HIV Infections in the Setting of Long-Acting Early Viral Inhibition: the LEVI Syndrome

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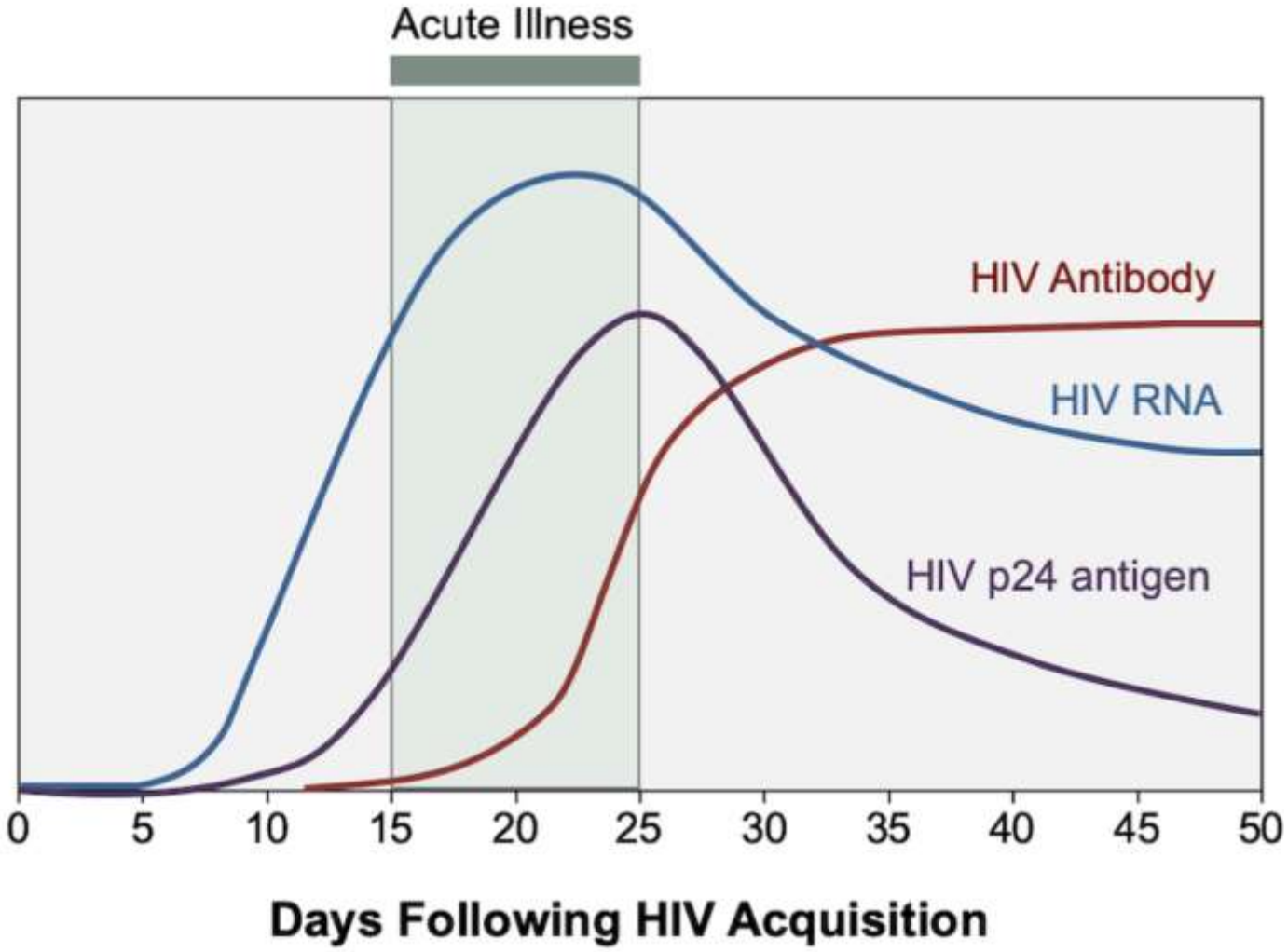
HPTN
HIV Prevention Trials Network

ANNUAL MEETING
2022

Acute HIV infection



https://www.hiv.uw.edu/go/screening-diagnosis/acute-recent-early-hiv/core-concept/all

New paradigm for HIV infections that occur in the setting of CAB-LA PrEP

Long-acting early viral inhibition (LEVI) syndrome

HPTN 083 and 084

These randomized clinical trials compared the efficacy of CAB-LA to daily oral TDF/FTC for HIV prevention

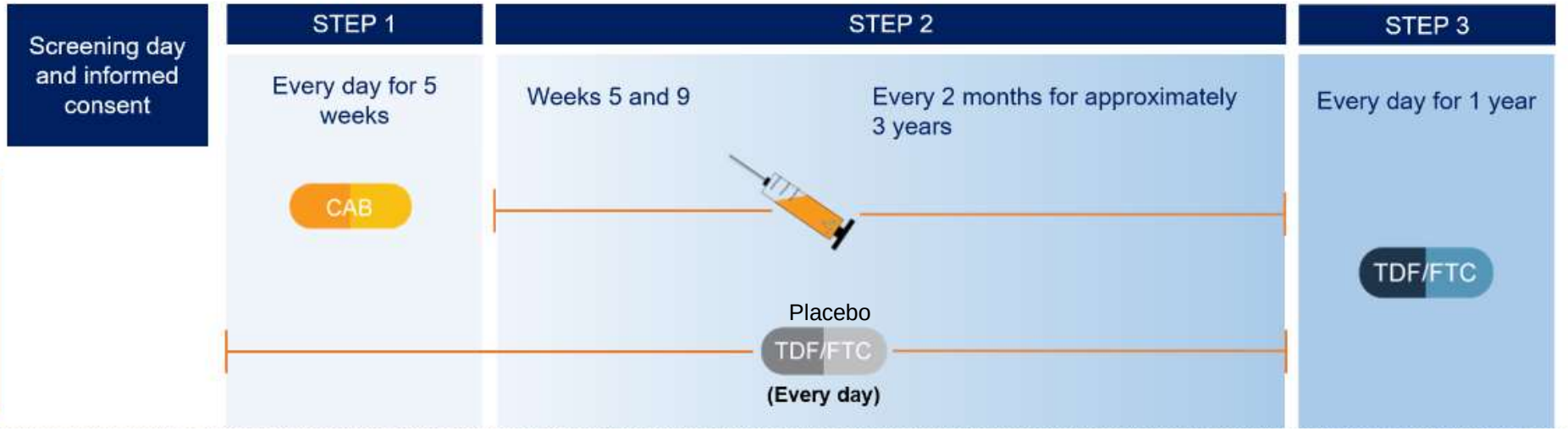
HPTN 083 enrolled >4,500 cisgender MSM and TGW at 43 sites in the US, Latin America, Asia and Africa

HPTN 084 enrolled >3,200 cisgender women at 20 sites in sub-Saharan Africa

Both trials were unblinded in 2020 because CAB LA was shown to be superior to oral TDF/FTC for HIV prevention

In Dec 2021, the US FDA approved CAB-LA for prevention of HIV sexual transmission (brand name: Apretude)

HPTN 083 and 084 – CAB arm



HIV testing at study sites

Negative HIV RNA test <14 days before enrollment

1 or 2 HIV rapid tests
Instrumented Ag/Ab test

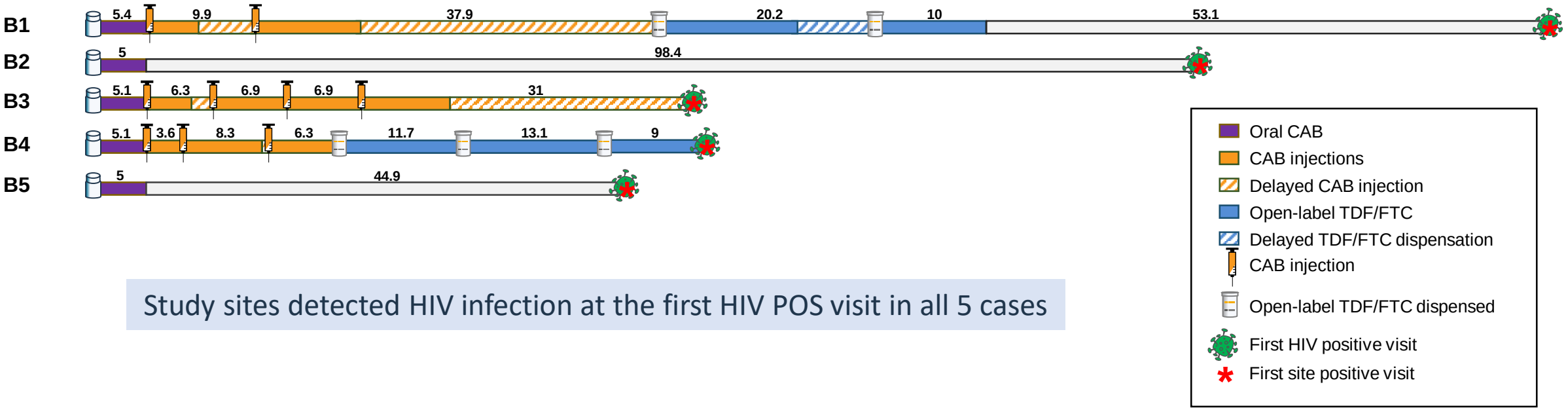
Reactive result → Clinical advisory committee

Locally-available RNA and/or Ab tests
Ultrasensitive DNA test (JHU, selected cases)
LLOD: 4.09 c/10^6 cells

Extended retrospective testing at the HPTN LC

APTIMA HIV-1 Qualitative RNA test (LLOD: 30 c/mL)
Architect Ag/Ab test
Geenius discriminatory test
Abbott RealTime HIV-1 viral load test
Single copy RNA test (U Pittsburgh, selected cases)

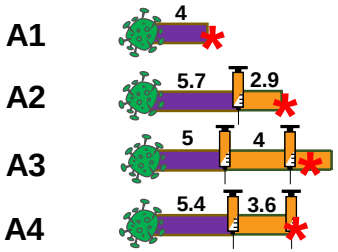
Incident cases with no CAB exposure in the past 6 months



Study sites detected HIV infection at the first HIV POS visit in all 5 cases

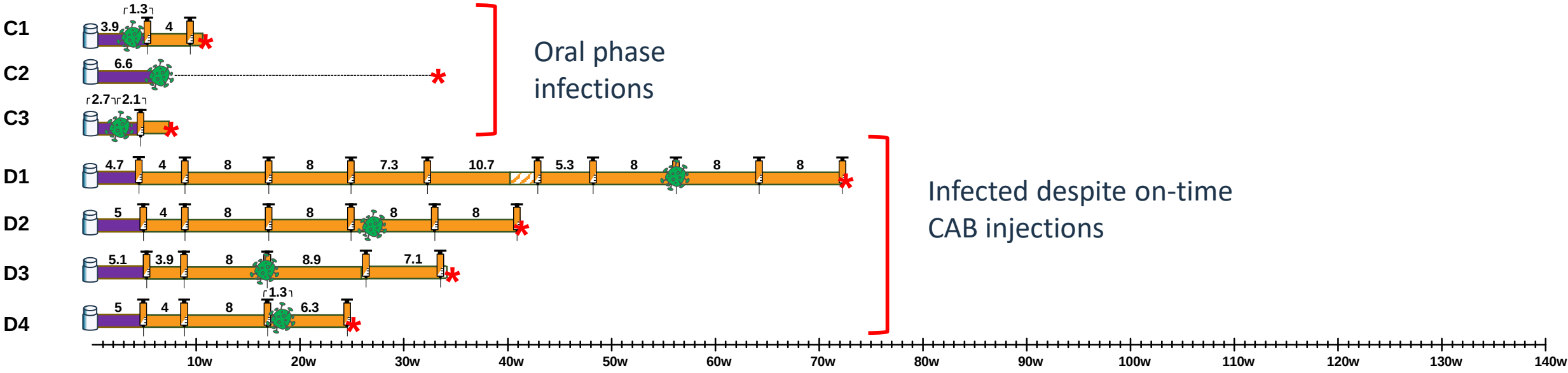
Baseline cases and incident cases with recent CAB exposure

Baseline infections



Detection of HIV infection at the study sites was delayed in all 11 cases

Incident infections

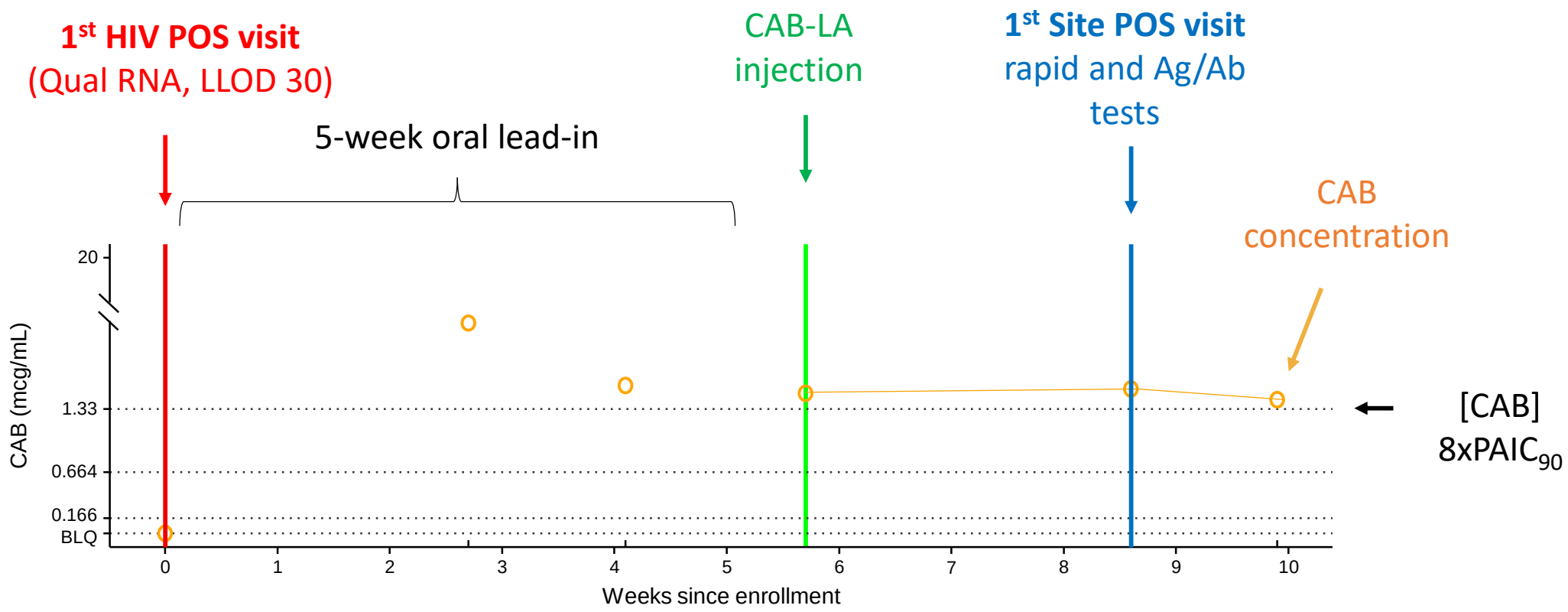


Oral phase infections

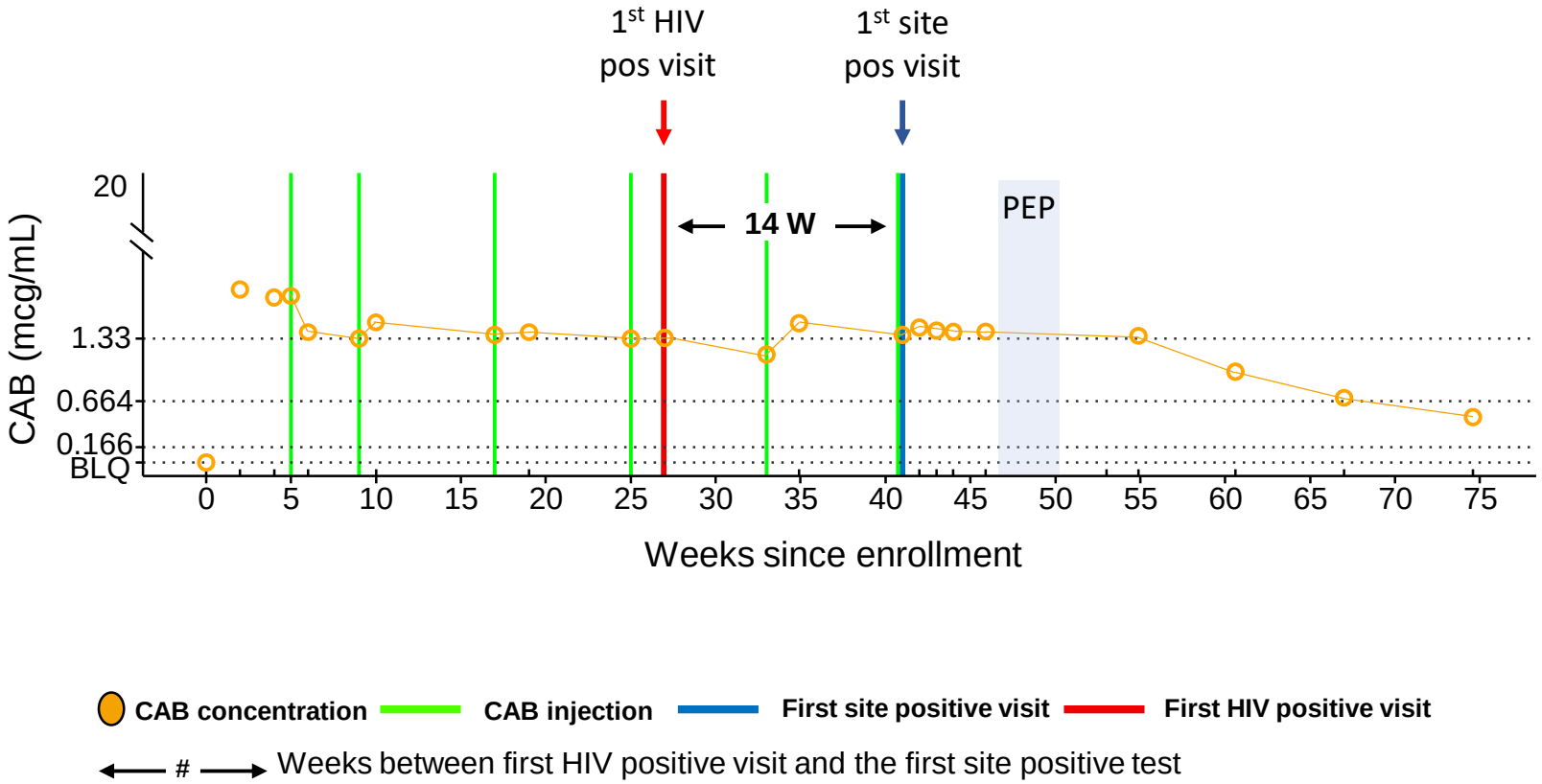
Infected despite on-time CAB injections

Case Studies

Case presentation



HPTN 083 – Case D2



Case D2

		Site Testing				
Visit type	Diagnosis visit type	Rapid 1 test	Ag/Ab test	DNA test	Viral load	Confirmatory Ab test
Enrollment		NR	NR			
Week 2		NR	NR			
Week 4		NR	NR			
Week 5		NR	NR			
Week 6		NR	NR			
Week 9		NR	NR			
Week 10		NR	NR			
Week 17		NR	NR			
Week 19		NR	NR			
Week 25		NR	NR			
Week 27		NR	NR			
Week 33		NR	NR			
Week 35		NR	NR			
Week 41	1st SITE POS	NR	R		ND	
Interim		R	R	Detect <LLOD	ND	
Interim		NR	R			
Week 43		NR	R			
Interim		NR	R	ND	ND	
Interim*		R	R	Detect <LLOD	ND	
Interim		NR	R			
Interim		NR	R	Detect 5.8	23	POS
Interim		R	R		23	

7 days

PEP

26 weeks

* Started a 30-day course of TDF/3TC/DRVr 7 days later for PEP

Case D2

	Visit type	Diagnosis visit type	Site Testing: Rapid 1 test	Site Testing: Ag/Ab test	Site Testing: DNA test	Site Testing: Viral load	Site Testing: Confirmatory Ab test	HPTN LC Testing: Ag/Ab test	HPTN LC Testing: Qualitative RNA test	HPTN LC Testing: Confirmatory Ab test	HPTN LC Testing: 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		
14 weeks	Week 27	1st HIV POS	NR	NR				NR	R		SCA 6.1
14 weeks	**Week 33**		NR	NR				NR	NR		
14 weeks	Week 35		NR	NR				NR	R		ND
14 weeks	**Week 41**	1st SITE POS	NR	R		ND		NR	NR		
48 weeks	Interim		R	R	Detect <LLOD	ND		R	NR	NEG	
48 weeks	Interim		NR	R				R	NR	NEG	
48 weeks	Week 43		NR	R				NR	NR		
48 weeks	Interim		NR	R	ND	ND		R	NR	INDET	
48 weeks	Interim*		R	R	Detect <LLOD	ND		NR	NR		
48 weeks	Interim		NR	R				R	NR	INDET	
48 weeks	Interim		NR	R	Detect 5.8	23	POS	R	R	NEG	<40
48 weeks	Interim		R	R		23		R	R	INDET	<40

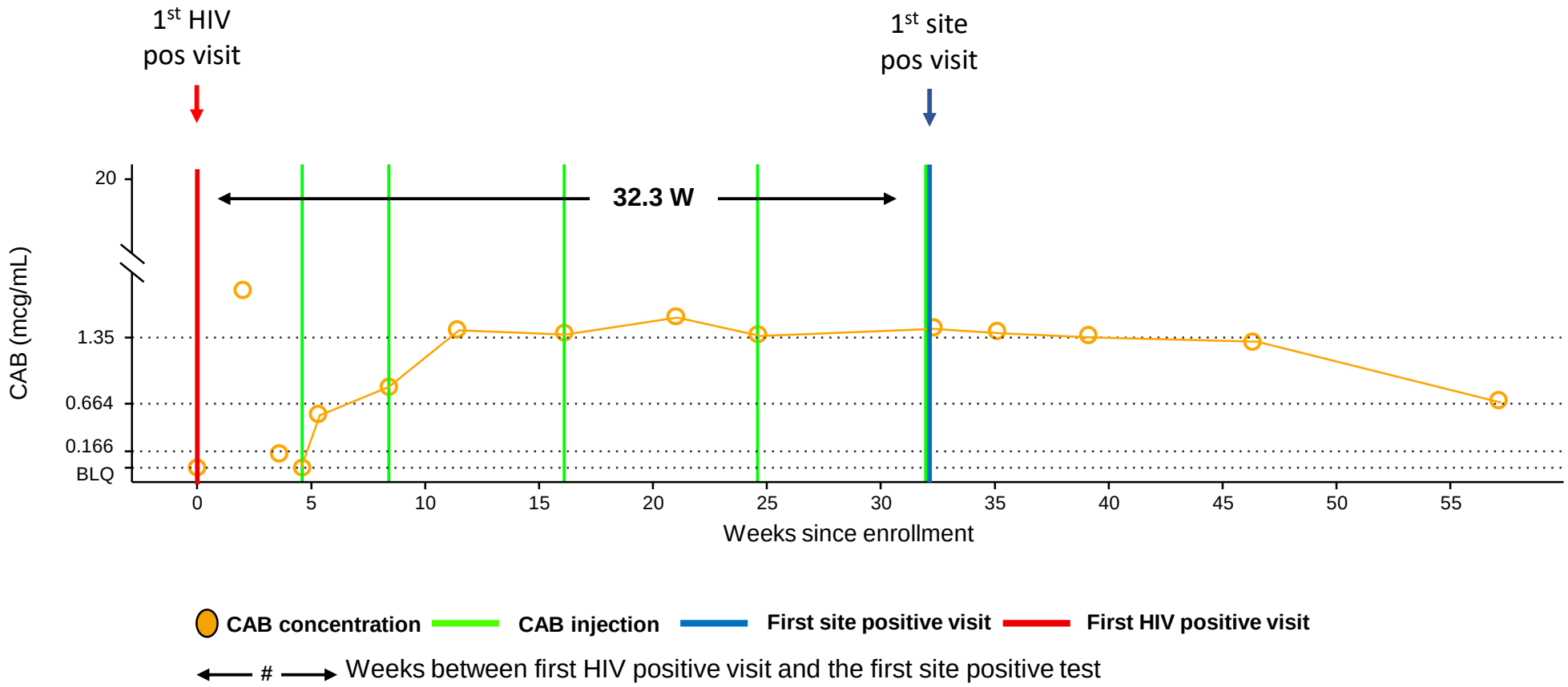
*Started a 30-day course of TDF/3TC/DRVr 7 days later for PEP; later started ART with TDF/3TC/DRVr with a viral load of 1700

Case D2

		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		R	R	Detect <LLOD	ND		R	NR	NEG	
Interim		NR	R				R	NR	NEG	
Week 43		NR	R				NR	NR		
Interim		NR	R	ND	ND		R	NR	INDET	
Interim*		R	R	Detect <LLOD	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

HPTN 084 – Case A1



Case A1

		Site Testing				
Visit type	Diagnosis visit type	Rapid 1 test	Rapid 2 test	Ag/Ab test	DNA test	Viral load
Enrollment		NR		NR		
Week 2		NR		NR		
Week 4		NR		NR		
Week 5		NR		NR		
Week 6		NR		NR		
Week 9		NR		NR		
Week 13		NR		NR		
Week 17		NR		NR		
Week 21		NR		NR		
Week 25		NR		NR		
Week 33	1st SITE POS	NR		R		ND
Interim Visit		NR		NR	<4.09	ND
Interim Visit		NR		R	4.6	ND
Interim Visit		NR	R	NR	4.4	ND
SC Week 24		NR	NR	NR		33

20 days

>5 months

Case A1

		Site Testing					HPTN LC Testing			
Visit type	Diagnosis visit type	Rapid 1 test	Rapid 2 test	Ag/Ab test	DNA test	Viral load	Ag/Ab test	Qualitative RNA test	Confirmatory Ab test	Viral load
Enrollment	1st HIV POS	NR		NR			NR	R		<40* SCA 21.4
Week 2		NR		NR			NR	R		500
Week 4		NR		NR			NR	R		1,740
Week 5		NR		NR			NR	R		6,300
Week 6		NR		NR			R	R	IND	87
Week 9		NR		NR			NR	NR		SCA NEG
Week 13		NR		NR			NR	NR		SCA NEG
Week 17		NR		NR			NR	NR		SCA NEG
Week 21		NR		NR			NR	NR		SCA NEG
Week 25		NR		NR			NR	NR		SCA NEG
Week 33	1st SITE POS	NR		R		ND	R	NR	IND	SCA NEG
Interim Visit		NR		NR	<4.09	ND	R	NR	IND	SCA NEG
Interim Visit		NR		R	4.6	ND	R	NR	IND	SCA NEG
Interim Visit		NR	R	NR	4.4	ND	R	NR	IND	SCA NEG
SC Week 24		NR	NR	NR		33	R	NR	IND	SCA NEG

Case A1

		Site Testing					HPTN LC Testing				
Visit type	Diagnosis visit type	Rapid 1 test	Rapid 2 test	Ag/Ab test	DNA test	Viral load	Ag/Ab test	Qualitative RNA test	Confirmatory Ab test	Viral load	
Enrollment	1st HIV POS	NR		NR			NR	R		<40* SCA 21.4	Oral CAB 5 weeks
Week 2		NR		NR			NR	R		500	
Week 4		NR		NR			NR	R		1,740	
Week 5		NR		NR			NR	R		6,300	
Week 6		NR		NR			R	R	IND	87	CAB injections 28 weeks
Week 9		NR		NR			NR	NR		SCA NEG	
Week 13		NR		NR			NR	NR		SCA NEG	
Week 17		NR		NR			NR	NR		SCA NEG	
Week 21		NR		NR			NR	NR		SCA NEG	
Week 25		NR		NR			NR	NR		SCA NEG	
Week 33	1st SITE POS	NR		R		ND	R	NR	IND	SCA NEG	
Interim Visit		NR		NR	<4.09	ND	R	NR	IND	SCA NEG	CAB tail 25 weeks
Interim Visit		NR		R	4.6	ND	R	NR	IND	SCA NEG	
Interim Visit		NR	R	NR	4.4	ND	R	NR	IND	SCA NEG	
SC Week 24		NR	NR	NR		33	R	NR	IND	SCA NEG	

Conclusions

HIV rapid tests and Ag/Ab tests often fail to detect HIV infection in the setting of CAB-LA PrEP

Suppression of viral replication and delayed antibody expression can persist for many months following HIV infection, even after injections are discontinued

Sensitive HIV RNA testing allows for earlier detection of infections in this setting

HIV RNA Testing with CAB-LA PrEP

Apretude (CAB-LA) package insert (US FDA):
Individuals must be tested for HIV-1 infection prior to initiating APRETUDE…and with each subsequent injection….using a test approved or cleared by the FDA for the diagnosis of acute or primary HIV-1 infection

US CDC/DHHS 2021: PrEP guidance for CAB-LA PrEP
Perform HIV RNA testing with the most sensitive test available

- Within 1 week before starting CAB PrEP
- 1 month after the 1st injection, then bi-monthly with each injection
- Quarterly for 12 months after stopping injections

Apretude package insert: https://www.accessdata.fda.gov

US CDC, DHHS. PrEP for the prevention of HIV infections in the United States – 2021 Update

FDA approved tests for diagnosis of acute HIV infection

Aptima HIV-1 Quant Dx Assay
Hologic, Panther platform, dual claim (detection, quantification)
Qualitative: LLOD - **30 copies/mL**, 700 uL serum or plasma

Cobas HIV-1/HIV-2 Qualitative Test
Roche, 6800/8800 systems
Qualitative: LLOD - **12.8 c/mL** (HIV-1), 650 uL serum or plasma

Impact of delayed HIV diagnosis in the setting of CAB-LA PrEP

Delayed detection of HIV infection
→ Unnecessary CAB-LA injections
→ Delayed ART initiation
→ Emergence of INSTI resistance
→ Potential to impact personal health or on-going HIV transmission

Emergence of INSTI resistance in the setting of CAB-LA PrEP

We evaluated INSTI resistance in the CAB arm of HPTN 083, and assessed whether earlier detection of HIV infection using a sensitive RNA assay for HIV screening would reduce INSTI resistance risk

GenoSure PRIme assay (Monogram Biosciences) – VL >500 c/mL
Low VL INSTI genotyping assay (Univ. of Pittsburgh) – VL <500 c/mL

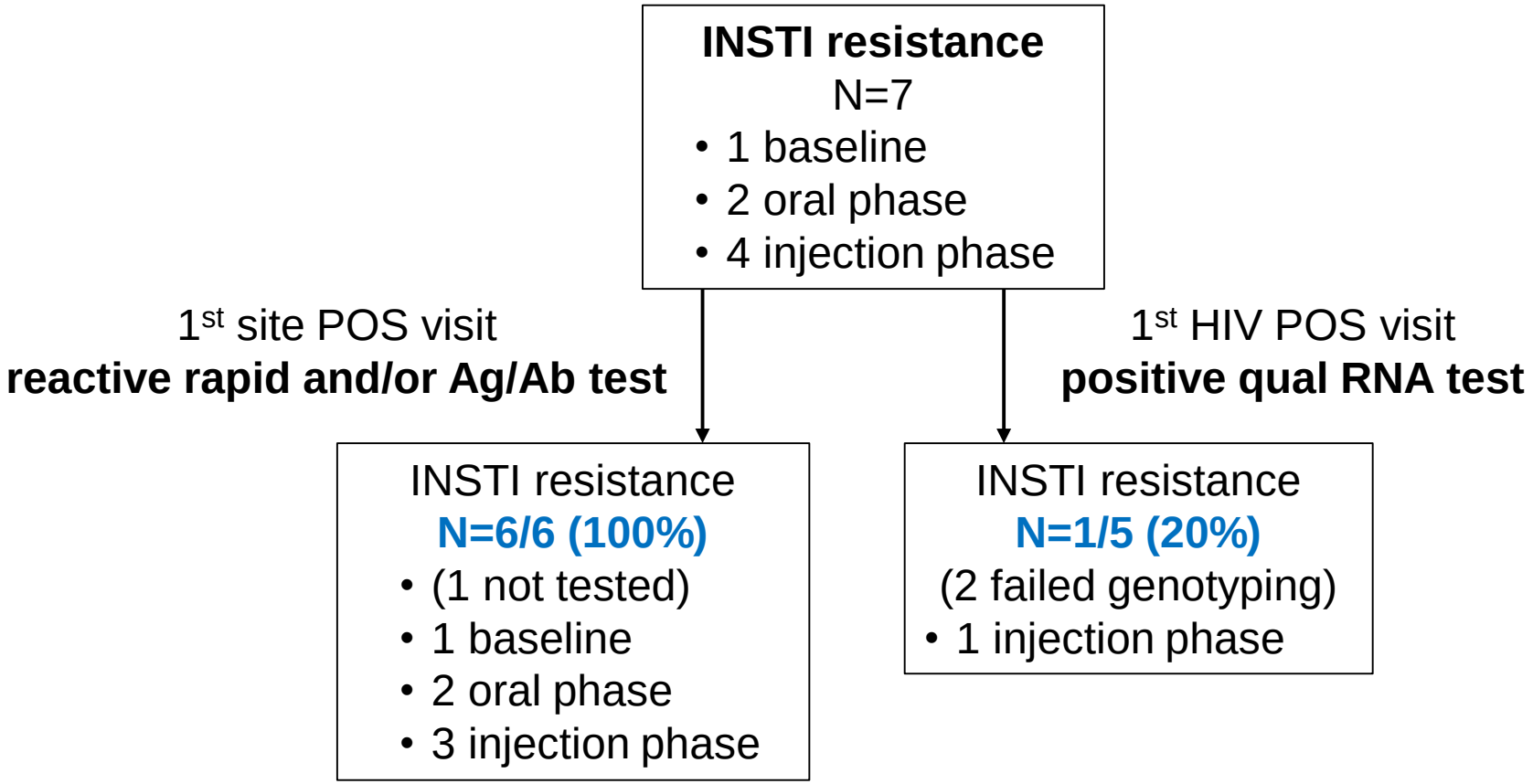
Emergence of INSTI resistance

In most cases, major INSTI resistance mutations (RAMs) were first detected:

- In samples with low VLs - not just in high VL "breakthrough" samples
  - <250 c/mL in 6/7 cases, <40 c/mL in 2/7 cases
- Close to the time of the first HIV positive visit
  - Median 38 days (range: 0-62 days)
- When CAB concentrations were high
  - 1.11-3.32 mcg/mL in 6/7 cases

Impact of HIV RNA screening on INSTI resistance

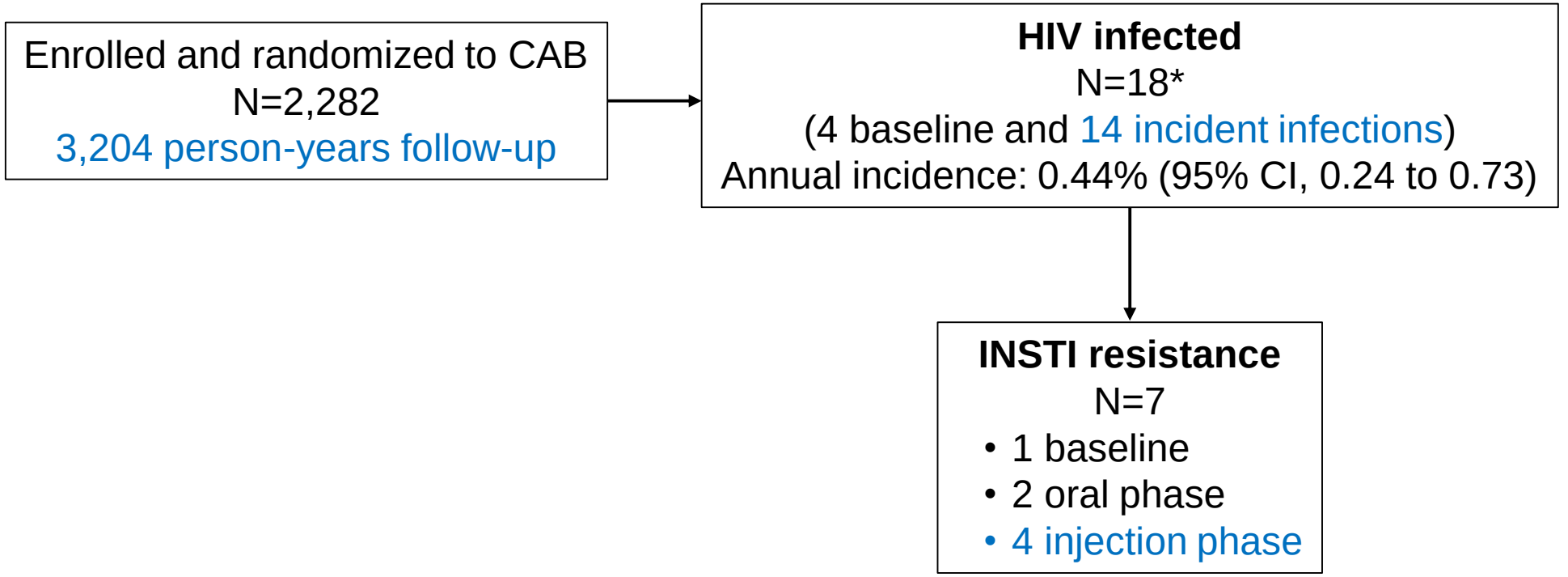
Use of an RNA assay for HIV screening would have detected infection before a **major** INSTI RAM was detected (4 cases) or before **additional major** INSTI RAMs accumulated (1 case)
This could not be evaluated in 2 cases since genotyping results were not obtained at the first HIV positive visit



Conclusions

Use of a sensitive RNA assay for HIV screening will help identify infections earlier
This may allow for earlier ART initiation, potentially reducing the risk of INSTI resistance
This testing should be performed using the most sensitive RNA assay available

HIV infection and INSTI resistance are rare events in the setting of CAB-LA PrEP



In the context of proven high efficacy, CAB-LA should also be considered for HIV PrEP in settings where HIV RNA screening is not readily available

Long-acting Early Viral Inhibition (LEVI)

Comparison of acute HIV infection (AHI) to infections that occur in the setting of long-acting early viral inhibition (LEVI)

	AHI	LEVI
Cause	Phase of natural HIV infection	Long-acting anti-viral PrEP agent (prototype: CAB-LA)
Onset	New infection	Infection during PrEP Initiation of PrEP agent during acute/early infection
Viral replication	Explosive	Smoldering
Symptoms	Fever, chills, rash, night sweats, muscle aches, sore throat, fatigue, swollen glands	Minimal, variable, often no symptoms reported
Detection	Ag/Ab assay, RNA assays (including less sensitive POC and pooled tests), DNA assays, total nucleic acid assays	Ultrasensitive RNA assay (often low or undetectable RNA, low/undetectable DNA, diminished/delayed Ab production)
Assay reversion	Rare	Common for many test types
Duration	1-2 weeks (until Ab detection)	Months (until viral breakthrough, cessation of anti-viral exposure or ART start)
Persistence	Rare*	Weeks-months after anti-viral agent is discontinued
Transmission	Very likely	Unlikely (except possibly through blood transfusion)
Drug resistance	No (unless transmitted)	Yes (can emerge early when viral load is low)

Acknowledgments

Study team and participants

Participating laboratories

Collaborators/Investigators

Citations

Landovitz NEJM 2021; 385:595
Marzinke JID 2021; 224:1581
Eshleman JID 2022; on-line ahead of print
Eshleman CROI 2022, Abstract LB95
Landovitz CROI 2022, Abstract LB96

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