The LEVI Syndrome: Characteristics of early HIV infection with cabotegravir for PrEP

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HPTN
HIV Prevention
Trials Network

HPTN 083 and 084

Randomized, double-blind, double-dummy trials
Compared CAB-LA to daily oral TDF/FTC for HIV PrEP

HPTN 083: >4500 cisgender MSM and TGW, US, Latin America, Asia and Africa
HPTN 084: >3200 cisgender women, sub-Saharan Africa

CAB arm: 5-week oral phase → loading injection → injections every 2 months for up to 3 years → daily oral TDF/FTC

Both trials demonstrated that CAB-LA was superior to daily oral TDF/FTC
CAB-LA was approved by the US FDA for HIV PrEP in Dec 2021 (Apretude)

This presentation will describe a new paradigm for early HIV infection in the setting of potent long-acting PrEP agents

Long-acting Early Viral Inhibition (LEVI) Syndrome

Marzinke, JID 2021; 224:1581
Eshleman, JID 2022; 225:1749
Eshleman, JID 2022; 226:2170
Marzinke, AAC 2023; In Press

HPTN 083 – CAB arm HIV infections

6 infections occurred despite on-time injections among 2,282 participants randomized to CAB-LA

Type of case	# Cases
Infected despite on-time injections	**6**
28 other infections	
No recent CAB exposure (within 6 months)	16
HIV+ at enrollment	4
Infected while receiving oral CAB	3
Infected after ≥ 1 delayed injection	3
Infected near the time of CAB re-initiation	2

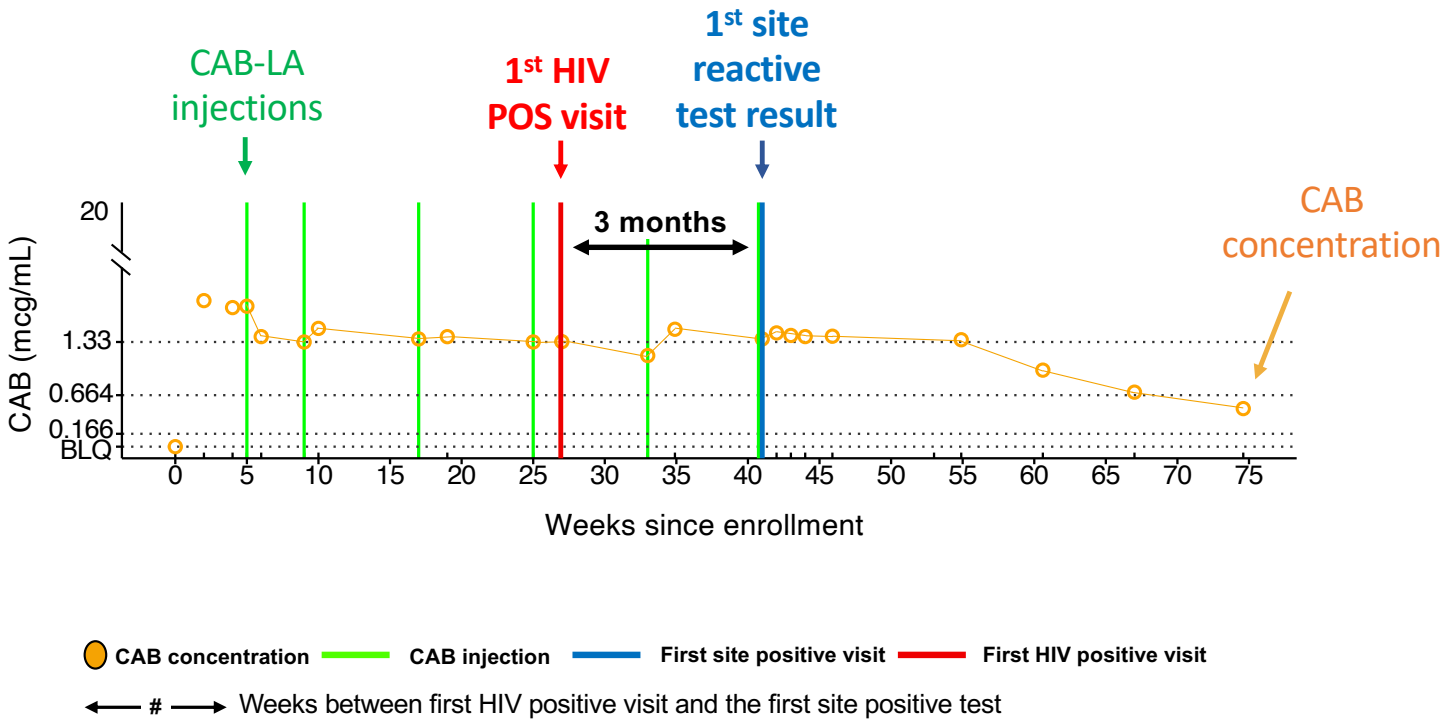
Delayed detection of HIV infection

- HIV rapid tests and Ag/Ab tests often fail to detect HIV infection in the setting of CAB-LA PrEP
- Viral suppression and delayed/diminished Ab expression can persist for months after infection, even after injections are discontinued

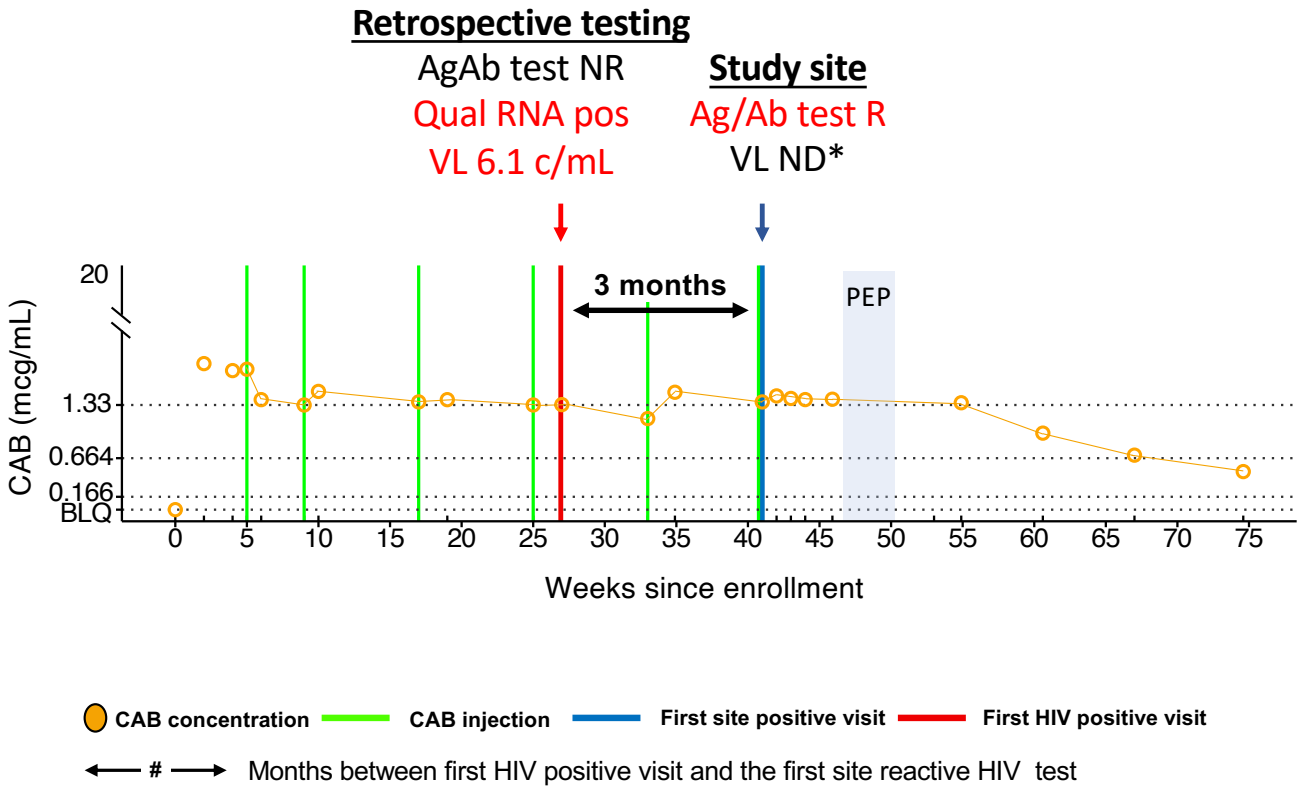
Delayed detection of HIV infection
→ Unnecessary CAB-LA injections
→ Delayed ART initiation
→ Potential to impact personal health or on-going HIV transmission
→ Emergence of INSTI resistance

- In HPTN 083, detection of infection was delayed in ~½ of the CAB arm infections
- This was rarely observed when infection occurred > 6 months after CAB administration

Case study


CAB-LA injections
1st HIV POS visit
1st site reactive test result
3 months
CAB concentration
CAB (mcg/mL)
20
1.33
0.664
0.166
BLQ
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
Weeks since enrollment
CAB concentration
CAB injection
First site positive visit
First HIV positive visit
#
Weeks between first HIV positive visit and the first site positive test

Case study: Detection of infection



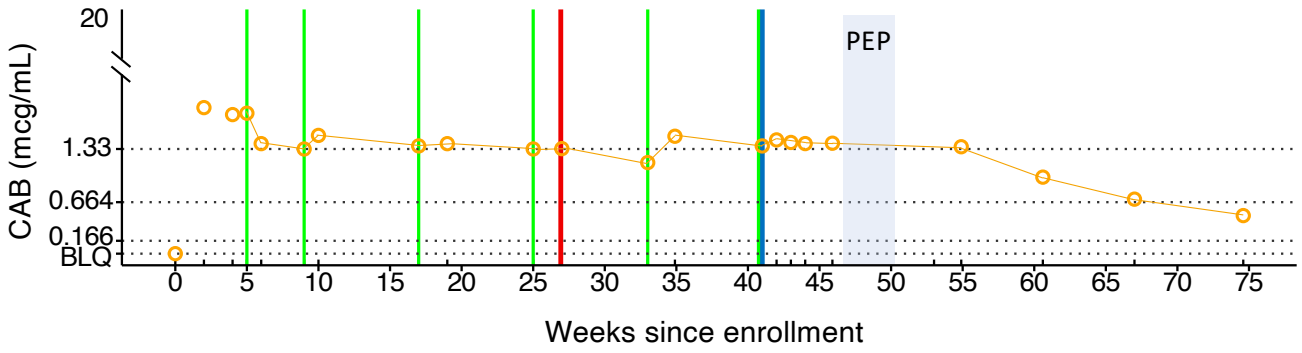
*LLOQ: 20 c/mL

Case Study: Confirmation of Infection

Retrospective testing
Ag/Ab test non-reactive
Qual RNA reactive
VL 6.1 c/mL
Genotyping failed

← 9 months →

Study site
Discrim Ab positive
Qual RNA reactive
VL 23
N155H + S230R



CAB concentration — CAB injection — First site positive visit — First HIV positive visit

← # → Months between first HIV positive visit and the first site confirmation of HIV infection

Assay Reversion

	Days since 1st HIV pos visit	Rapid test	Ag/Ab test	Qualitative RNA test LLOD 30 c/mL	Confirmatory Ab test	Viral load LLOQ 40 c/mL or single copy	DNA test LLOD 4.09 c/10^6 cells
11 months	0	NR	NR	R		6.1	
	42	NR	NR	NR			
	55	NR	NR	R		ND	
	98	NR	NR	NR			
	105	R	R	NR	NEG		Detect <LLOD
	112	NR	R	NR	NEG		
	119	NR	NR	NR			
	132	NR	R	NR	INDET		ND
	195	R	NR	NR			Detect <LLOD
	235	NR	R	NR	INDET		
	280	NR	R	R	NEG	<40	Detect 5.8
	333	R	R	R	INDET	<40	

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, drug clearance, or ART start); can persist months after the 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)

INSTI resistance

In HPTN 083, INSTI resistance emerged in 10/18 cases with CAB administration within 6 months of the 1st HIV positive visit

INSTI resistance was not observed when the 1st HIV positive visit was >6 months after CAB administration

Retrospective testing with a sensitive RNA assay detected most infections before INSTI resistance emerged

HIV RNA screening

RNA testing can be used to screen for HIV infection with CAB-LA PrEP

- Included in the US FDA package insert
- Recommended by the US CDC
- Not included in the WHO guidelines

We are evaluating the use of RNA screening in the on-going 083 and 084 open-label studies

Further research is needed to evaluate the pros and cons of HIV RNA screening with CAB-LA PrEP

Conclusions

- Infections with on-time CAB-LA injections are rare
- Detection of infection in the setting of CAB-LA is often delayed using rapid and Ag/Ab tests for screening
- RNA assays detect infections earlier, often before resistance emerges
- Further research is needed to evaluate use of HIV RNA screening in this setting
- Future studies will be needed to determine if the LEVI syndrome occurs with other potent, long-acting PrEP agents

Acknowledgments

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