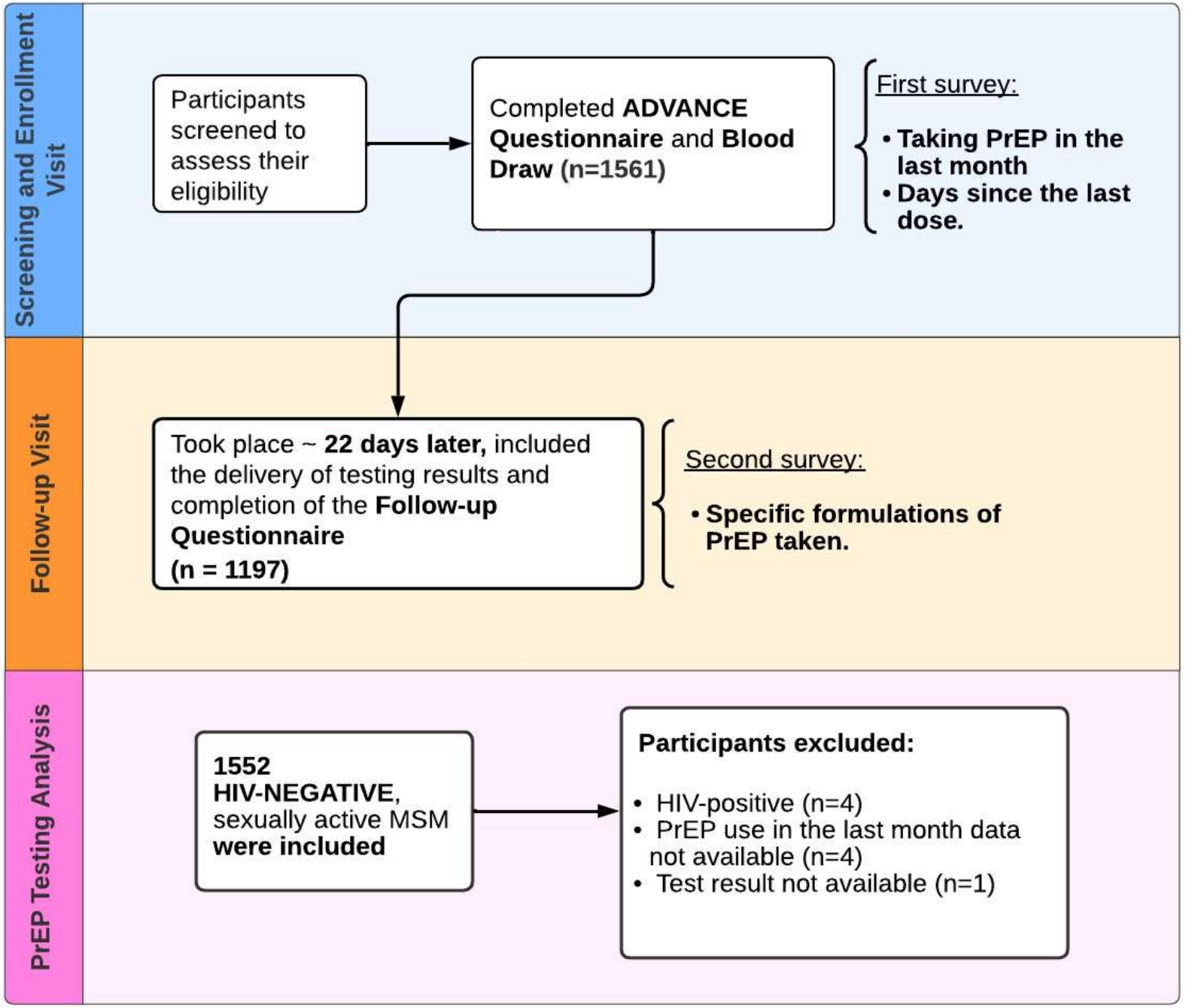


Yager JL, et al. *AIDS* 2021; **35**: 2481-7.
Lee WA, et al. *Antimicrob Agents Chemother* 2005; **49**: 1898-906.
Birkus G, *et al. Antimicrob Agents Chemother* 2007; **51**: 543-50.
Castillo-Mancilla JR, et al. *AIDS Res Hum Retroviruses* 2013; **29**: 384-90.

ADVANCE Study

Participant Selection and Data Collection

Provides insights into the relationship between self-reported PrEP use and laboratory testing among MSM interested in blood donation



OraSure Colorimetric Tenofovir (OCT) – ELISA Testing

To assess the presence of tenofovir, the first generation research use only (RUO) colorimetric TFV ELISA developed by OraSure (Bethlehem, PA) for WB and plasma

- **Whole blood** - Lower limit of detection of 50% inhibition corresponds 50-100 ng/mL of TFV (from TFV and cleaved intracellular TFV-DP)

- **Plasma** - Lower limit of inhibition of 50% inhibition corresponds 25-50 ng/mL of TFV

WB samples were tested in duplicate, and the average of the results reported

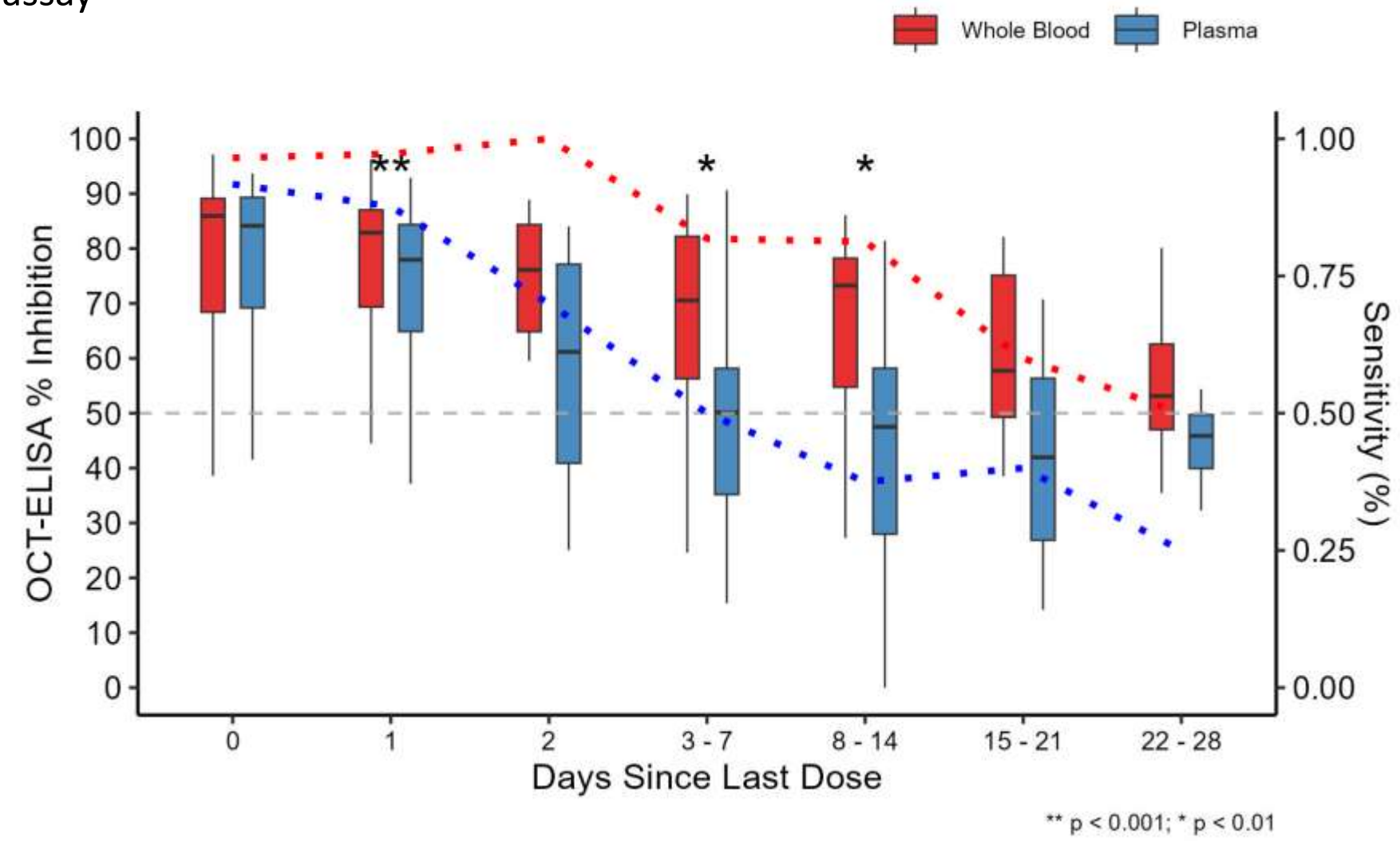
OCT-ELISA Detection Rates & Time Since Last PrEP Intake

As the interval since the last reported dose increases, the percent inhibition decreases, reducing the sensitivity of the OCT-ELISA assay

Whole Blood:

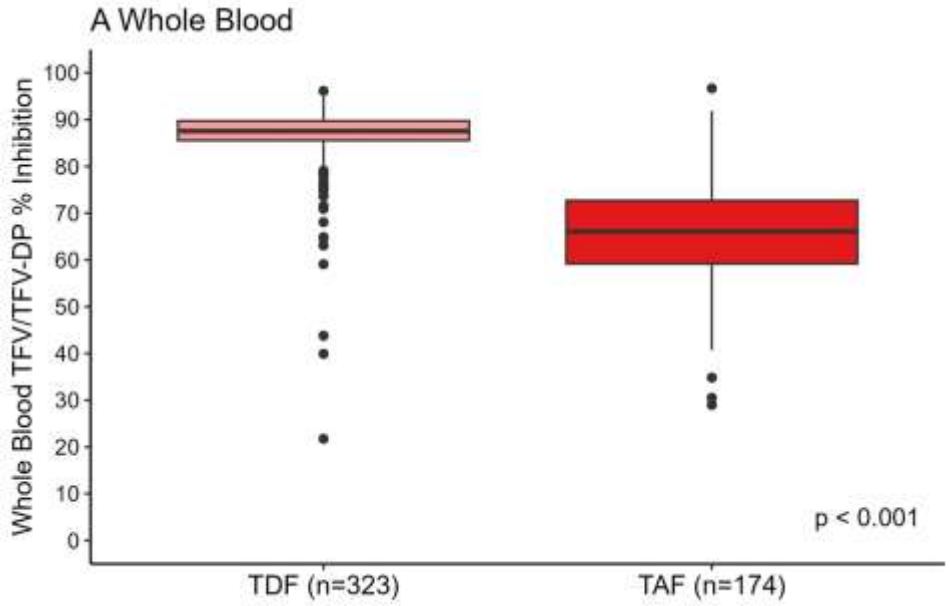
→ This detection decrement is particularly noticeable **when the interval since the last dose extends to three or more days.**

→ Maintains an extended detection window, **holding a reasonable sensitivity of 81% up to 14 days after the last dose.**

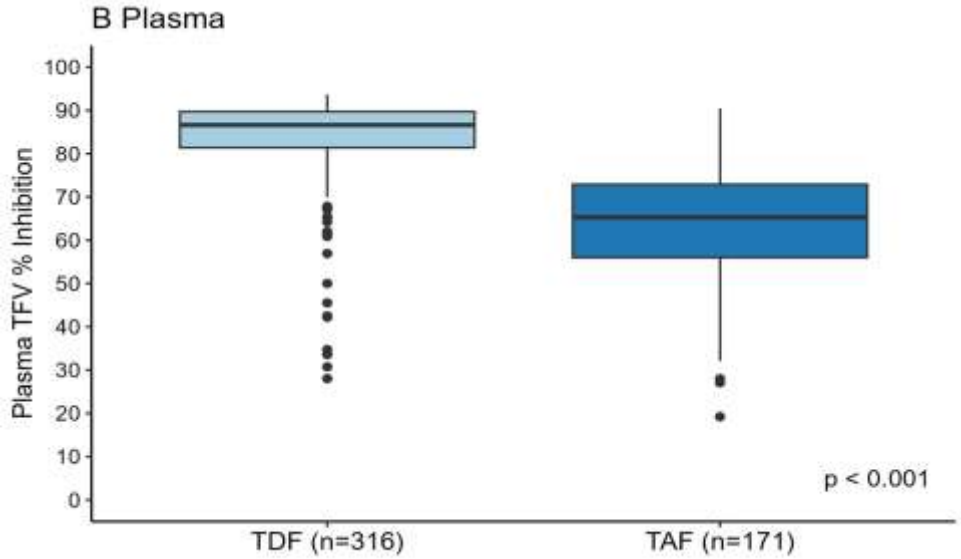


OCT-ELISA Performance for Participants on TDF/FTC and TAF/FTC based Regimens

Whole Blood



Plasma



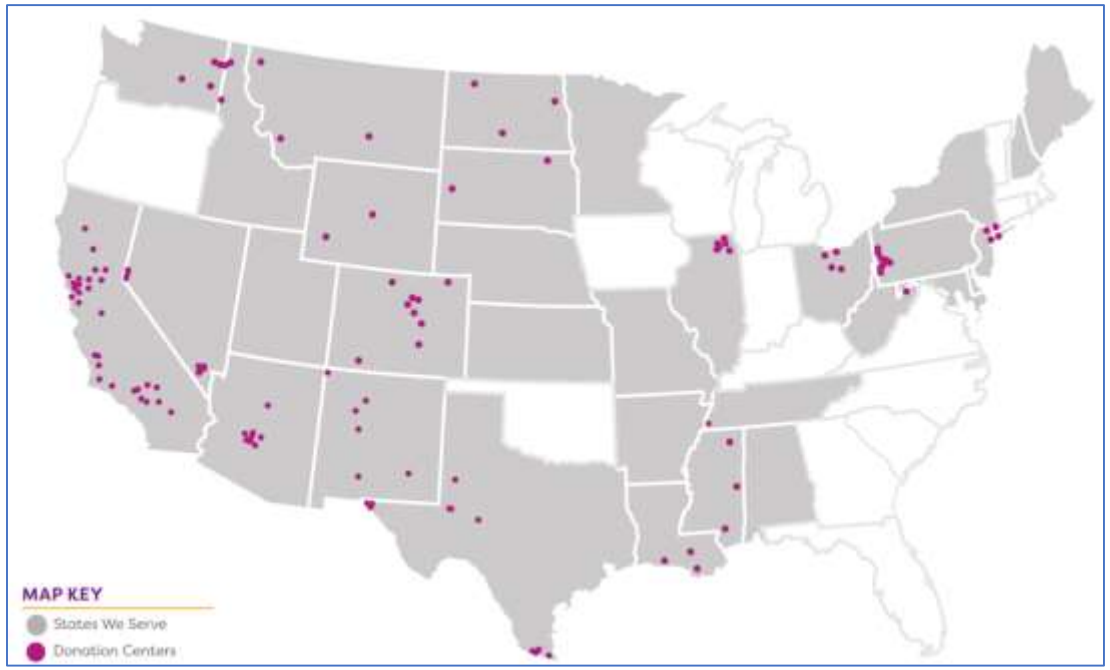
Key Findings:

- → Participants on the **TDF/FTC** regimen had a **higher detection rate** and significantly **higher percent inhibition**
- → **Plasma** results - Consistent with existing literature documenting significantly **lower TFV concentrations in individuals using TAF**
- → **WB** results:
  - → Previous studies have indicated oral administration of TAF leads to a **marked accumulation of TFV-DP within PBMCs**
  - → Pilot study showed TAF dosing **reduces red blood cell TFV-DP concentrations (~7x)**

Yager JL, et al. *J Acquir Immune Defic Syndr*. 2020 Jul 1;84(3):323-330.

Assessment of risk of HIV TT following PrEP breakthrough infection

Individual Donor Assessment (IDA) Adopted mid-year 2023 at most blood centers in the US



Responses on Vitalant donor history questionnaire: August 2023 – March 2024, N=810,666 allogeneic donor responses:

Oral PrEP/PEP use in last 3 months (Yes or Unsure)

Sex	All Donations * n/N (%)	First-time * n/N (%)	Repeat * n/N (%)	Tests of Proportion
Male	152/434,128 (0.035)	**118/87,879 (0.134)**	34/346,249 (0.0098)	* $p < 0.001$ (more common in males)
Female	22/376,700 (0.0058)	16/92,410 (0.017)	6/284,290 (0.0021)	

Injected PrEP use in the last 2 years (Yes or Unsure)

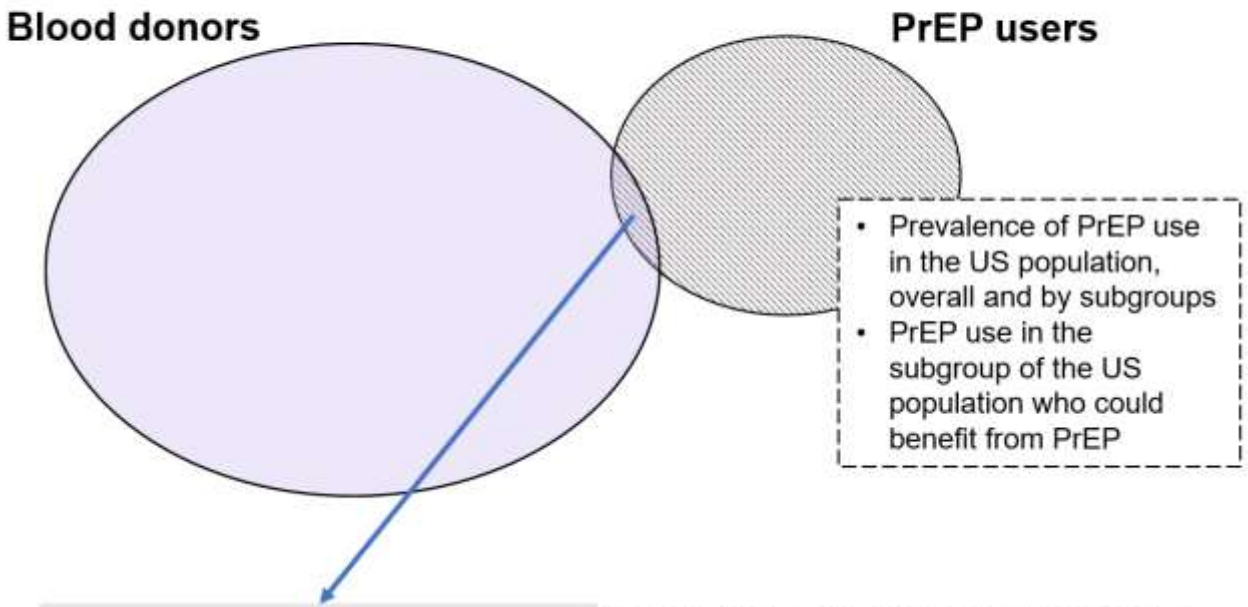
Sex	All Donations * n/N (%)	First-time n/N (%)	Repeat n/N (%)	Tests of Proportion
Male	71/434,070 (0.016)	61/87,839 (0.069)	10/346,231 (0.0029)	* $p < 0.001$ (more common in females)
Female	107/376,657 (0.028)	**91/92,389 (0.099)**	16/284,268 (0.0056)	

US Transfusion Transmitted Infections Monitoring System (TTIMS) Assessment of Undisclosed PrEP/PEP Use in Donors

Donor Group	Sample Size
First-Time Males	5500
First-Time Females	2250
Repeat Males	2250
Total	11,000

- Sample collection sites: Boston, Chicago, Los Angeles, Orlando, Memphis, Miami, New York City, San Francisco, Washington DC
- Whole blood and plasma aliquots collected and stored
- All samples currently being tested for tenofovir using the WB-OCT ELISA
- A subset will be tested using LC-MS/MS

Model for PrEP users



Non-disclosure of PrEP use at the time of donation
- Donor history questionnaire

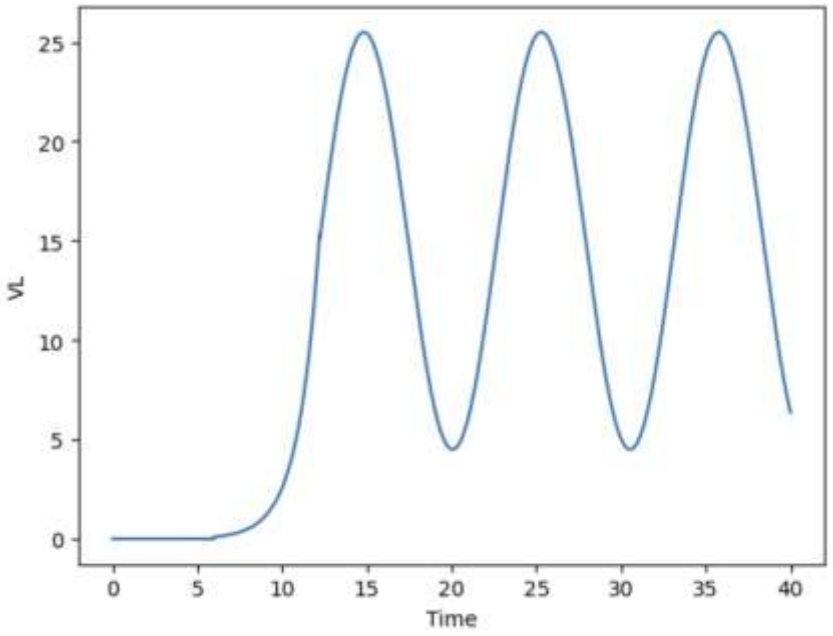
Missed HIV infection detection in blood donation laboratory screening
- Type of screening assay(s)
- Time between HIV acquisition and testing
- Type of PrEP (oral vs. injectable)

Infectivity of the blood unit
- HIV viral load
- Presence/type of antiretrovirals in the unit
- Leukapheresis/storage time

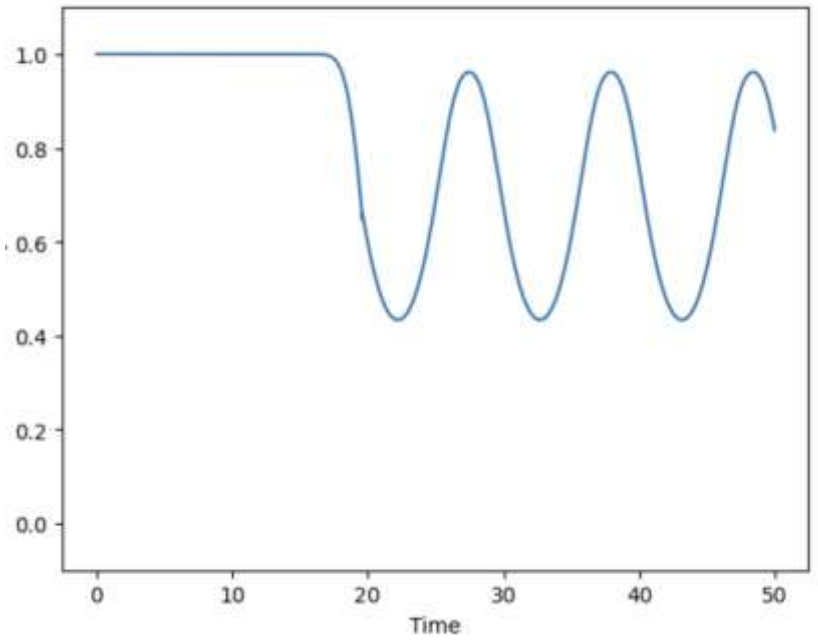
Transfusion-transmitted HIV

Conceptual (idealized) Curves Defining Risk Day Equivalent Distributions

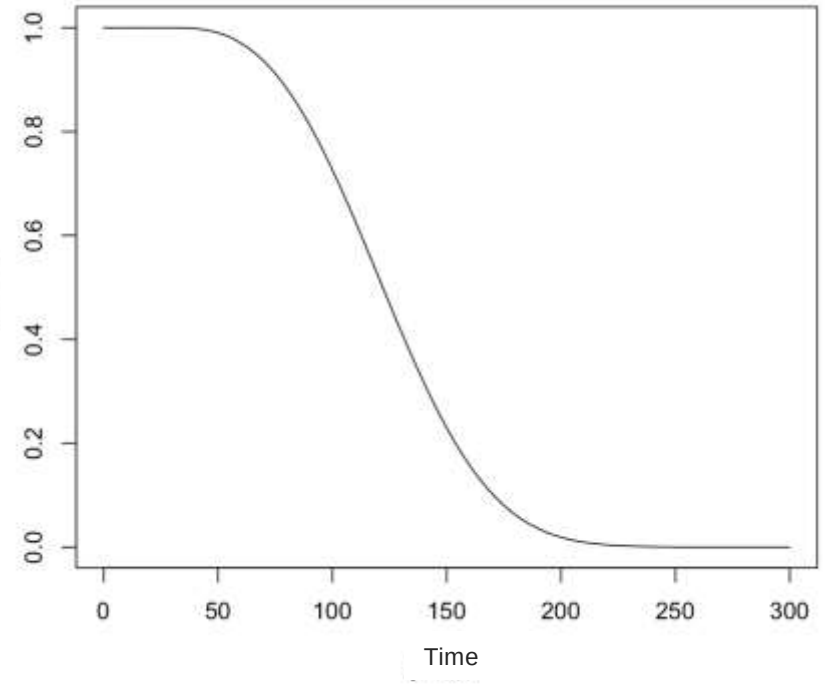
Viral load over time post breakthrough



Probability infectious & non-detectable by NAT

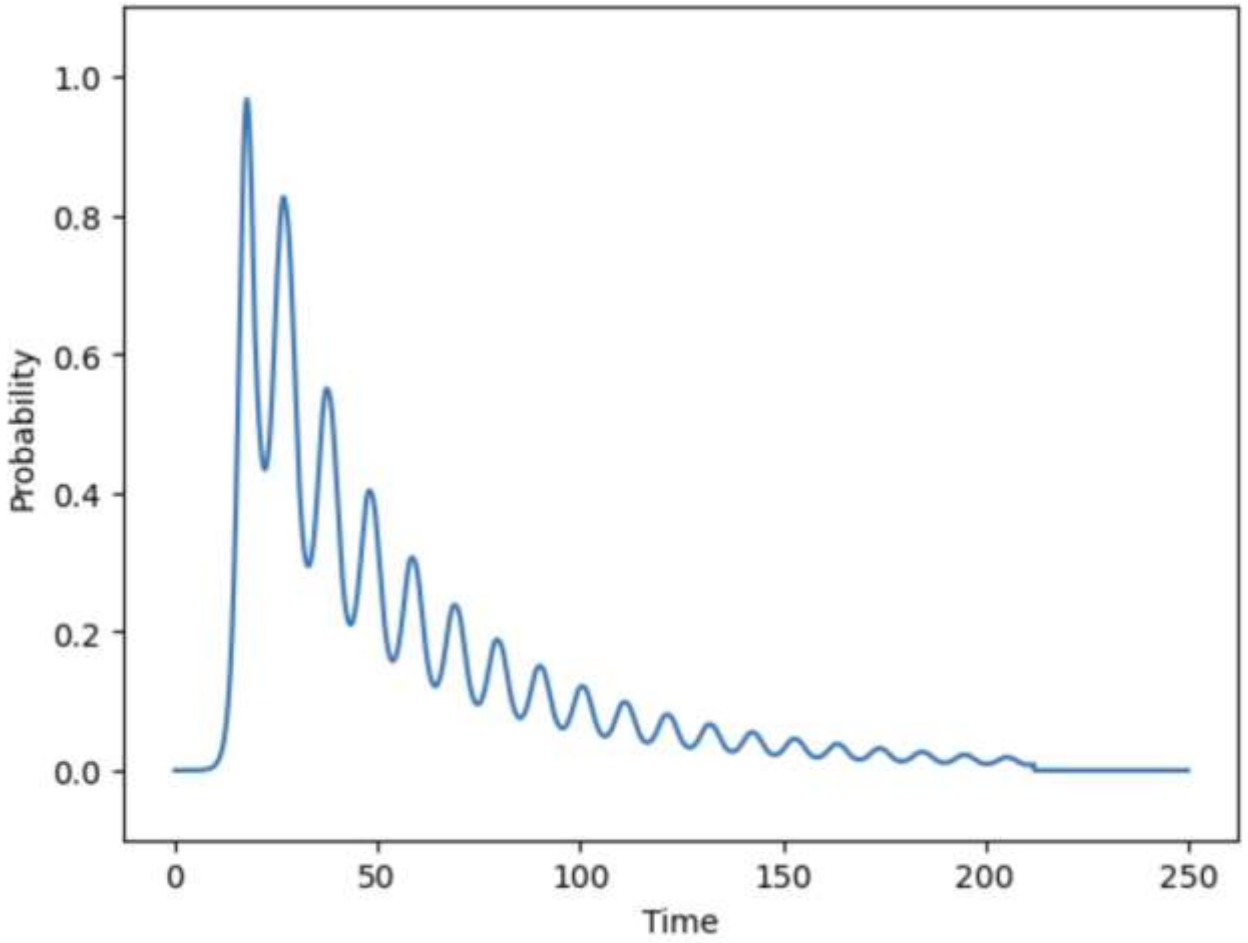


Probability non-detectable by serology



Generalized Shape of Probability of Infectiousness, Non-detection by NAT, and Non-detection by Serology

The area under the curve gives risk day equivalents



Ranges of Risk Day Estimates

PrEP form	Blood Product	Range	95% Credible Interval	Mean	Median
Oral PrEP	RBC	1.0–40.1	3.7–13.1	6.0	**5.5**
	Plasma	4.0–42.8	6.5–15.9	8.7	**8.2**
Injectable PrEP	RBC	2.1–99.1	4.0–24.6	7.1	**5.7**
	Plasma	4.0–104.7	6.5–28.0	9.8	**8.2**

Parameters varied over 10,000 iterations:

- volume of plasma transfused (as for no ARV)
- eclipse period (before viral outgrowth)
- doubling time during initial viral outgrowth
- Transmissibility - based on FDA dose response model *(J Acquir Immune Defic Syndr 2023 Feb 1;92(2):173-179. doi: 10.1097/QAI.0000000000003115)*
- viral load "set point" around which VL oscillates
- NAT detection limits (as for no ARV)
- *serologic delay based on single curve set to range of delays in literature, capturing inter-subject variability*

Assumptions for Scenarios

"Optimistic" Scenario – somewhat favorable assumptions

- Male FTD undisclosed PrEP use is 20% of the 0.6% *(Blood 2020 Sep 10;136(11):1351-1358. doi: 10.1182/blood.2020006890.)* – other donor groups scaled in proportion)
- Incidence = half of what was observed in PrEP clinical and post-surveillance studies (assumed donor behavioral effect, includes disclosure of other deferrable risks)
- Risk days = median from simulations
- Drug presence effect: 25% reduction in infectivity

"Pessimistic" Scenario – adverse assumptions

- Male FTD undisclosed PrEP use is 33% of the 0.6% (other donor groups scaled in proportion)
- Incidence = what was observed in studies PrEP clinical and post-surveillance studies
- Risk days = median from simulations
- Drug presence effect: none

Preliminary Risk Estimates

Scenario	PrEP formulation	N undisclosed PrEP donations / year	Incidence in PrEP users	N PrEP b/t cases donating and not disclosing (stratified sex, FT/RPT, aggregated)	Probability of b/t per donation	Risk day equivalents (IWP) RBC / Plasma	Transmission probability / Residual Risk in RBC per million (m)	Overall Residual Risk in RBC	Transmission probability / Residual Risk in Plasma (FFP)	Overall Residual Risk in Plasma (FFP)	N trans-missions (WB donors, 1 RBC & 1 FFP product)
No PrEP comparison (existing RR estimates			3-month PrEP deferral estimates			4.5 / 7.3		1 in 8.6 m		1 in 5.3 m	3
Optimistic case	Injectable (10%)	548	Stratified by male / female and oral / injected PrEP use	1	1.0777×10^{-7}	5.7 / 8.2	0.0012/m 1 in 798 m	0.0553/m 1 in 18.1 m	0.0018/m 1 in 550 m	0.0814/m 1 in 12.3 m	2
	Oral (90%)	5,070		53	4.7511×10^{-6}	5.5 / 8.2	0.0540/m 1 in 18.5 m		0.0796/m 1 in 12.6 m		
Pessimistic case	Injectable (10%)	904		4	3.556×10^{-7}	5.7 / 8.2	0.0055/m 1 in 181 m	0.3582/m 1 in 4.1 m	0.0080 1 in 125 m	0.4306/m 1 in 2.3 m	7
	Oral (90%)	8,365		175	1.568×10^{-5}	5.5 / 8.2	0.2376/m 1 in 4.2 m		0.3503 1 in 2.9m		

Preliminary Risk Estimates

Simplified summary table

Scenario	Modeled Undetectable Infectious Risk Days [injected PrEP / oral PrEP-PEP]		Modeled Residual Risk (1 TT HIV in X million transfusions)	
	RBC	Plasma	RBC	Plasma
Baseline (no PrEP)	4.5	7.3	8.6 m	5.3 m
Additional PrEP breakthrough HIV risk				
Optimistic	5.7/5.5	8.2/8.2	18.1 m	12.3 m
Pessimistic			4.1 m	2.3 m

Summary

- PrEP changes the ability to detect HIV RNA and Abs
  - Different PrEP formulations have different effects making the situation increasingly challenging
- Intermittent adherence to dosing drives the risk of breakthrough HIV infection
- Donors are disclosing PrEP use in the US
  - We do not yet have data on undisclosed PrEP using during the period of individual donor assessment
- Detection of undisclosed PrEP use through biomarker testing is still not the answer
  - No high throughput assays
  - No assays beyond LC-MS/MS that cover all drugs of interest (FTC, TVF, CAB)
  - ARV detection in plasma ≠ intracellular ARV concentration and is therefore misleading
- Initial assessment of additional risk suggests low but evident risk of TT HIV
  - More insights to come as we refine the residual risk model

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