

# Considerations for HIV diagnosis in the context of PrEP

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# Background

- Current PrEP guidelines require quarterly HIV testing
  - 100,000 – 105,000 current PrEP users in South Africa
  - Potential for false positive or negative test results
- Presence of antiretrovirals for PrEP at time of infection may alter
  - Dynamics of viremia
  - Associated immune response
  - Present challenges to diagnosis
  - Potential to be more complicated with longer acting systemic products
- Accurate resolution of ambiguous results important for clinical management
  - Reduce harms e.g. resistance, psychological stress

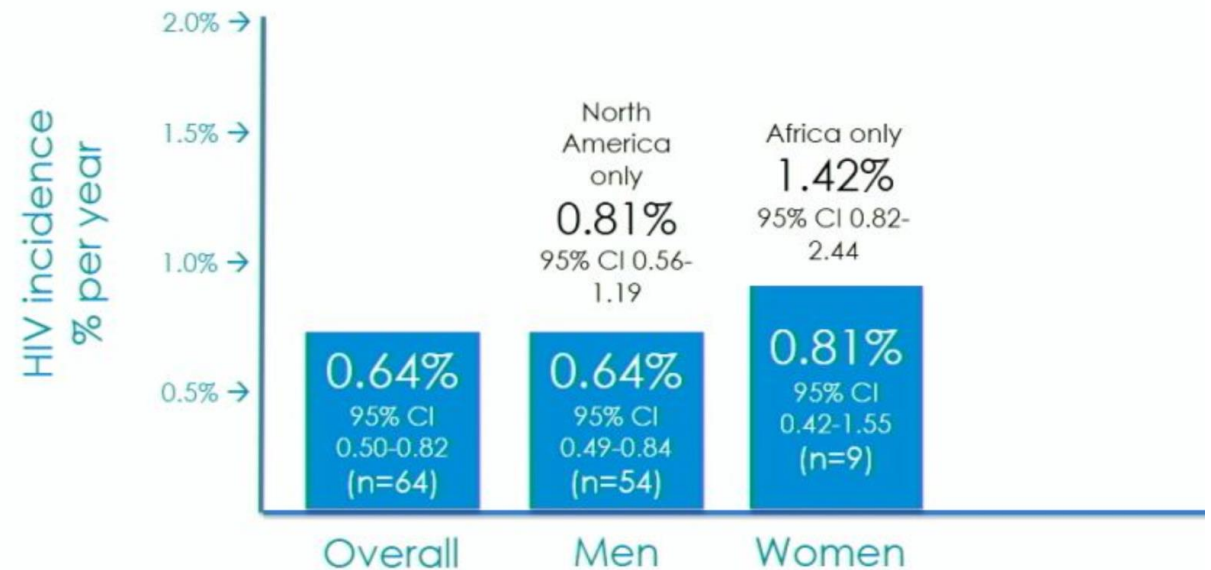
# Frequency of HIV infection among persons on PrEP

- 46 individual studies of TDF/FTC as PrEP
- 10, 609 HIV-1 negative participants
- 9,936 person-years

## Results

- 91 new HIV infections
- Incidence 0.92/100 py
- 36% new infections >30 days post-PrEP dose
- Adherence is key to PREP effectiveness – most infections appeared to occur in the absence of consistent PrEP use
- Period of vulnerability – acute infection at time of initiation

## Results: HIV incidence



# Case 1

- 23 year old woman
- Initiated oral TDF/FTC for HIV prevention May 2019
- Attended clinic visits
  - M1, M3, M6, **M9** – HIV detected at this visit on two rapid tests
  - Participant reported missing PrEP pills during travel (6-8 weeks previously)
  - Restarted PrEP on return from travel 1 mo prior to diagnosis
- At HIV diagnosis,
  - HIV RNA 1177, CD4+ 365
- Started FDC EFV/TDF/FTC 2 weeks after diagnosis

# Case 1 – additional test results

- 23 year old woman
  - Initiated oral TDF/FTC for HIV prevention May 2019
  - Attended clinic visits
    - M1, M3, M6, M9 – HIV detected at this visit on two rapid tests
    - Participant reported missing PrEP pills during travel (6-8 weeks previously)
    - Restarted PrEP on return from travel 1 mo prior to diagnosis
    - **TFV-DP 2190 fmol/punch**
  - At HIV diagnosis,
    - HIV RNA 1177, CD4+ 365
    - **ART drug resistance profile – susceptible**
  - Started FDC EFV/TDF/FTC 2 weeks after diagnosis
- *Important to ask about treatment interruptions and potential risk exposures*

# Potential for false positive testing

- False positive rate (FPR) = 1- specificity
- Each rapid test has different performance characteristics
- Rigorous licensing and manufacturing ensure false positive rare
  
- E.g. assume in SA
  - Specificity rapid test in high risk population is 99.7% (95% CI 99.0 - 100%) for whole blood.
  - FPR 0.3 % (0-1%)
  - 0.3% X 4 tests X 100,000 users = **1,200 false positive tests**

# Case 2

- 25 yo woman
- On PrEP for 41 weeks, self-reported adherence good
- Rapid test 1 negative, rapid test 2 **positive**
- PrEP hold, repeat testing

## **Additional testing**

- HIV 4<sup>th</sup> gen ELISA non reactive
- HIV RNA not detectable (LDL)
- HIV 1/2 Genius negative

# Case 2 - continued

- Repeat testing – 1 week later

## Confirmatory Sample date:

Rapid test 1

Negative

Rapid test 2

Positive

HIV ELISA

Non Reactive

Viral Load copies/ml

LDL

Geenius

Negative

CD4

1433cells/UL



# Case 2 - continued

- Repeat testing – 1 week later

## Confirmatory Sample date:

Rapid test 1	Negative
Rapid test 2	Positive
HIV ELISA	Non Reactive
Viral Load copies/ml	LDL
Geenius	Negative
CD4	1433cells/UL

- Repeat testing (delayed >4 weeks)

## Week 4 Visit date

22 Aug 19

Rapid test 1	N/A
Rapid test 2	Positive
HIV ELISA	Negative
Viral Load copies/ml	LDL
Geenius	Negative
Final status	Negative

Restarted PrEP 3 months after first positive

# Case 3

- 24 yo young woman,
- Started PrEP, RPR 1:32 at initiation, treated
- M6 visit – rapids negative, HIV 1/2 4<sup>th</sup> gen **positive**, RPR 1:8
- Good self-reported adherence, confirmed on drug level testing
- PrEP held at first positive test

# Case 3 - additional testing

2 weeks later	Interim	HIV Rapids	Neg / Neg
	Interim	HIV-1/2 (4th Gen)	Indeterminate
	Interim	PCR - HIV Viral Load ABBOTT	Not detected
	Interim	CD4 CELL COUNT	869
4 weeks later	Interim	HIV Rapids	Neg / Neg
	Interim	HIV-1/2 (4th Gen)	REACTIVE
	Interim	Geenius Confirmatory	NEGATIVE
	Interim	Alere Determine 4th Generation Rapid	NEGATIVE
	Interim	GeneXpert HIV -1 Viral	Not detected
	Interim	PCR - HIV DNA Qualitative	NEGATIVE
	Interim	PCR - HIV Viral Load ABBOTT	Not detected
	Interim	QUANT HIV LOG VIRAL LOAD	Not applicable
	Interim	Western Blot HIV1	NEGATIVE

- Determined to be false positive, possibly because of RPR+
- Chavez, 2011 reported specificity 98.78% (95% CI: 98.51-99.01)

# Potential for false negative testing: 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
- 
- May be further complicated with long acting products e.g. CAB LA
  - Need more empiric data!

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

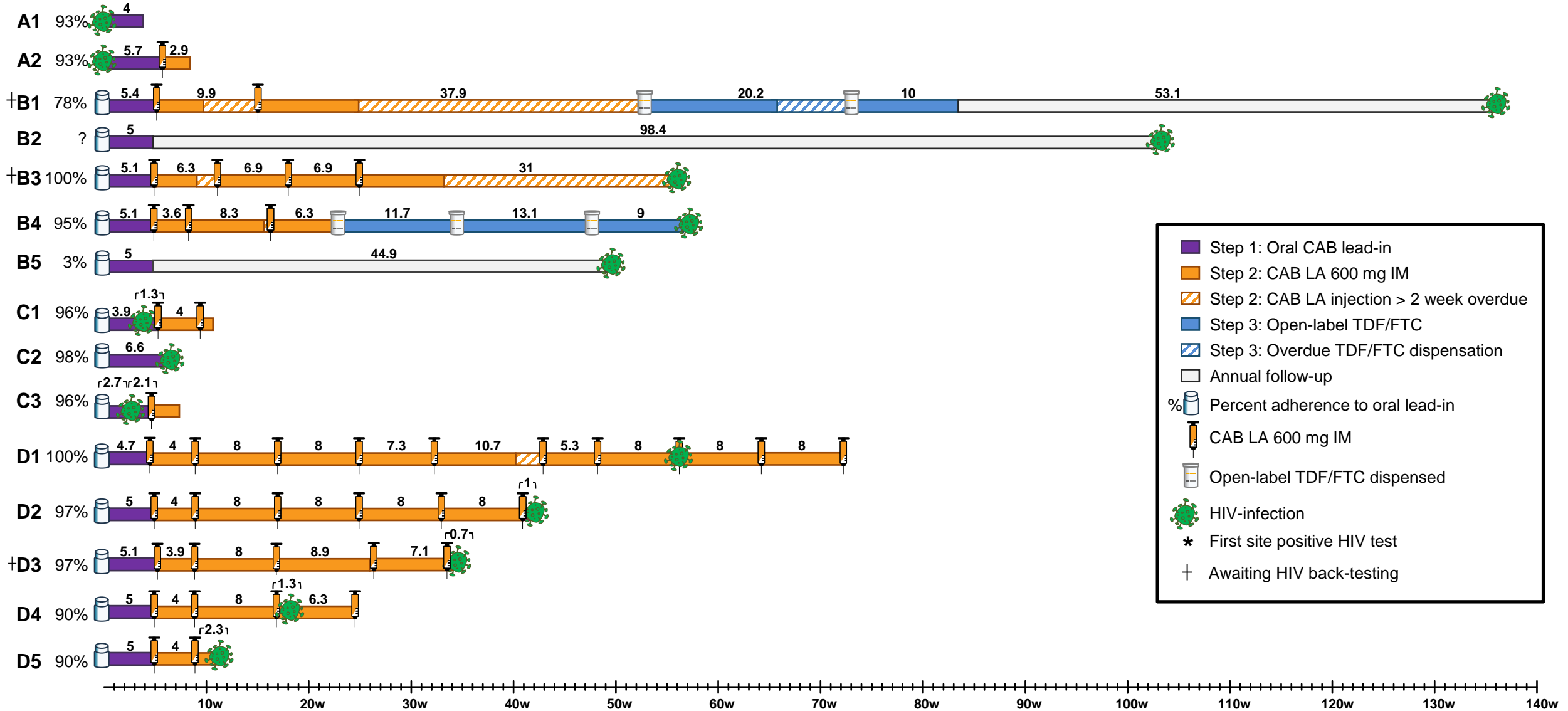
Deborah Donnell<sup>a,c</sup>, Eric Ramos<sup>b</sup>, Connie Celum<sup>c,d,e</sup>, Jared Baeten<sup>c,d,e</sup>,  
Joan Dragavon<sup>b</sup>, Jordan Tappero<sup>g</sup>, Jairam R. Lingappa<sup>c,e,f</sup>,  
Allan Ronald<sup>h</sup>, Kenneth Fife<sup>i</sup>, Robert W. Coombs<sup>b</sup>,  
for the 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.

# 13 Incident HIV Infections

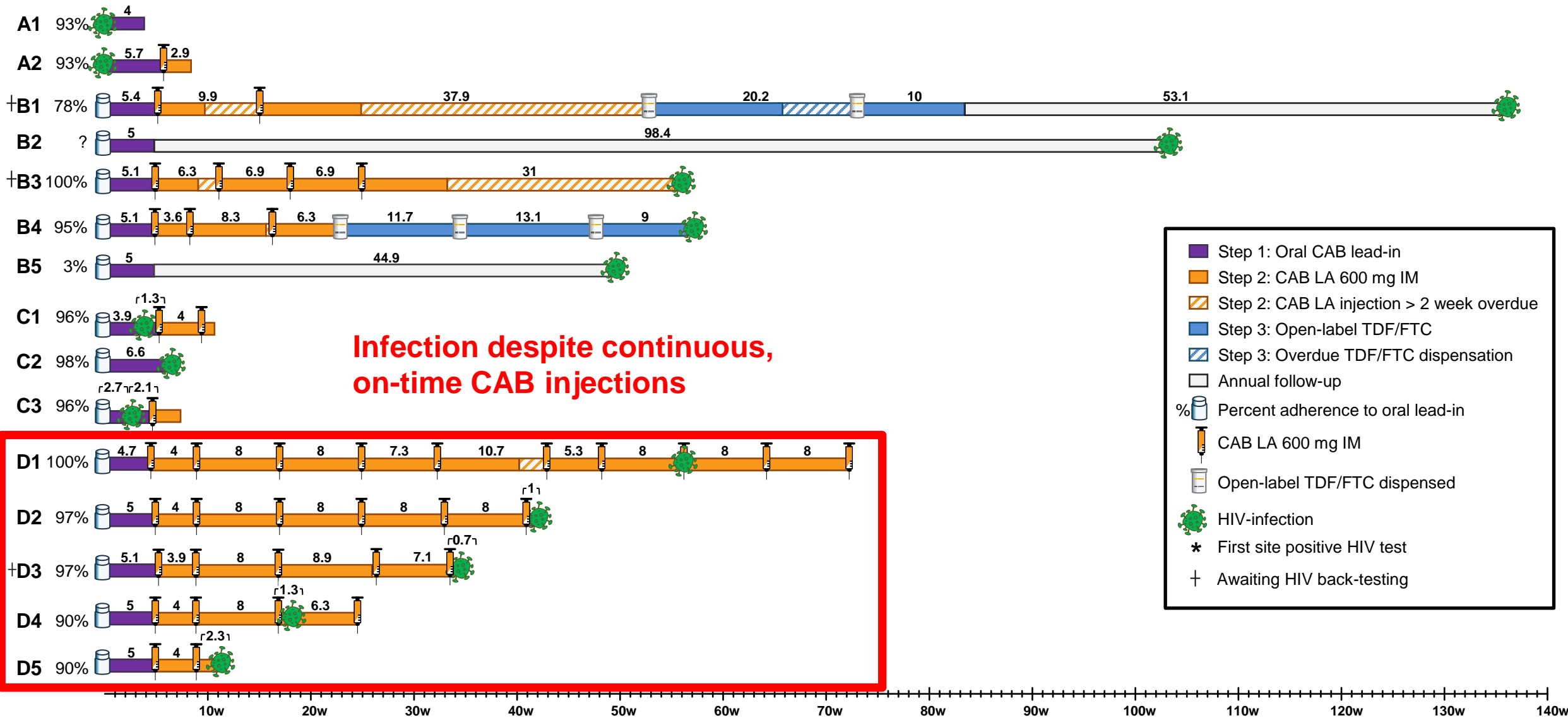
## Cabotegravir



- Step 1: Oral CAB lead-in
- Step 2: CAB LA 600 mg IM
- Step 2: CAB LA injection > 2 week overdue
- Step 3: Open-label TDF/FTC
- Step 3: Overdue TDF/FTC dispensation
- Annual follow-up
- % Adherence to oral lead-in
- CAB LA 600 mg IM
- Open-label TDF/FTC dispensed
- HIV-infection
- \* First site positive HIV test
- + Awaiting HIV back-testing

# 13 Incident HIV Infections

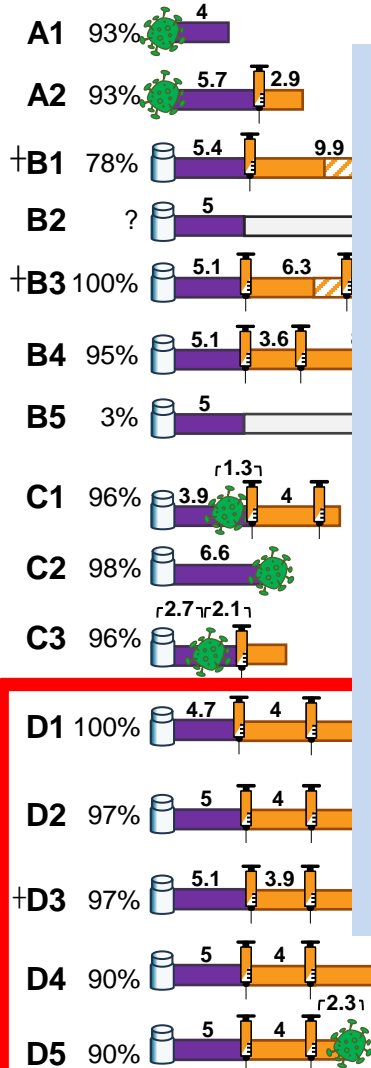
## Cabotegravir



**Infection despite continuous, on-time CAB injections**

# 13 Incident HIV Infections

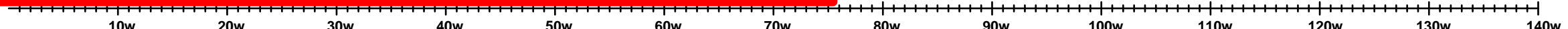
## Cabotegravir



Look out for upcoming presentations and papers in 2021 at CROI, IAS

With additional data on PK and resistance profiles of CAB seroconverters

- oral lead-in
- mg IM
- ation > 2 week overdue
- DF/FTC
- F/FTC dispensation
- dispensed
- test
- sting



# How to Manage Ambiguous HIV Test Results during PrEP

Client on PrEP  
Quarterly screening

More experience needed to manage ambiguous tests results

To resolve false-positive results:

Repeat testing, discussion between clinicians and virologists  
Seek expert opinion

**Continue PrEP  
if PrEP adherence**

Maintains protection  
**Risk for resistance**

**Stop PrEP  
Reassess HIV status**

Facilitate diagnosis  
**Risk of infection**

**Initiate ART  
if no PrEP adherence**

Drug-related AEs  
**Confirm diagnosis**



# Summary

- ART PrEP is highly effective in preventing HIV
- PrEP may interfere with interpretation of current HIV testing algorithms
  - Important to be aware of reasons for positive test
- Long acting products may further complicate testing interpretation
  - New data available in 2021 will be informative
- Clinicians will need to make important decisions about whether to stop/start PrEP and start ART
  - Need for additional testing, seek expert advice

# Acknowledgements

- PrEP recipients
- Raphael Landovitz
- Connie Celum