

Rischio di resistenze nella PrEP con Cabotegravir

Firenze, 28 gennaio 2025

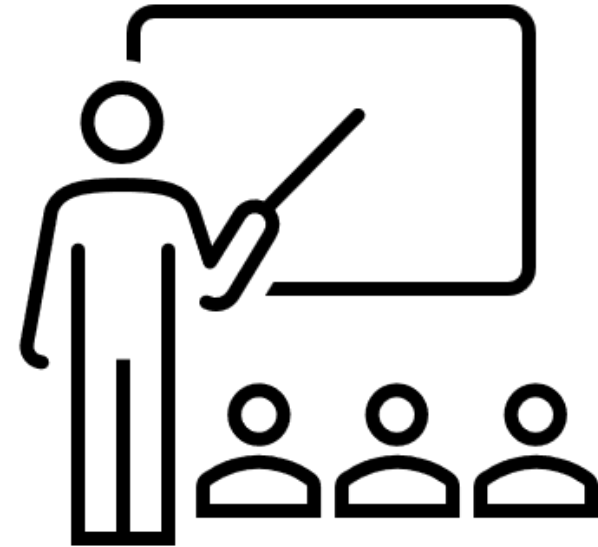
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Disclosures (last 2 years)

- Grants for research activities
 - Gilead Sciences
 - Merck Sharp and Dohme
- Personal fees for advisory boards and educational activities
 - Gilead Sciences
 - Merck Sharp and Dohme
 - ViiV Healthcare

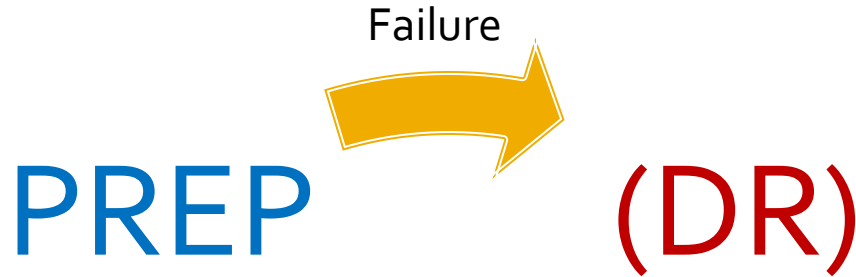
CAB LA PrEP and drug resistance

- **Basics on PrEP & drug resistance**
- What happened in CAB LA PrEP clinical trials
- What's happening in the real world
- Hints for management



Drug resistance from PrEP to ART and back

- All current and upcoming PREPs are single-class*
- High genetic barrier difficult to obtain



- All common ART regimens are dual-class
- Genetic barrier usually high (2nd gen INSTIs)

*

TXF/FTC
LA CAB
DPV vaginal ring
LEN
MK-8527

Drug resistance from PrEP to ART and back

- All current and upcoming PREPs are single-class*
- High genetic barrier difficult to obtain

PREP

DR

Failure

Transmission

DR

ART

Failure

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*

TXF/FTC

LA CAB

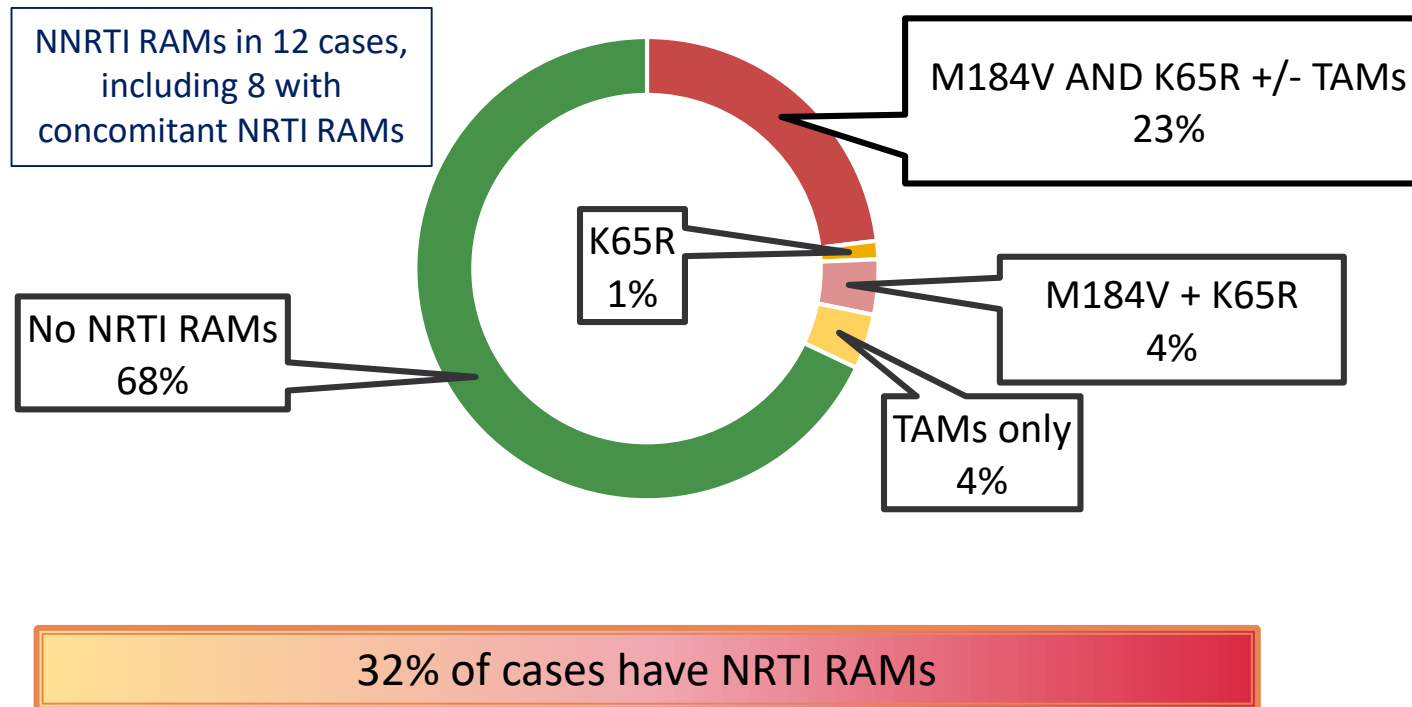
DPV vaginal ring

LEN

MK-8527

HIV-1 Incidence, Adherence, and Drug Resistance in Individuals Taking Daily TDF/FTC for HIV-1 PreP: Pooled Analysis From 72 Global Studies

Distribution of NRTI RAMs in 78 cases



- **72 TDF/FTC PrEP studies, 17,274 individuals**
- **101** acquired HIV-1 after PrEP initiation and within 60 days of PrEP discontinuation
 - HIV-1 IR **0.77** per 100 person-years
 - **78** with available HIV-1 genotype

How could HIV-1 drug resistance impact preexposure prophylaxis for HIV prevention?

Table 1. Seroconversions in Studies and Cohorts of Individuals Prescribed TDF/FTC PrEP for HIV Prevention

Type of study	No. with PrEP-associated resistance/No. HIV Positive (%) at a Study Follow-Up Visit ^e	No. with PrEP-associated resistance/No. HIV positive (%) at Enrollment into Study ^f
Clinical Trials ^a	12/222 (5%)	13/20 (65%)
On-Demand PrEP ^b	1/14 (7%)	2/5 (40%)
Open-Label/Demonstration Project ^c	2/45 (4%)	3/6 (50%)
Cohort/Population ^d	44/202 (22%)	–

5.3%

58.1%

^aStudies included are as follows: FEM-PrEP [30], iPrEX [31], TDF2 [32], Partners PrEP [33], VOICE [34], DISCOVER [15[■]] and HPTN-083 [16[■]].

^bStudies included are as follows: IPERGAY [17], IPERGAY OLE [18], HPTN-067 [19].

^cStudies/projects included are as follows: PROUD [20], HPTN-073 [21], USA DEMO [22], HPTN-082 [23], iPrEX OLE [24], ATN 110 [25].

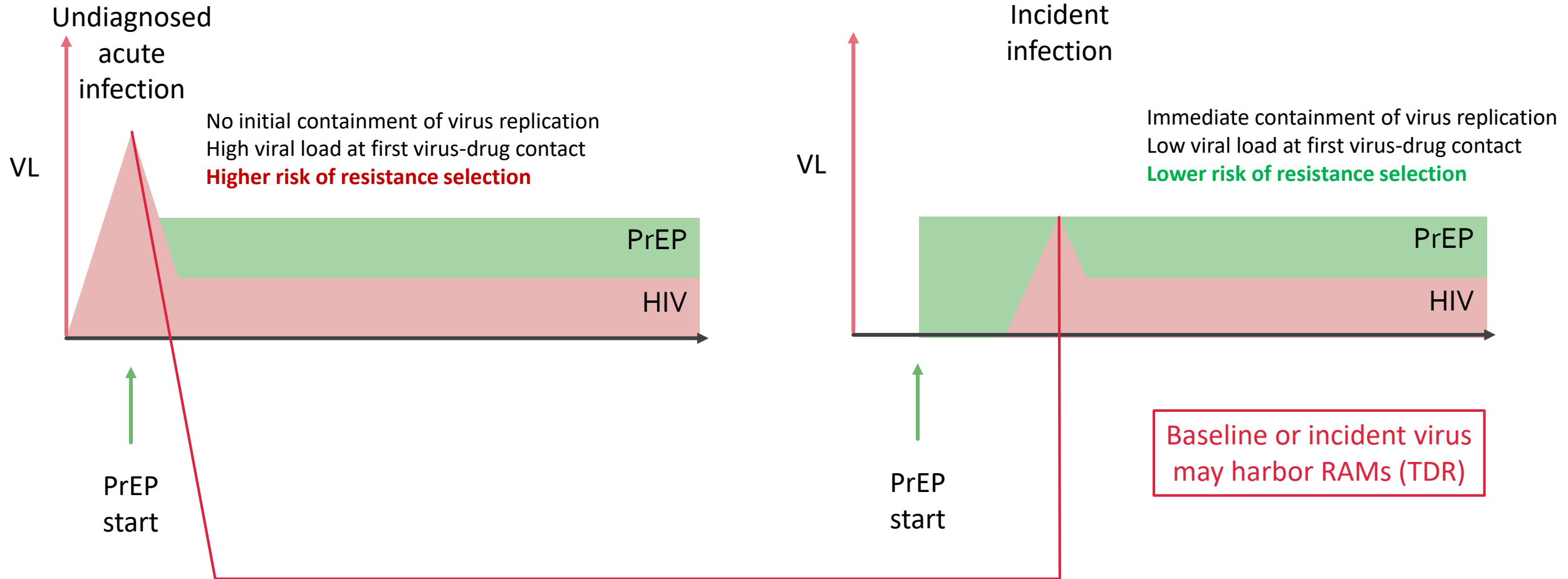
^dProjects included are as follows: SEARCH [1[■]], GEMS [27], IAVI-Kenya [28], VHA [29], Princess PrEP [35], 56 Dean Street [36].

^eProportion with PrEP-associated resistance is the aggregate number of participants with tenofovir disoproxil fumarate (TDF) or emtricitabine (FTC)-associated mutations (K65R, M184I or V, K70E) at their follow-up visit from all referenced studies, over the aggregate total of HIV positive cases identified at follow-up visits from all referenced studies.

^fProportion with PrEP-associated resistance is the aggregate number of participants from all referenced studies with tenofovir disoproxil fumarate (TDF) or emtricitabine (FTC)-associated mutations (K65R, M184I or V, K70E) who were retrospectively determined by detectable HIV RNA to be HIV positive at enrollment into the study, over the aggregate total of HIV positive cases at enrollment from all referenced studies.

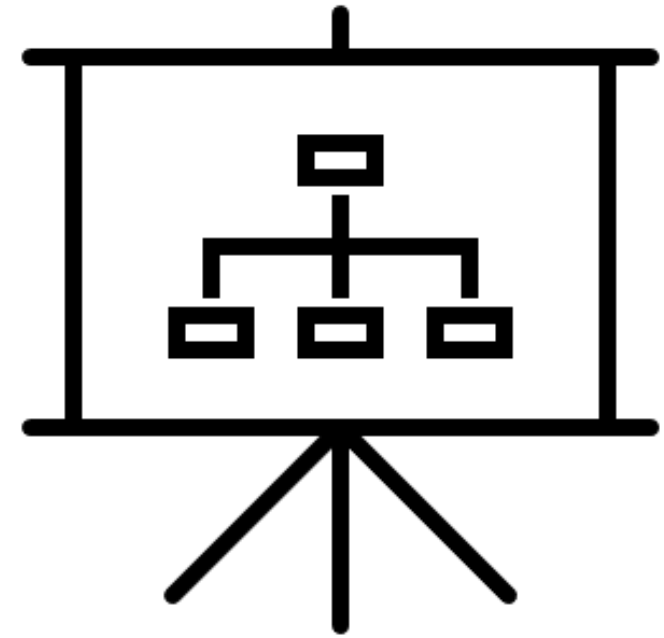
PrEP and antiretroviral resistance

What to expect



CAB LA PrEP and drug resistance

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HPTN 084: Characteristics of HIV acquisitions and resistance (blinded phase)



Timing of HIV acquisition		CAB (3,205 PYs)		TDF/FTC (4,596 PYs)	
		4 HIV acquisitions	0 with INSTI RAMs	36 HIV acquisitions	1 with NRTI RAMs
A	BL HIV acquisition	1	0	0	0
B	No recent CAB exposure*	2	0	–	–
BR	CAB restarted after HIV acquisition**	0	0	–	–
C	During CAB OLI phase	0	0	–	–
D	On-time CAB LA injections	0	0	–	–
DX	Delayed CAB LA injections***	1	0	–	–
0	During daily oral TDF/FTC	–	–	36	1

No INSTI resistance detected in the CAB arm

*Acquisitions detected >6 months after the last CAB injection;

Acquisitions detected >6 months after the last injection that were identified when LA PrEP was restarted in the open-label study *Acquisitions in the setting of at least one inter-injection delay of ≥10 weeks but not meeting group B criteria

Delany-Moretlwe, Lancet 2022
Delany-Moretlwe, IAC 2022

HPTN 084: Characteristics of HIV acquisitions and resistance (blinded plus unblinded phase)



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0	During daily oral TDF/FTC	–	–	36	1

No INSTI resistance detected in the CAB arm (+ 3 incident cases without resistance info in the unblinded phase)

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HPTN 083: Characteristics of HIV acquisitions and resistance (combined period: blinded and 1-year unblinded phases)



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D	On-time CAB LA injections	6	6	–	–
DX	Delayed CAB LA injections***	3	0	–	–
O	During daily oral TDF/FTC	–	–	73	10
		34%		16%	

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Landovitz, Lancet HIV 2023

Marzinke, J Infect Dis 2021

Marzinke, Antimicrob Agents Chemother 2023

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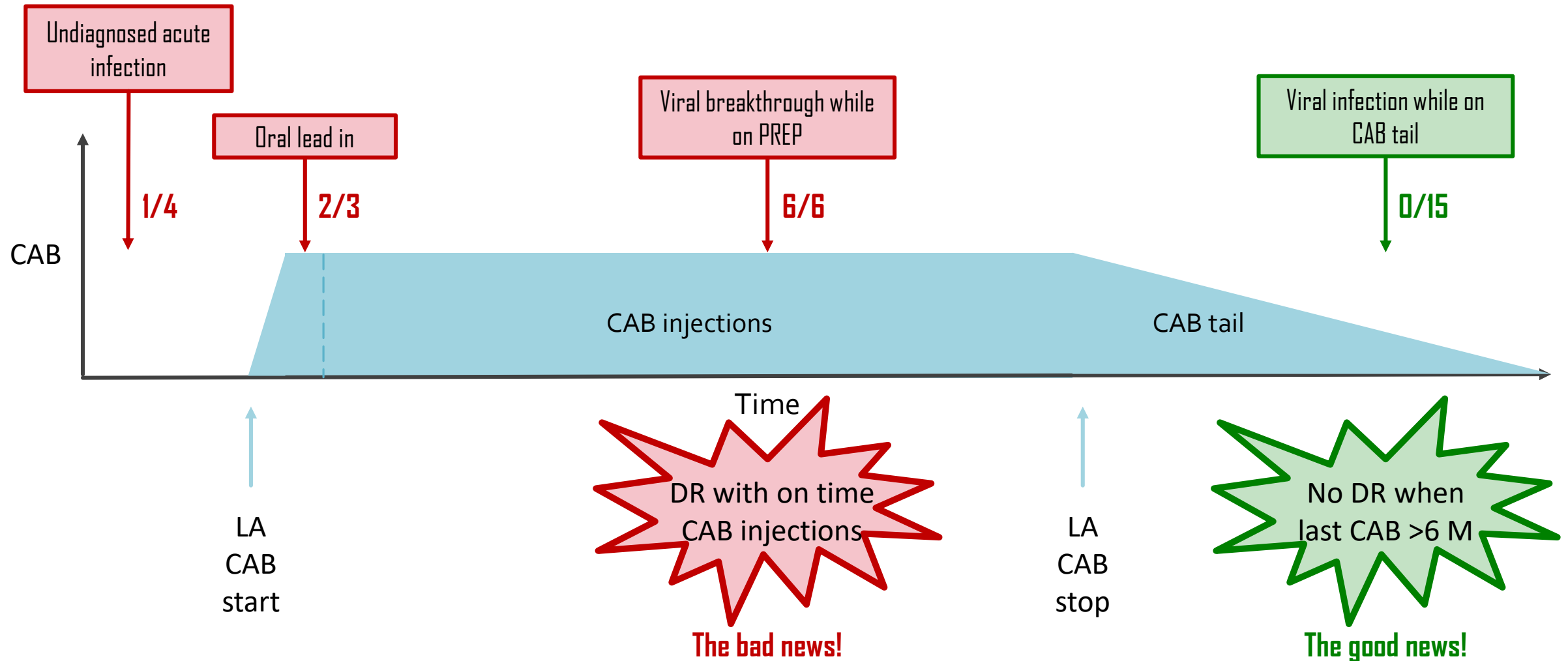
6 participants acquired HIV and developed INSTI resistance whilst adherent to CAB LA injections

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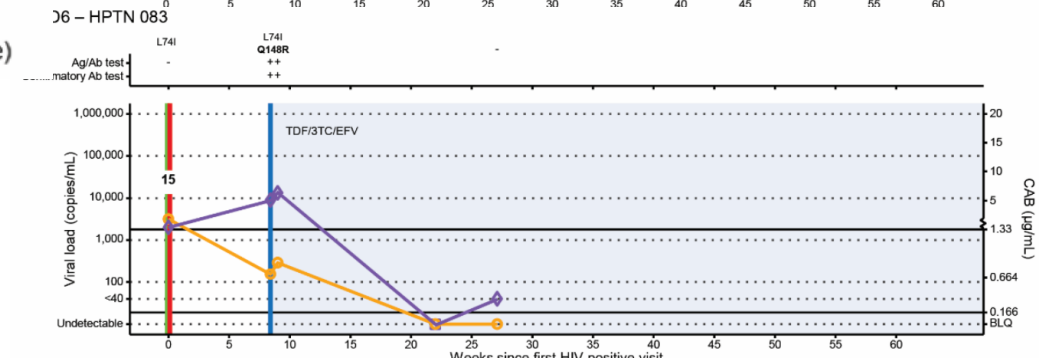
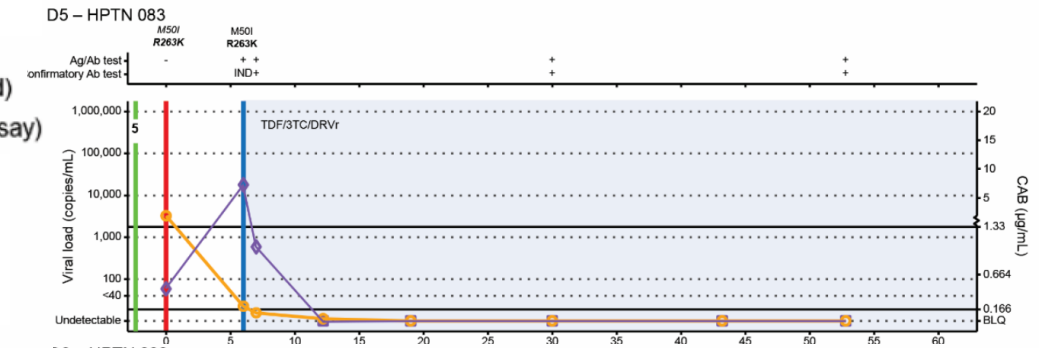
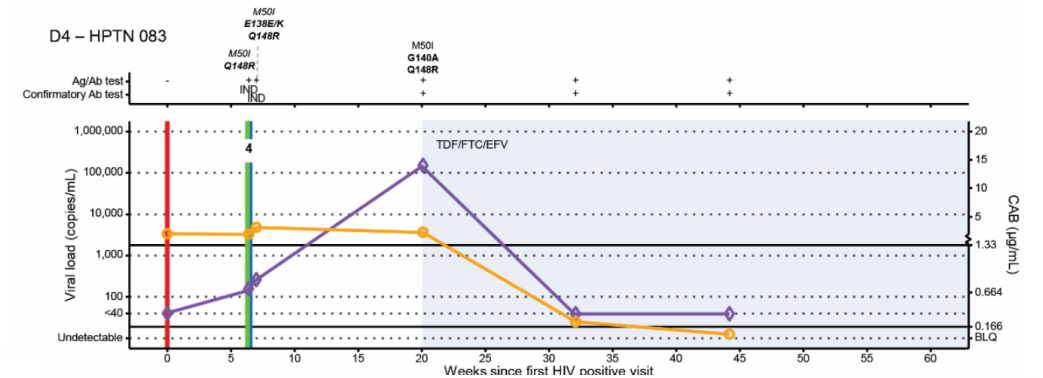
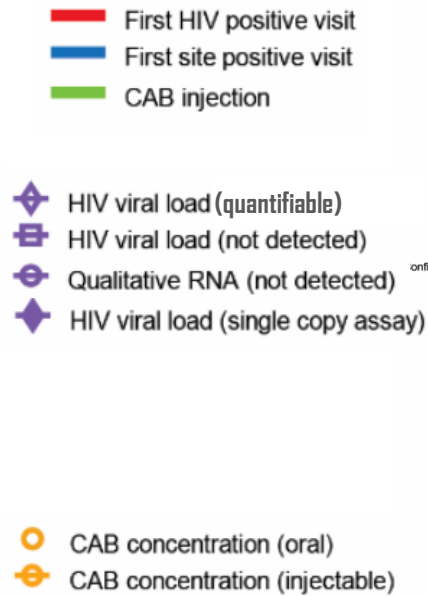
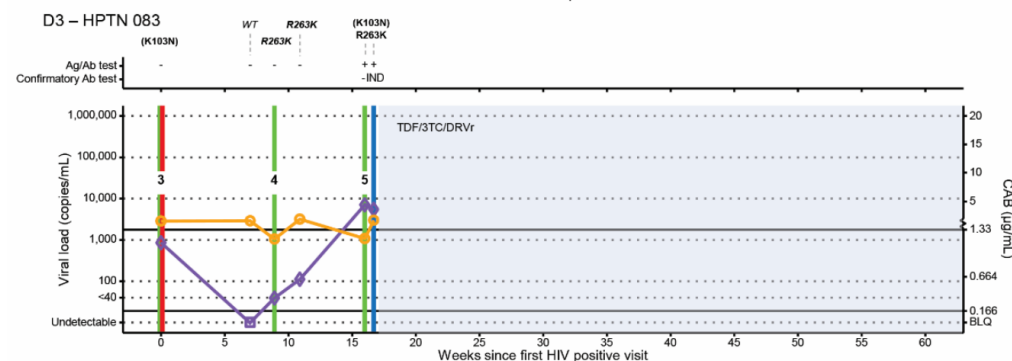
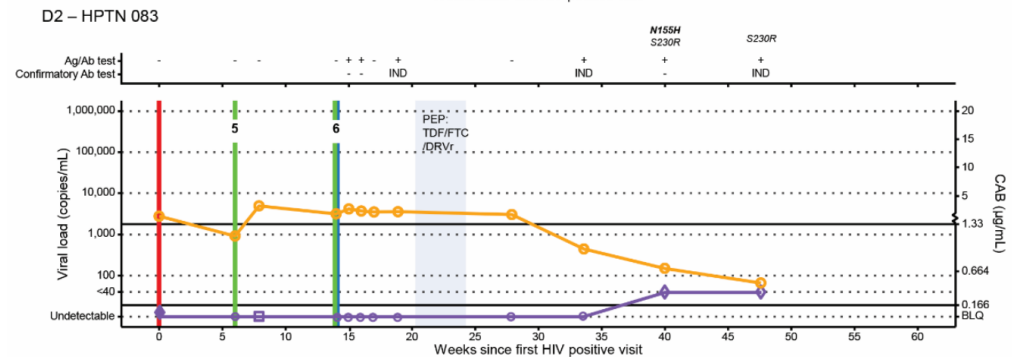
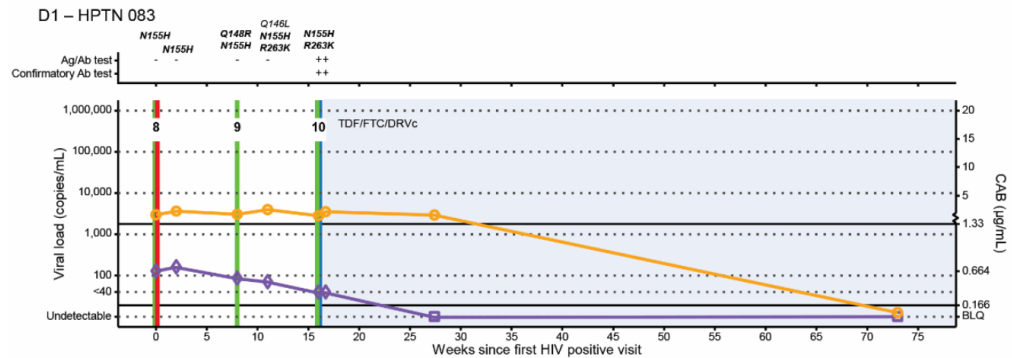
LA CAB and potential for emergent INSTI resistance:

When do drug and virus meet and may end up with resistance?

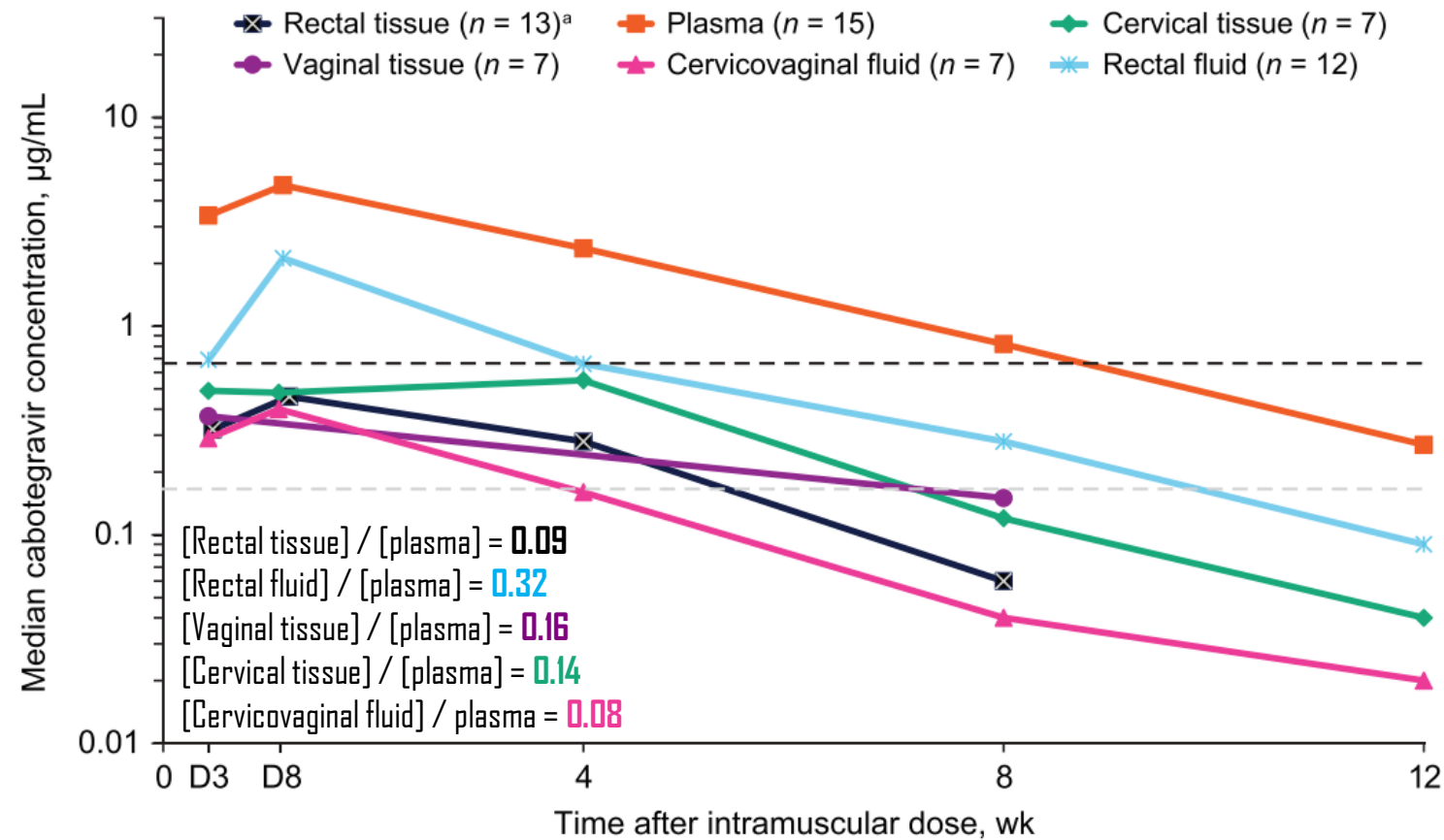


HPTN 083: HIV Infections in Cabotegravir Arm

Cases D1-D6



Multicompartmental pharmacokinetic evaluation of LA CAB in healthy adults for HIV preexposure prophylaxis



- 16 participants followed through week 52
- Median plasma CAB concentrations exceeded the in vitro PA-IC90 through Week 12
- Strong correlations between tissue and plasma CAB concentrations

Median CAB concentration–time profiles presented by matrix following a single, ultrasound guided CAB LA 600-mg intramuscular gluteal injection

Delayed detection of HIV infection under CAB shield



Minimal or no
symptoms



Very low viral load

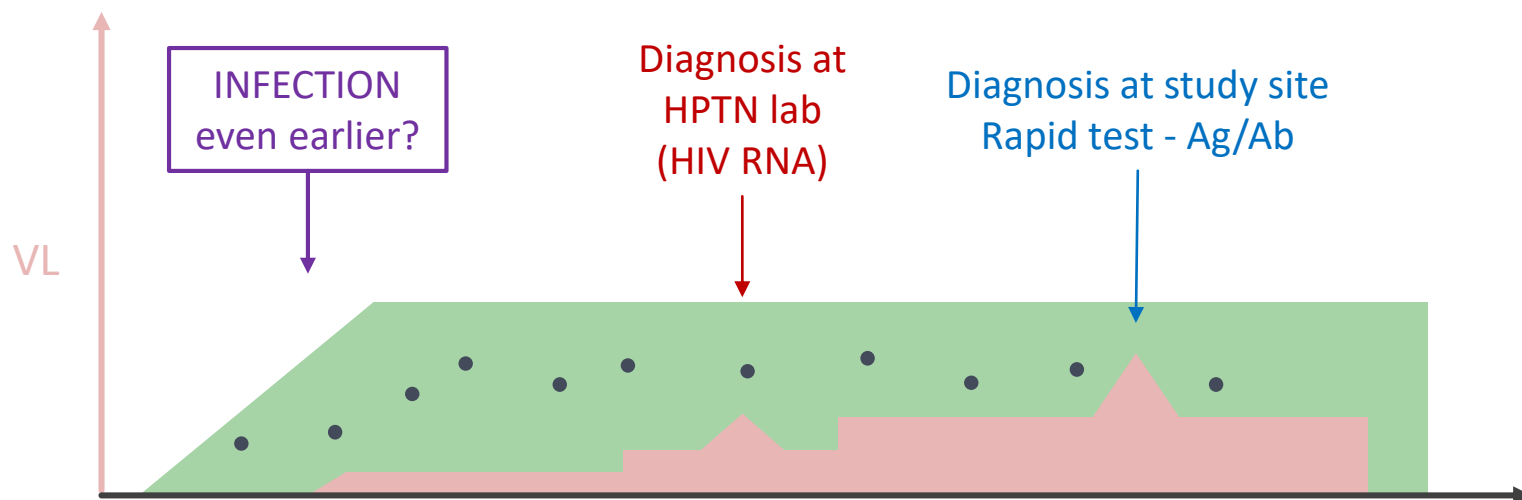


Decreased/delayed
antibody

Long-acting early viral inhibition syndrome (LEVI)

Why emergent INSTI resistance with on time CAB injections?

- HIV testing based on rapid test plus Ab/Ag combo at study site
- Ab/Ag combo plus qualitative HIV-1 RNA at HPTN lab



- CAB measurements

PrEP
HIV

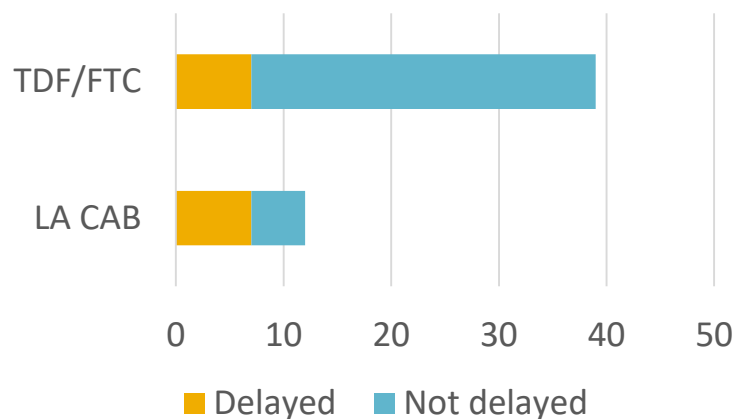
CAB

- ✓ Potent drug
- ✓ Immediate containment of virus replication
- ✓ Low (hard to detect) viral load in peripheral blood

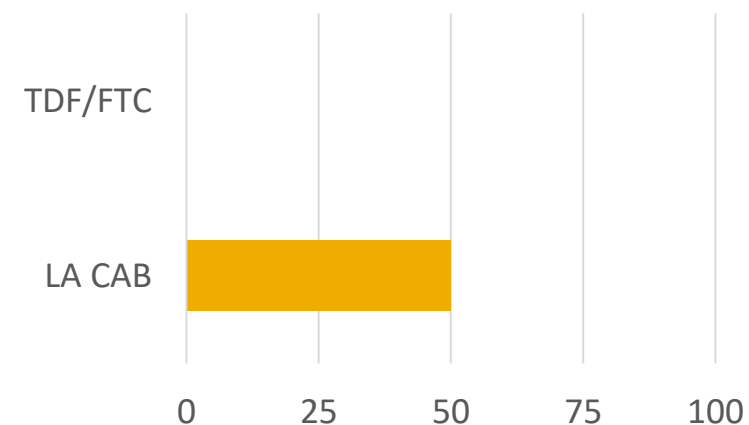
- Overall, it seems high CAB concentration is needed to select for drug resistance
- Could infection have occurred even earlier than detected at HPTN lab?
- How was CAB concentration at that time?

Delayed detection of incident HIV infections in HPTN 083 (blinded phase)

Cases with delayed diagnosis

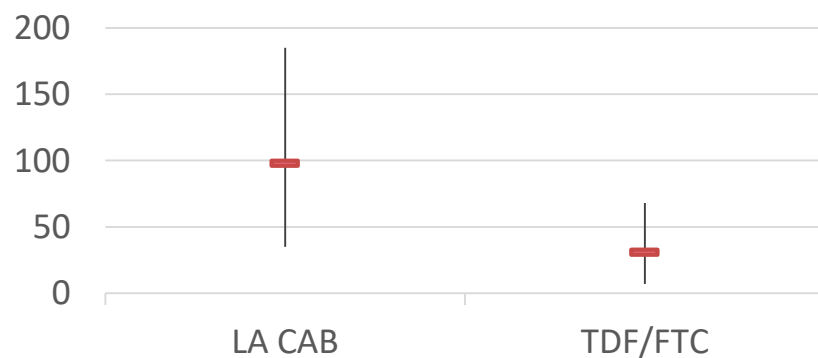


% with prolonged VS

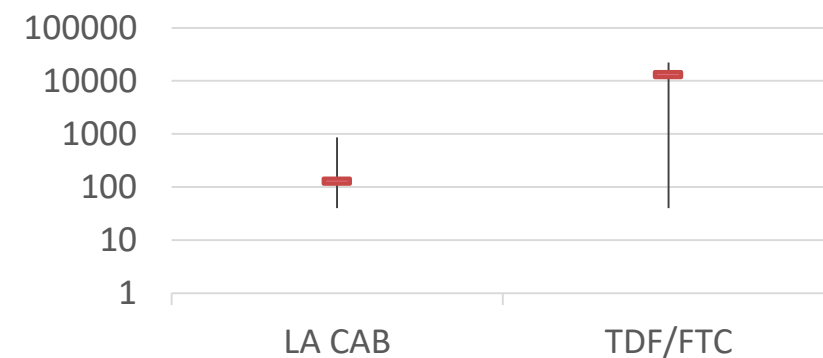


Delayed HIV diagnosis much more prominent with LA CAB compared to oral TDF/FTC
(increased drug class potency)

Median delay (days)

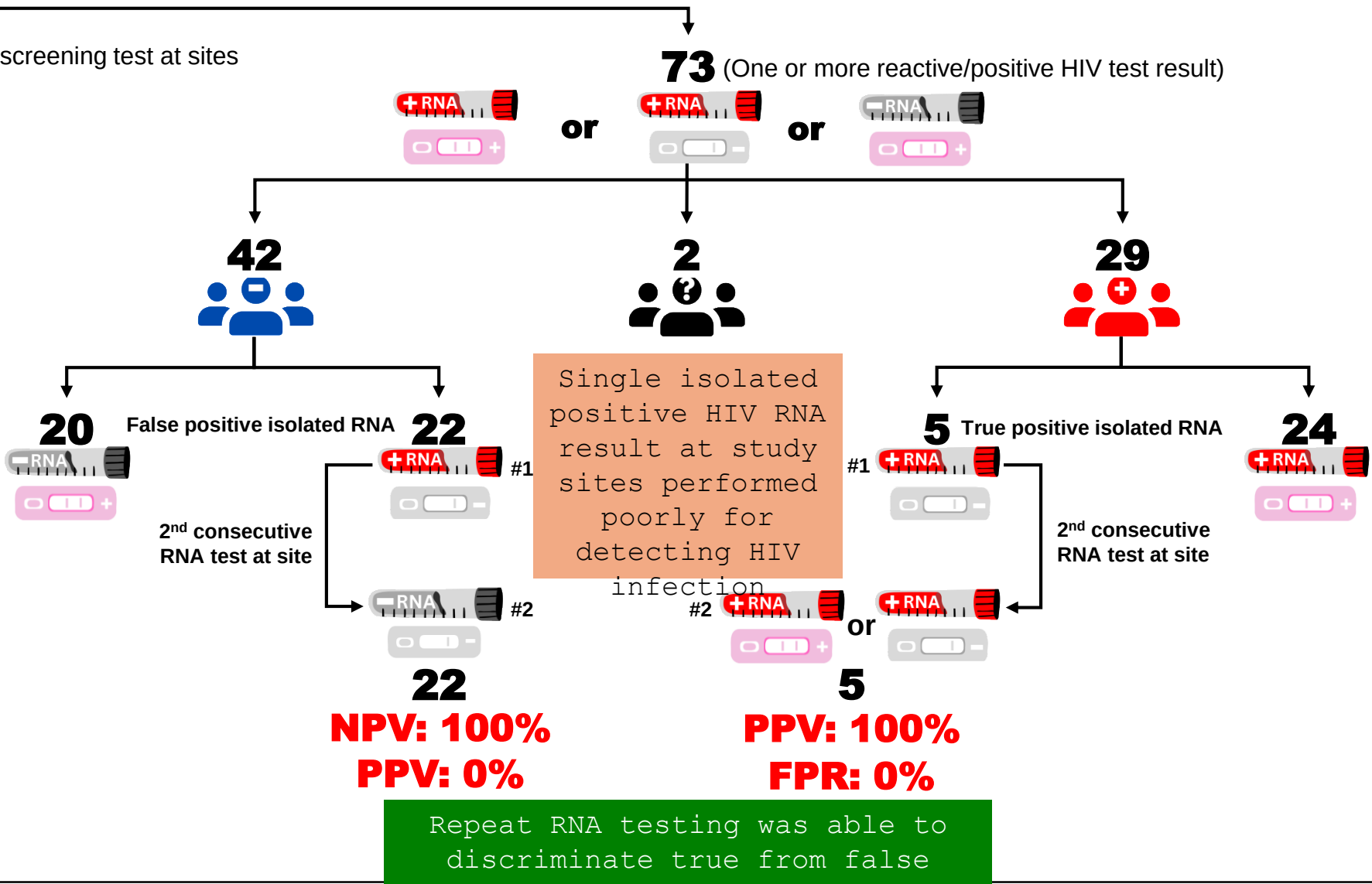


Median VL at first HIV+ visit



26,528

Visits with an RNA screening test at sites



Landovitz, IAC

2024



ADJUDICATED
NEGATIVE



ADJUDICATED
POSITIVE



ADJUDICATION STATUS
NOT DETERMINED



POSITIVE HIV
RNA TEST



NEGATIVE HIV
RNA TEST



POSITIVE NON-RNA
HIV TEST



NEGATIVE NON-RNA
HIV TEST



NO CAB-LA W/ IN
THE LAST 6 MONTHS



CAB-LA W/ IN
THE LAST 6 MONTHS

HIV DNA Levels in Persons Who Acquired HIV in the Setting of LA CAB for HIV Prevention: Analysis of Cases from HPTN 083 and 084

TABLE 2. CHARACTERISTICS OF PERSONS WITH HIV WITH ONE OR MORE DNA TEST RESULT^a

Study arm	Study	Case ^b	Detection delay ^c	VL at 1 st HIV pos visit (c/mL)	TDF/FTC adherent at 1 st HIV pos visit ^d	First visit with DNA results ^e			
						Days since 1 st HIV pos visit	HIV RNA ^f	DNA (c/10 ⁶ PBMC)	ARV drug concentration ^g
CAB (7 cases)	083	A1	Yes	4,010	—	41	Detected <40	4.2	3.68
		A3	Yes	1,360	—	81	NR	Detected <LLOD	3.37
		A4	Yes	44,180	—	70	NR	97.8	4.90
		C1	Yes	120	—	51	2,549	81.5	3.65
		D2	Yes	6.1	—	105	NR	Detected <LLOD	2.67
		BR1	Yes	450	—	83	100,260	682	1.29
		A1	Yes	21.4	—	246	SCA negative	Detected <LLOD	2.16
TDF/FTC (14 cases)	083	E2	No	34,180	No	3	50,050	166	BLQ (3 days prior)
		E9	No	505,690	No	9	82,397,780	6672	BLQ (9 days prior)
		E25	No	36,976,550	No	13	13,150,570	2,782	BLQ
		E32	No	11,310	No	14	14,360	132	BLQ
		E71	No	711,390	No	4	674,200	1,988	BLQ (4 days prior)
		E74	No	358	No	29	Not detected	20.0	BLQ (29 days prior)
		E17	No	2,706,990	No	3	2,144,273	3,906	BLQ
	084	E21	No	15,800	No	11	7,400	2,978	36.6
		E27	No	1,005,760	No	5	11,600	12.1	BLQ
		E31	Yes	71	Inconsistent	84	SCA 0.8	Not detected	432
		E36	No	Not detected	Partial	11	SCA negative	6.9	541
		E37	Yes	9,160	No	127	NR	99.0	1,051
		E42	No	Not detected	No	115	SCA negative	7.0	BLQ
		E47	No	113,080	No	4	33,165	101	BLQ

HIV RNA-negative, HIV DNA-

HIV RNA-positive, HIV DNA-

negative

Major INSTI RAMs detected at study site vs. centralized lab

Case ID	HIV subtype	First HIV+ visit at centralized lab	First HIV+ visit at study site
A2	C	None	E138K Q148K
C1	B	None	Q148R → E138K G140S Q148R
C3	B	None	E138A Q148R
D1	Likely B	N155H	Q148R N155H → N155H R263K
D2	Likely B	NA	N155H
D3	BF	None	R263K
D4	C	NA	Q148R → E138K Q148R → G140A Q148R
D5	F	R263K	R263K
D6	AE	None	Q148R
BR1	Median viral load at first detection of resistance: 148 c/mL (IQR: 77-1,011)	None	Q148R

Major INSTI RAMs detected at study site vs. centralized lab

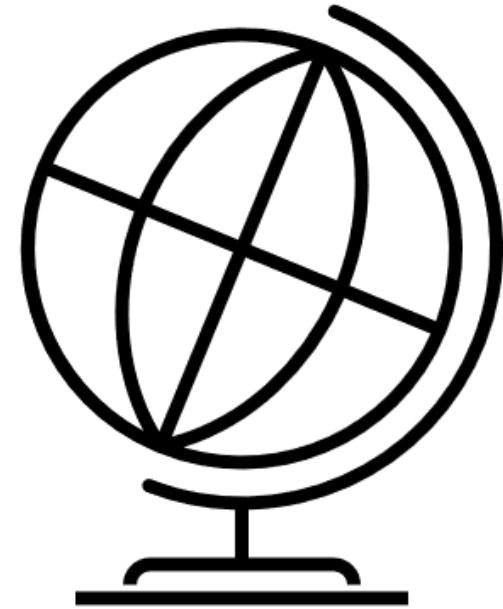
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D5	F	R263K	R263K
D6	AE	None	Q148R
BR1	BC	None	Q148R
Retrospective testing detected most infections before INSTI resistance emerged			

Major INSTI RAMs detected at study site vs. centralized lab

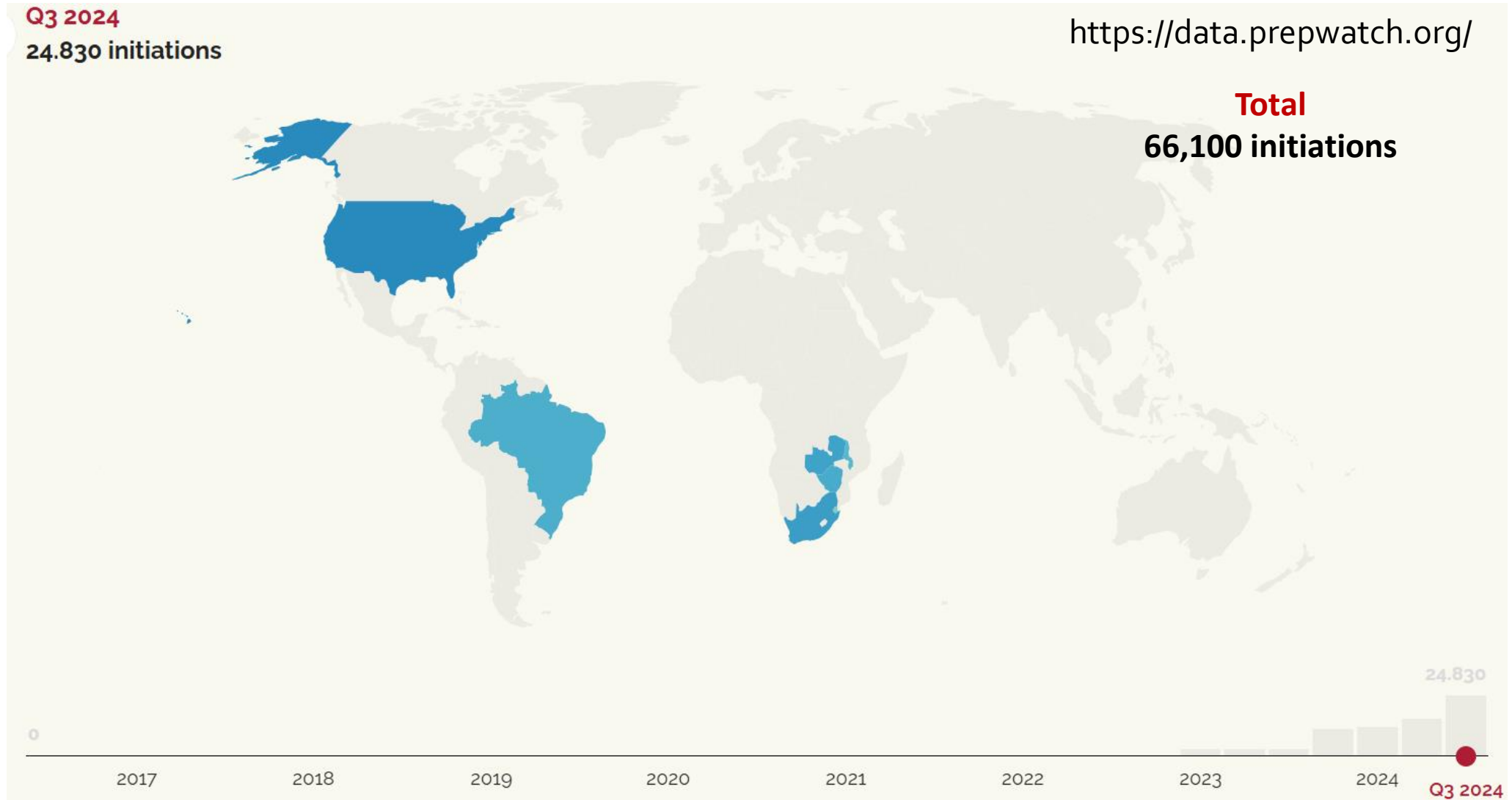
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D5	F	R263K	R263K		
D6	AE	None	Q148R		
BR1	BC	None Predicted impact on dolutegravir activity	Q148R		
Susceptible		Potential low-level R	Low-level R	Intermediate R	High-level R

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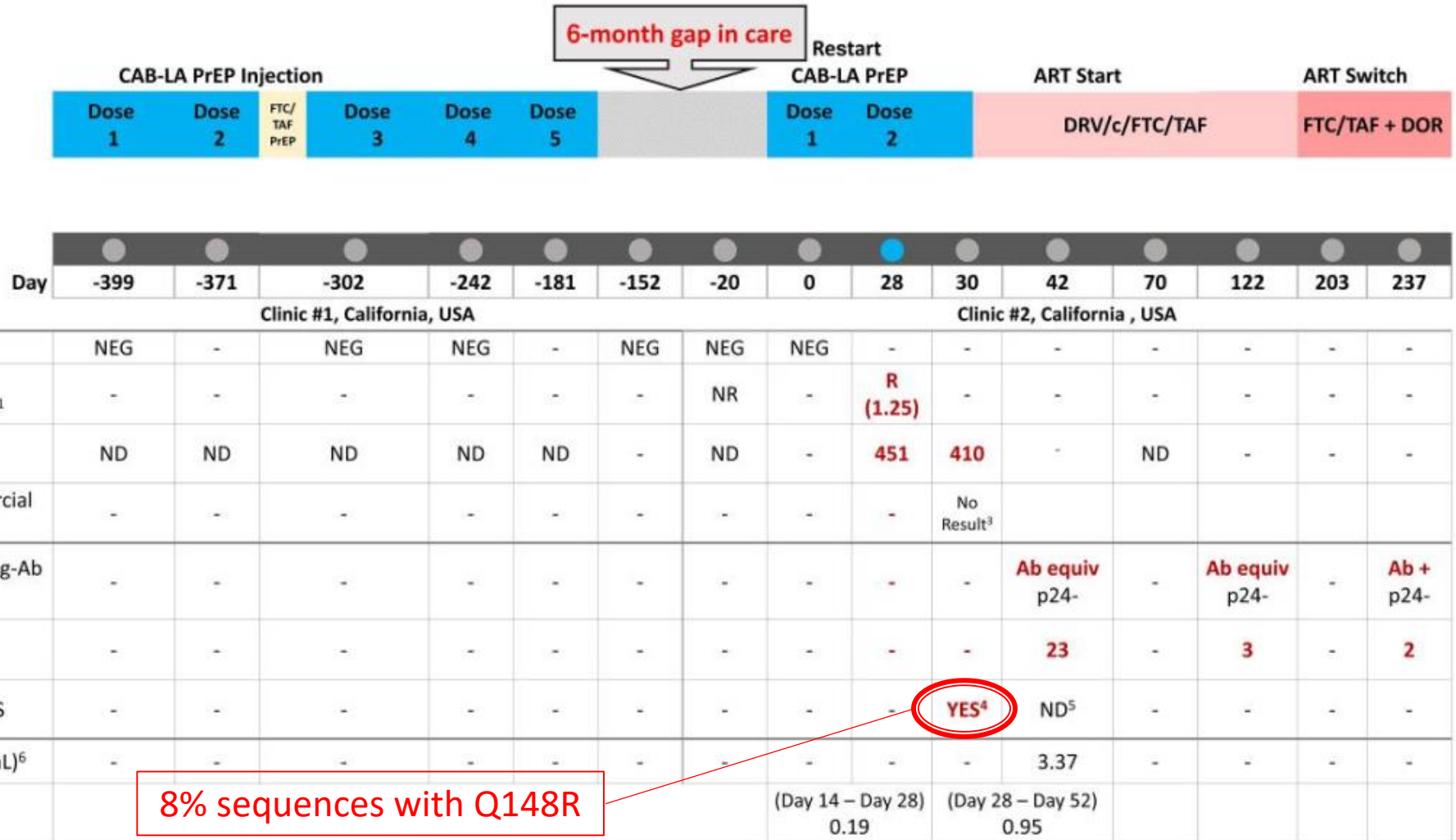


Worldwide use of LA CAB PrEP



First Case of HIV Seroconversion With Integrase Resistance Mutations on Long-Acting Cabotegravir for Prevention in Routine Care (SeroPrEP)

SeroPrEP registry and biobank of individuals who acquire HIV on PrEP in the US



SeroPrEP: Treatment Outcomes Following HIV Acquisition While on LA CAB PrEP

Assessment Method	Case A	Case B	Case C
Sanger genotyping			
▪ Sample collection, days post diagnosis	7	13	6
▪ INSTI mutations detected	None	None	None
Single-genome sequencing			
▪ Sample collection, days post diagnosis	Unavailable	7	10
▪ Signature INSTI mutations detected, n/N sequences	Unavailable	E138K (1/56)	Q148R (10/33)
▪ Accessory INSTI mutations detected, n/N sequences	Unavailable	N155K (1/43)	None

HIV incident infections in a PrEP cohort

[ClinSex, Buenos Aires]



N=517

Individuals who started PrEP
at a sexual health clinic

Outcomes

RAMs and virologic outcomes of HIV incident cases among PrEP users



June 2018–
June 2024

Baseline Characteristics of Individuals Starting PrEP

Characteristic	N=517
Age, years, median (IQR)	31 (27, 37)
Gender, n (%)	
Cisgender MSM	512 (99)
TGW	5 (1)
ART used for PrEP, n (%)	
F/TDF	391 (76)
Q2M IM CAB	126 (24)
PrEP days, median (IQR)	545 (318, 967)

Adherence and RAMs in HIV Incident Cases Among Individuals Receiving PrEP

ART for PrEP	n/N (%)	Adherence	Major RAMs
Q2M IM CAB	2/126 (1.6%)	Good in 2/2	In 2/2 (INSTI in 2; NNRTI in 1)
F/TDF	4/391 (1.0%)	Irregular ^a in 3/4 Good in 1/4	In 1/4 (NRTI)

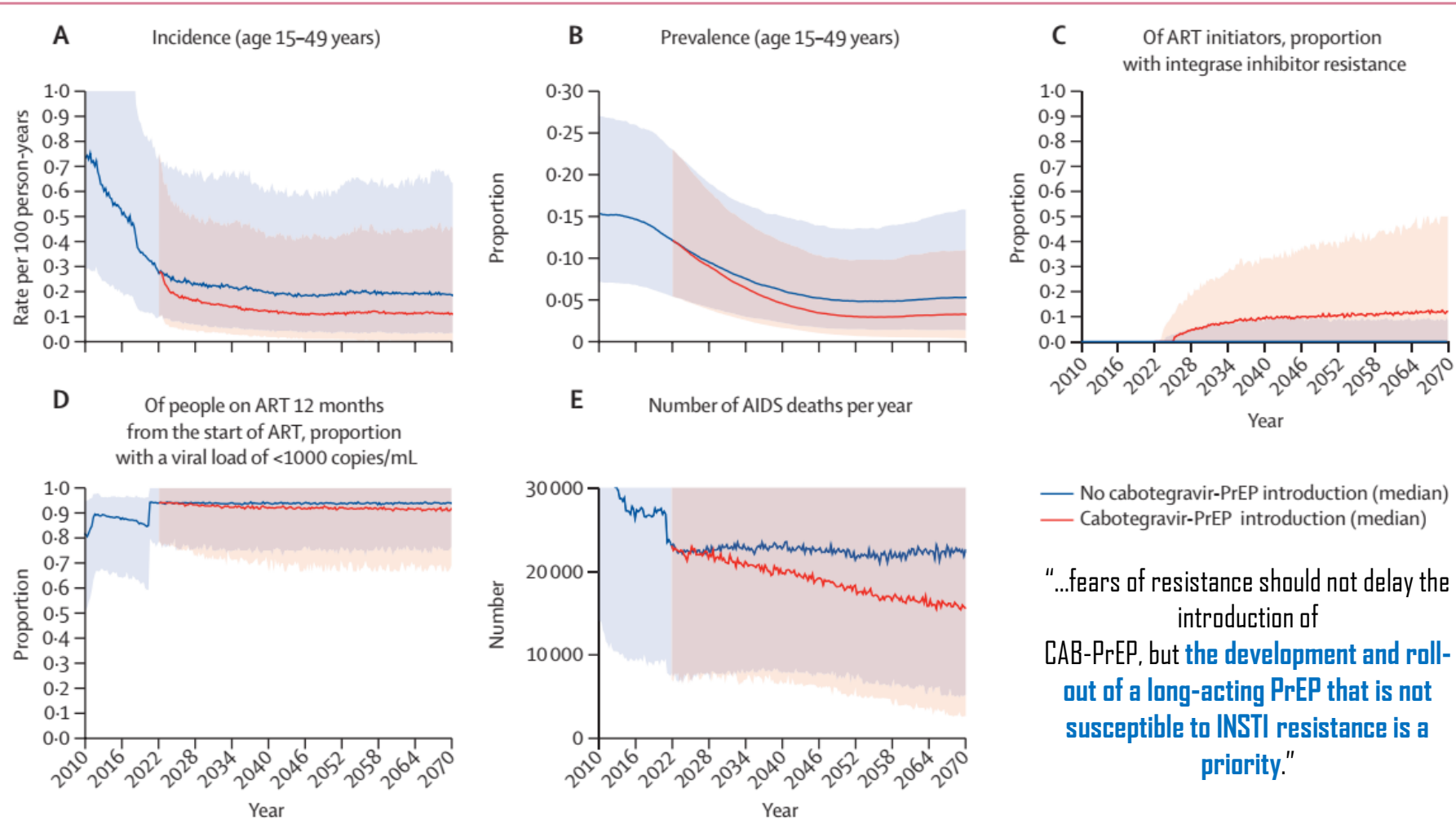
Although PrEP is highly effective, infrequent HIV acquisition can occur. Major INSTI RAMs occurred in 2/2 (100%) individuals on Q2M IM CAB and NRTI RAMs in 1/4 (25%) individuals on F/TDF with incident HIV

^aDue to missed doses and intolerance

N/A, not available; Q2M, every 2 months; TGW, transgender women

Pastor I, et al. HIV Glasgow 2024, Poster 026

Predicted effects of the introduction of long-acting injectable cabotegravir pre-exposure prophylaxis in sub-Saharan Africa: a modelling study



Predicted effects of introduction of LA CAB in SSA by HIV Synthesis modeling:

- Increased PrEP use
- Increased proportion of INSTI resistance
- Small decrease in proportion of PWH with VL <1000 cps/mL
- Decreased HIV incidence and mortality
- Little benefit from NAT over Ag/Ab assays

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Virological management of LA CAB PrEP



Aug 2024

Screening and at least every 3 months: HIV Ag/Ab and HIV-1 RNA tests



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Sep 2023

Screening and at each subsequent injection: HIV Ag/Ab and HIV-1 RNA tests



Mar 2024

Le persone devono essere sottoposte al test per l'HIV-1, prima di iniziare cabotegravir e a ogni successiva iniezione di cabotegravir [...]. Un test combinato antigene/anticorpo e un test HIV-RNA devono risultare entrambi negativi.

Virological management of LA CAB PrEP

- ✓ Nucleic acid testing detects infection earlier than Ab/Ag assays and rapid tests
- ✗ Extremely sensitive NAT may generate false positives

Repeated testing with routine HIV1 RNA (and non-routine HIV DNA) assays helps distinguish true from false positives

- ✓ Early diagnosis may limit the risk of emergent INSTI resistance
- ✗ Sequencing at low HIV RNA copy numbers is challenging and not commonly and readily available

Switch proactively to bDRV based ART as soon as diagnosis is confirmed
Optionally adjust ART based on GRT, if available

PrEP and antiretroviral resistance

TXF/FTC vs. LA CAB

Feature	Oral TXF/FTC	LA CAB
Impact of TDR	Limited but tangible	Virtually none
Vulnerability of PK tail	Low	Moderate to high
Impact of adherence	High	Low
Drug class potency	Low	High
Drug combination	Two compounds but one class	One compound
Major causes for resistance	TDR, erratic adherence	To be defined

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6 participants acquired HIV and developed INSTI resistance whilst adherent to CAB LA injections

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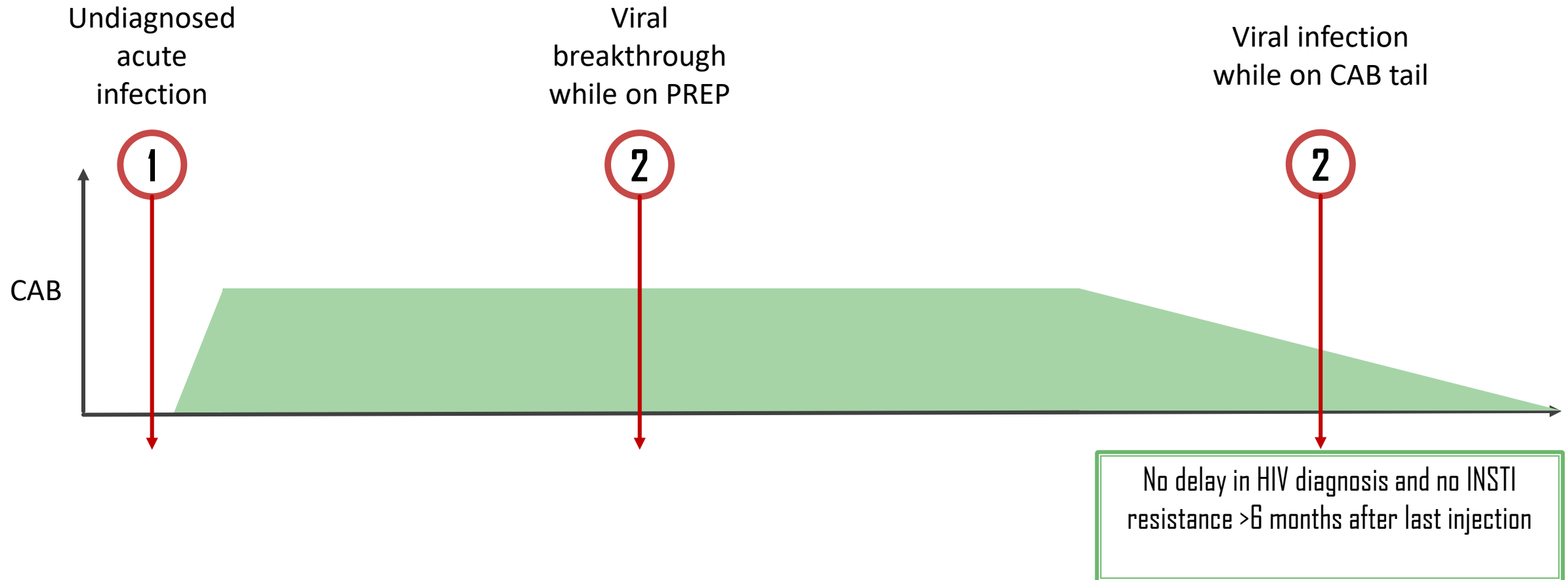
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Landovitz, Lancet HIV 2023

Marzinke, J Infect Dis 2021

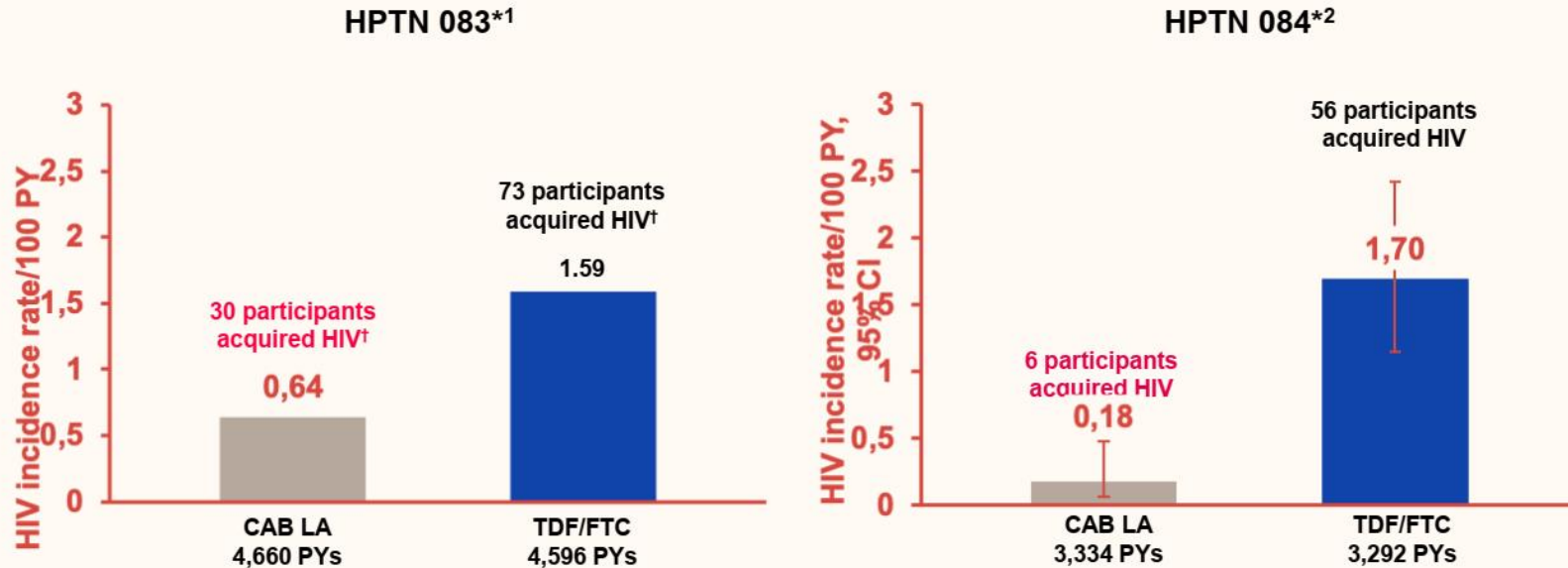
Marzinke, Antimicrob Agents Chemother 2023

LA CAB and potential for emergent INSTI resistance: *When do drug and virus meet?*



The beginning of the LA PREP era

HPTN 083 and 084: Incident HIV acquisitions after 4 years (blinded and unblinded phases)



CAB LA was superior to daily oral TDF/FTC at preventing new HIV acquisitions in HPTN 083 and HPTN 084

*Data analysed following post hoc, centralised testing of stored samples from the blinded phase and Year 1 unblinded phase

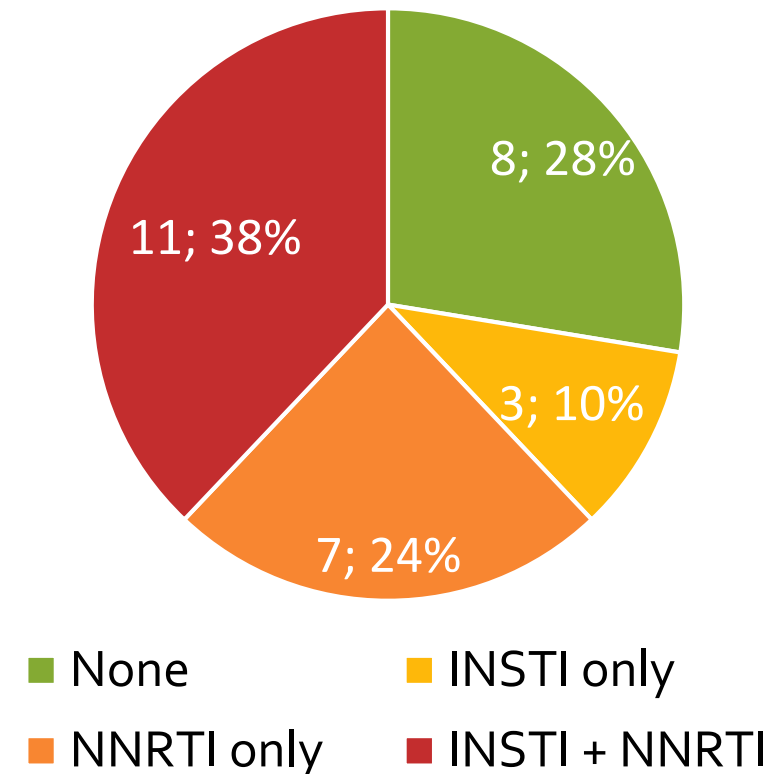
†Standard deviation not reported

1. Marzinke MA, et al. HIV Glasgow 2022. Oral O21
2. Delany-Moretlwe S, et al. AIDS 2022. Oral OALBX0108

Virological failure rate and emergent resistance in real-world studies evaluating long-acting cabotegravir and rilpivirine in people with baseline viral suppression

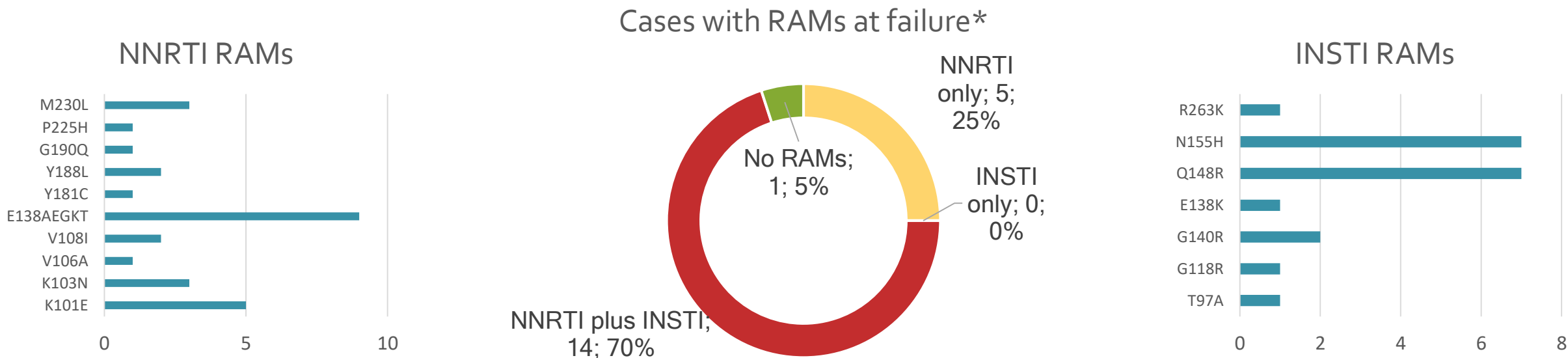
- **Real-world studies** that identified VFs and reported RAM testing results at VF among people who were virologically suppressed at CAB+RPV LA initiation
 - 13 studies representing 2934 PWH
- **21 of 29 (72%) VFs had treatment-emergent resistance** reported across 11 studies
 - 18 (46%) had treatment-emergent NNRTI RAMs
 - 14 (36%) had treatment-emergent INSTI RAMs
 - Most common major INSTI RAMs included **Q148R** (n=5), **N155H** (n=5), **E138K** (n=3), **R263K** (n=2), and **G140S** (n=2)
 - 11 (38%) had treatment emergent resistance to both INSTI and NNRTI

Distribution of emergent resistance



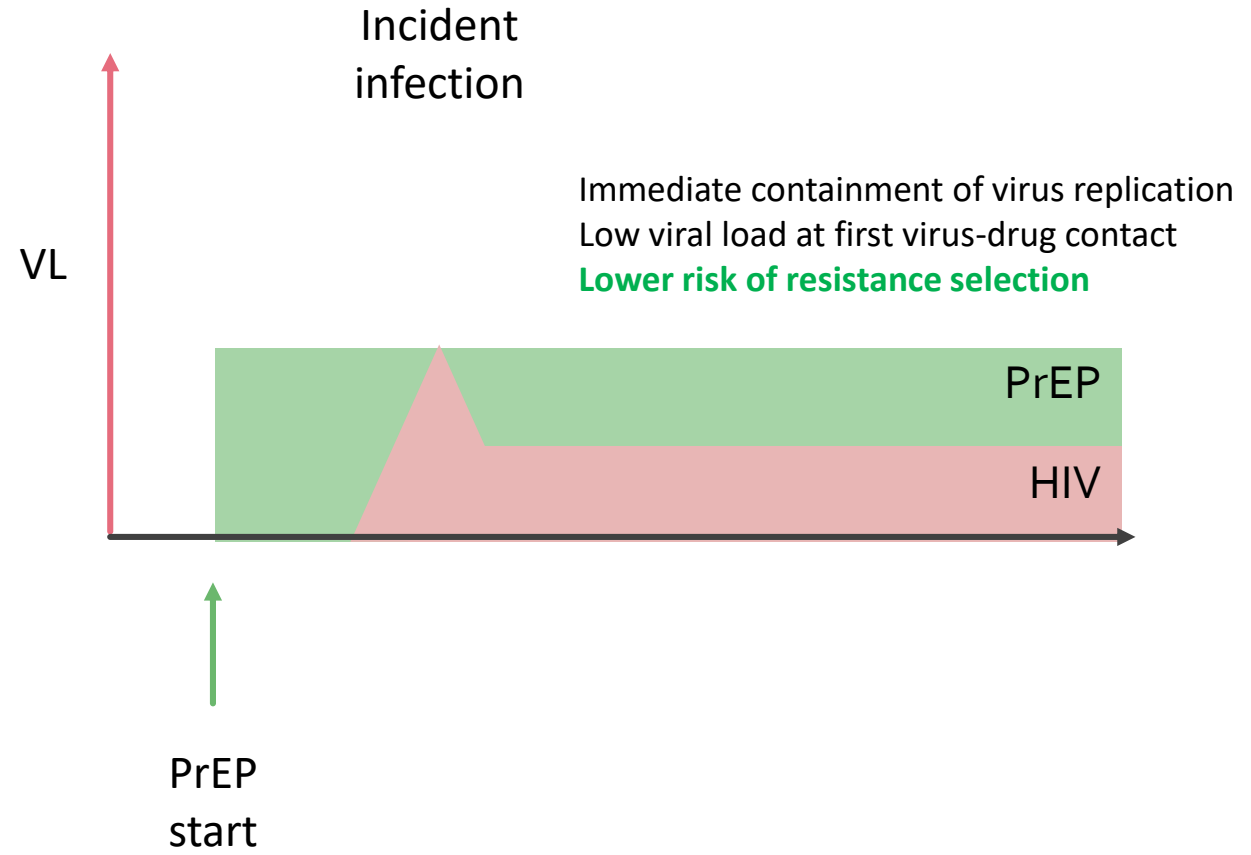
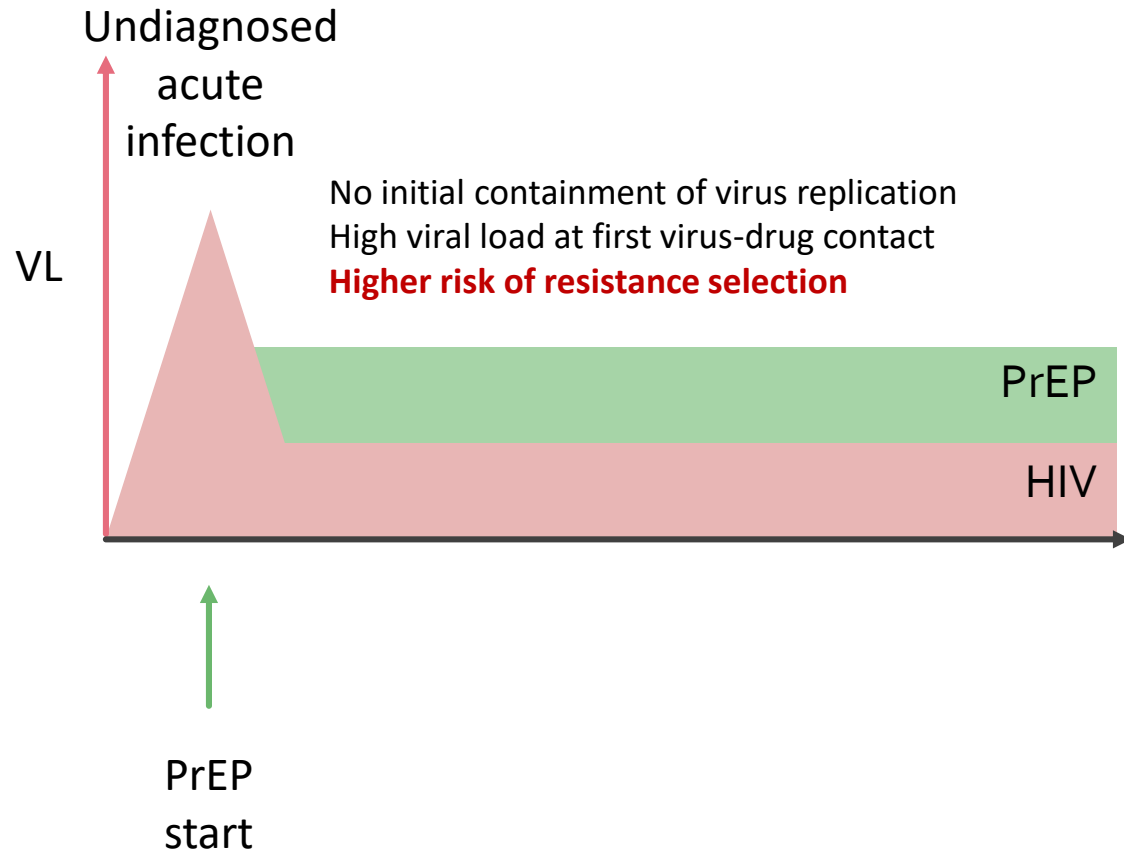
Emergent resistance at failure of LA CAB RPV in key RCTs

RCT (participants on CAB/RPV)	VFs with genotype	Genotypes with NNRTI RAMs (cases with same RAMs at baseline)	Genotypes with INSTI RAMs (cases with same RAMs at baseline)
FLAIR (283)	3	3 (2)	1 (0)
ATLAS (308)	4	4 (0)	4 (0)
ATLAS 2M (1045)	11	10 (5)	7 (0)
SOLAR (447)	2	2 (0)	2 (0)

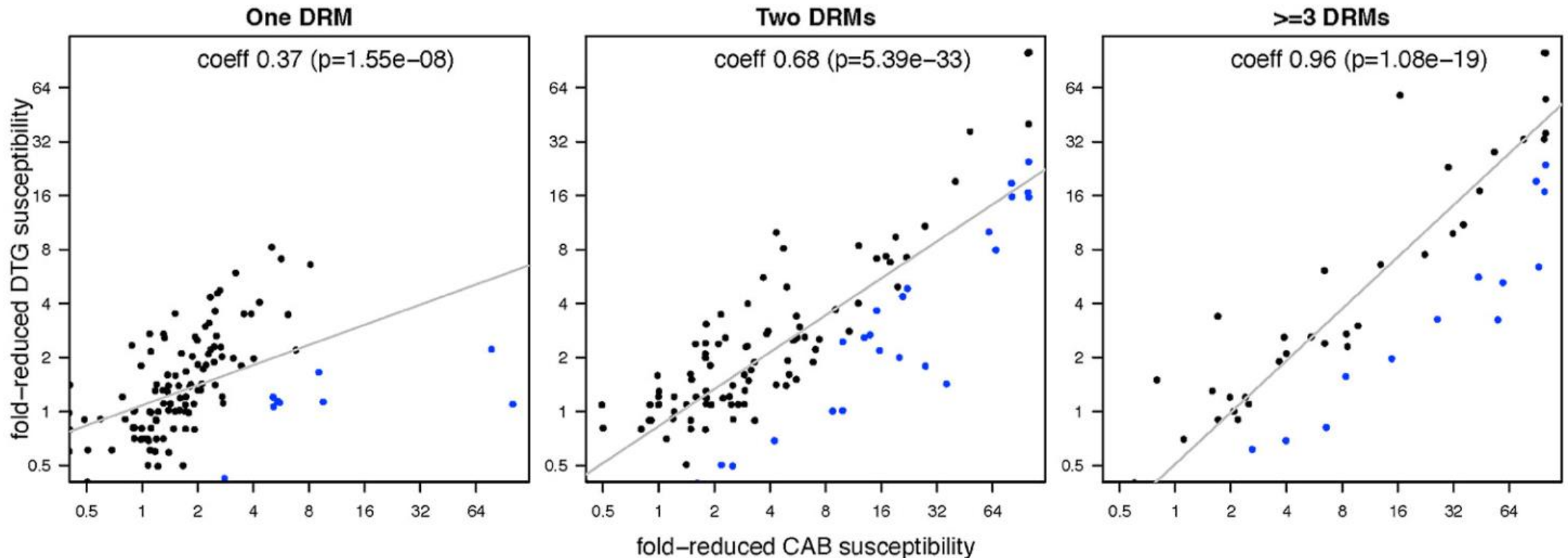


PrEP and antiretroviral resistance

What to expect



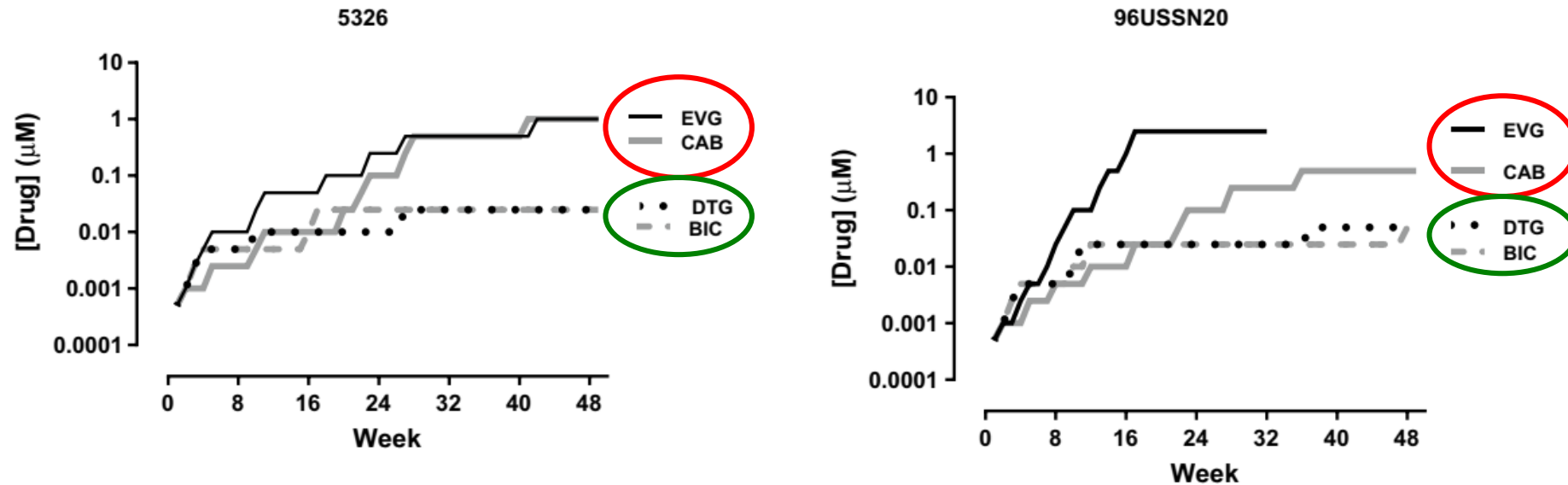
Impact of integrase mutations selected at CAB failure



Correlation between reduced CAB and DTG susceptibility. Susceptibility results on both axes are shown on a log2 scale according to whether the tested isolates contained one, two, or three or more INSTI-resistance mutations.

- Fold-change resistance to CAB $\geq 4\times$ fold-change resistance to DTG

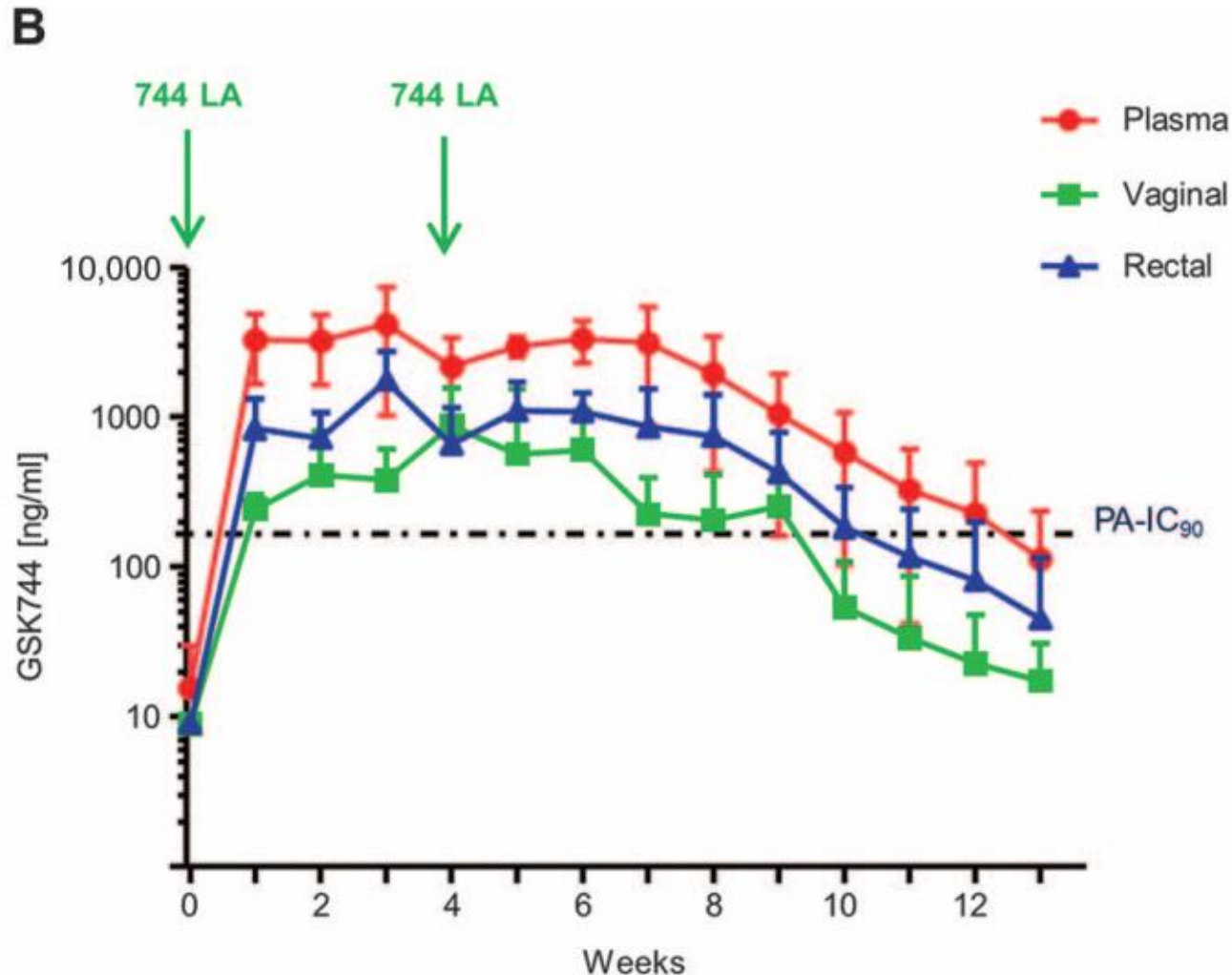
In vitro drug resistance selection by Cabotegravir



HIV Isolate	Drug	Acquisition of resistance mutations			
		Week 8	Week 16	Week 24-30	Week 43-46
5326	DTG	wt	wt	wt	H51HY
96USSN20	DTG	wt	R263K	R263K	R263K
5326	BIC	wt	S153Y	S153Y	S153Y
96USSN20	BIC	wt	E157K	E157K, S153FS	E157EK, S153FS
5326	CAB	S153FS	Q148K	T97AT, G140S, S147GS, Q148K	L74M, G140S, S147G, Q148K
96USSN20	CAB	R263KR	R263KR, Q148R, E138EK	L74LM, R263K, Q148R, E138K	L74LM, R263K, Q148R, E138K
5326	EVG	wt	wt	R263K, S153A	R263K, S153A
96USSN20	EVG	T66I	T66I, S147G, G163GR	T66I, S147G, G163GR	T66I, Q146R, S147G, Q95R

Fig. 1 Growth of 5326 and 96USSN20 clinical isolates in escalating concentrations of dolutegravir (DTG), bictegravir (BIC), cabotegravir (CAB) and elvitegravir (EVG). The rise in drug concentrations were related to the acquisition of resistance mutations at the designated weeks of selection

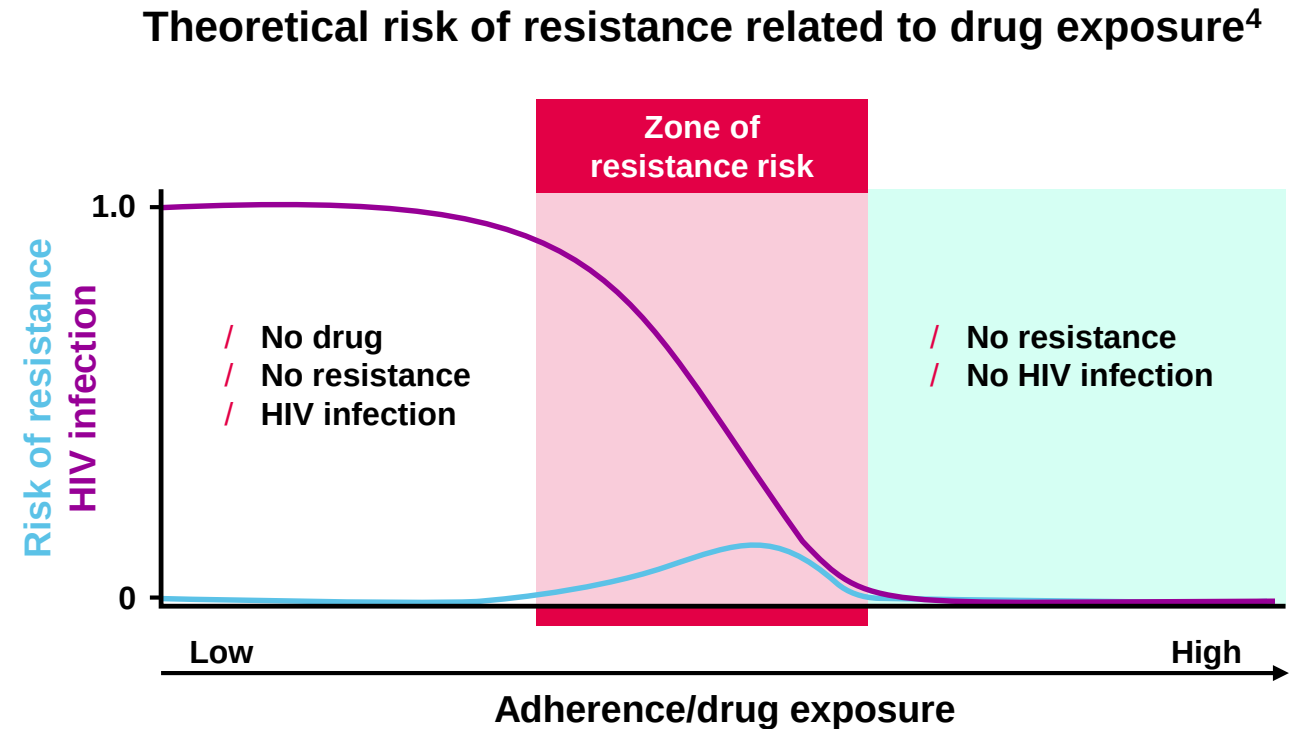
The long-acting integrase inhibitor GSK744 protects macaques from repeated intravaginal SHIV challenge



- Intravaginal inoculations of SHIV twice a week for up to 11 weeks in 6 pigtail macaques
- CAB injection every 4 weeks
- All 6 macaques protected from infection
- Vaginal and plasma drug concentrations remained above CAB PA-IC₉₀

CAB LA PrEP: Potential zone of resistance risk during PK tail

- / During the PK tail phase, CAB levels will eventually fall below the protective threshold, but CAB can remain in circulation for an extended period^{1,2}
- / There is a theoretical risk of developing resistance to CAB LA if an individual acquires HIV during this period³

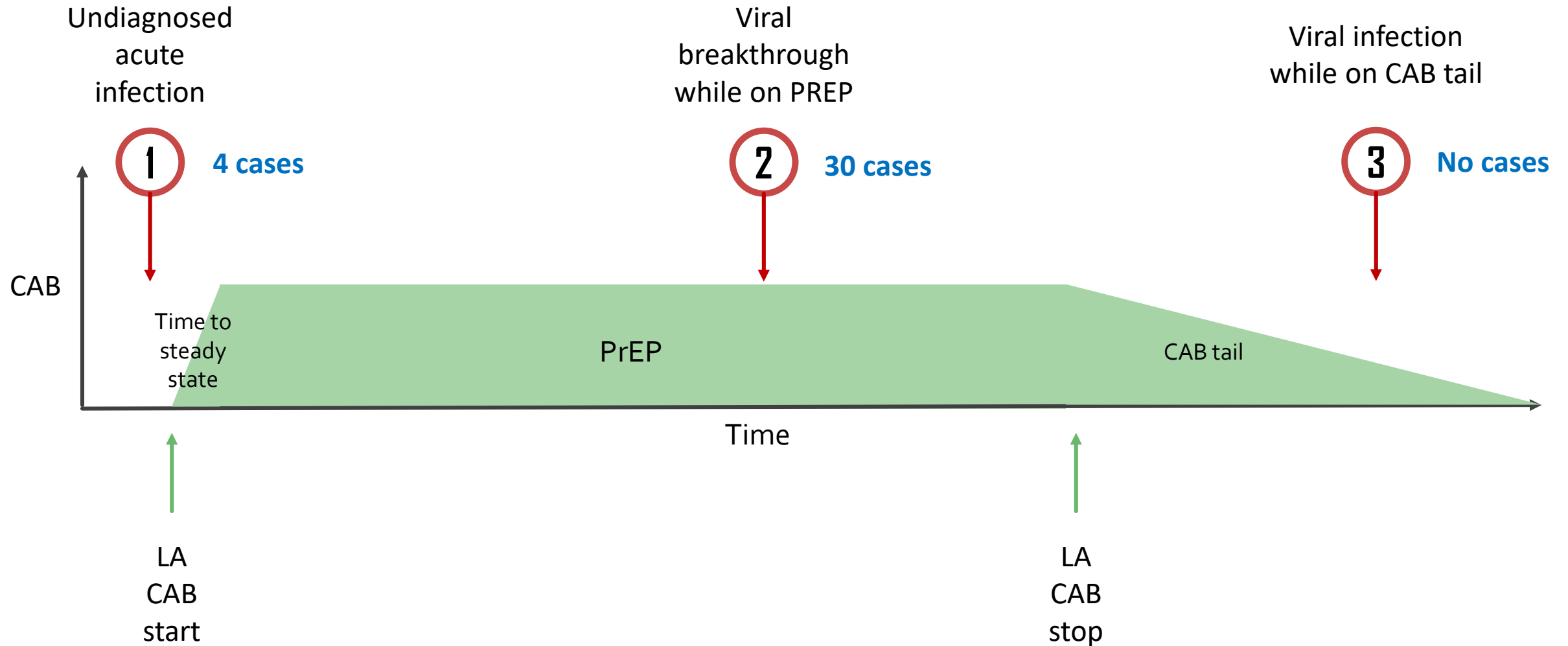


No participant in HPTN 083 and 084 who acquired HIV-1 during the PK ‘tail phase’* was found to have developed resistance to CAB or other INSTIs^{5–7}

*16 cases of HIV acquisition that occurred >6 months since the last CAB exposure

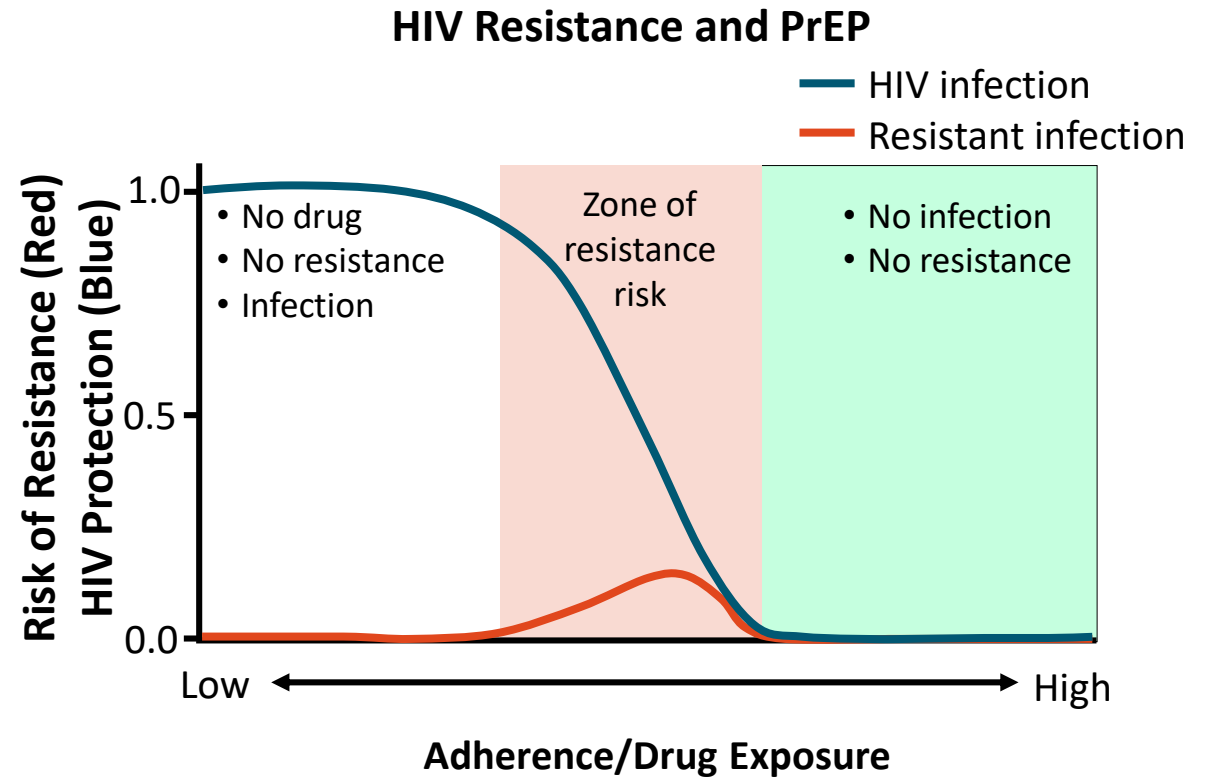
1. Landovitz RJ, et al. Lancet HIV 2020;7:e472–81; 2. Ford SL, et al. CROI 2020. Poster 466; 3. Radzio-Basu J, et al. Nat Commun 2019;10:2005
 4. DHHS/CDC Clinical Practice Guideline: PrEP for the Prevention of HIV Infection in the United States. Updated 2021
 5. WHO. Guidelines on Long-acting injectable cabotegravir for HIV prevention. Jul 2022
 6. Landovitz RJ, et al. N Engl J Med 2021;385:595–608; 7. Marzinke MA, et al. Antimicrob Agents Chemother 2023;e0005323 (and suppl. appendix)

LA CAB and potential for emergent INSTI resistance: *When do drug and virus meet?*

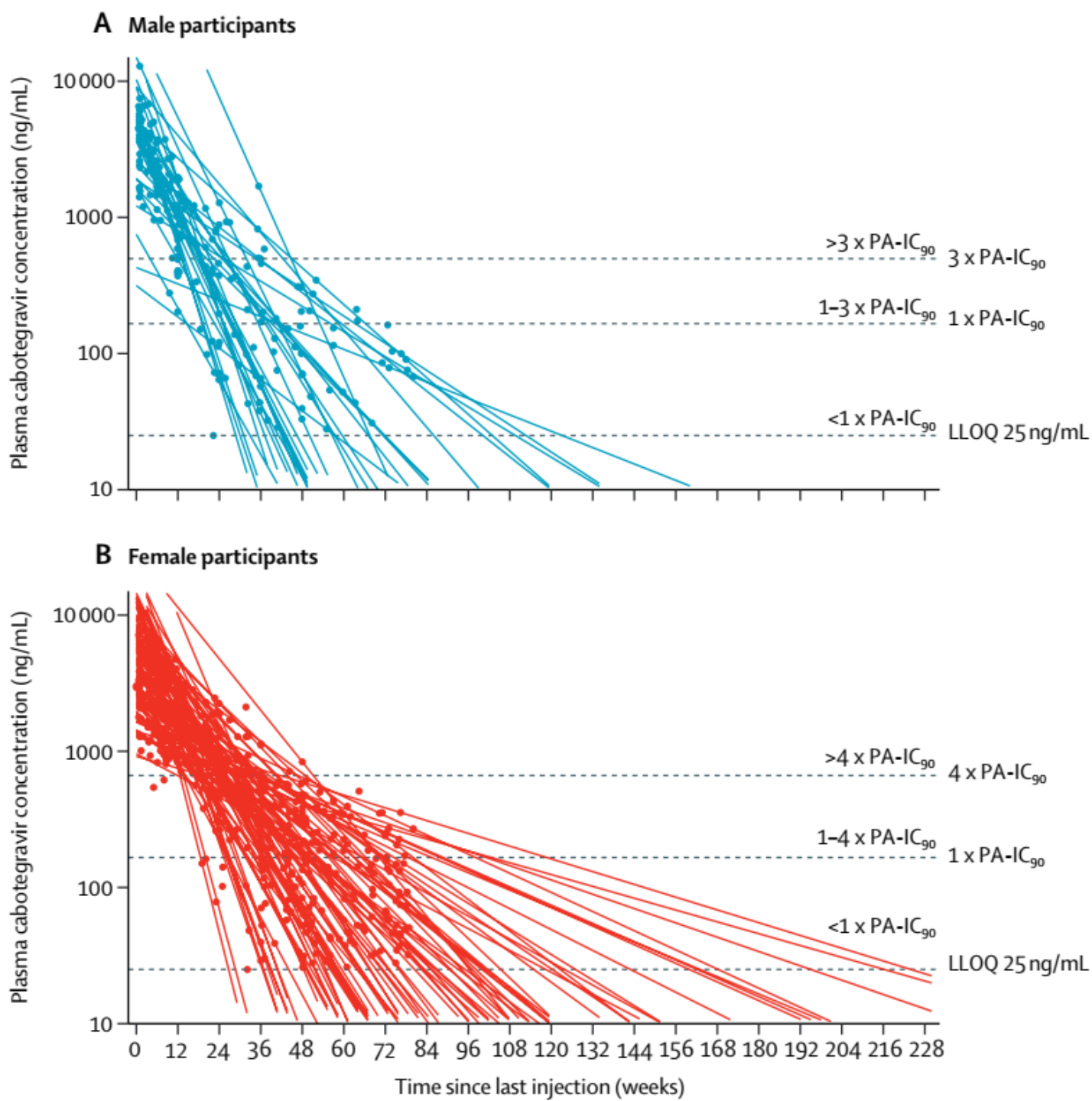


Stopping LA CAB for PrEP

- Assess for ongoing risk of HIV exposure
- Counsel about long duration of declining CAB levels and risk of resistance if HIV acquisition occurs
- Give oral PrEP if it is indicated; FTC/TDF or FTC/TAF can begin within 8 wk after last CAB injection
- Continue follow-up quarterly for 12 mo to assess PrEP needs, and complete HIV testing



Tail-phase safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in HIV-uninfected adults: a secondary analysis of the HPTN 077 trial



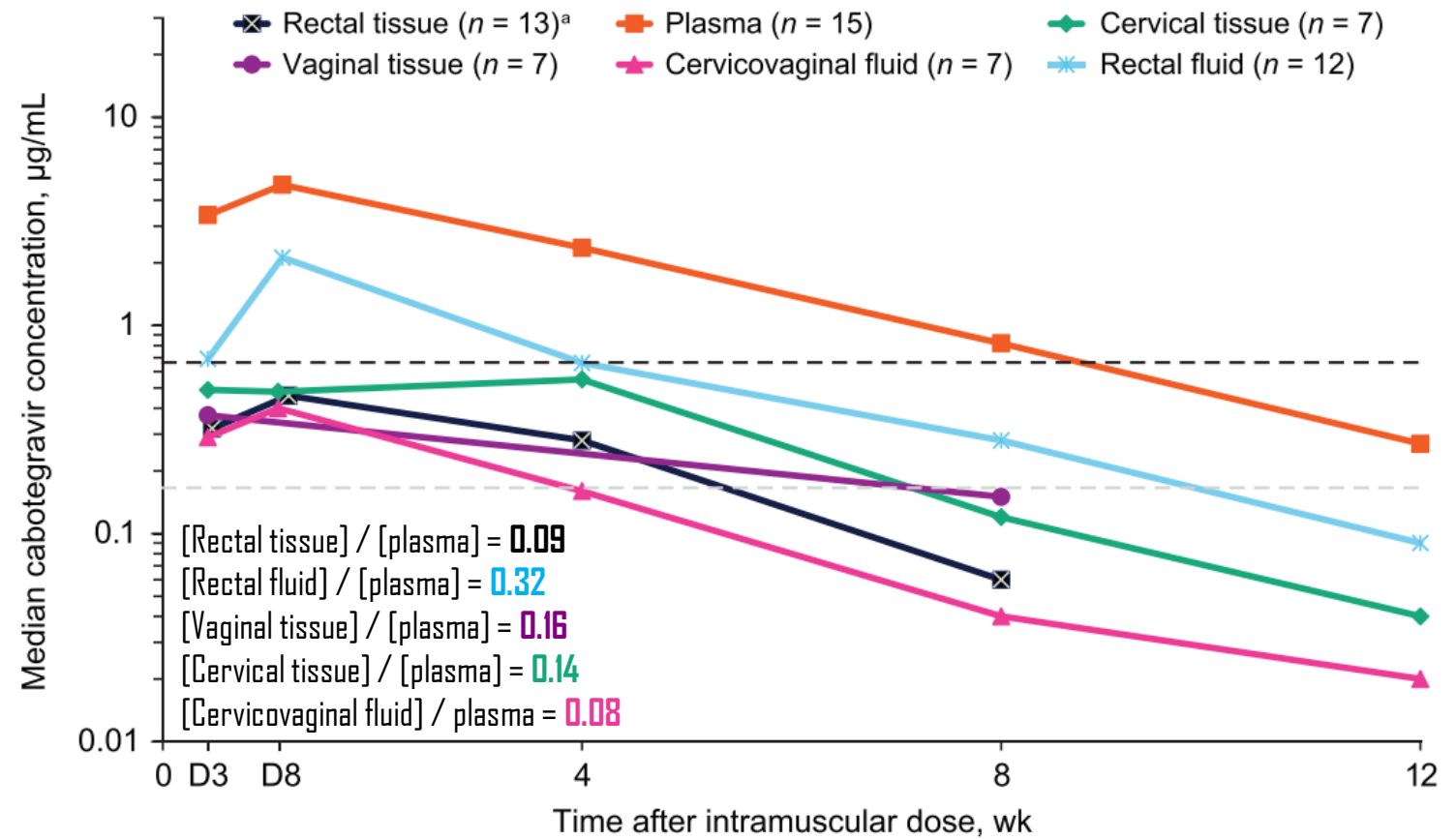
- HPTN 077, 8 sites in Brazil, Malawi, South Africa, and the USA
- 134 adults in CAB group
- CAB still detectable after final injection:
 - at 52–60 weeks, in 9 (23%) males vs. 52 (63%) females
 - at week 76, 4 (13%) males vs. 27 (42%) females
- Median time to undetectability of CAB was 43.7 weeks for males vs. 67.3 weeks for females ($p=0.0003$)
- Apparent CAB half life was longer for females than males (FC 1.33; $p=0.014$), and longer for participants with a high BMI than those with a low BMI (1.31; $p=0.015$)

Multicompartmental pharmacokinetic evaluation of LA CAB in healthy adults for HIV preexposure prophylaxis

Parameter	Participants in overall population (n = 19)	Participants in evaluable pharmacokinetic population (n = 15) ^a
Age (y)		
Mean (SD)	33.3 (9.1)	30.1 (7.0)
Range	22.0–53.0	22.0–46.0
Sex, n (%)		
Female	10 (53)	7 (47)
Male	9 (47)	8 (53)
Body mass index (kg/m ²)		
Mean (SD)	27.2 (3.3)	26.9 (2.9)
Range, min-max	21.4–33.1	21.4–31.1
Height, mean (SD), cm	171.1 (10.2)	171.8 (9.0)
Weight, mean (SD), kg	79.4 (11.5)	79.1 (9.0)
Race and ethnicity, n (%)		
Not Hispanic and not Latino	19 (100)	15 (100)
Asian	1 (5)	1 (7)
Black and African American	6 (32)	5 (33)
White	12 (63)	9 (60)

SD, standard deviation.

^aFour participants did not have evaluable pharmacokinetic data: 2 withdrew before receiving intramuscular injection; 1 had injection maladministration into the retroperitoneal cavity; and 1 was hospitalized for non-study drug-related serotonin syndrome.



Median CAB concentration–time profiles presented by matrix following a single, ultrasound guided CAB LA 600-mg intramuscular gluteal injection

Shaik, Brit J Clin Pharmacol 2022

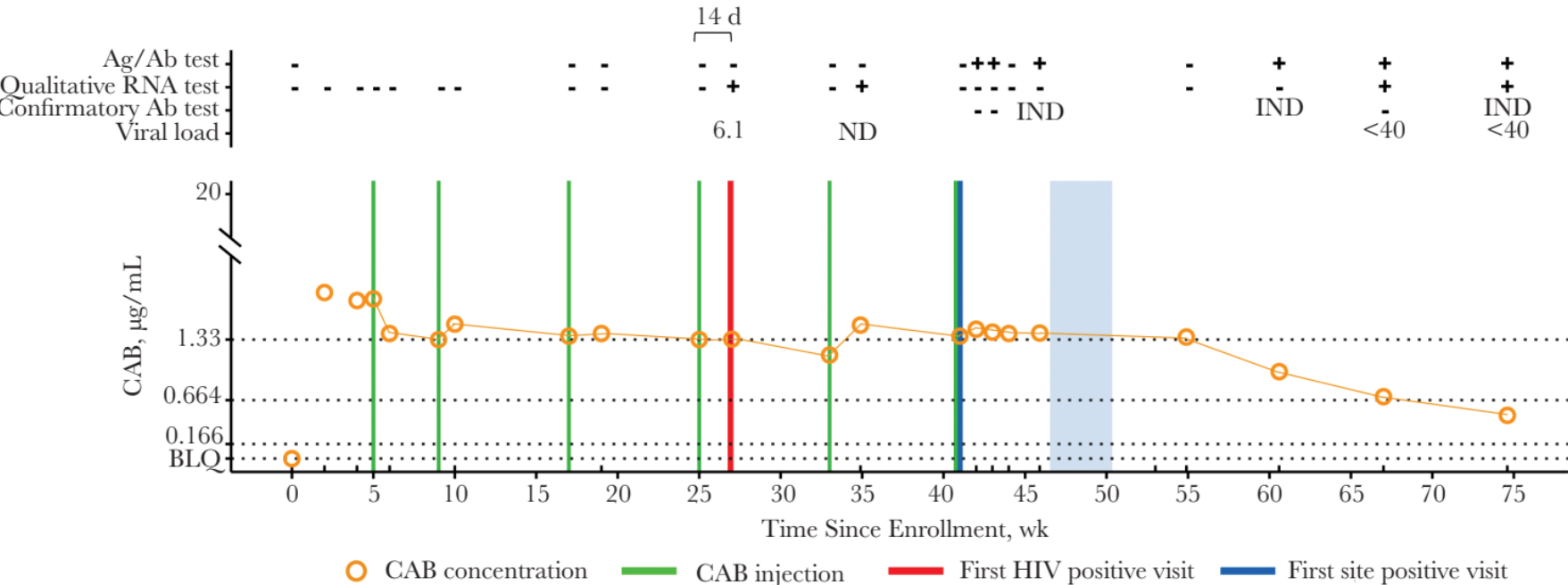
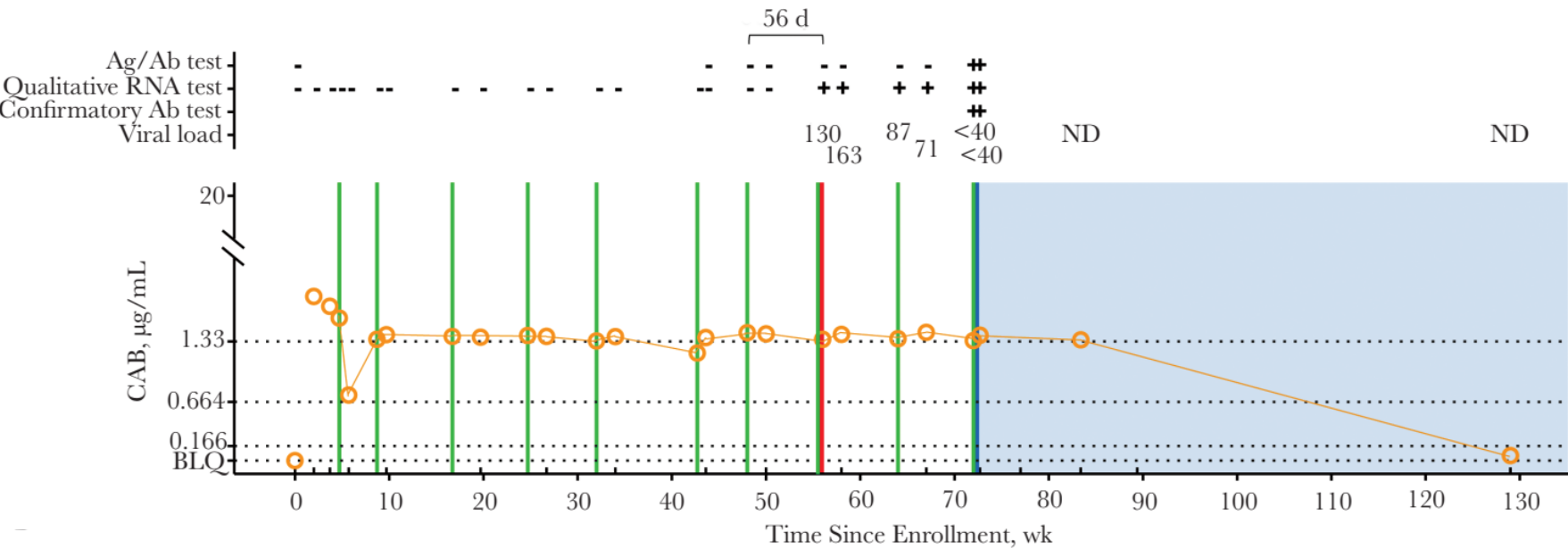
D1

HPTN 083: breakthrough HIV Infections in CAB Arm

- 4 participants acquired HIV despite mostly **on-time CAB-LA injections** (group D)
- 2–7 injections before the first HIV-positive visit
- Median CAB concentration at that visit was 1.56 (1.48–1.71) µg/mL
- ≥8× PA-IC90 at 83%** and **≥4× PA-IC90 at 95%** of the evaluable visits before the first HIV-positive visit

D1

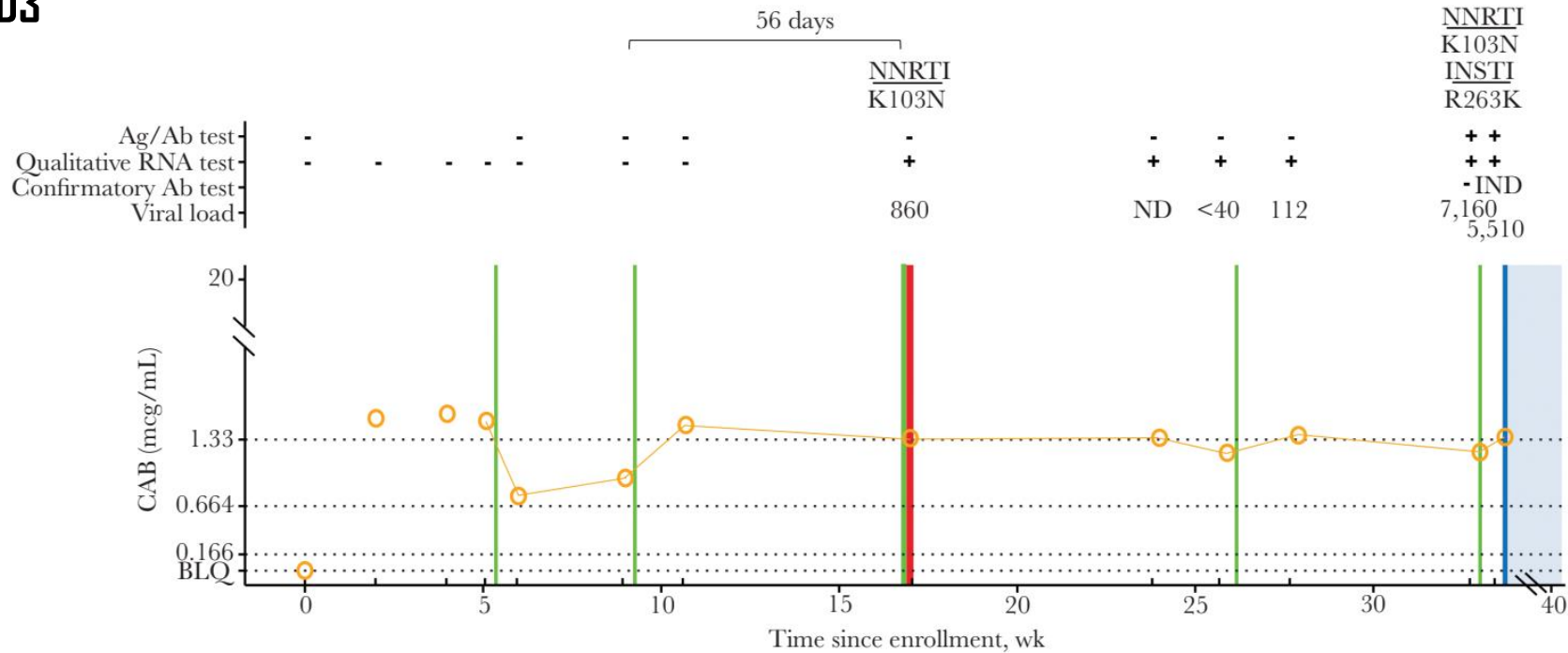
D2



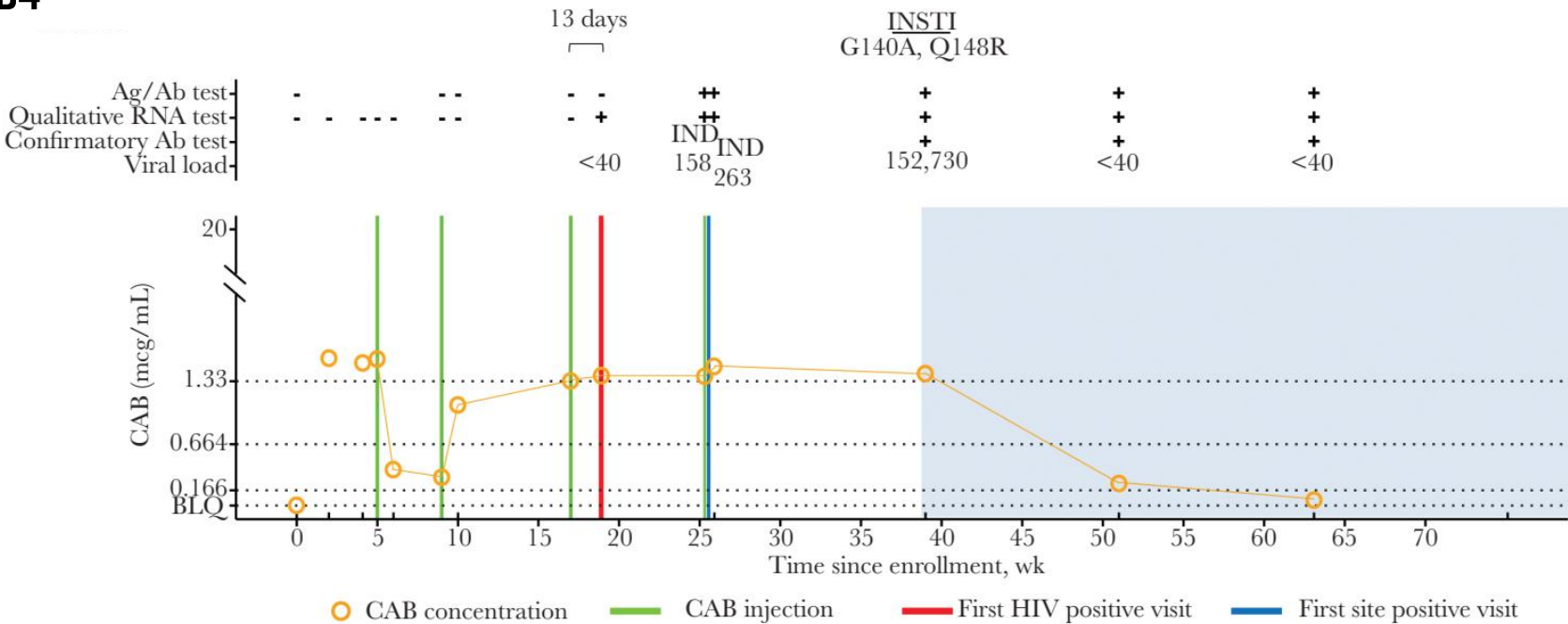
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D3

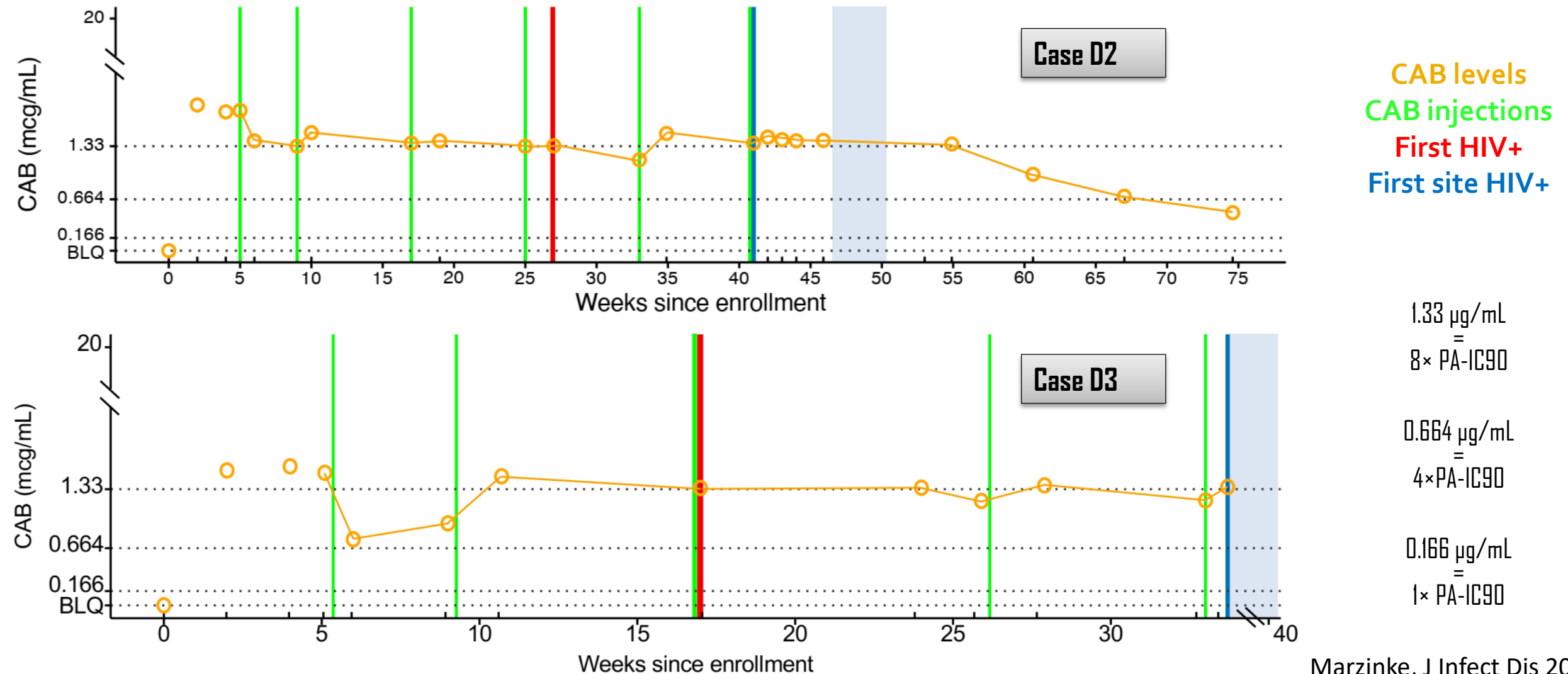


D4



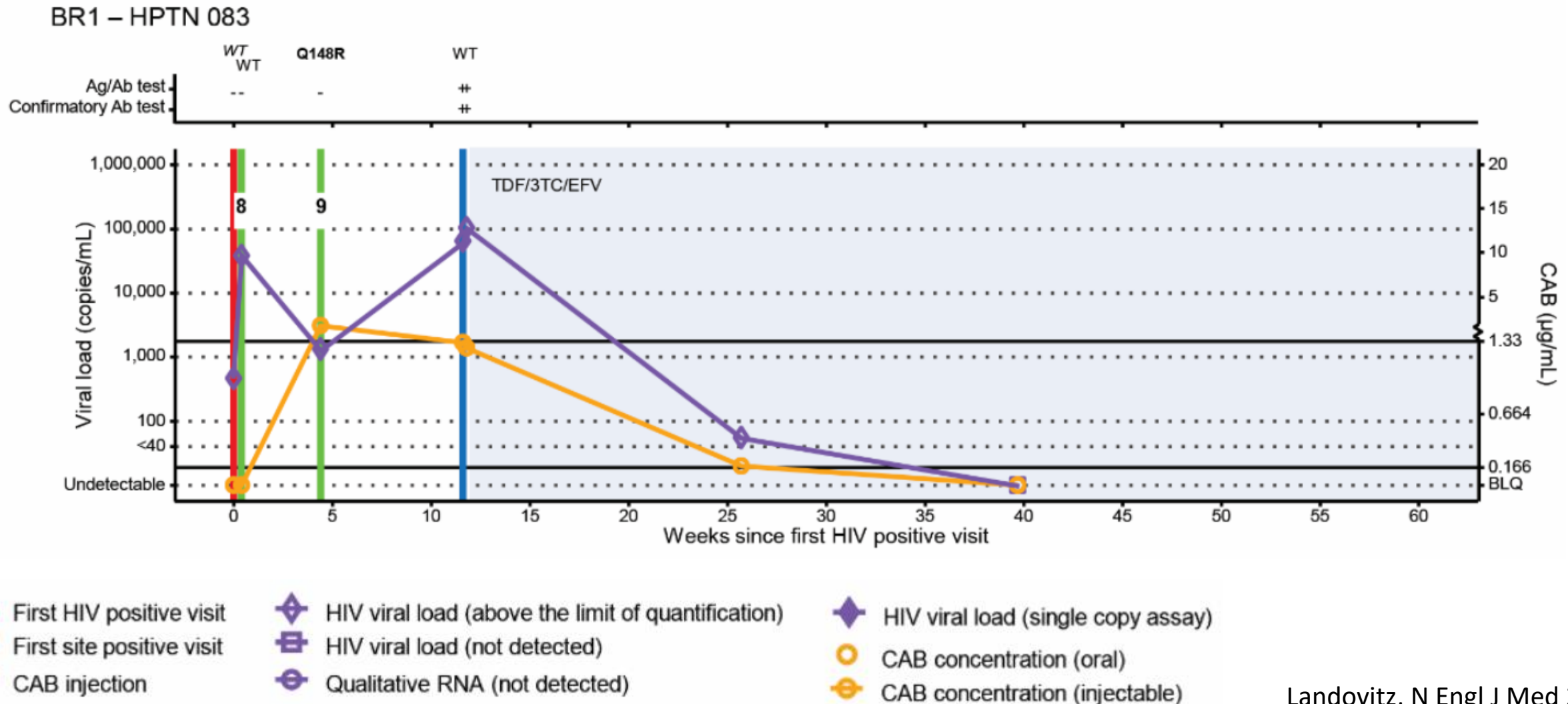
HPTN 083: study drug concentration in incident HIV-1 infections

Cases D2 and D3 (on time injections with adequate CAB levels)



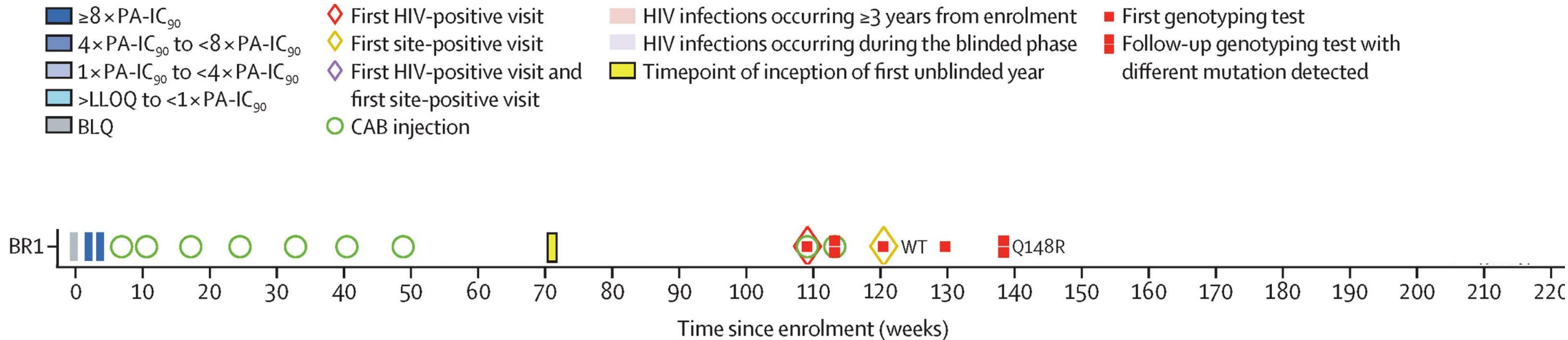
HPTN 083: HIV Infections in Cabotegravir Arm

Case BR1



HPTN 083: HIV Infections in Cabotegravir Arm

Case BR1



CAB LA tail phase was technically defined as >10 to <66.6 weeks after a cabotegravir injection, and for which post-hoc pharmacological assessment suggested that the infection was likely to have been acquired while cabotegravir was quantifiable in plasma; this excludes participants re-exposed to injectable cabotegravir subsequent to infection

HIV RNA Screening Reduces INSTI Resistance Risk in Persons Receiving LA CAB for HIV Prevention (HPTN-083)

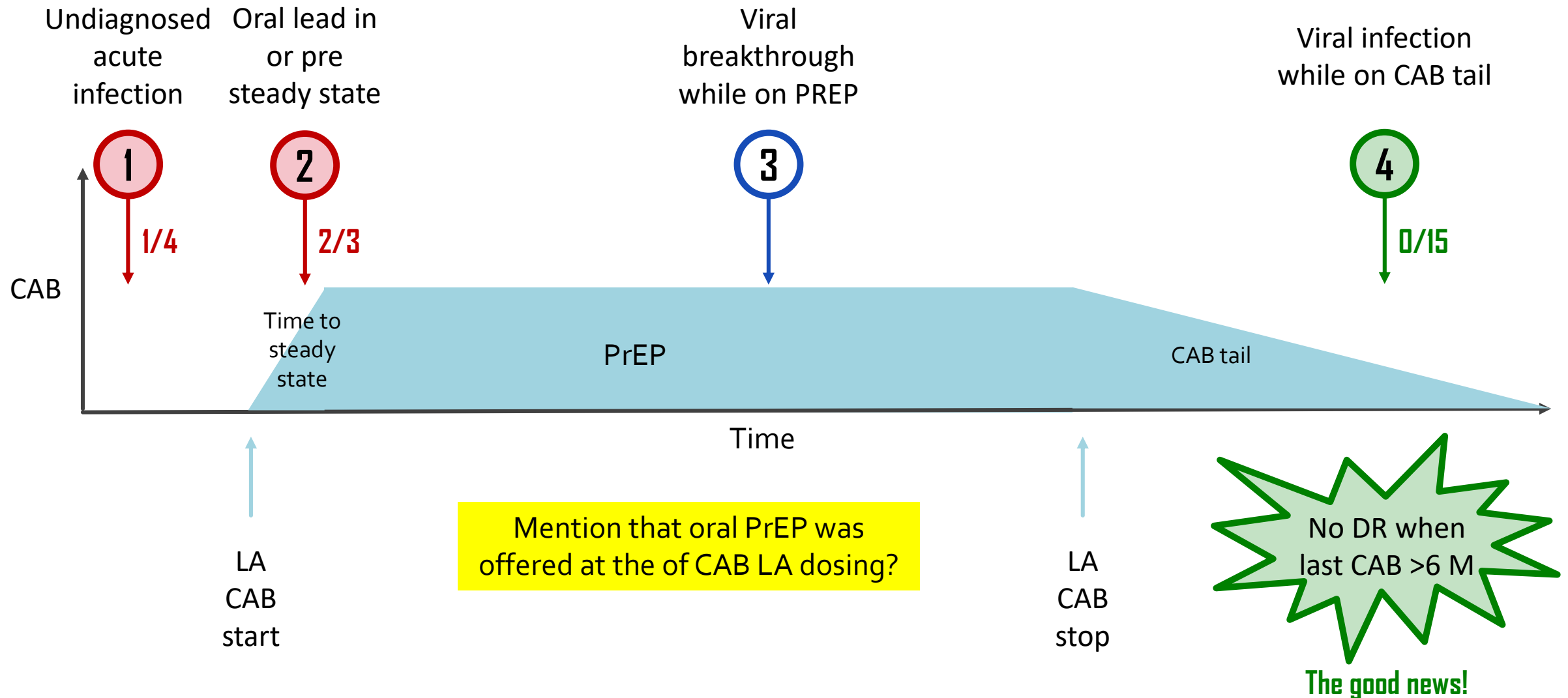
Table 2. Characteristics of the first visit with a major INSTI RAM detected.

Timing of infection	Case	Viral load (copies/mL)	Major INSTI RAMs detected	Timing			CAB concentration (µg/mL) ^a
				Relative to injections	Relative to the 1 st site pos visit	Days since the 1 st HIV pos visit	
Enrollment	A2	204	E138E/K, Q148K/R	1 st injection visit	Before	40	3.318
While receiving oral CAB	C1	137	Q148Q/R	8 days after the 1 st injection	Before	17	1.219
	C3	102,329	E138A, Q148R	20 days after the 1 st injection	Same visit	35	1.108
While receiving CAB injections	D1	130	N155H	8 th injection visit	Before	0	1.613
	D2	<40	N155H	182 days after the 6 th injection	After ^b	280 ^b	0.703
	D3	<40	R263K	4 th injection visit	Before	62	1.213
	D4	158	Q148R	4 th injection visit	Same visit ^c	45	1.930

^aThe concentration of cabotegravir associated with protection against HIV infection (PAIC90) is 1.330 µg/mL.

LA CAB and potential for emergent INSTI resistance:

When do drug and virus meet and may end up with resistance?



Major INSTI RAMs detected at study site vs. centralized lab

Case ID	HIV subtype	First HIV+ visit at centralized lab	First HIV+ visit at study site
A2	C	None	E138K Q148K
C1	B	None	Q148R → E138K G140S Q148R
C3	B	None	E138A Q148R
D1	Likely B	N155H	Q148R N155H → N155H R263K
D2	Likely B	NA	N155H
D3	BF	None	R263K
D4	C	NA	Q148R → E138K Q148R → G140A Q148R
D5	F	R263K	R263K
D6	AE	None	Q148R
BR1	BC	None	Q148R

- Retrospective testing with a sensitive RNA assay detected most infections before INSTI resistance emerged
- Median viral load at first detection of resistance: 148 c/mL (IQR: 77-1,011)

Antiretroviral resistance and management after pre-exposure to prophylaxis

	Previous PrEP use (n=22)	No previous PrEP use (n=917)	p value
Age (years)	31 (23–52)	32 (18–74)	0.97
Gender and sexual behaviour			
Men who have sex with men	22 (100%)	878 (96%)	0.38
Men who don't have sex with men	0 (0%)	26 (3%)	..
Women	0 (0%)	13 (1%)	..
Baseline viral load (copies per mL)	7700 (<20–320 000)	58 000 (<20–1 000 000)	0.0004
Presence of Met184Val or Met184Ile	5 (23%)	5 (1%)	<0.0001
Unable to amplify genotypic resistance test	4 (18%)	20 (2%)	0.002
Data are median (range) and n (%). Data represent documented PrEP use in the 12 months before HIV diagnosis.			
Table: Demographics and genotypic resistance test results of patients with HIV			

Retrospective analysis of data from 939 patients attending a sexual health and HIV clinic in central London

PrEP Use History in People With Antiretroviral Resistance at HIV Diagnosis (New York City, 2015–2022)

Characteristic	Cases with M184I/V at Baseline (%)	Total cases	P Value (χ^2 Test)
All	98 (2)	4246	
PrEP use history			<.001
Recent PrEP use	19 (14)	136	
Past PrEP use	10 (8)	124	
No known PrEP use	69 (2)	3986	

- New York City surveillance and partner services data to measure the effect of TXF/FTC PrEP history on the baseline prevalence of M184I/V at HIV diagnosis in 2015–2022
- PrEP use categorized as “recent” (stopped ≤ 90 days before diagnosis), “past” (PrEP > 90 days before diagnosis), or “no known use”

PrEP Use History in People With Antiretroviral Resistance at HIV Diagnosis (New York City, 2015–2022)

PrEP Use History	aRR (95% CI) ^a	
	AHI	No AHI
Recent PrEP use	5.86 (2.49–13.77)	7.26 (3.98–13.24)
Past PrEP use	2.77 (.66–11.64)	4.46 (2.15–9.24)
No known PrEP use	1.00 (Reference)	1.00 (Reference)

Abbreviations: AHI, acute human immunodeficiency virus infection; aRR, adjusted relative risk; CI, confidence interval; PrEP, preexposure prophylaxis.

^aAdjusted for transmission category: men who have sex with men versus other (heterosexual, contact, injection drug use, transgender with sexual contact, unknown risk).

- New York City surveillance and partner services data to measure the effect of TXF/FTC PrEP history on the baseline prevalence of M184I/V at HIV diagnosis in 2015–2022
- PrEP use categorized as “recent” (stopped ≤90 days before diagnosis), “past” (PrEP >90 days before diagnosis), or “no known use”

Drugs resistance due to PrEP use

Table 1. HIV-1 resistance to tenofovir or emtricitabine in oral tenofovir disoproxil fumarate/emtricitabine preexposure prophylaxis trials

Study	TDF/FTC Arm	Tenofovir Resistance ^a		FTC Resistance ^b	
		Standard genotype	Sensitive genotype	Standard genotype	Sensitive genotype
Infection after enrollment					
FEM-PrEP	33	0	0	4	1
iPrEx	36	0	0	0	2
TDF2	9	0	0	0	0
Partners PrEP	21	0	1	0	5
VOICE	61	0	0	1	2
Total	160	0 (0%)	1 (0.6%)	5 (3%)	10 (6%)
Acute infection at enrollment					
FEM-PrEP	1	0	–	0	–
iPrEx	2	0	–	2	–
TDF2	1	1	–	1	–
Partners PrEP	4	0	–	2	–
VOICE	9	0	–	2	–
Total	17	1 (6%)	–	7 (41%)	–

PeEP, preexposure prophylaxis; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

^aK65R or K70E detected by standard population genotype or above 1% frequency by sensitive genotype (allele-specific PCR or 454 sequencing).

^bM184V or M184I detected by standard population genotype, or above 1% frequency by sensitive genotype (allele-specific PCR or 454 sequencing).

Daily F/TDF PrEP and antiretroviral resistance

	Number with Resistance/Total Number Infected			
	Infected At Study Entry		Incident Infection	
	PrEP	Placebo	PrEP	Placebo
iPrEx	2/2	1/8	0/48	0/83
Partners PrEP	1/3	0/6	0/13	0/52
TDF2	1/1	0/2	0/9	0/24
FEM-PrEP	0/1	0/1	4/33	1/35
VOICE	2/9	0/1	1/61	0/60
Total	6/16	1/18	5/164	1/254

P=0.035

P=0.037

P<0.001

- Resistance was rare in PrEP clinical trials
 - Overall risk: 0.05% (5/9222)
- Resistance favoured in people with undiagnosed **acute HIV infection at study entry**
 - risk: 37% in this setting

Clinical Genotypic Drug Resistance With Daily F/TDF in the Setting of PrEP

- Resistance was rare in PrEP clinical trials
 - Overall risk: 0.05% (5/9222)
 - Number needed to treat to harm: 1844
 - All resistance occurred in people with undiagnosed acute HIV infection at study entry (risk: 37% in this setting)
- Multiple HIV infections were averted for every case of resistance
 - Overall
 - Daily PrEP prevented >8 HIV infections for every FTC-resistant HIV infection
 - Partners PrEP
 - Daily PrEP prevented 25 HIV infections for every drug-resistant infection

F/TDF: emtricitabine/tenofovir disoproxil fumarate.

Gibas KM, et al. *Drugs*. 2019;79:609-619.

**Number Infected and Resistance/
Total Number Infected**

	Infected At Study Entry		Incident Infection	
	PrEP	Placebo	PrEP	Placebo
iPrEx	2/2	1/8	0/48	0/83
Partners PrEP	1/3	0/6	0/13	0/52
TDF2	1/1	0/2	0/9	0/24
FEM-PrEP	0/1	0/1	4/33	1/35
VOICE	2/9	0/1	1/61	0/60
Total	6/16	1/18	5/164	1/254

How could HIV-1 drug resistance impact preexposure prophylaxis for HIV prevention?

Table 1. Seroconversions in Studies and Cohorts of Individuals Prescribed TDF/FTC PrEP for HIV Prevention

Type of study	No. with PrEP-associated resistance/No. HIV Positive (%) at a Study Follow-Up Visit ^e	No. with PrEP-associated resistance/No. HIV positive (%) at Enrollment into Study ^f
Clinical Trials ^a	12/222 (5%)	13/20 (65%)
On-Demand PrEP ^b	1/14 (7%)	2/5 (40%)
Open-Label/Demonstration Project ^c	2/45 (4%)	3/6 (50%)
Cohort/Population ^d	44/202 (22%)	–

^aStudies included are as follows: FEM-PrEP [30], iPrEX [31], TDF2 [32], Partners PrEP [33], VOICE [34], DISCOVER [15[■]] and HPTN-083 [16[■]].

^bStudies included are as follows: IPERGAY [17], IPERGAY OLE [18], HPTN-067 [19].

^cStudies/projects included are as follows: PROUD [20], HPTN-073 [21], USA DEMO [22], HPTN-082 [23], iPrEX OLE [24], ATN 110 [25].

^dProjects included are as follows: SEARCH [1[■]], GEMS [27], IAVI-Kenya [28], VHA [29], Princess PrEP [35], 56 Dean Street [36].

^eProportion with PrEP-associated resistance is the aggregate number of participants with tenofovir disoproxil fumarate (TDF) or emtricitabine (FTC)-associated mutations (K65R, M184I or V, K70E) at their follow-up visit from all referenced studies, over the aggregate total of HIV positive cases identified at follow-up visits from all referenced studies.

^fProportion with PrEP-associated resistance is the aggregate number of participants from all referenced studies with tenofovir disoproxil fumarate (TDF) or emtricitabine (FTC)-associated mutations (K65R, M184I or V, K70E) who were retrospectively determined by detectable HIV RNA to be HIV positive at enrollment into the study, over the aggregate total of HIV positive cases at enrollment from all referenced studies.

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Cohort/Population ^d	44/202 (22%)	–

5.3%

58.1%

^aStudies included are as follows: FEM-PrEP [30], iPrEX [31], TDF2 [32], Partners PrEP [33], VOICE [34], DISCOVER [15[■]] and HPTN-083 [16[■]].

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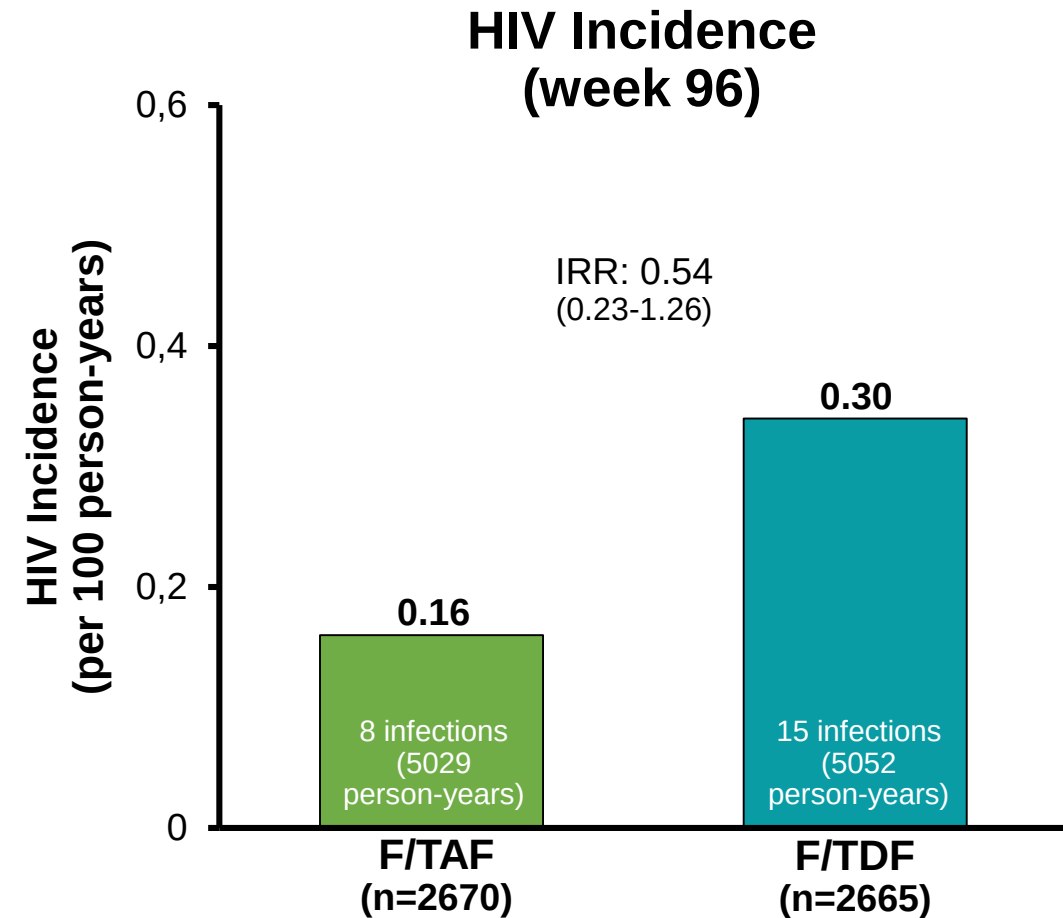
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DISCOVER Trial: HIV Incidence at Week 96 With Daily F/TAF or F/TDF for HIV PrEP

- F/TAF was non-inferior to F/TDF for HIV prevention at both week 48 and 96
- HIV infections: 23 in 10,081 person-years of follow-up
 - F/TAF (n=8): suspected baseline infection (n=1), low TFV-DP levels (n=6), medium TFV-DP levels (n=1)
 - No FTC or TAF resistance
 - F/TDF (n=15): suspected baseline infection (n=4), low TFV-DP levels (n=10), high TFV-DP levels (n=1)
 - FTC resistance: 4/13 who were genotyped



Prevalence of HIV Drug Resistance in People Newly Diagnosed with HIV who have used Pre-exposure Prophylaxis in Europe; the PrEPaRe study

Table 1. Resistance among PLHIV exposed to PrEP

		Prevalence (n/N)	95% confidence interval
Major antiretroviral drug resistance mutation to FTC or TDF detected with frequency above 15% (K65REN, M184VI, K70E)		24% (12/50)	(12% - 36%)
	M184VI exclusively	10	
	K103N exclusively	1	
	L10I, L33I, E35D, N37S, R41K, L63T, A71T, I93L, A98S, D123E, E204A, Q207E, R211K, K277R	1	

- Observational study across 10 European countries
- 1,725 new HIV diagnoses, Oct 2020 to Mar 2024
- Main reason (60%) for diagnosis was regular testing
- 70 had used PREP, genotype available for 50

GEMS: Study Design

- Observational cross-sectional study
- Blood samples (whole blood for plasma or dried blood spots) collected from participants diagnosed with HIV on PrEP
- Demographics and self-reported adherence obtained through a questionnaire
- HIV drug resistance mutations revealed by Sanger sequencing of reverse transcriptase and analyzed using Stanford HIVdb v9.0
- Tenofovir-diphosphate levels measured by liquid chromatography–mass spectrometry

GEMS: Characteristics of Patients Who Seroconverted on PrEP

- 229 reported seroconversions on PrEP between December 2017 and June 2021
- 208 (91%) patients provided a sample
 - South Africa: 79 (38%)
 - Kenya: 65 (31%)
 - Zimbabwe: 36 (17%)
 - Eswatini: 28 (13%)

Characteristic	Patients (N = 208)
Female sex, n (%)	155 (75)
Age category at seroconversion, n (%)	
■ 16-24	108 (52)
■ ≥25	95 (46)
■ Unknown	5 (2)
Population, n (%)	
■ Adolescent girl/young woman	87 (42)
■ Serodifferent couple	50 (23)
■ Female sex worker	20 (10)
■ Men who have sex with men	15 (7)
■ Transgender woman	12 (6)
■ Pregnant or lactating	8 (4)
■ Incarcerated	1 (<1)

GEMS: Time From PrEP Initiation to Seroconversion

Time from PrEP Initiation to Seroconversion, mo	Patients, % (N = 208)
0-3	35
3-6	20
6-12	20
12+	18
Unknown	8

GEMS: Analysis of Resistance and Adherence Level

- 118/208 samples (57%) successfully sequenced
 - Insufficient HIV-1 RNA (30% of samples) most common reason for no result

Resistance	No Resistance Mutations 65/118 (55%)		
	Low*	Moderate [†]	High [‡]
Adherence	34/41 (82%)	1/41 (2%)	6/41 (15%)

Resistance	Resistance Mutations Not Associated With PrEP 26/118 (22%)		
	Low*	Moderate [†]	High [‡]
Adherence	12/20 (60%)	1/20 (5%)	7/20 (35%)

Resistance	Resistance Mutations Associated With PrEP (K65R, K70E, M184IV) 27/118 (23%)		
	Low*	Moderate [†]	High [‡]
Adherence	2/18 (11%)	2/18 (11%)	14/18 (78%)

* <350 fmol/punch, <2 doses/week.

[†] 350-699 fmol/punch, 2-3 doses/week.

[‡] ≥700 fmol/punch, 4-7 doses per week.

GEMS: Analysis of Resistance Mutations

Resistance Pattern	Patients, n
PrEP mutation only	14
▪ K65R, K70E, M184V	1
▪ M184I/V	13
PrEP and NNRTI mutations	13
▪ K65R, M184V + L100I, K103N	1
▪ K65R, M184V + K101E, V106M, E138A, G190A	1
▪ K65R + K103N	1
▪ M184I/V + various NNRTI mutations	10

HIV-1 Incidence, Adherence, and Drug Resistance in Individuals Taking Daily TDF/FTC for HIV-1 PreP: Pooled Analysis From 72 Global Studies

Table 1. HIV-1 Incidence Rates After Up to 96 Weeks in 72 Post-Approval Studies of F/TDF for PrEP in 28 Countries, 2011–2021

	HIV-1 Diagnosis		No HIV-1 Diagnosis		IR (95% CI) per 100 Person-years
	n	Mean Person-years	n	Mean Person-years	
All (n = 17 274)	101	0.59	17 173	0.76	.77 (.63, .94)
Age at PrEP initiation 14 to <18 y (n = 368)	4	0.51	364	0.56	2.0 (.73, 5.2)
Age at PrEP initiation 18 to <35 y (n = 11 453)	87	0.58	11 366	0.70	1.1 (.88, 1.3)
Age at PrEP initiation 35+ y (n = 4766)	8	0.88	4758	0.85	.20 (.10, .39)
TFV-DP in DBSs not collected	47	0.40	10 629	0.66	.67 (.50, .89)
TFV-DP (fmol/punch) in DBSs available	54	0.76	6544	0.92	.89 (.68, 1.2)
<350 (<2 doses/wk)	45	0.81	1335	0.83	3.9 (2.9, 5.3)
350 to <700 (2–3 doses/wk)	2	0.9	934	0.89	.24 (.060, .96)
700 to <1250 (4–6 doses/wk)	6	0.35	2352	0.94	.27 (.12, .60)
≥1250 (≥7 doses/wk)	1 ^a	0.67	1923	0.96	.054 (.008, .38)
Cisgender men (n = 10 946)	65	0.66	10 881	0.82	.73 (.57, .93)
Cisgender women (n = 5502)	33	0.41	5469	0.63	.96 (.68, 1.4)
Transgender women (n = 405)	2	1.03	403	0.75	.66 (.16, 2.6)
Transgender (n = 337) ^b	1	1.3	336	1.03	.29 (.041, 2.0)

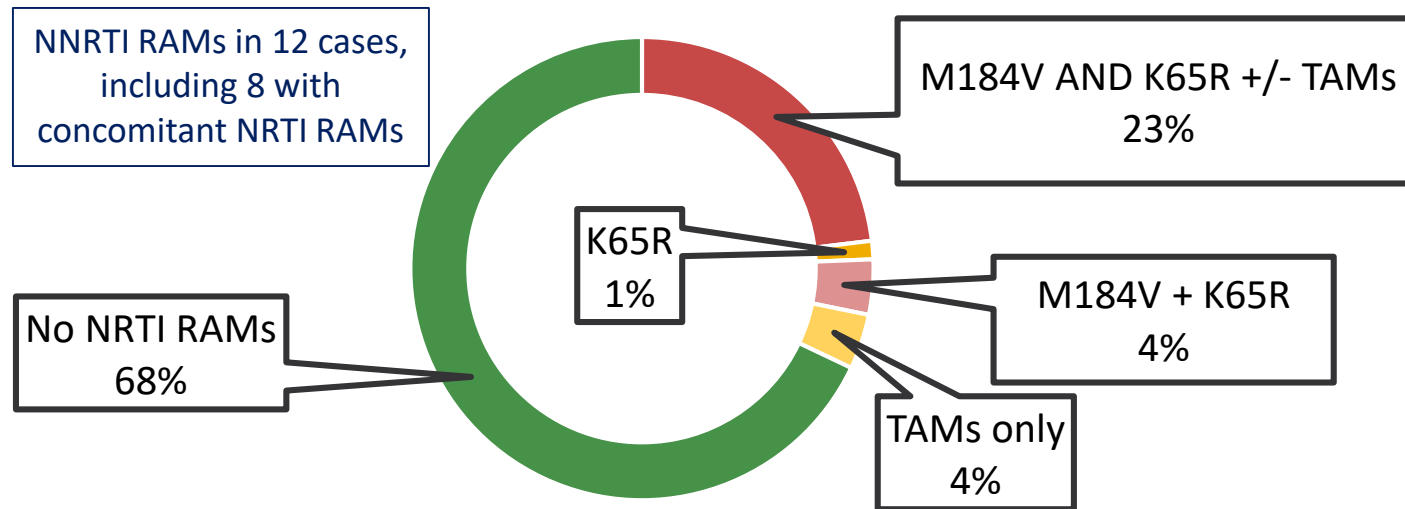
Abbreviations: CI, confidence interval; DBS, dried blood spots; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HIV-1, type 1 human immunodeficiency virus; IR, incidence rate; PrEP, pre-exposure prophylaxis; TFV-DP, tenofovir diphosphate.

^aThe participant, a cisgender man who had sex with men, had average TFV-DP DBS concentrations of 2234 and 2258 fmol/punch at 6 months after the start of F/TDF for PrEP and at time of HIV-1 diagnosis, respectively [23]; to date, this is the only reported infection with wild-type HIV infection while taking oral daily PrEP with documented daily adherence.

^bIndividuals were categorized as transgender, but no specific gender identity data were available.

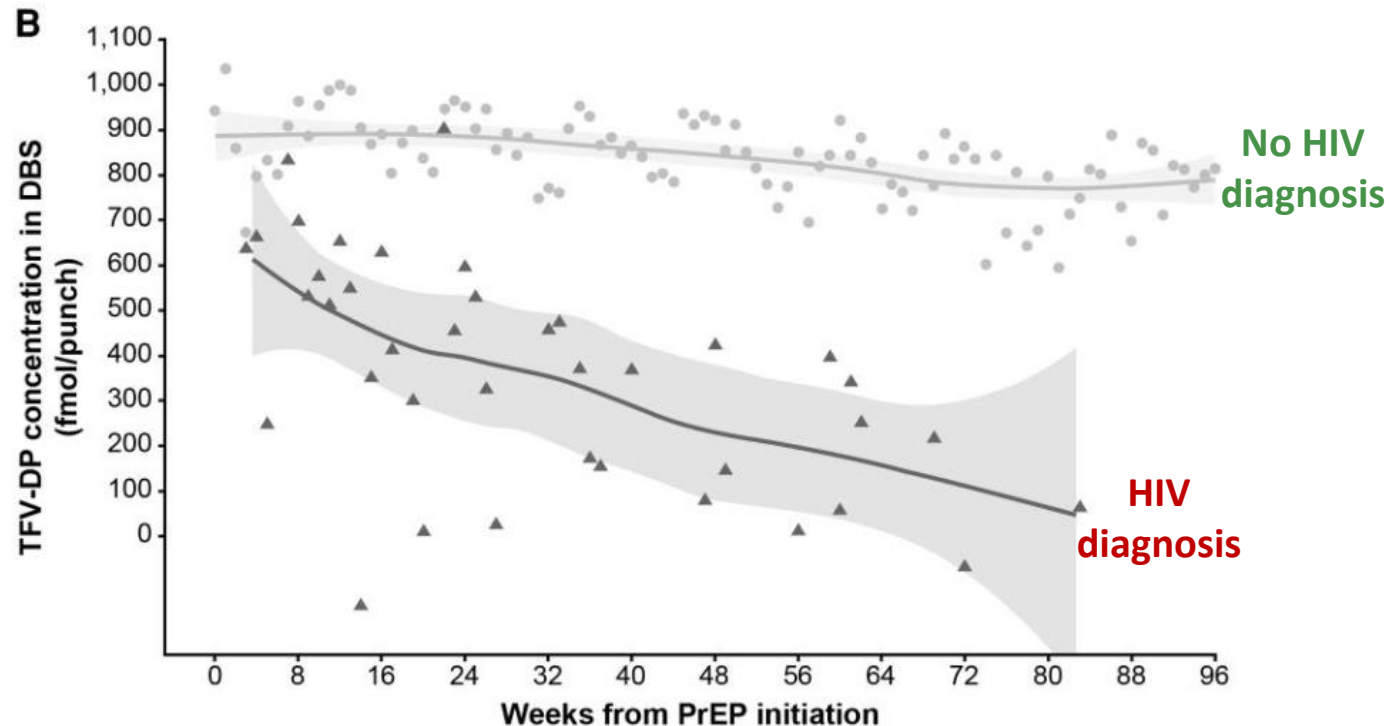
HIV-1 Incidence, Adherence, and Drug Resistance in Individuals Taking Daily TDF/FTC for HIV-1 PreP: Pooled Analysis From 72 Global Studies

Distribution of NRTI RAMs in 78 cases



- 72 TDF/FTC PrEP studies, 17,274 individuals
- 101 acquired HIV-1 after PrEP initiation and within 60 days of PrEP discontinuation
 - HIV-1 IR 0.77 per 100 person-years
 - 78 with available HIV-1 genotype

HIV-1 Incidence, Adherence, and Drug Resistance in Individuals Taking Daily TDF/FTC for HIV-1 PreP: Pooled Analysis From 72 Global Studies



- Adherence measured by TFV-DP in DBS. Least-squares means by week for individuals diagnosed with HIV-1 and individuals not diagnosed
- TFV-DP concentration data in DBSs were available for 9 participants with M184V/I and/or K65R
 - Including 4 with high adherence, diagnosed 28 to 84 days after PrEP initiation (PrEP started during unrecognized acute infection?)

Adherence group	HIV incidence rate per 100 PYs
Low (<2 doses/week)	2.39
Medium (2-3 doses/week)	0.24
High (consistent daily dosing)	0.05

Characterization of HIV Seroconverters in a TDF/FTC PrEP Study: HPTN 067/ADAPT

TABLE 1. Participants Who Seroconverted at the HPTN 067/ADAPT Trial

Case	Study Arm	HIV Infection Detected		PrEP Exposure	Resistance to Study Drug
		Retrospective Testing (HPTN LC)	Study Site		
1	Not randomized, acute at enrollment	Enrollment*	w4	Once-weekly DOT only (4 doses)	K65R
2	Not randomized, acute at enrollment	Enrollment*	w4	Once-weekly DOT only (4 doses)	M184I
3	Not randomized, acute at enrollment	Enrollment*	w4	Once-weekly DOT only (4 doses)	Not detected
4	Not randomized, infected by 6 wk	w4	w5	Once-weekly DOT only (5 doses)	Not detected
5	Not randomized, infected by 6 wk	w4	w4	Once-weekly DOT only (4 doses)	Not detected
6	Not randomized, pregnant	w26	w26	Once-weekly DOT only (5 doses)	Not detected
7	Daily arm	w6*	w22	DOT plus daily PrEP; low adherence	Not detected
8	Daily arm	w14*	w18	DOT plus daily PrEP; low adherence	Not detected
9	Time-driven arm	w22	w22	DOT plus time-driven PrEP; low adherence	Not detected
10	Time-driven arm	w14*	w18	DOT plus time-driven PrEP; adherent with a missing dose (7-day period with no drug before acute infection)	K65R, M184I
11	Event-driven arm	w30*	w34	DOT plus infrequent event-driving dosing	Not detected
12	Event-driven arm	w18*	w22	DOT plus infrequent event-driving dosing	Not detected

Twelve participants seroconverted in the HPTN 067/ADAPT trial. The table shows the randomization status and study arm for each participant. The table also shows the first HIV-positive study visit, which was determined by retrospective testing performed at the HPTN Laboratory Center (LC), and the study visit where HIV infection was first detected at the study site using HIV rapid tests.

All participants were exposed to once-weekly directly observed therapy (DOT). The 6 randomized participants were also exposed to self-administered PrEP with one of 3 dosing regimens (daily, time-driven, and event-driven). Information on PrEP exposure during the self-administered phase of the trial was obtained by retrospective ARV drug testing and review of self-reported data on dosing that were collected during the trial. HIV mutations that confer resistance to TDF/FTC (study drug) were detected in 3 participants (at the week 4 study visit in cases 1 and 2, and at the week 19 study visit in case 10).

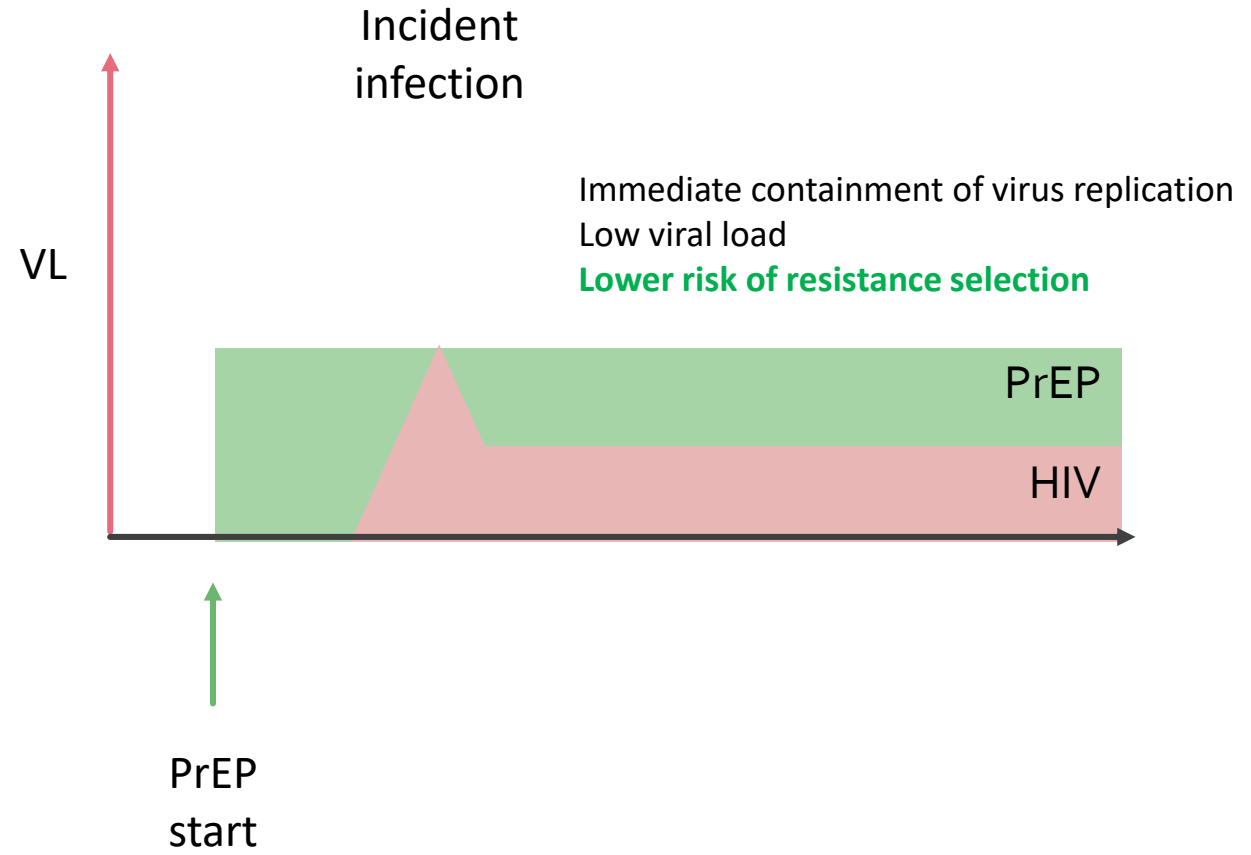
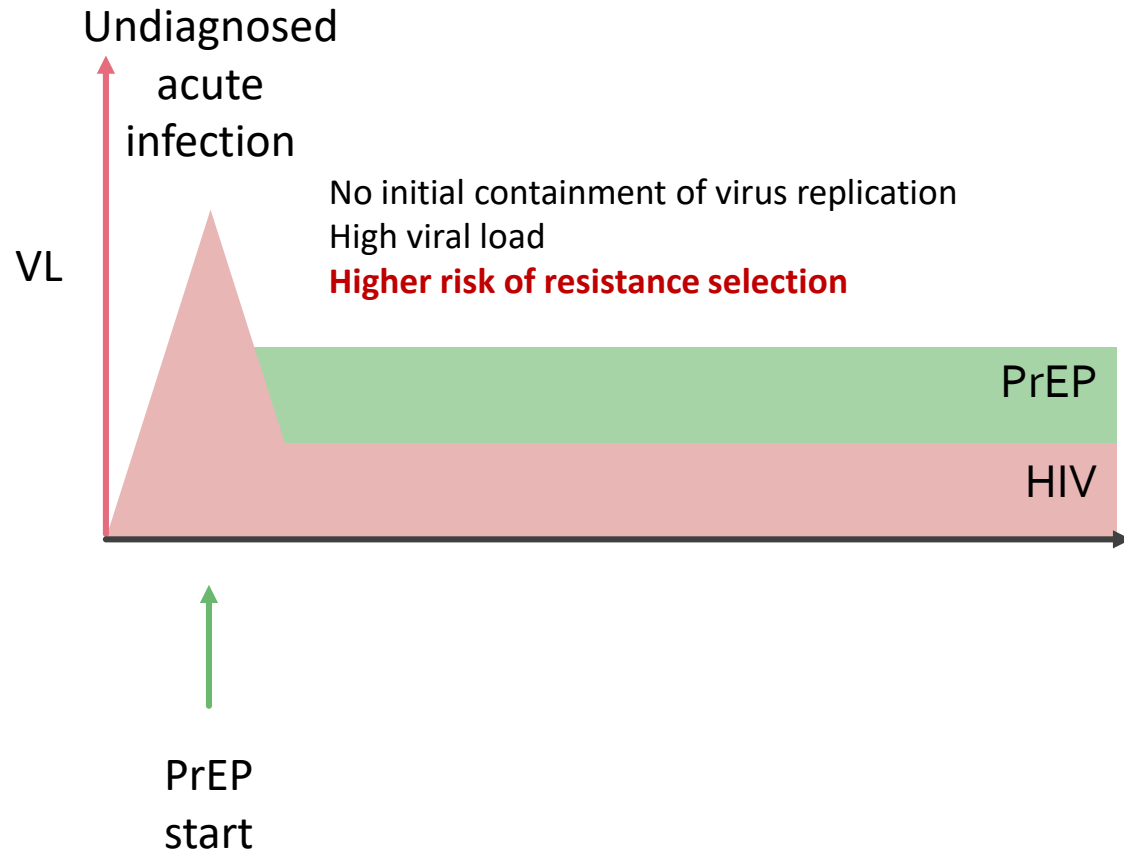
*Participant had acute HIV infection at the first HIV-positive study visit.

DOT, directly observed therapy; HPTN, HIV Prevention Trials Network; LC, Laboratory Center; w, week.

- TDF/FTC PrEP) in women (South Africa) and MSM (Thailand, US)
- Once-weekly DOT of TDF/FTC, then randomization to daily, time-driven, or event-driven PrEP
- 12 HIV seroconversion events
- Sensitive assays improved detection of HIV infection
- Drug resistance mostly detected by NGS

PrEP and antiretroviral resistance

What to expect



PrEP and antiretroviral resistance

TXF/FTC vs. LA CAB

Feature	Oral TXF/FTC	LA CAB
Impact of TDR	Limited but tangible	Virtually none
Vulnerability of PK tail	Low	Moderate to high
Impact of adherence	High	Low
Drug class potency	Low	High
Drug combination	Two compounds but one class	One compound
Major causes for resistance	TDR, erratic adherence	To be defined

The beginning of the LA PREP era

LA CAB superior to reference TDF/FTC PrEP in both trials



HPTN 083¹

- N = 4566 MSM and TGW
- 13 incident infections with LA CAB vs 39 with oral FTC/TDF
 - 4 with on-time CAB injections
 - 1 CAB infection later determined to be baseline infection
- HR for CAB vs FTC/TDF:
0.34 (95% CI: 0.18-0.62)



HPTN 084²

- N = 3224 cisgender women
- 4 incident infections with LA CAB vs 36 with oral FTC/TDF
 - 0 with on-time CAB injections
 - 1 CAB infection later determined to be baseline infection
- HR for CAB vs FTC/TDF:
0.12 (95% CI: 0.05-0.31)

1. Landovitz. NEJM. 2021;385:595.

2. Delany-Moretlwe. Lancet. 2022;399:1779.

The beginning of the LA PREP era

- International, randomized, double-blind phase IIb/III (083) and phase III (084) trials
- LA IM CAB met criteria for **superiority** vs daily oral FTC/TDF in both trials

HPTN 083¹



- N = 4566 MSM and TGW
- 13 incident infections with LA CAB vs 39 with oral FTC/TDF
 - **4 with on-time CAB injections**
 - 1 CAB infection later determined to be baseline infection
- HR for CAB vs FTC/TDF:
0.34 (95% CI: 0.18-0.62)

HPTN 084²



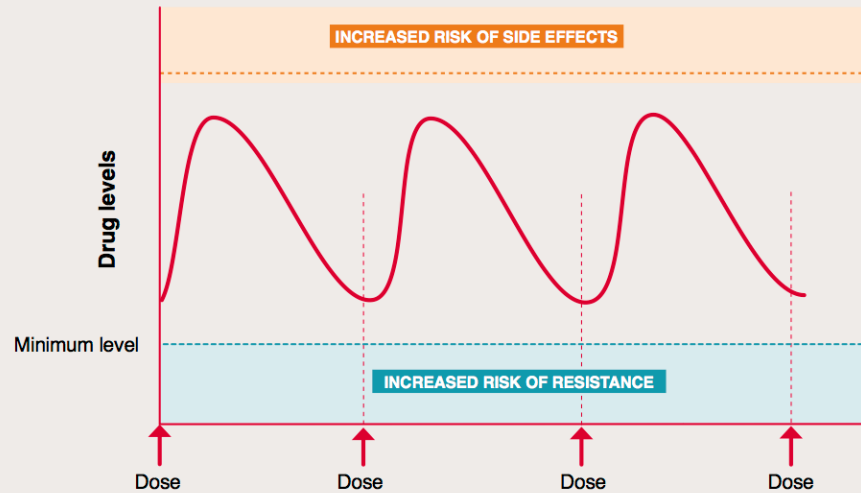
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1. Landovitz. NEJM. 2021;385:595.

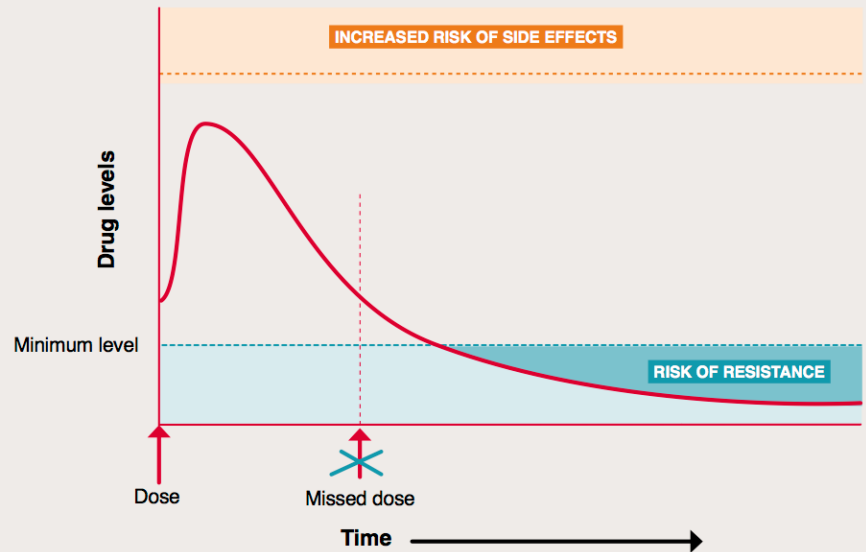
2. Delany-Moretlwe. Lancet. 2022;399:1779.

Adherence and drug levels

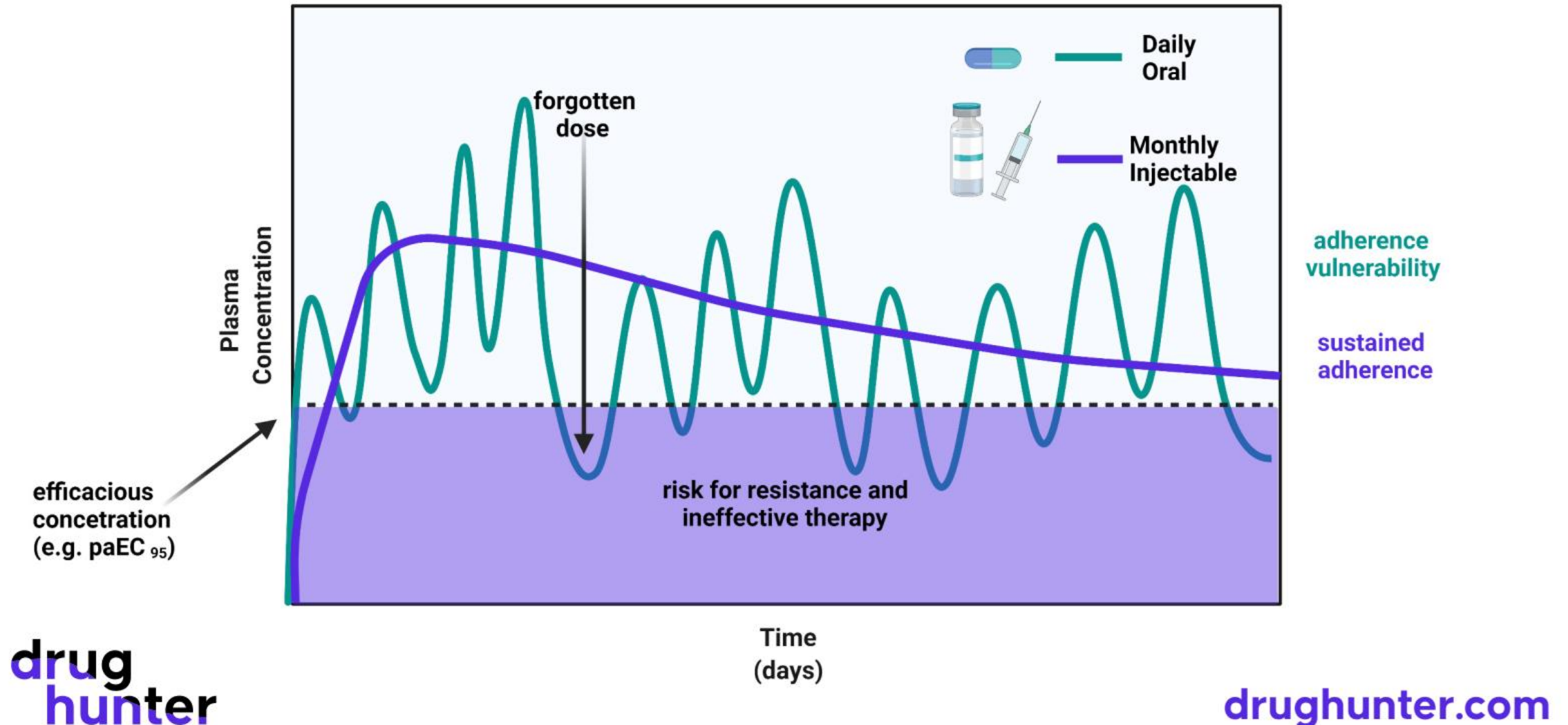
Taking meds on time



Missing a dose or taking it late

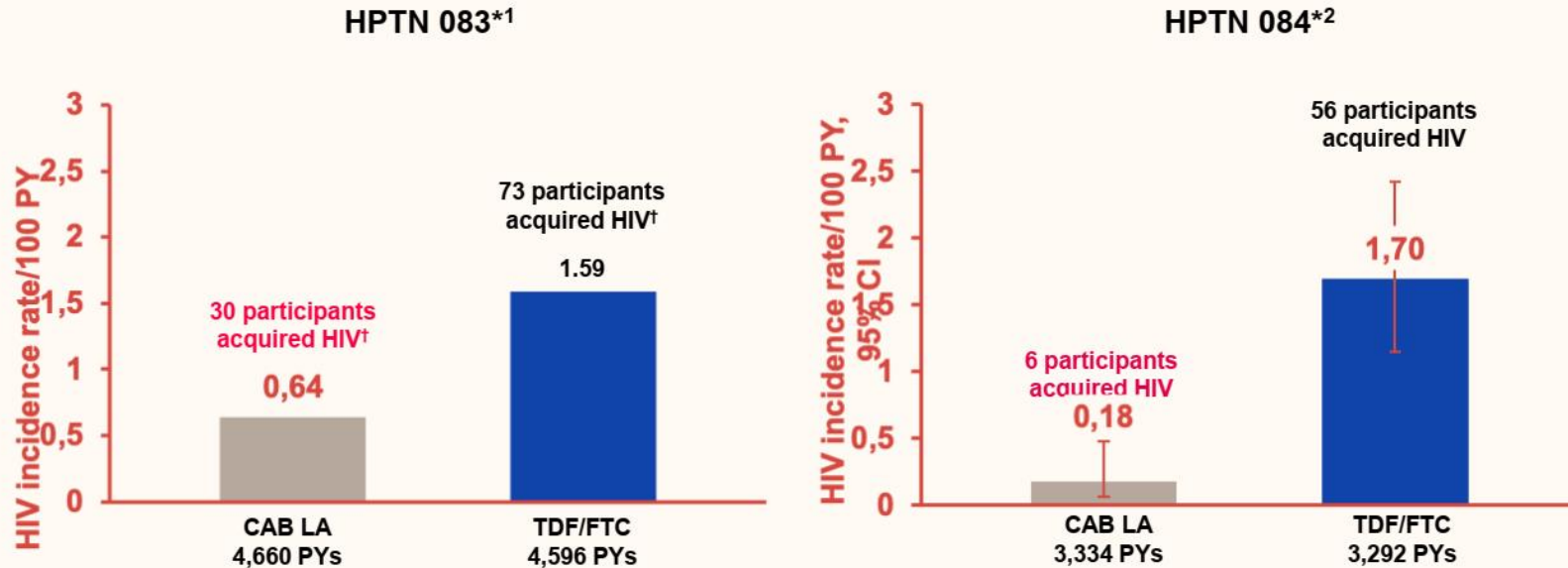


Daily Oral vs. Monthly Injectable Dosing for HIV



The beginning of the LA PREP era

HPTN 083 and 084: Incident HIV acquisitions after 4 years (blinded and unblinded phases)



CAB LA was superior to daily oral TDF/FTC at preventing new HIV acquisitions in HPTN 083 and HPTN 084

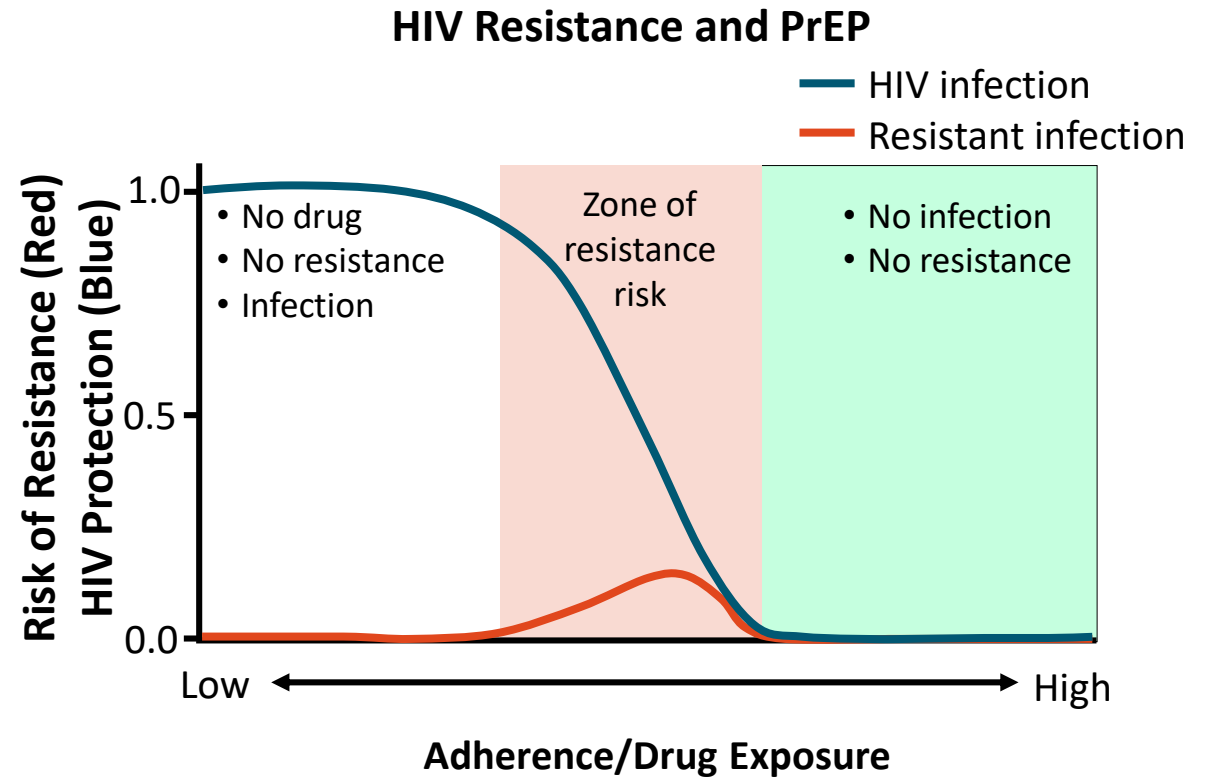
*Data analysed following post hoc, centralised testing of stored samples from the blinded phase and Year 1 unblinded phase

†Standard deviation not reported

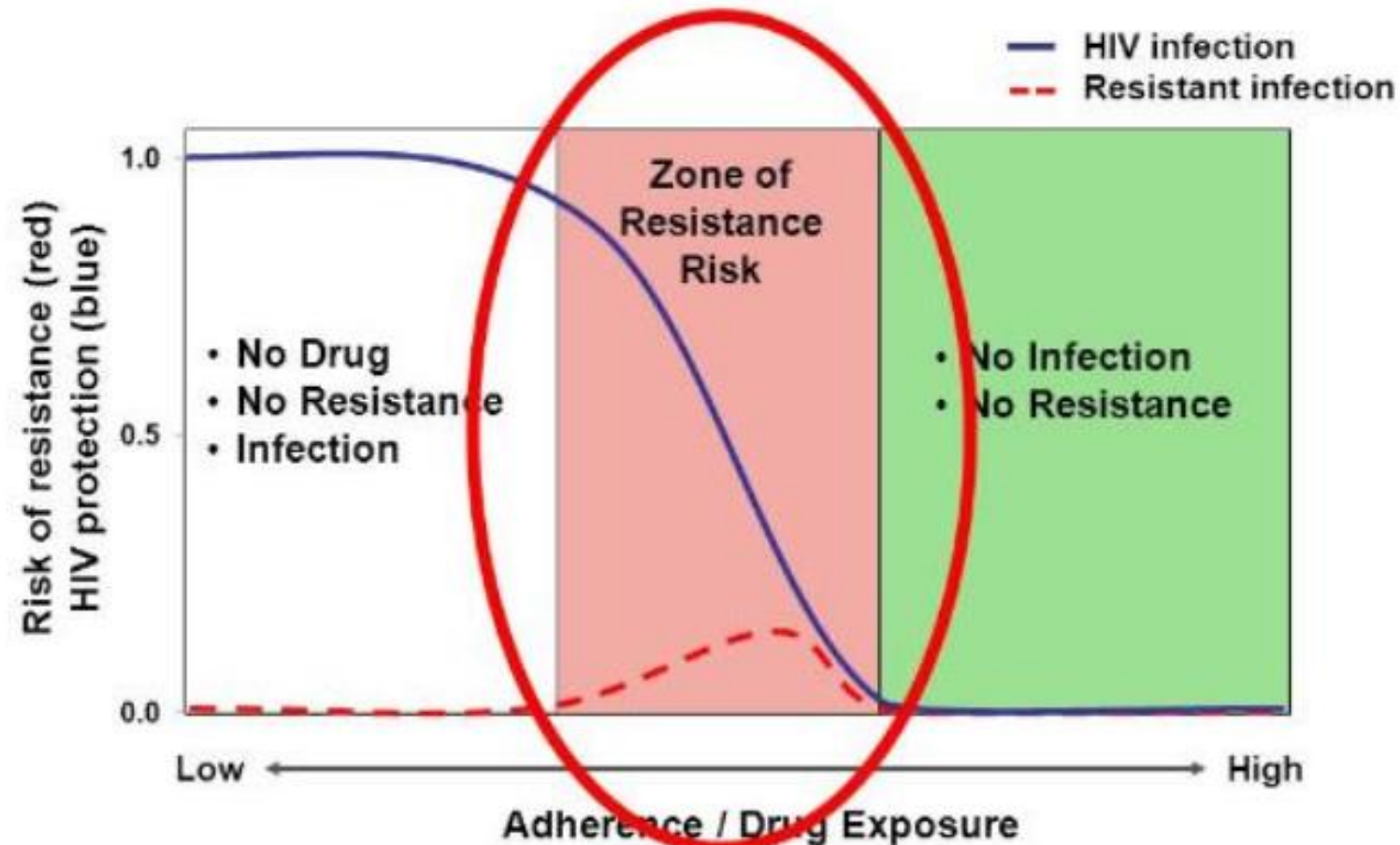
1. Marzinke MA, et al. HIV Glasgow 2022. Oral O21
2. Delany-Moretlwe S, et al. AIDS 2022. Oral OALBX0108

Stopping LA CAB for PrEP

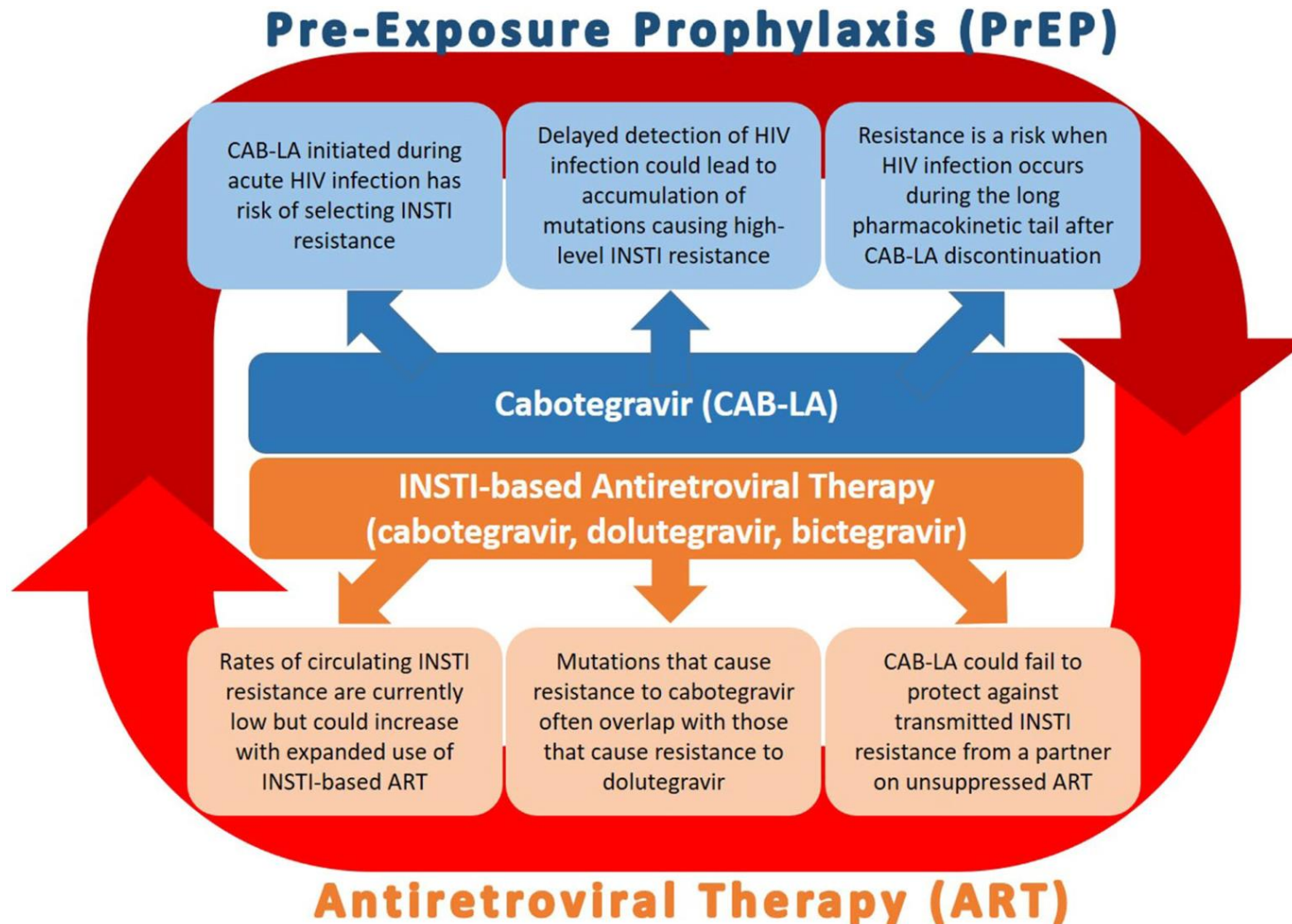
- Assess for ongoing risk of HIV exposure
- Counsel about long duration of declining CAB levels and risk of resistance if HIV acquisition occurs
- Give oral PrEP if it is indicated; FTC/TDF or FTC/TAF can begin within 8 wk after last CAB injection
- Continue follow-up quarterly for 12 mo to assess PrEP needs, and complete HIV testing



Adherence / drug exposure vs. risk of emergent resistance

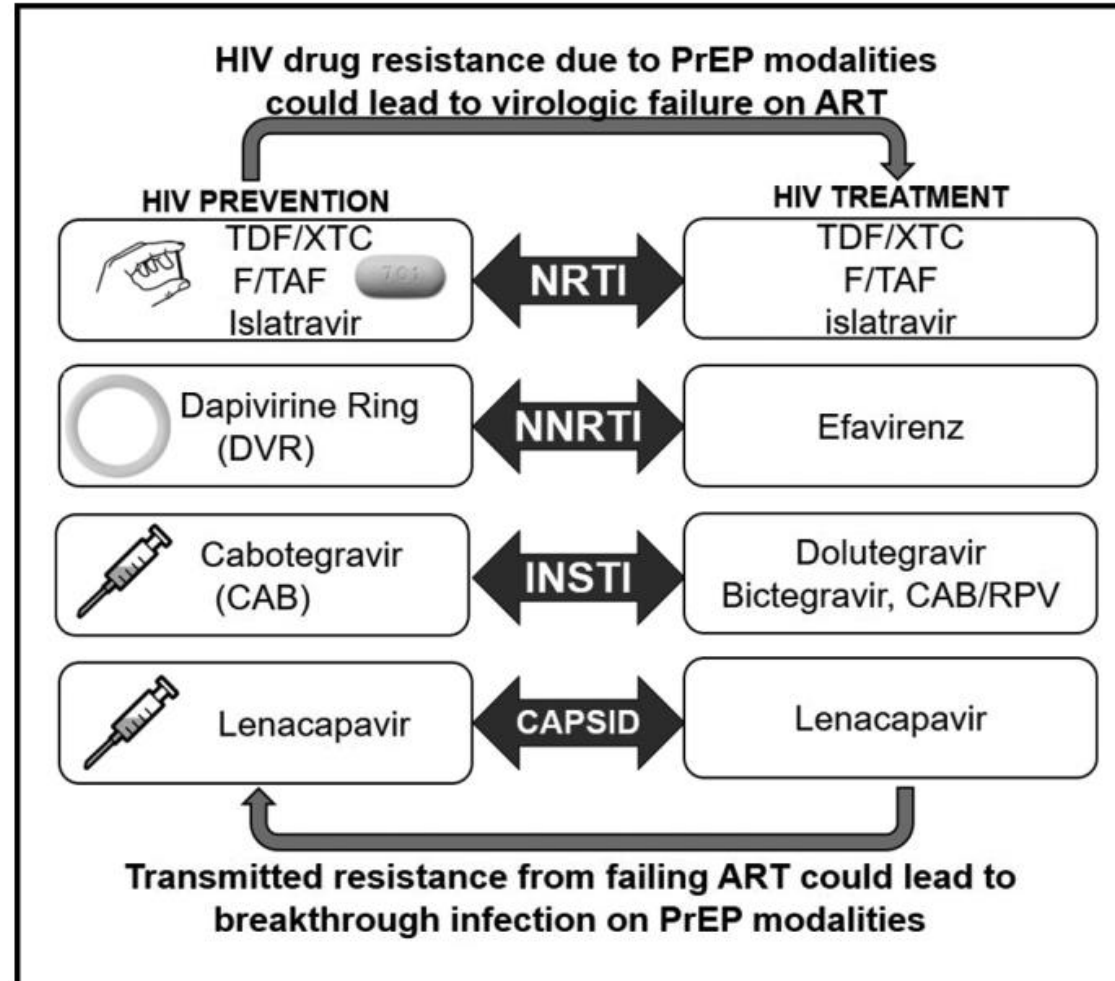


INSTI resistance from PrEP to ART and back

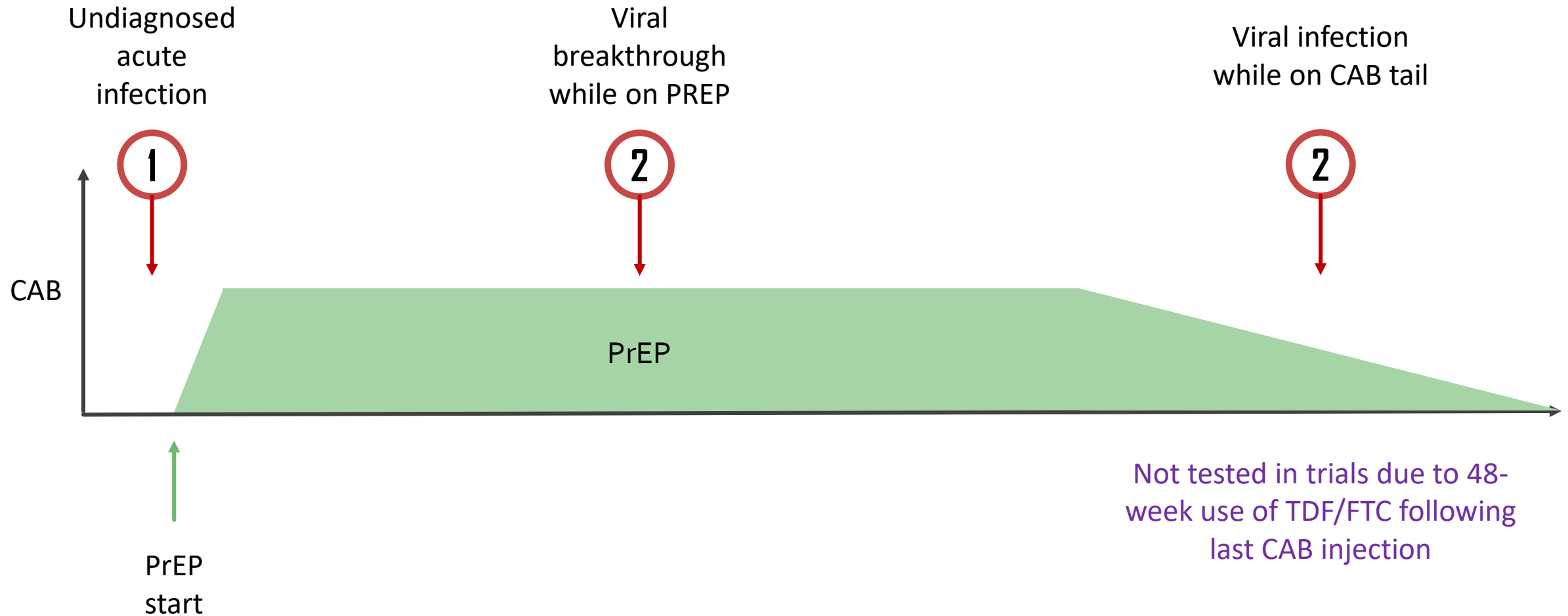


Using the same drugs and drug classes for both prevention and treatment increases the risk of resistance and failure of both approaches

INSTI resistance from PrEP to ART and back



LA CAB and potential for emergent INSTI resistance: *When do drug and virus meet?*



In vitro drug resistance selection by Cabotegravir

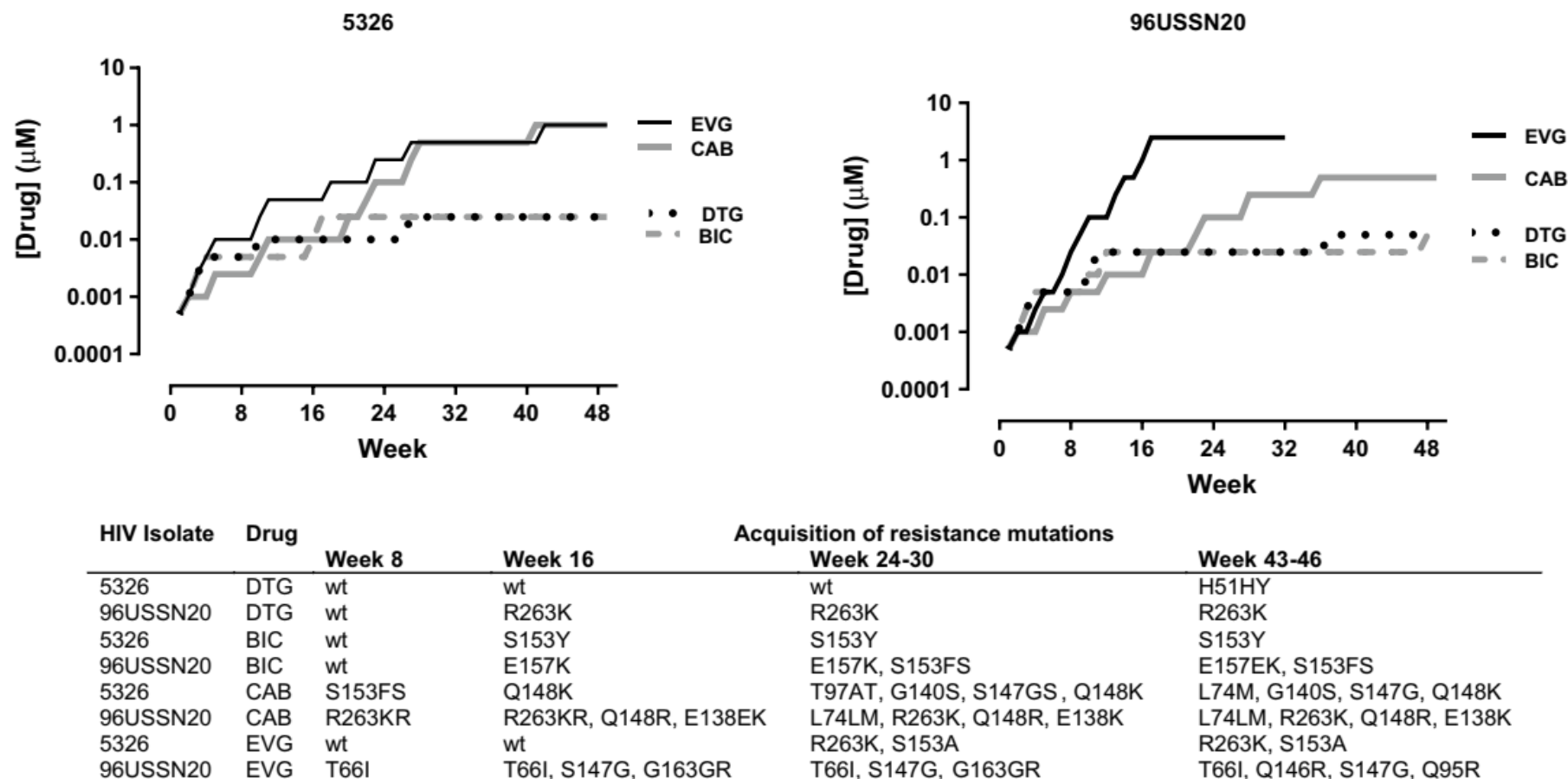
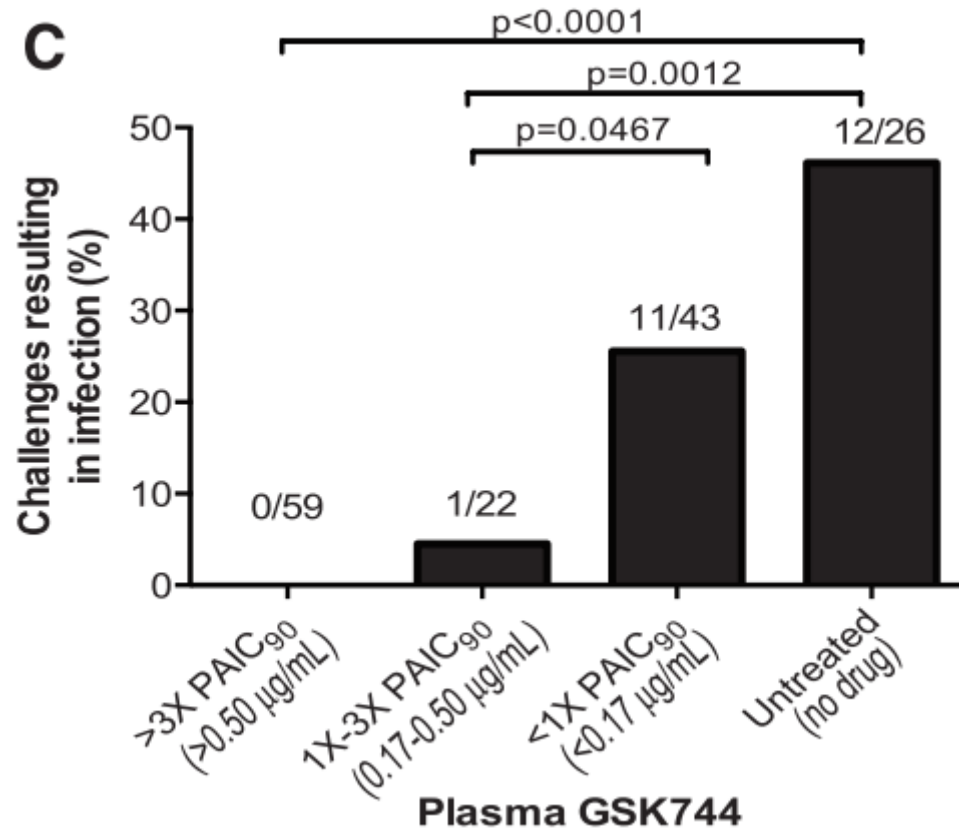


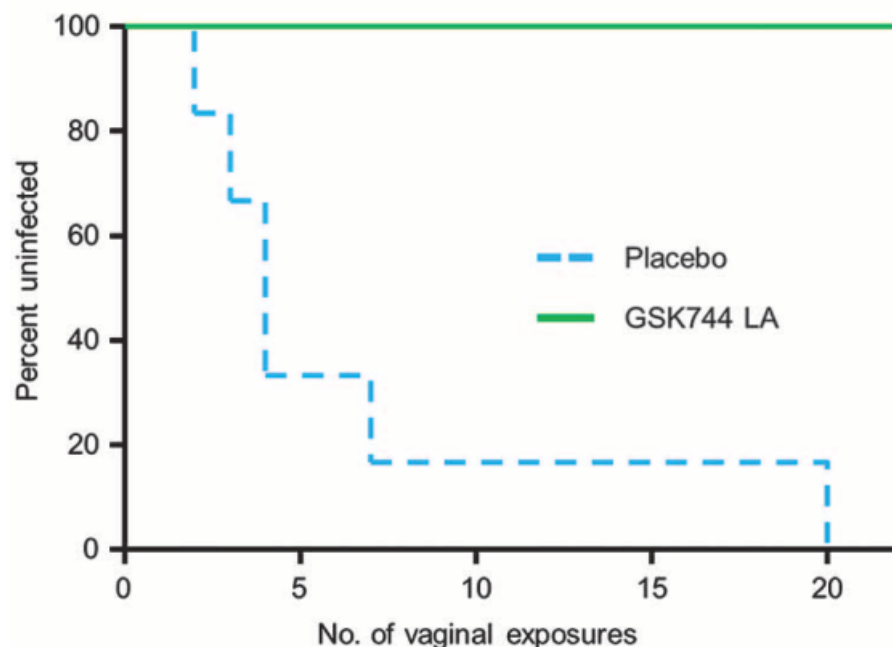
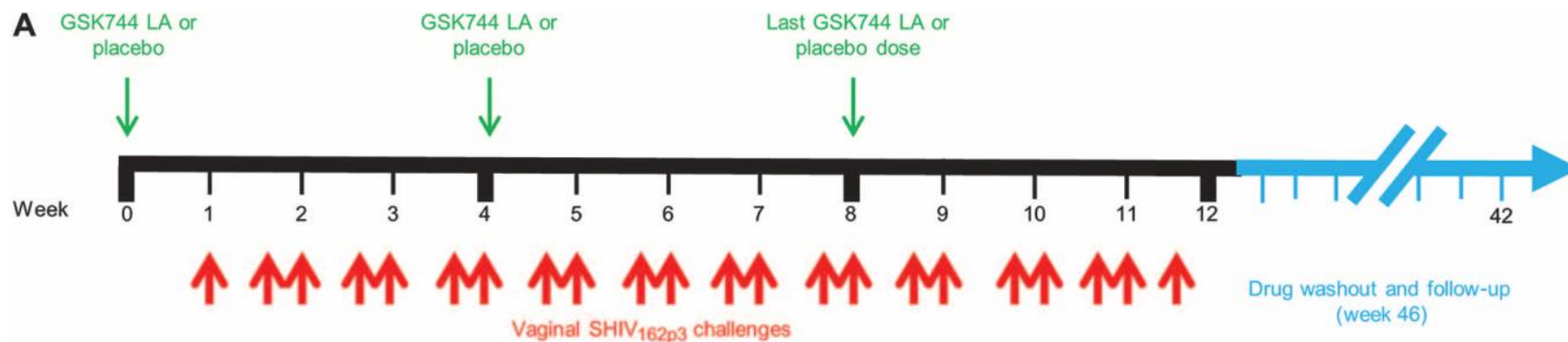
Fig. 1 Growth of 5326 and 96USSN20 clinical isolates in escalating concentrations of dolutegravir (DTG), bictegravir (BIC), cabotegravir (CAB) and elvitegravir (EVG). The rise in drug concentrations were related to the acquisition of resistance mutations at the designated weeks of selection

LA CAB protects macaques from intrarectal SHIV



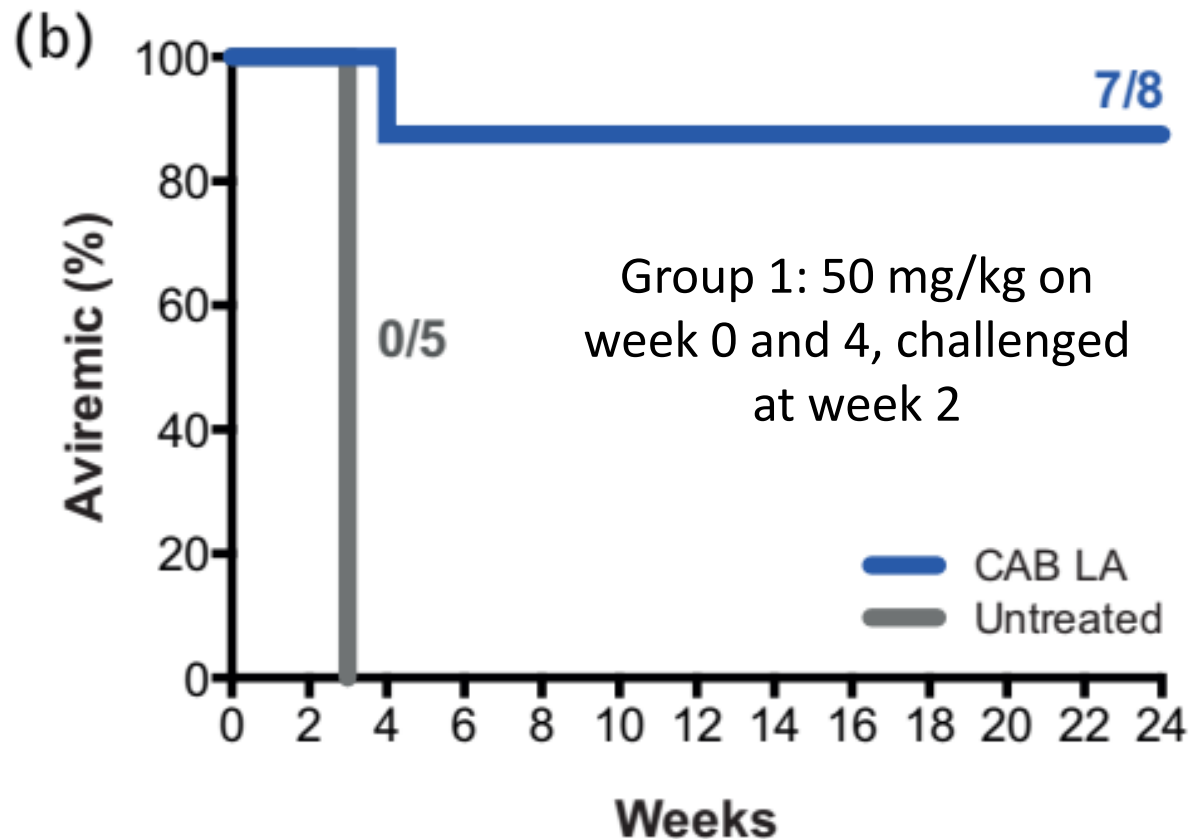
- LA CAB administered at two time points 4 weeks apart
- Macaques challenged weekly for 8 weeks starting 1 week after last CAB injection
- All animals protected at CAB plasma concentrations achievable with quarterly injections in humans
- Repeated challenging until infection occurred showed protection decreased over time and correlated with the plasma drug levels

LA CAB protects macaques from repeated intravaginal SHIV challenge



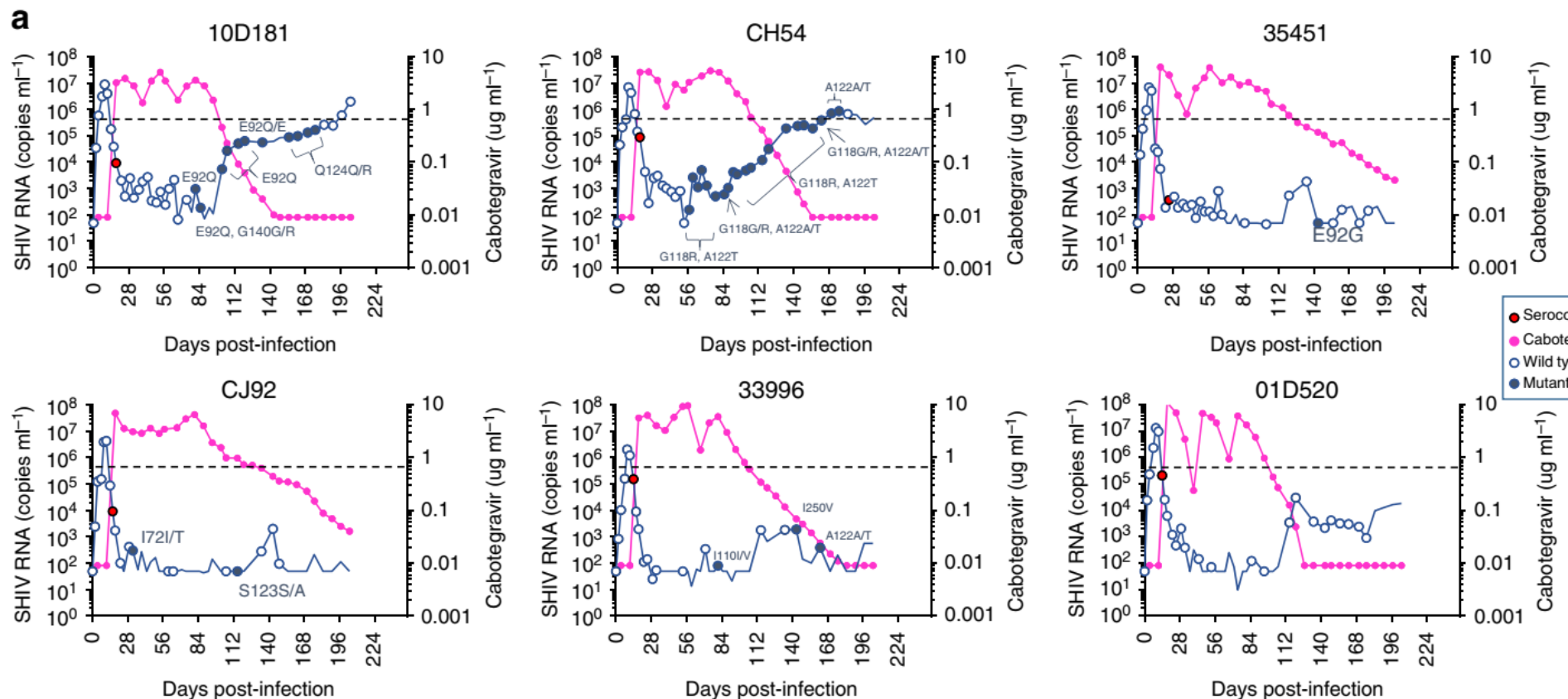
- 12 female pigtail macaques were exposed to 22 intravaginal inoculations of SHIV, twice a week for up to 11 weeks
- 6 animals received LA CAB injections 50 mg/kg at 0, 4, 8 weeks, and 6 received placebo
- LA CAB, at plasma concentrations achievable with quarterly injections in humans, **protected all six macaques from infection**

LA CAB injection protects macaques against intravenous challenge with SIVmac251



- Three groups of rhesus macaques (n=8 per group) injected intramuscularly with LA CAB
 - Group 1: 50 mg/kg on week 0 and 4
 - Group 2: 50 mg/kg on week 0
 - Group 3: 25 mg/kg on week 0 and 50 mg/kg on week 4
- Challenged intravenously with 17 animal ID50 SIVmac251 on week 2
- 21/24 LA CAB treated macaques remained aviremic (88% protection)

Drug resistance emergence in macaques administered LA CAB for PrEP during acute SHIV infection



- 6 macaques infected with SHIV received CAB-LA before seroconversion
- Integrase mutations G118R, E92G/Q, or G140R in plasma from 3/6 macaques as early as day 57
- G118R and E92Q in viruses from vaginal and rectal fluids

The long-acting integrase inhibitor GSK744 protects macaques from repeated intravaginal SHIV challenge

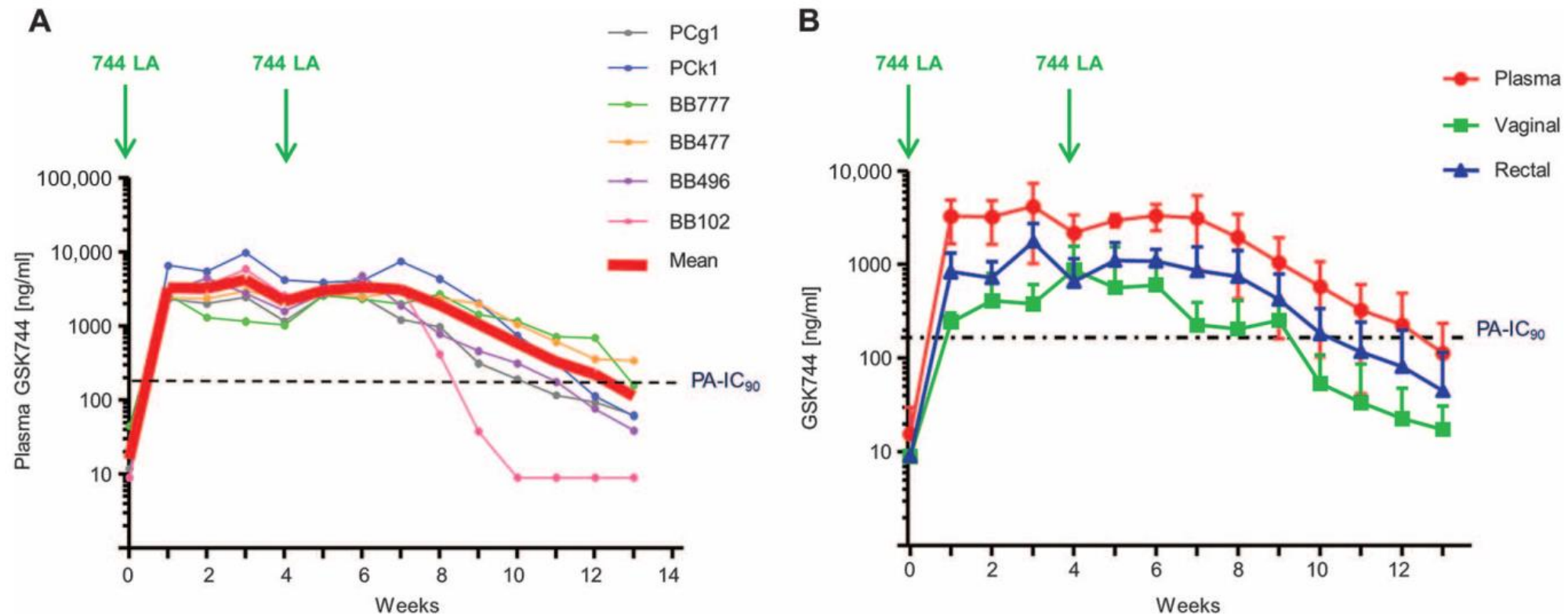
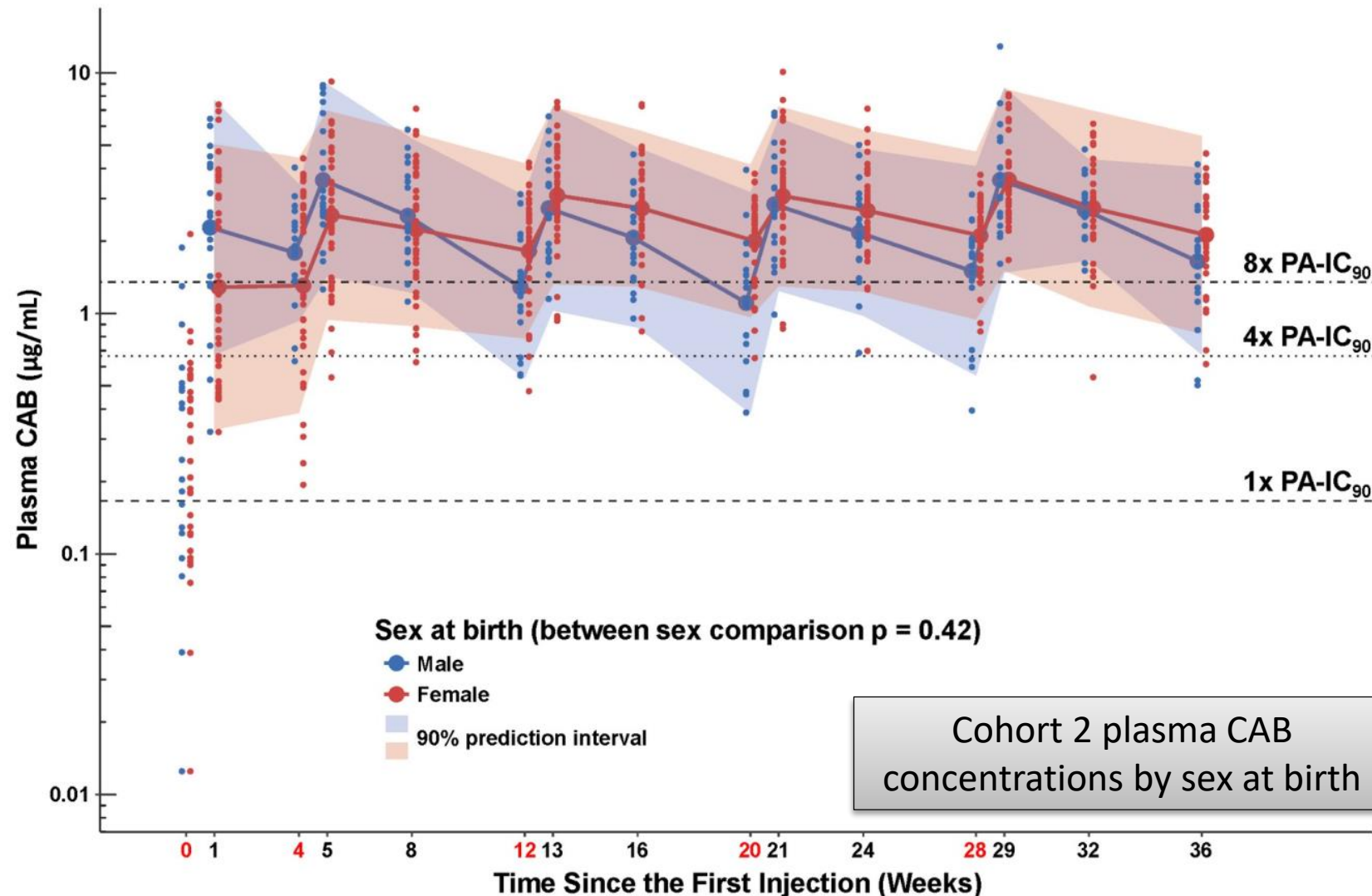


Fig. 1. Pharmacokinetic profile of GSK744 LA in pigtail macaques. Female macaques ($n = 6$; 11 years old and 6 kg on average) received two GSK744 LA doses (50 mg/kg) 4 weeks apart, followed by weekly measurements of drug concentrations in blood and in vaginal and rectal secretions. (A) GSK744 concentrations in each macaque. Red line denotes the mean plas-

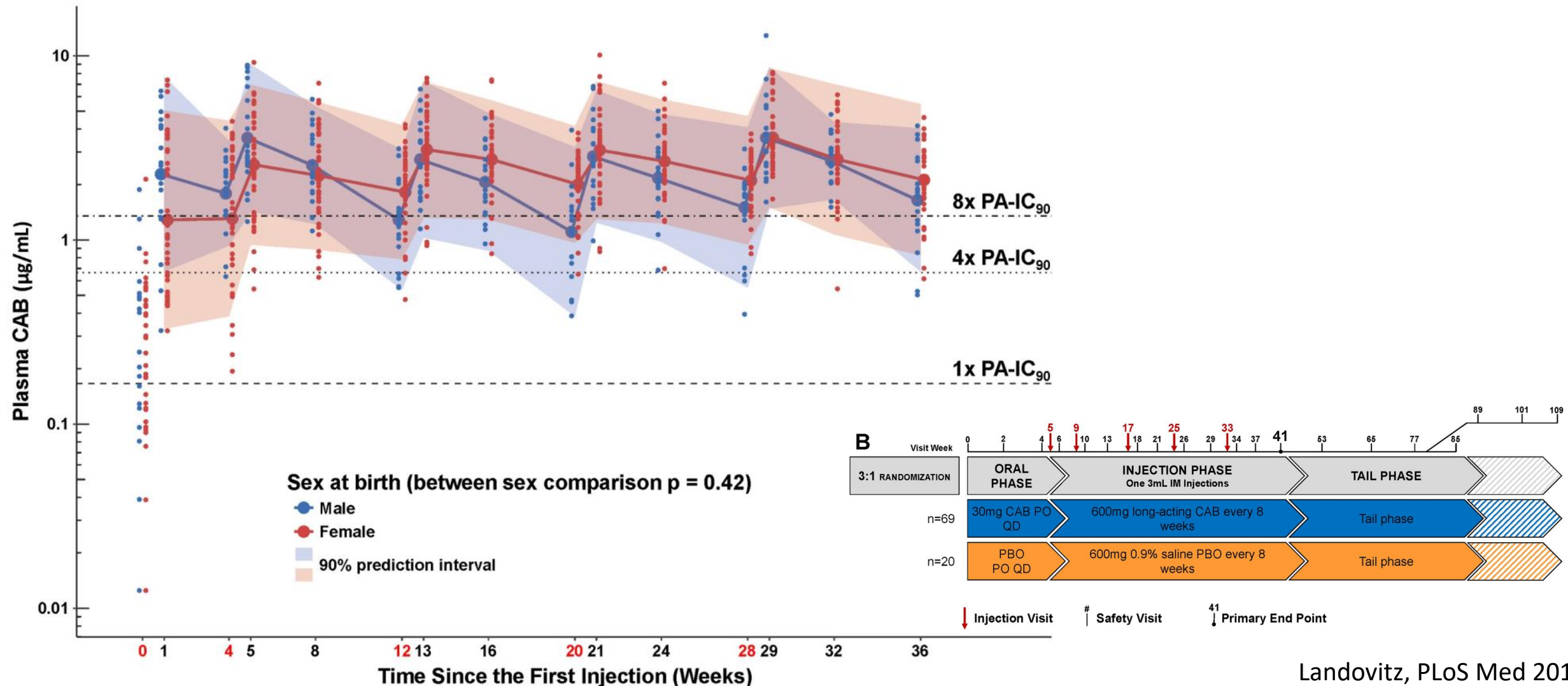
ma drug concentrations. (B). GSK744 concentrations in blood plasma and in rectal and vaginal secretions. Values denote means $\pm$ SEM. GSK744 concentrations were measured by high-performance liquid chromatography (HPLC) tandem mass spectrometry (MS/MS) as described (13). This assay has a limit of quantification of 10 ng/ml. Horizontal dotted lines denote the $PA-IC_{90}$.

Safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in low-risk HIV-uninfected individuals: HPTN 077, a phase 2a randomized controlled trial

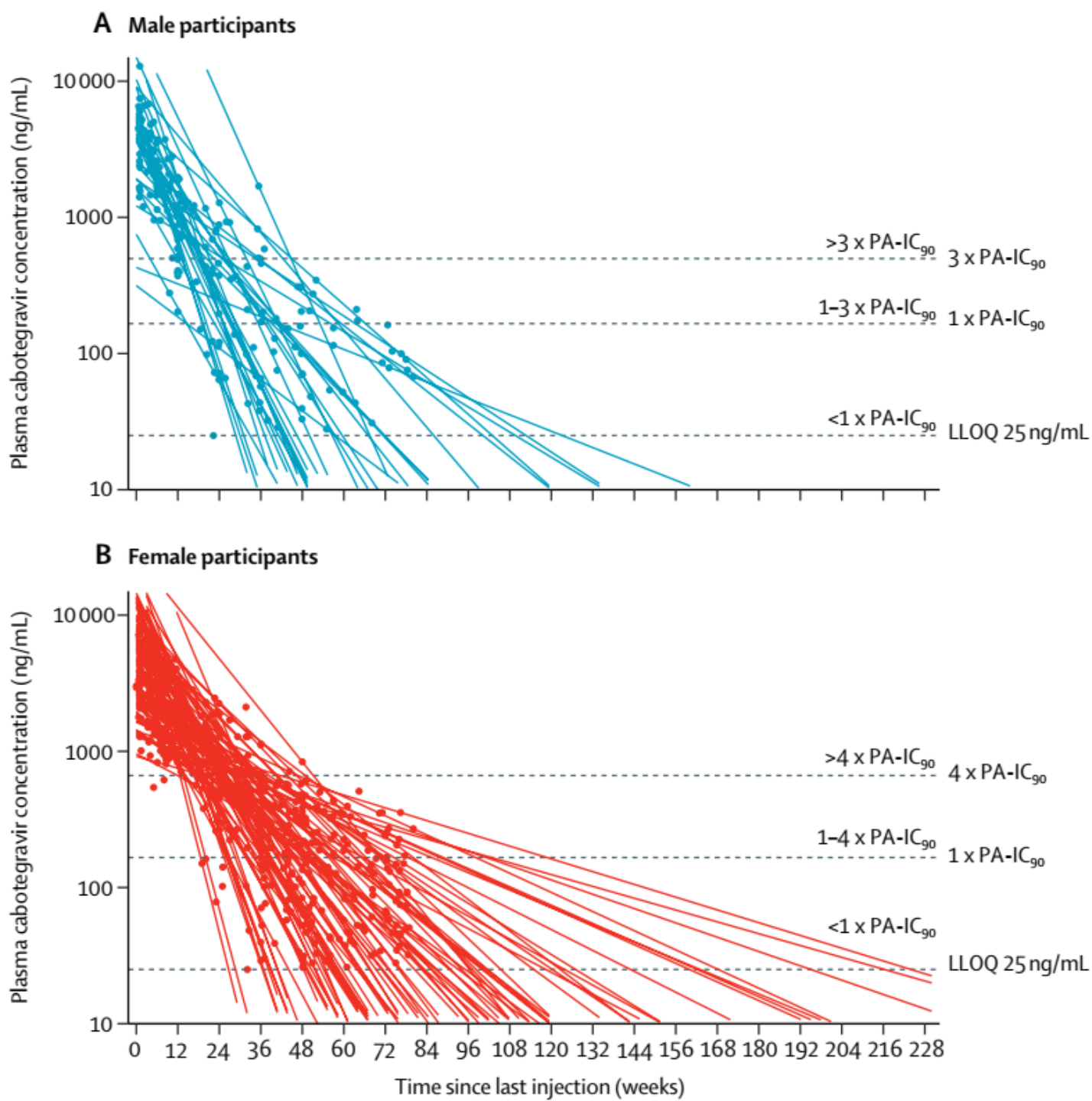


- HPTN 077: double-blind, placebo-controlled phase 2a trial
- Healthy individuals aged 18–65 years at low HIV risk randomized (3:1) to receive CAB or placebo (PBO)
- In the initial oral phase, participants received 1 daily oral tablet (CAB or PBO) for 4 weeks
- Cohort 1: 3 injections of CAB LA 800 mg or 0.9% saline as PBO IM every 12 weeks for 3 injection cycles
- Cohort 2: CAB LA 600 mg or PBO IM for 5 injection cycles; the first 2 injections in Cohort 2 were separated by 4 weeks, the rest by 8 weeks

Safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in low-risk HIV-uninfected individuals: HPTN 077, a phase 2a randomized controlled trial

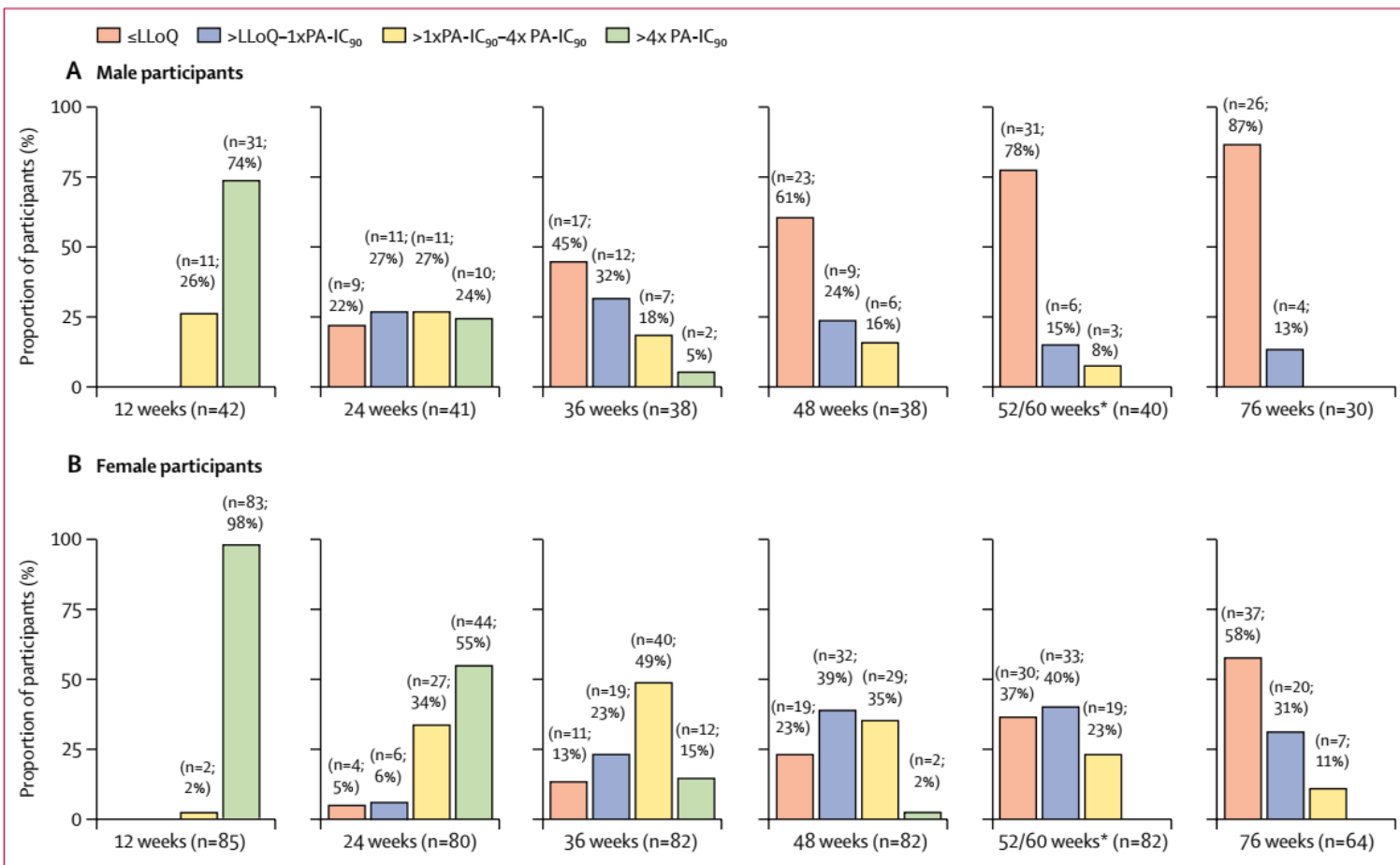


Tail-phase safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in HIV-uninfected adults: a secondary analysis of the HPTN 077 trial



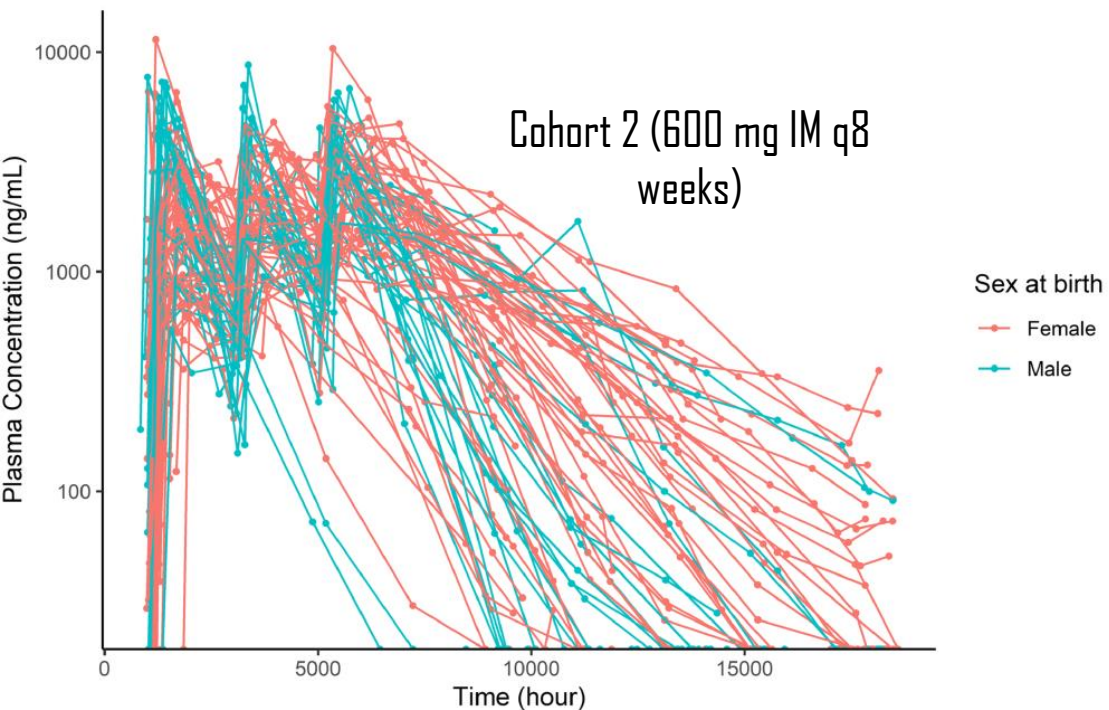
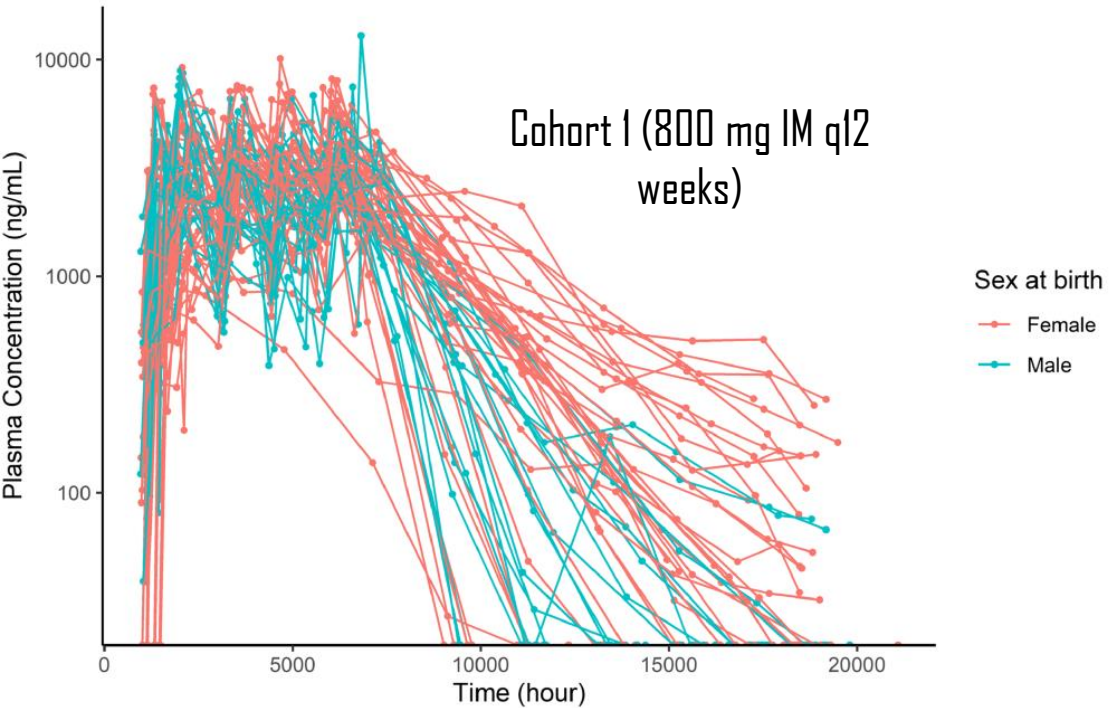
- HPTN 077, 8 sites in Brazil, Malawi, South Africa, and the USA
- 134 adults in CAB group
- CAB still detectable after final injection:
 - at 52–60 weeks, in 9 (23%) males vs. 52 (63%) females
 - at week 76, 4 (13%) males vs. 27 (42%) females
- Median time to undetectability of CAB was 43.7 weeks for males vs. 67.3 weeks for females ($p=0.0003$)
- Apparent CAB half life was longer for females than males (FC 1.33; $p=0.014$), and longer for participants with a high BMI than those with a low BMI (1.31; $p=0.015$)

Tail-phase safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in HIV-uninfected adults: a secondary analysis of the HPTN 077 trial



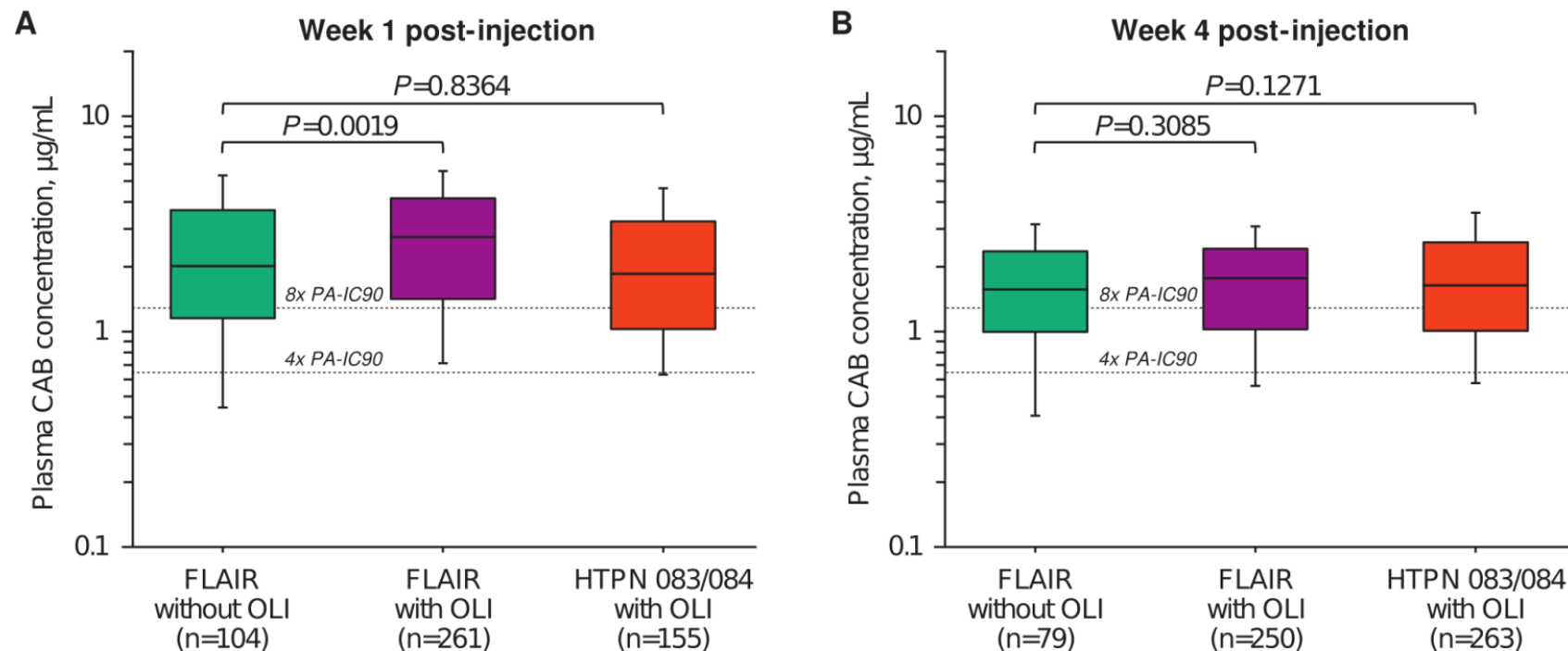
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A population pharmacokinetic model based on HPTN 077 of long-acting injectable cabotegravir for HIV PrEP



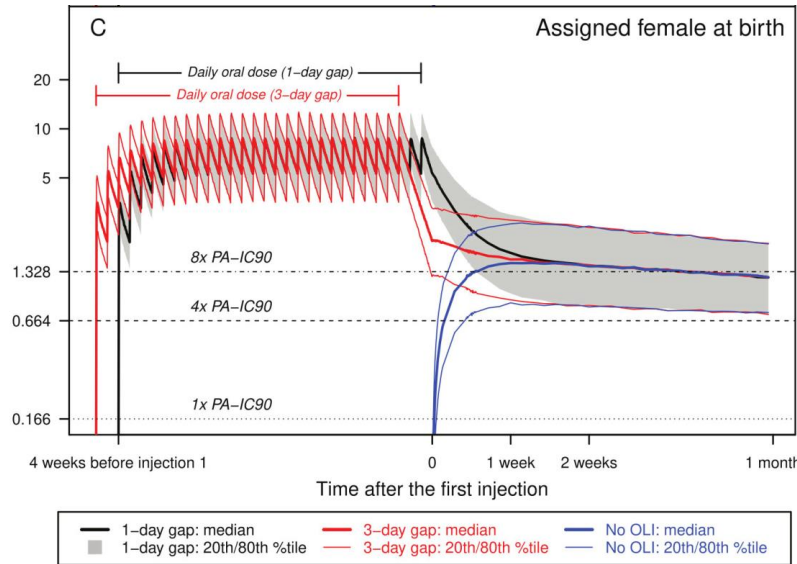
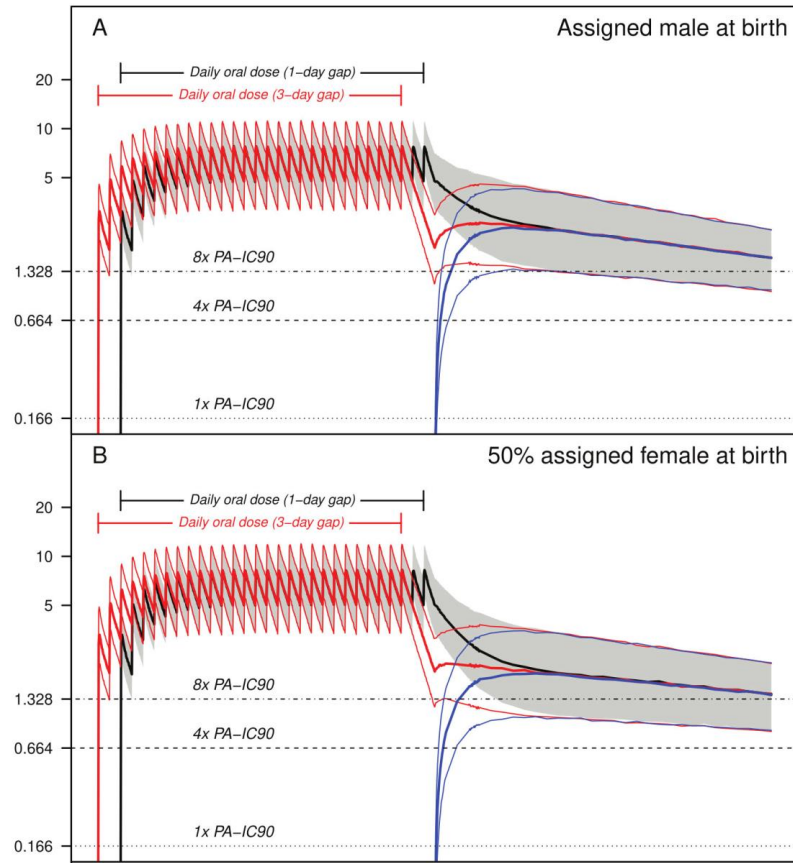
- PK measurements from 133 participants in the HIV Prevention Trials Network (HPTN) 077 trial
- **Between-occasion variability (BOV)** identified as a significant covariate affecting the absorption rate (contribution of BOV to PK variability on the absorption rate k_a of 38.5%)
- **Sex and body weight** were identified as significant covariates influencing the absorption rate and apparent clearance of CAB-LA after intramuscular injection at various doses and frequencies
- Male participants had 67% higher k_a than female participants.

Long-acting cabotegravir pharmacokinetics with and without oral lead-in for HIV PrEP



- HIV-positive participants initiating injections with (n = 278) or without (n = 110) OLI in phase III treatment study FLAIR
- HIV-negative participants using OLI (n = 263) in pivotal pre-exposure prophylaxis studies HPTN 083 and HPTN 084

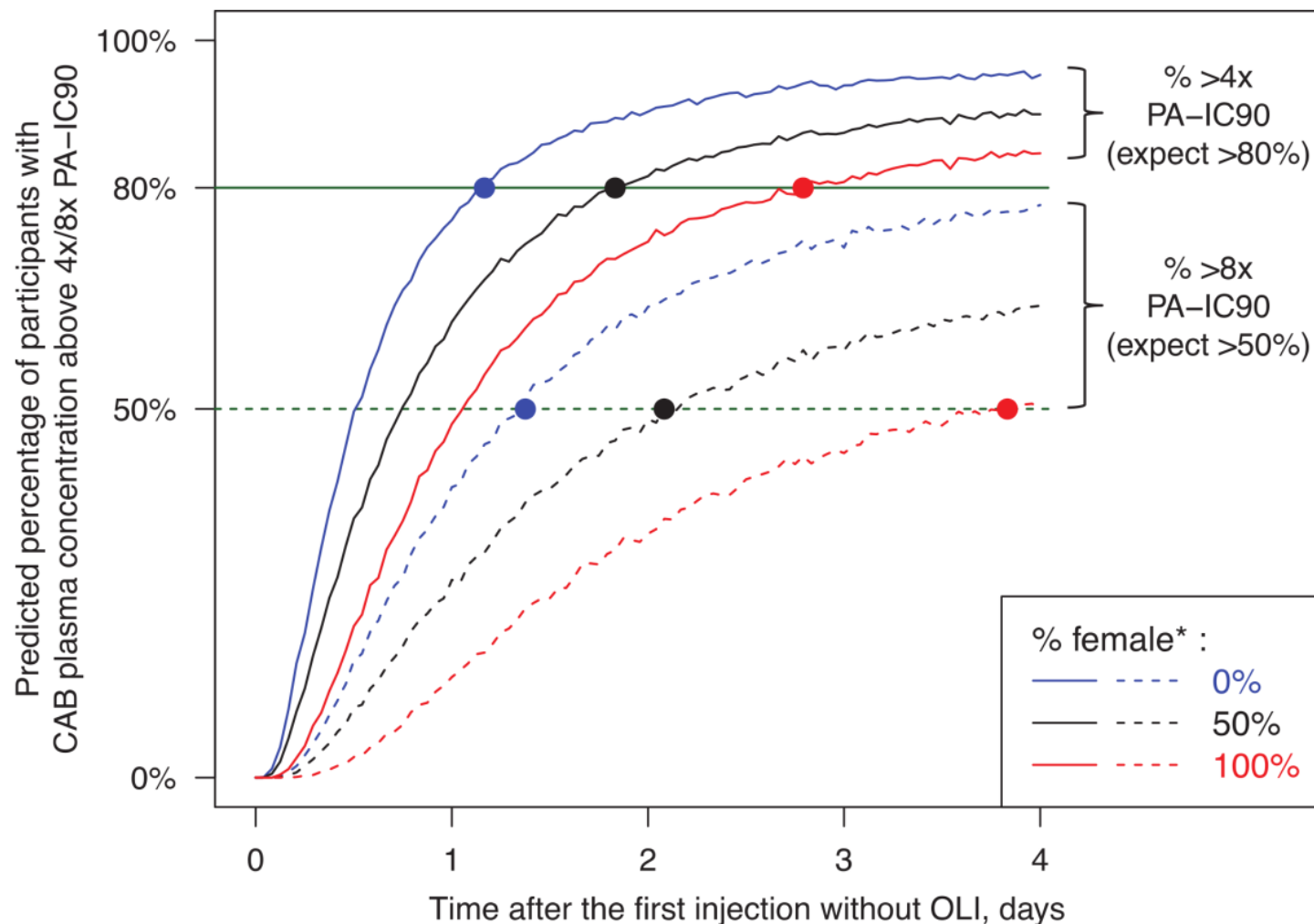
Long-acting cabotegravir pharmacokinetics with and without oral lead-in for HIV PrEP



Simulated cabotegravir concentration-time profiles when the first injection is given with a 1-day or 3-day gap after the final OLI dose or without OLI in a population (A) assigned male at birth, (B) 50% assigned female at birth, and (C) assigned female at birth. The first injection is administered at time 0.

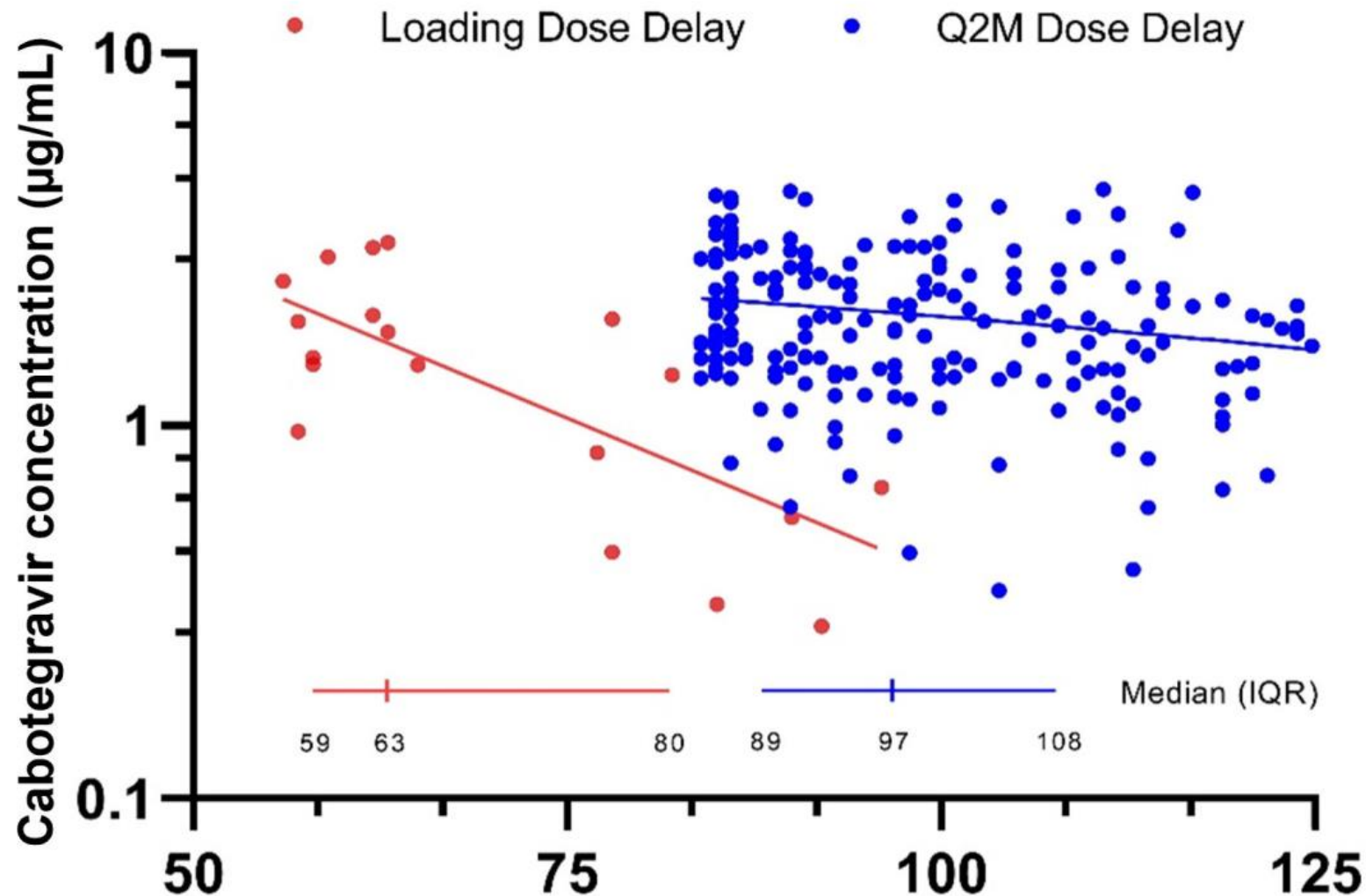
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Long-acting cabotegravir pharmacokinetics with and without oral lead-in for HIV PrEP



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Pharmacologic evaluation of delayed LA CAB administration among cisgender women in HPTN 084

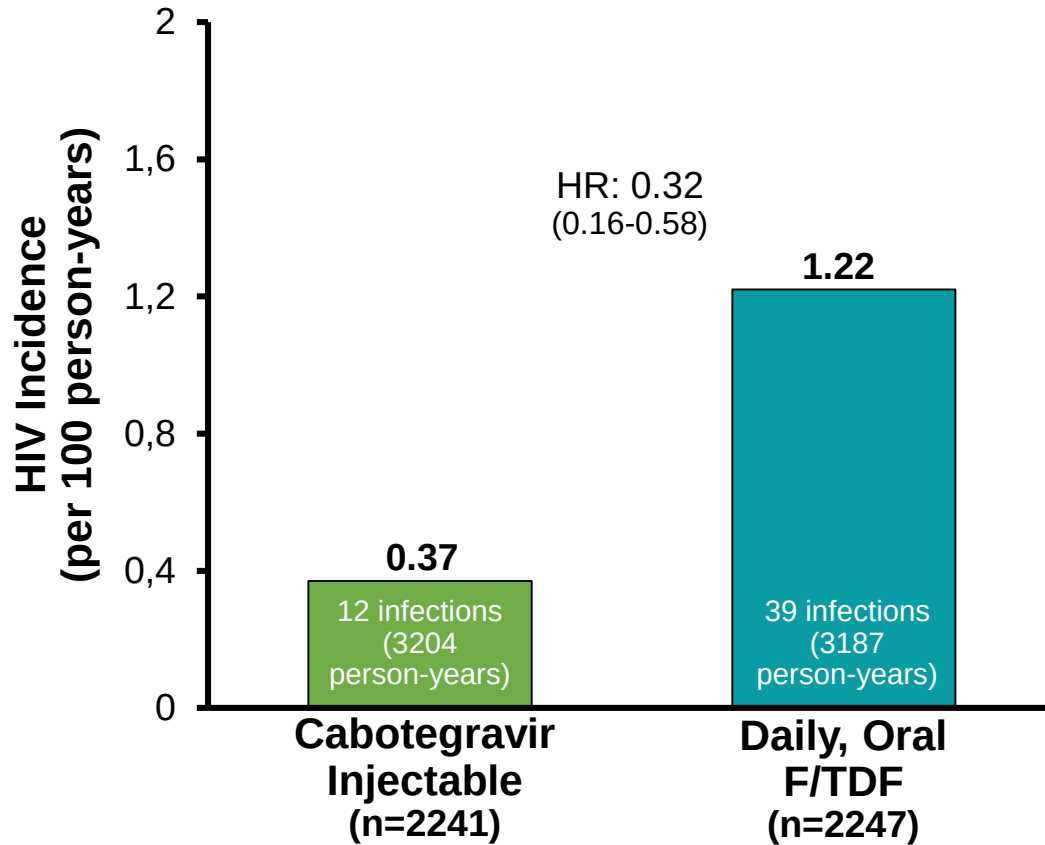


- 194 participants randomized to CAB-LA experienced at least one injection delay
- Plasma CAB concentrations were maintained above 4x PA-IC90 for all loading dose and 98% of Q2M delays when injections were administered up to 6 weeks late
- In population PK models, Q3M injections in females were predicted to yield higher steady-state exposures than in males on the approved Q2M regimen

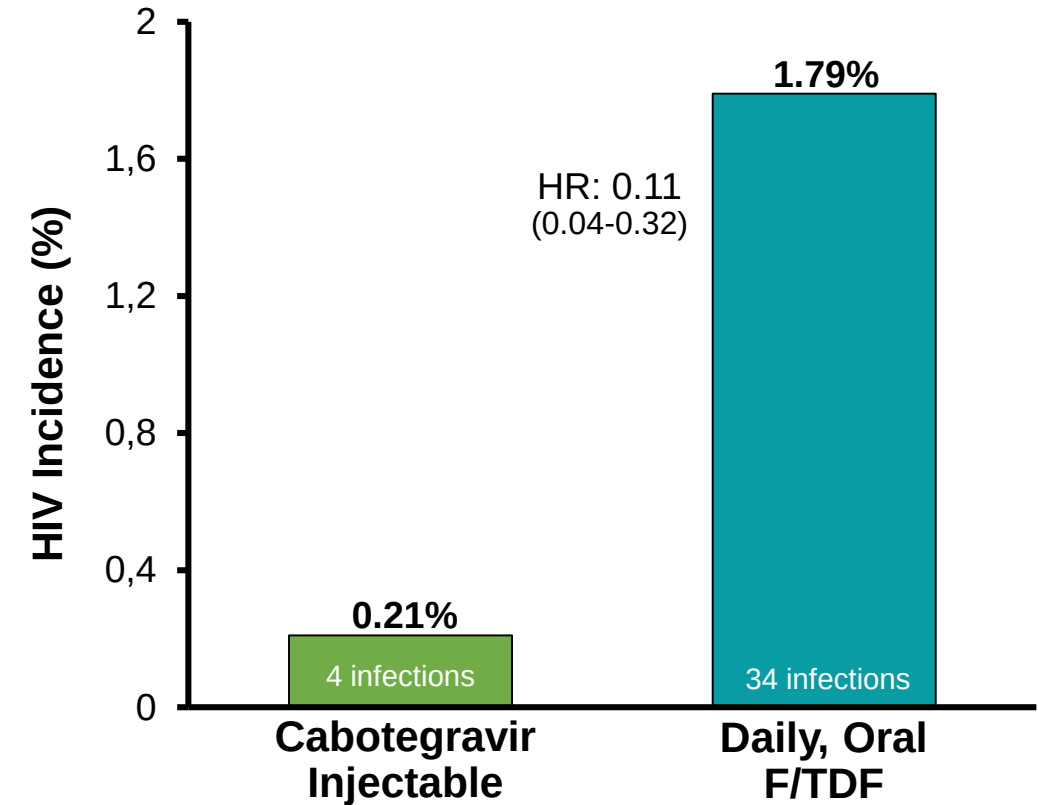
HPTN 083 and 084: Incident HIV Infections With Long-Acting Injectable Cabotegravir for PrEP

Updated
Citation

MSM/Transgender Women
(median follow-up: 1.4 years)

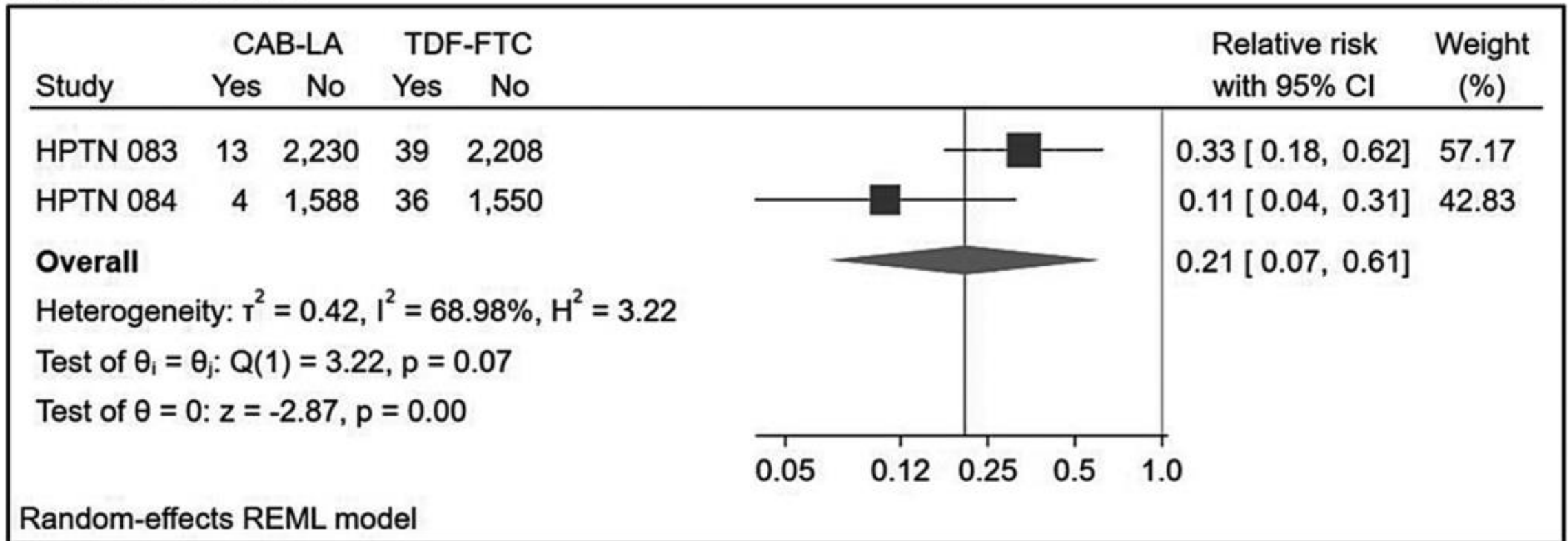


Cisgender Women



Safety and efficacy of long-acting injectable cabotegravir as preexposure prophylaxis to prevent HIV acquisition

Panel A: HIV Infection

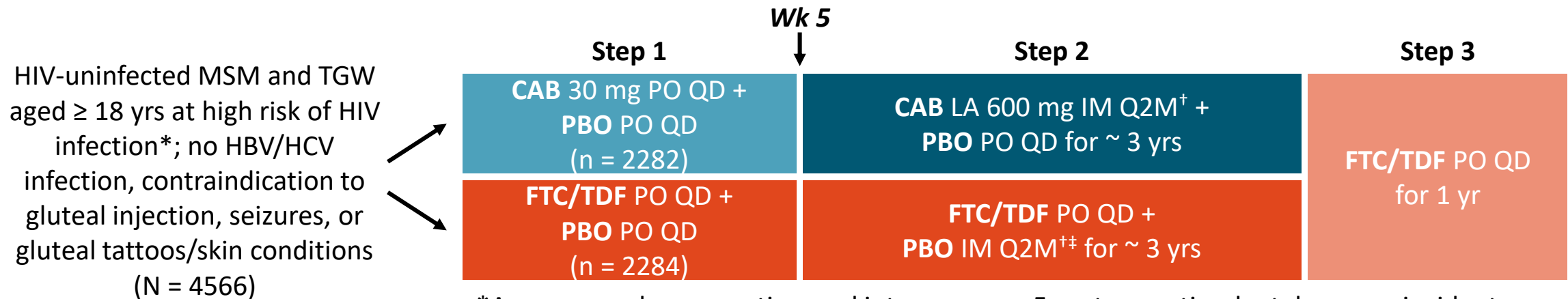


CAB DR summary

Source	Cases with DR
2024_CCO_ART Initiation After HIV Seroconversion on PrEP__6949_ART Class_CF Module #1	10/32 cases HPTN 083 0/4 HPTN 084
2023__CCO_2023CMOH_Downloadable_4	10/34 cases HPTN 083
Marzinke_AAC_2023_HPTN_083_extended_analysis.pdf	/34 cases HPTN 083 (blinded plus one year unblinded)

HPTN 083: Study Design

- International, randomized, double-blind phase IIb/III study
 - At interim analysis on May 14, 2020, with 25% of endpoints accrued, DSMB recommended termination of blinded study due to crossing of prespecified O'Brien-Fleming stopping bound
 - Planned N = 5000, with $\geq 50\%$ aged < 30 yrs; $\geq 10\%$ TGW; $\geq 50\%$ black participants in US



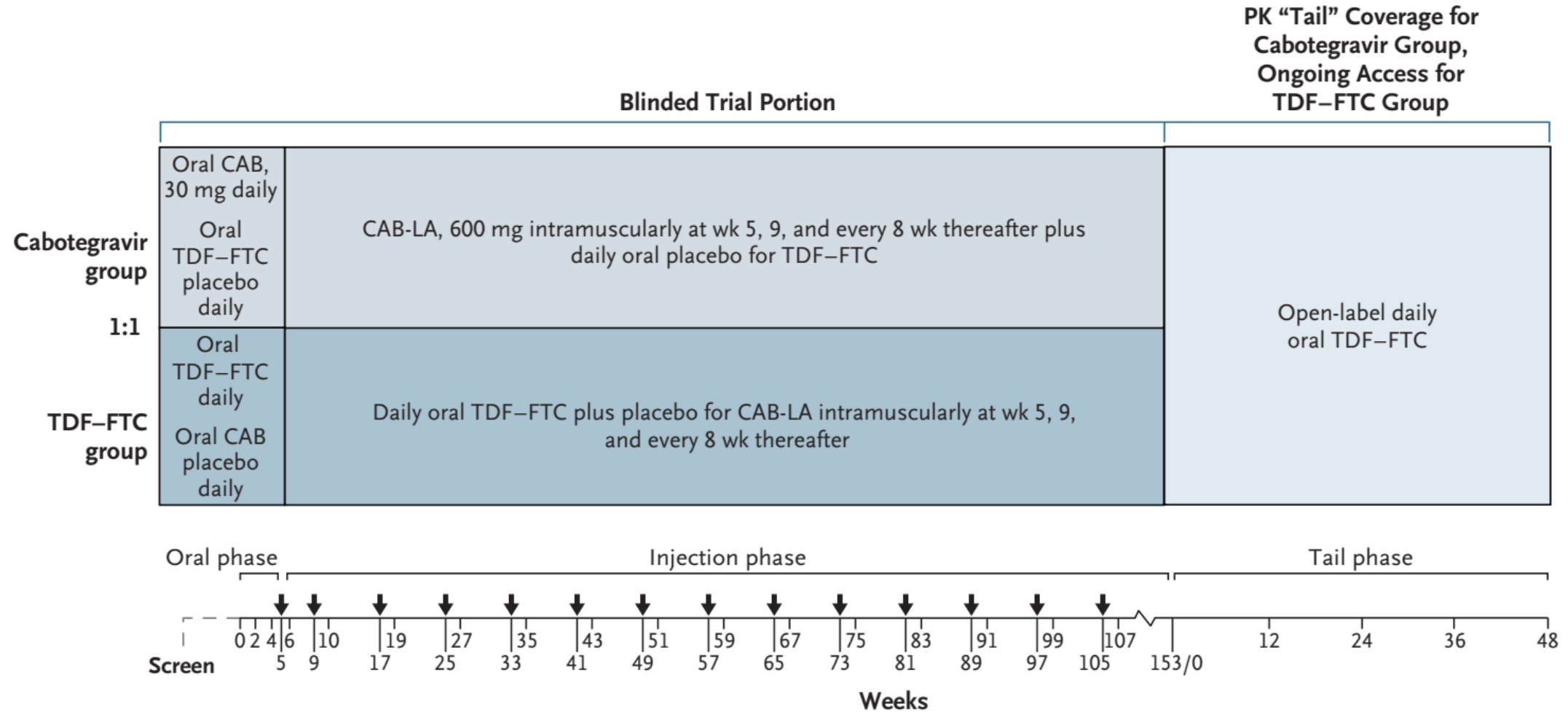
*Any noncondom receptive anal intercourse, > 5 partners, stimulant drug use, incident rectal or urethral STI or incident syphilis in past 6 mos; or SexPro Score ≤ 16 (US only).

⁺First 2 doses given in Wks 5 and 9 then every 2 mos thereafter.

⁺⁺PBO for CAB injection was a 20% intralipid solution.

- Primary endpoints: incident HIV infections, grade ≥ 2 clinical and laboratory events

HPTN 083: Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women



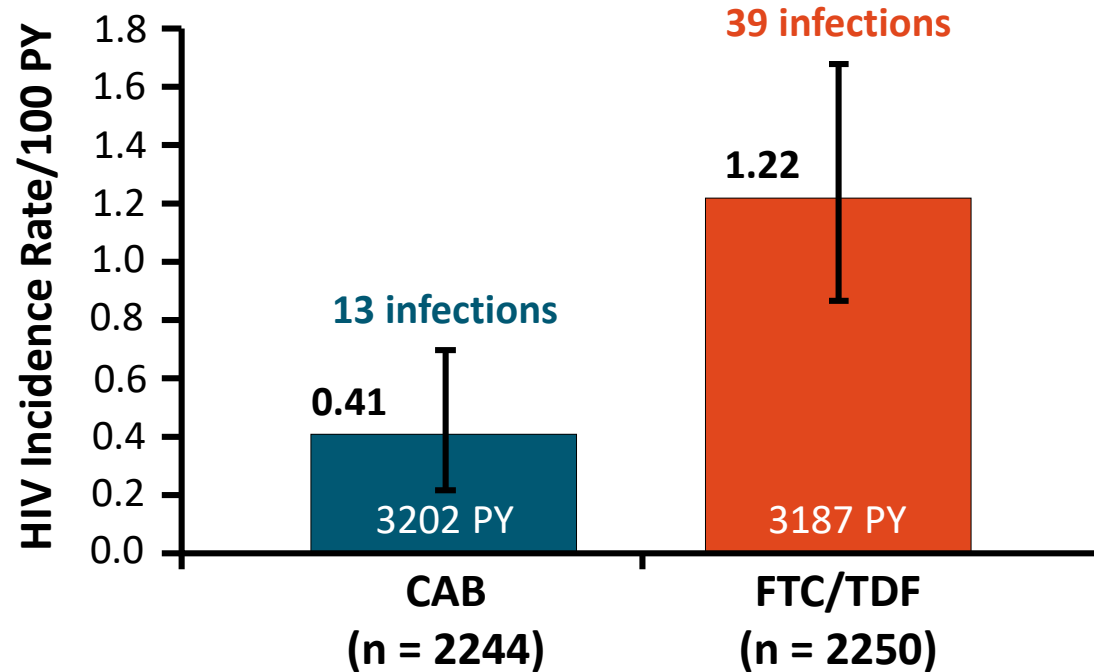
HPTN 083: Baseline Characteristics

Race or Ethnicity, n (%)	CAB (n = 2282)	FTC/TDF (n = 2284)	Total (N = 4566)
United States	849 (37.2)	849 (37.2)	
▪ Black/African American	411 (48.9)	433 (51.0)	844 (49.7)
▪ White/Asian/Native/ other	438 (51.1)	416 (49.0)	854 (50.4)
▪ Latinx	149 (17.6)	154 (18.1)	303 (17.8)
Latin America	980 (42.9)	984 (43.2)	1964 (43.0)
▪ Black/Afro-Caribbean	199 (20.3)	196 (19.9)	395 (20.1)
▪ Native	433 (44.2)	425 (43.2)	858 (43.7)
▪ White/Asian/Other	348 (35.5)	363 (36.8)	711 (59.6)
▪ Latinx	893 (91.1)	912 (92.7)	1805 (91.9)
Asia	375 (16.5)	377 (16.5)	752 (16.5)
▪ Asian	374 (99.7)	375 (99.5)	749 (99.6)
▪ Other	1 (0.3)	2 (0.5)	3 (0.4)
Africa	78 (3.4)	74 (3.2)	152 (3.3)
▪ Black	62 (79.5)	57 (77.0)	119 (78.3)
▪ Other	2 (2.6)	3 (4.1)	5 (3.3)

Characteristic	CAB (n = 2282)	FTC/TDF (n = 2284)	Total (N = 4566)
Gender identity, n (%)			
▪ MSM	2014 (88.3)	1981 (86.7)	3995 (87.5)
▪ TGW	265 (11.6)	302 (13.2)	567 (12.4)
Median age, yrs (IQR)	26 (22-32)	26 (22-32)	26 (22-32)
Age, n (%)			
▪ 18-29 yrs	1571 (68.8)	1508 (66.0)	3079 (67.4)
▪ 30-39 yrs	499 (21.9)	550 (24.1)	1049 (23)
▪ 40-49 yrs	145 (6.4)	170 (7.4)	315 (6.9)
▪ 50-59 yrs	60 (2.6)	50 (2.2)	110 (2.4)
▪ ≥ 60 yrs	7 (0.3)	6 (0.3)	13 (0.3)
Postsecondary education, n (%)	1762 (77.2)	1715 (75.1)	3477 (76.1)
Single, n (%)	1887 (82.7)	1863 (81.6)	3750 (82.1)

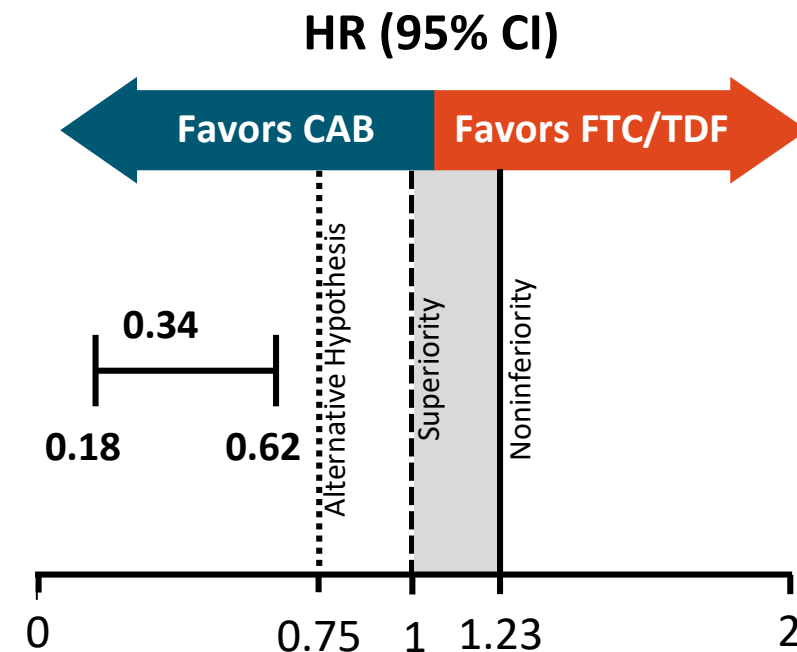
HPTN 083: HIV Incidence

- Pooled incidence: 0.81 per 100 PY (95% CI: 0.61-1.07)
 - 52 HIV infections in 6389 PYFU

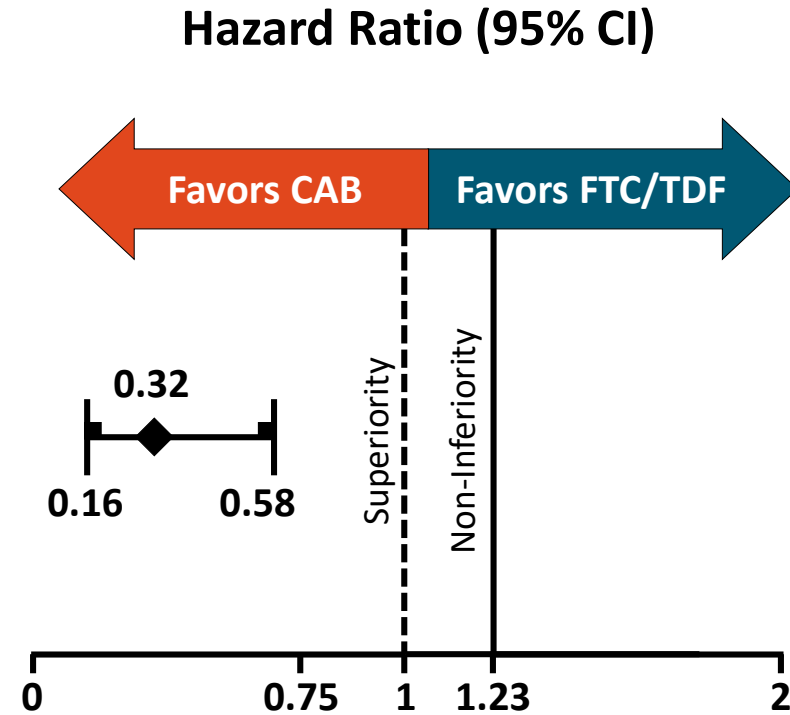
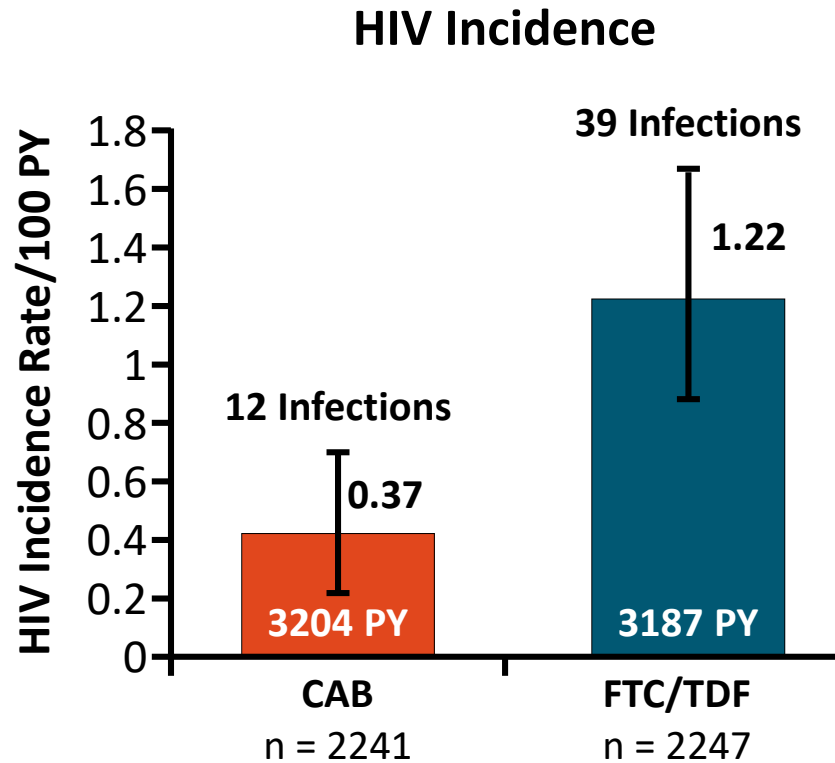


Median follow-up per participant: 1.4 yrs (IQR: 0.8-1.9).

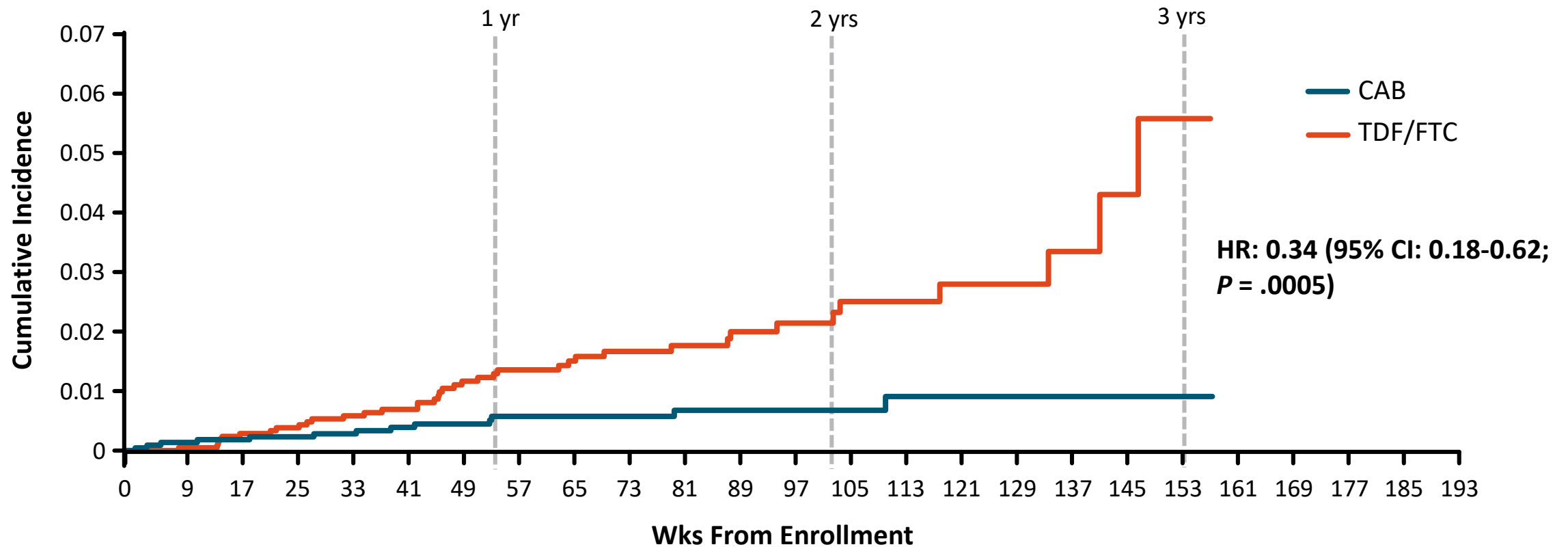
- LA CAB met alternative hypothesis (HR: 0.75) and demonstrated statistically significant superiority vs FTC/TDF



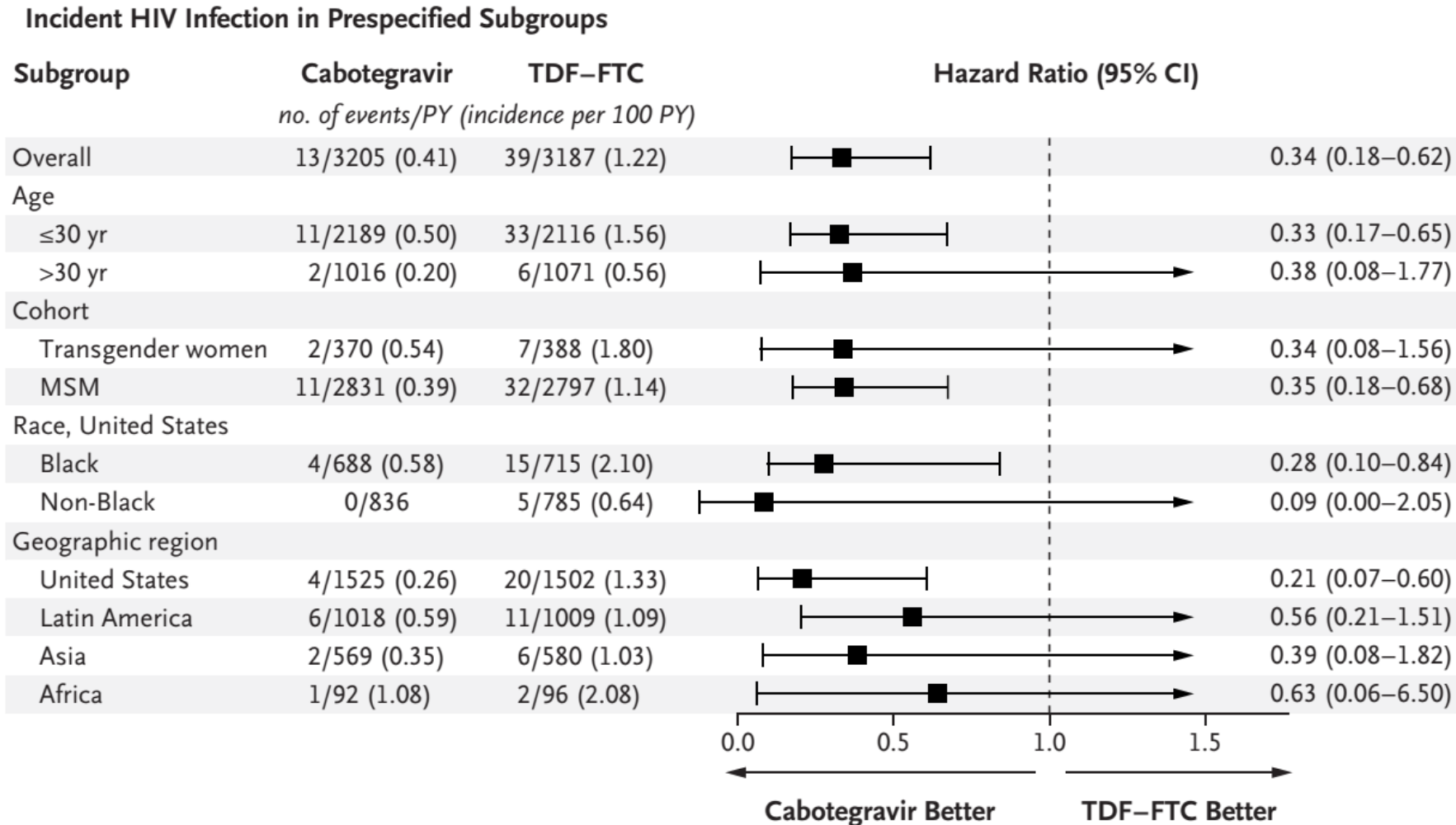
HPTN 083: HIV Incidence



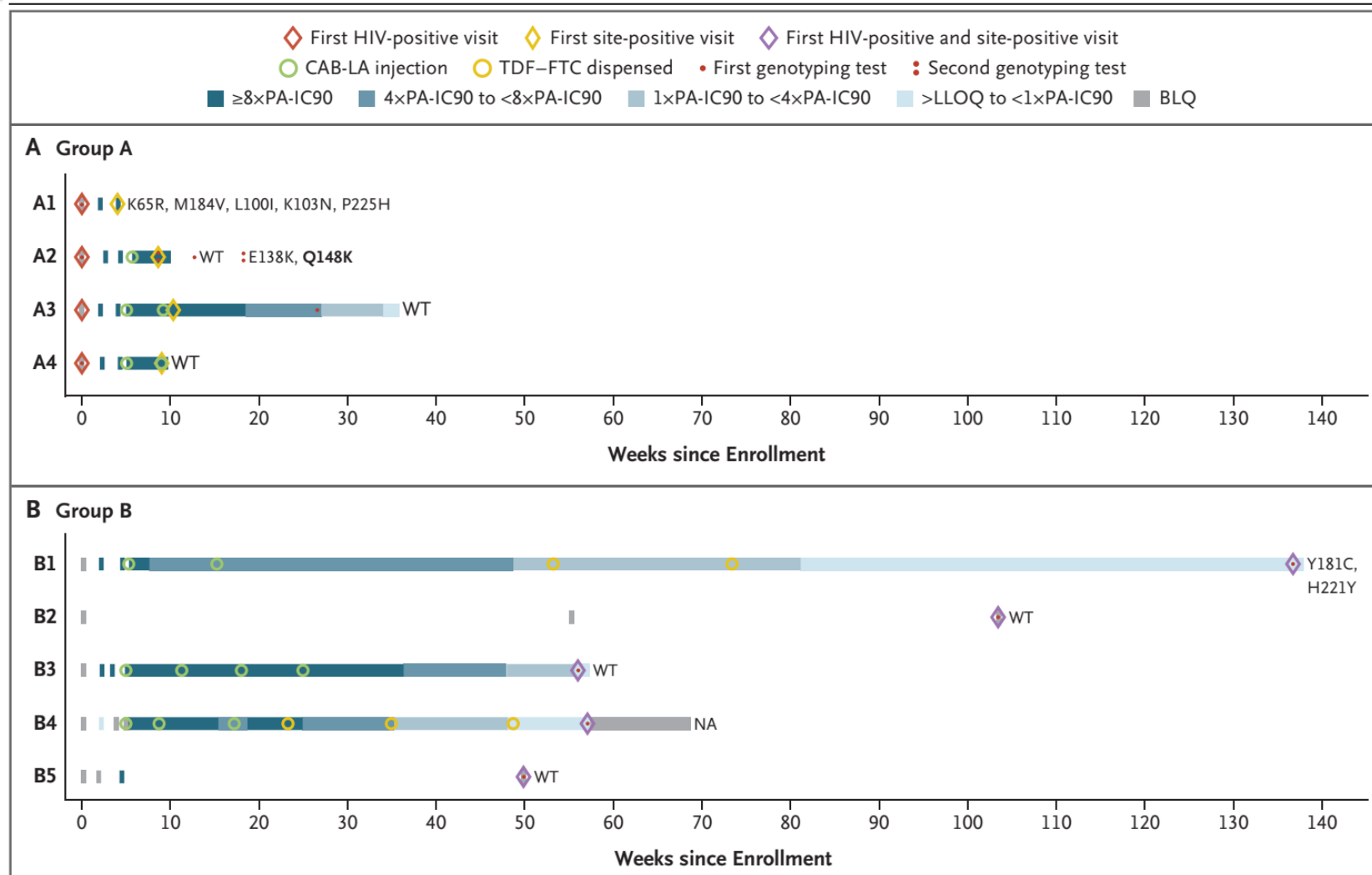
HPTN 083: HIV Incidence in ITT Population



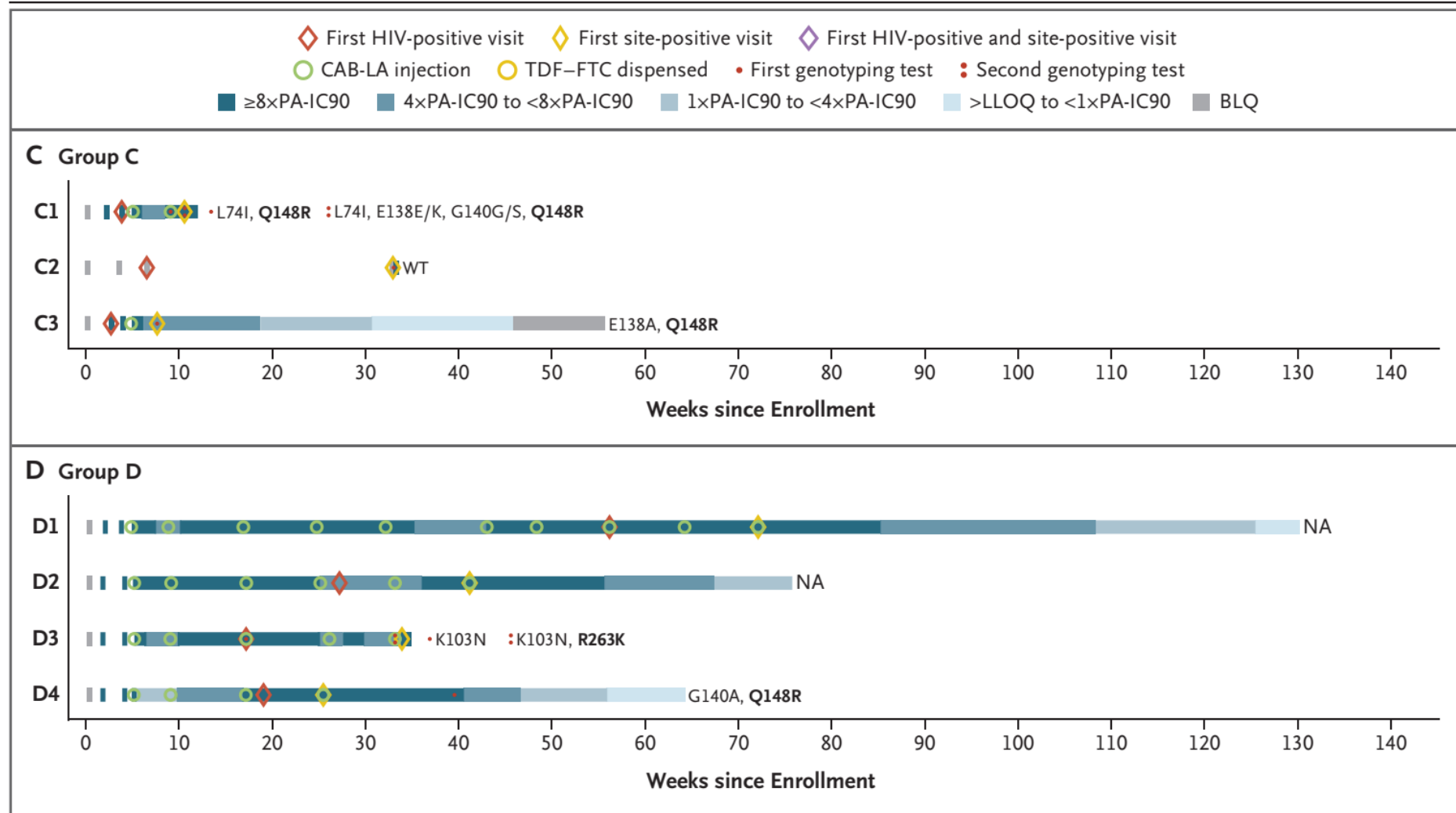
HPTN 083: Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women



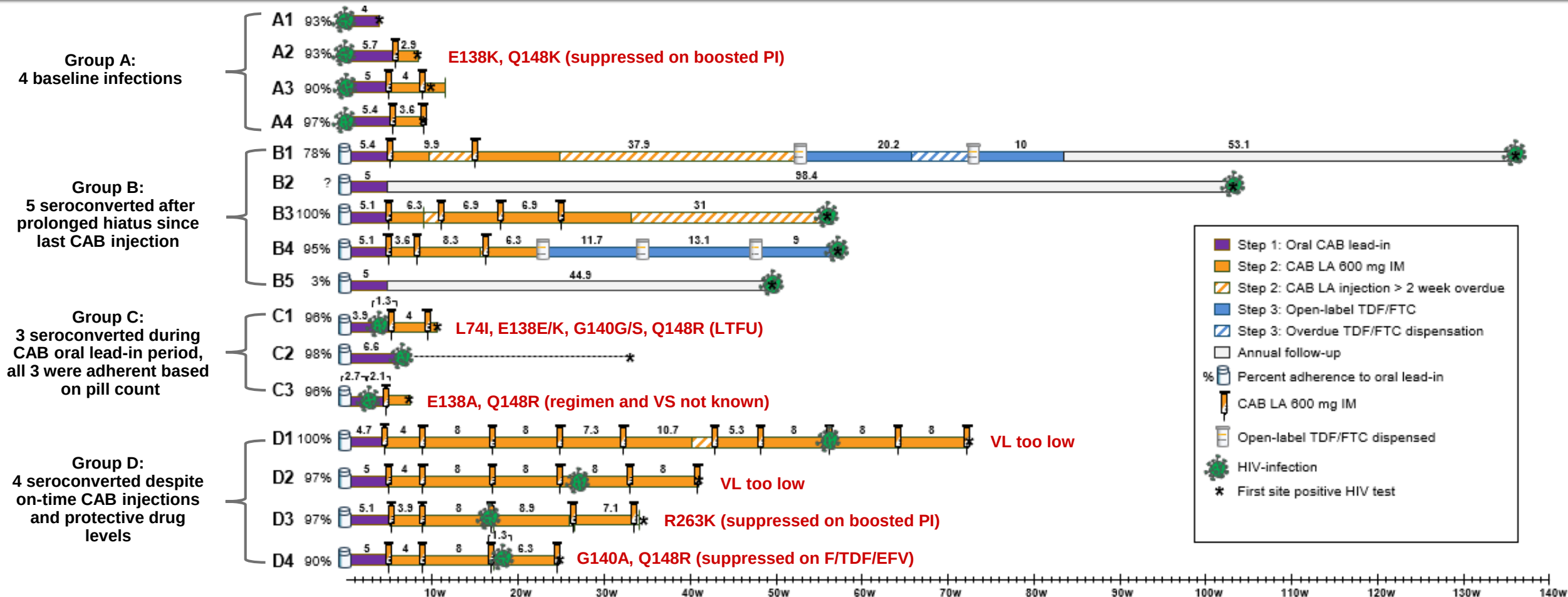
HPTN 083: Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women



HPTN 083: Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women

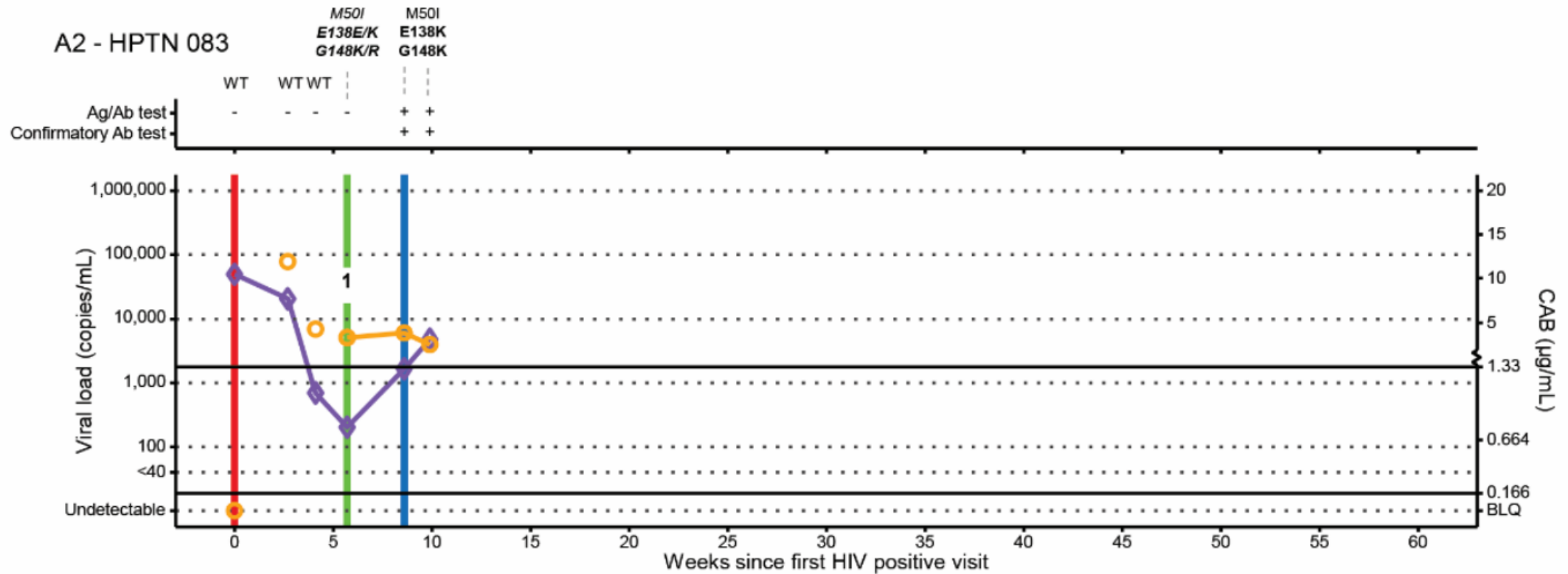


HPTN 083: HIV Infections in Cabotegravir Arm



HPTN 083: HIV Infections in Cabotegravir Arm

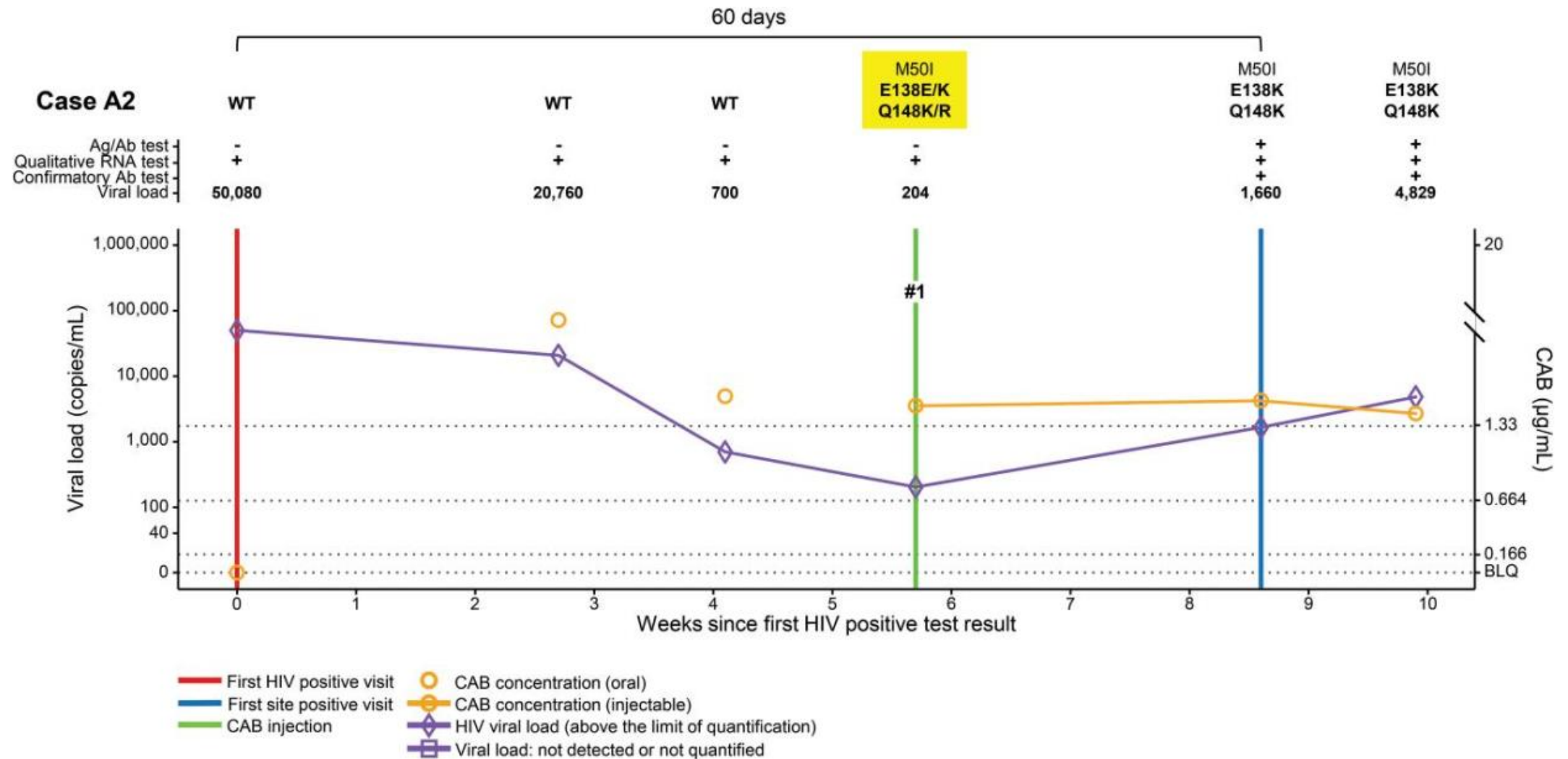
Case A2



- First HIV positive visit
- First site positive visit
- CAB injection
- HIV viral load (above the limit of quantification)
- HIV viral load (not detected)
- Qualitative RNA (not detected)
- HIV viral load (single copy assay)
- CAB concentration (oral)
- CAB concentration (injectable)

HPTN 083: HIV Infections in Cabotegravir Arm

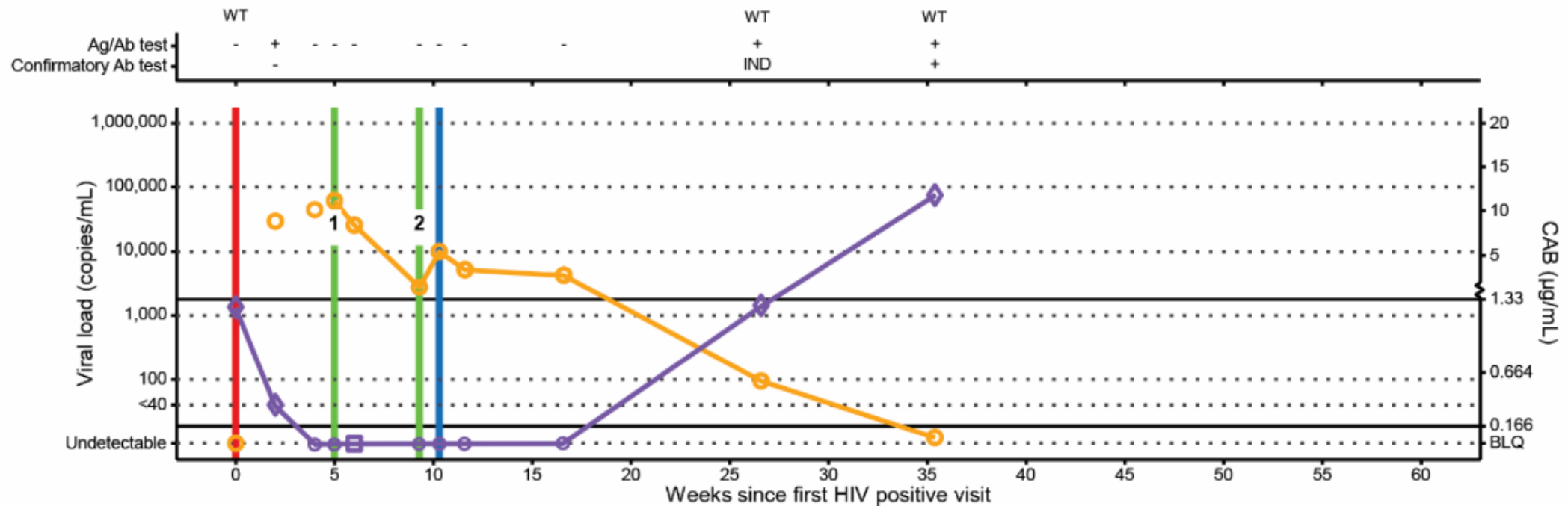
Case A2



HPTN 083: HIV Infections in Cabotegravir Arm

Case A3

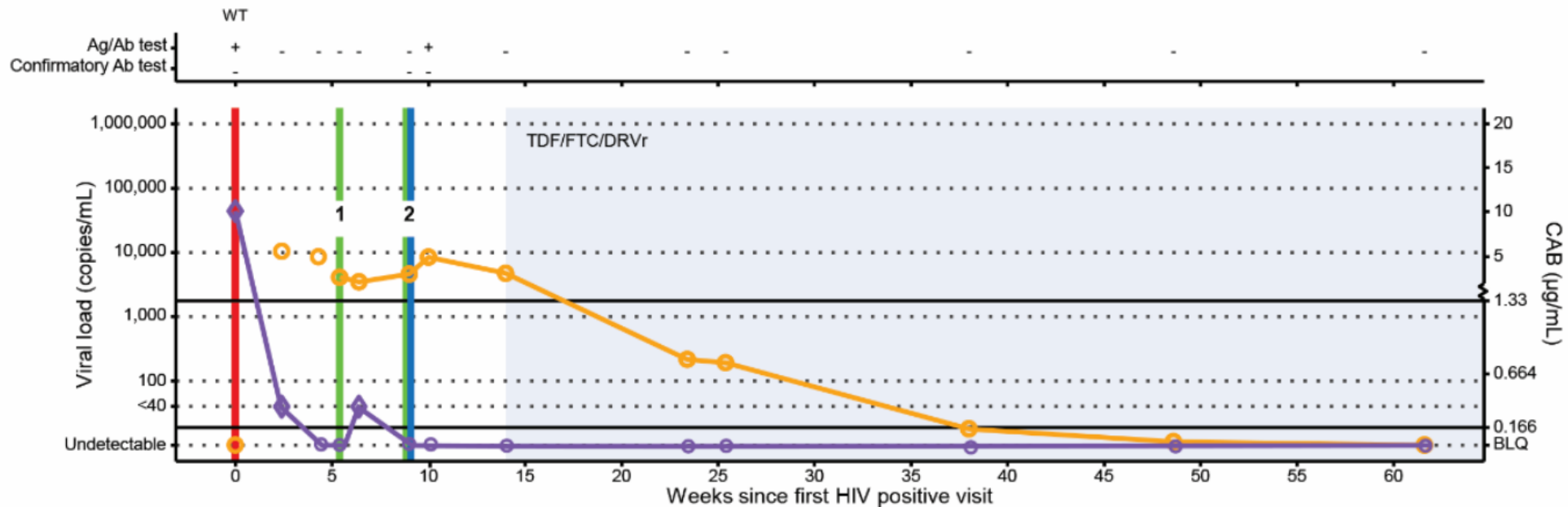
A3 – HPTN 083



HPTN 083: HIV Infections in Cabotegravir Arm

Case A4

A4 – HPTN 083

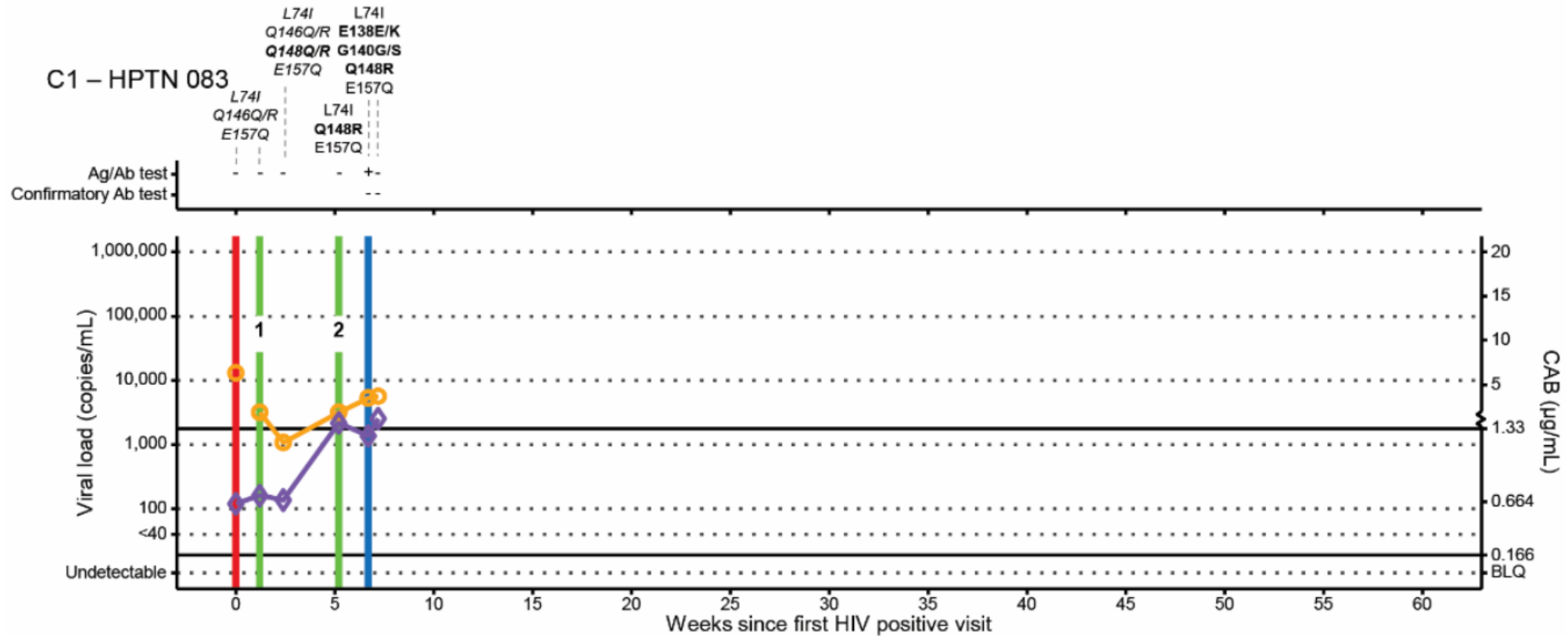


First HIV positive visit
 First site positive visit
 CAB injection
 HIV viral load (above the limit of quantification)
 HIV viral load (not detected)
 Qualitative RNA (not detected)
 HIV viral load (single copy assay)
 CAB concentration (oral)
 CAB concentration (injectable)

First HIV positive visit
 First site positive visit
 CAB injection
 HIV viral load (above the limit of quantification)
 HIV viral load (not detected)
 Qualitative RNA (not detected)
 HIV viral load (single copy assay)
 CAB concentration (oral)
 CAB concentration (injectable)

HPTN 083: HIV Infections in Cabotegravir Arm

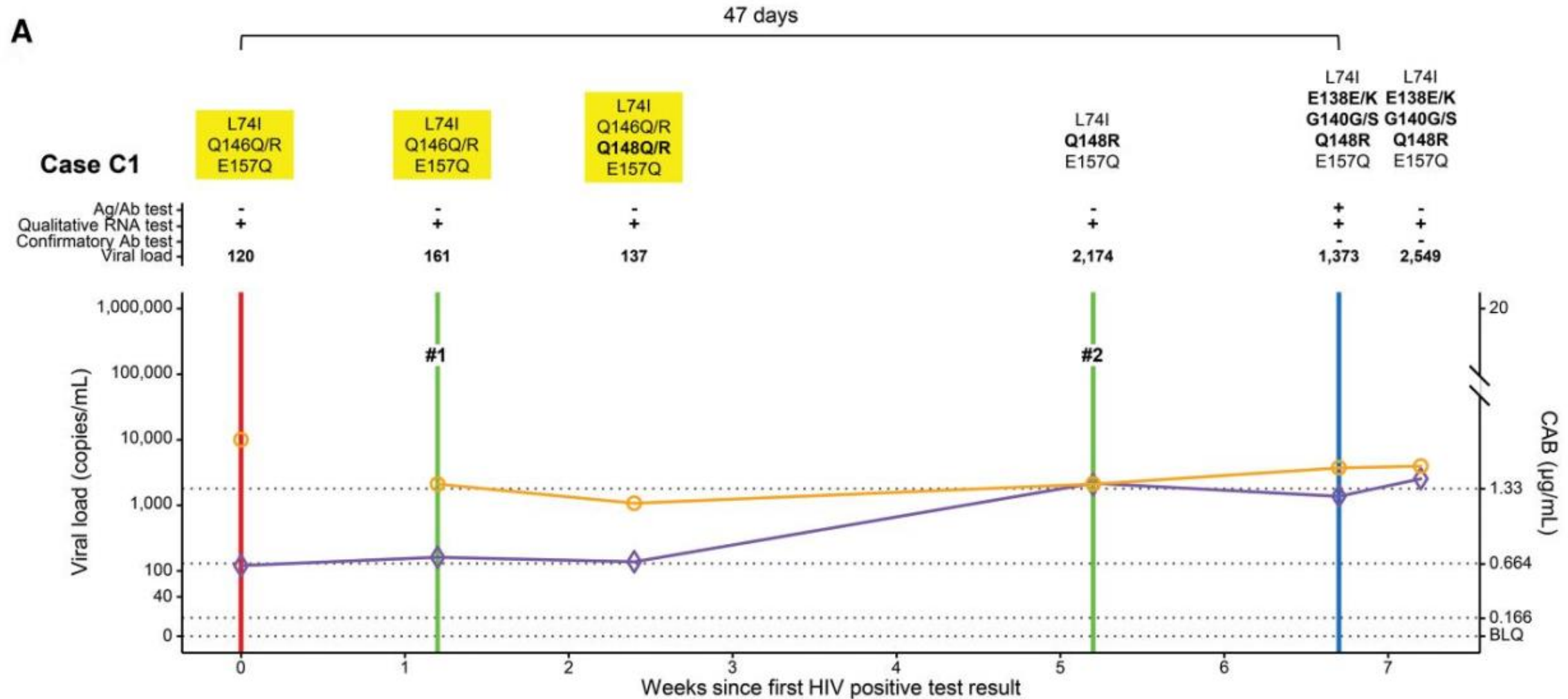
Case C1



-  First HIV positive visit
 First site positive visit
 CAB injection
-  HIV viral load (above the limit of quantification)
 HIV viral load (not detected)
 Qualitative RNA (not detected)
-  HIV viral load (single copy assay)
 CAB concentration (oral)
 CAB concentration (injectable)

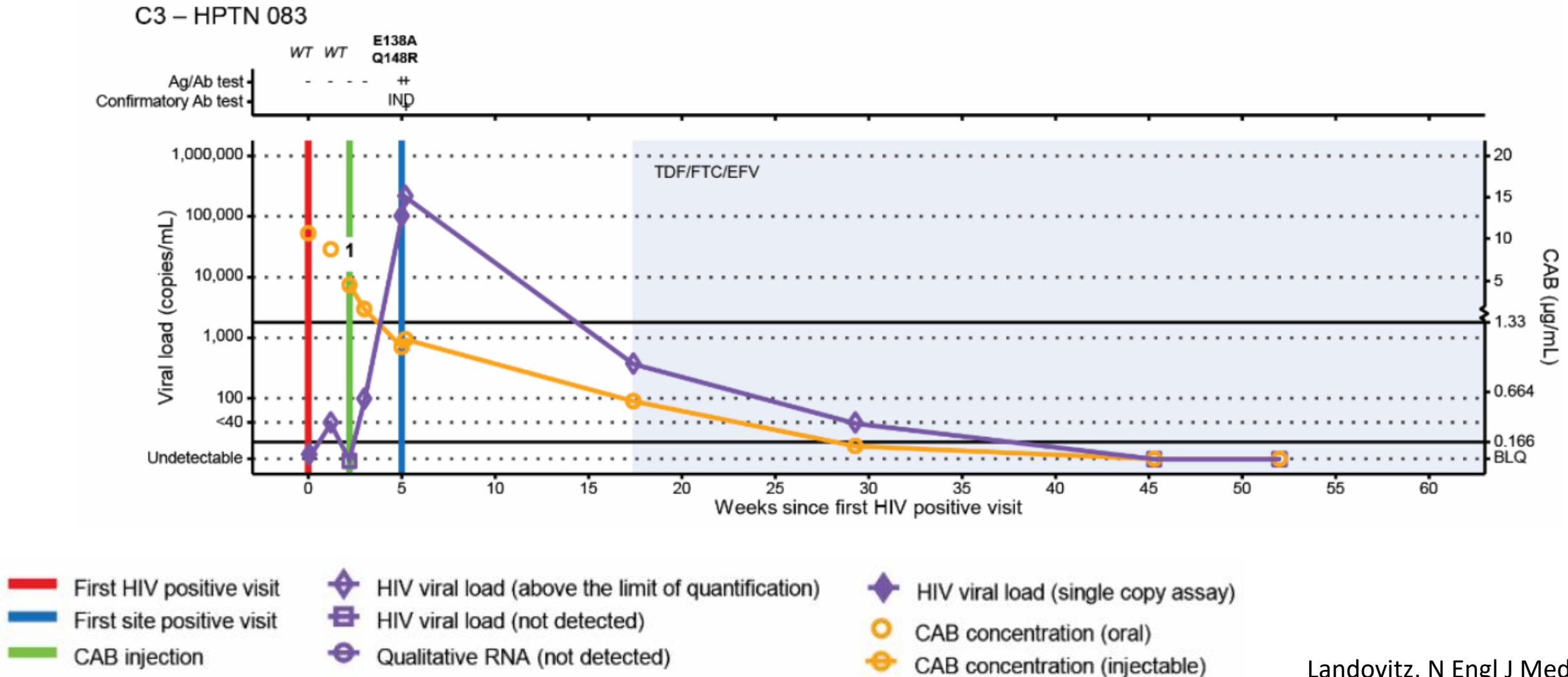
HPTN 083: HIV Infections in Cabotegravir Arm

Case C1



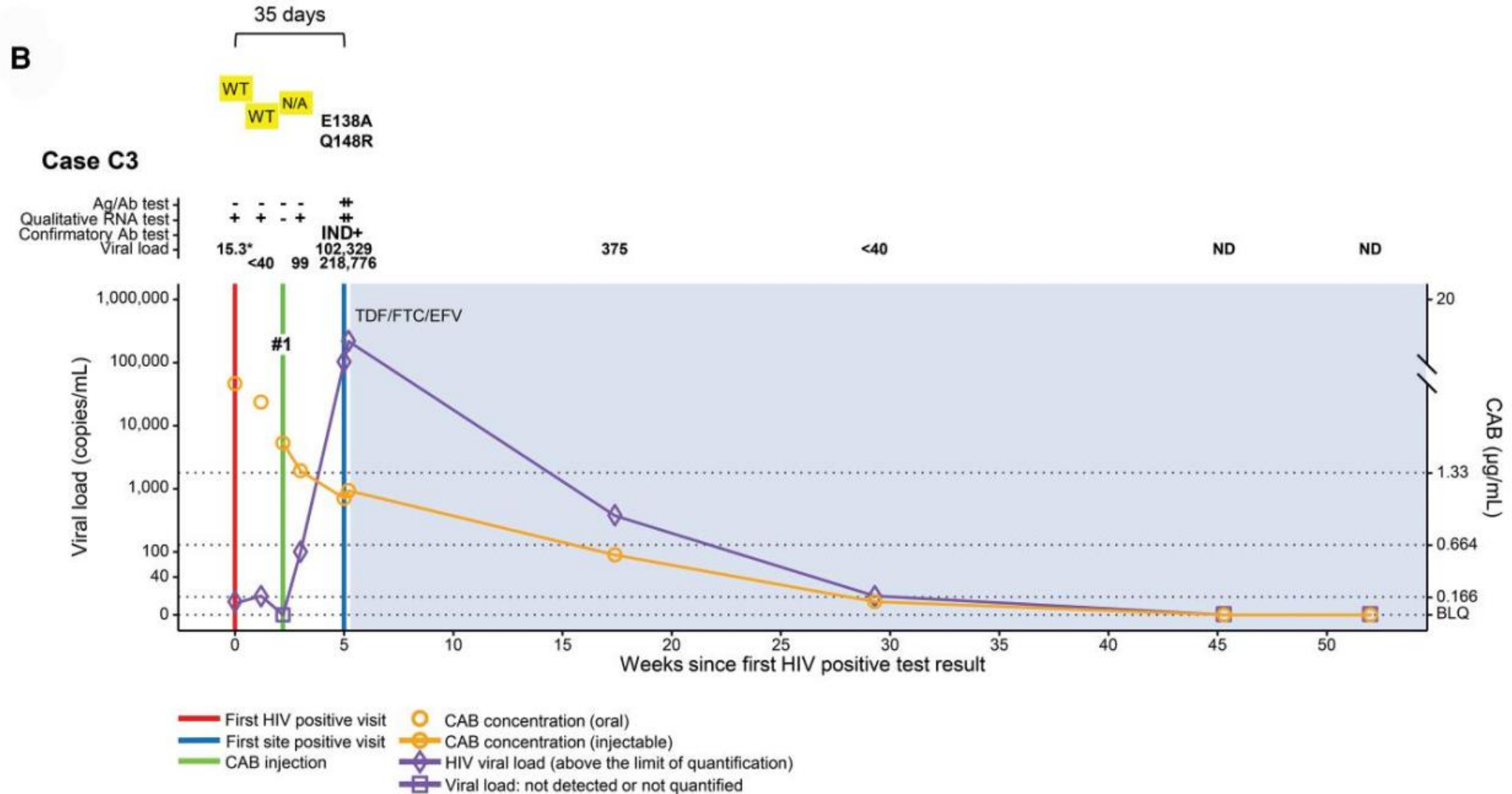
HPTN 083: HIV Infections in Cabotegravir Arm

Case C3



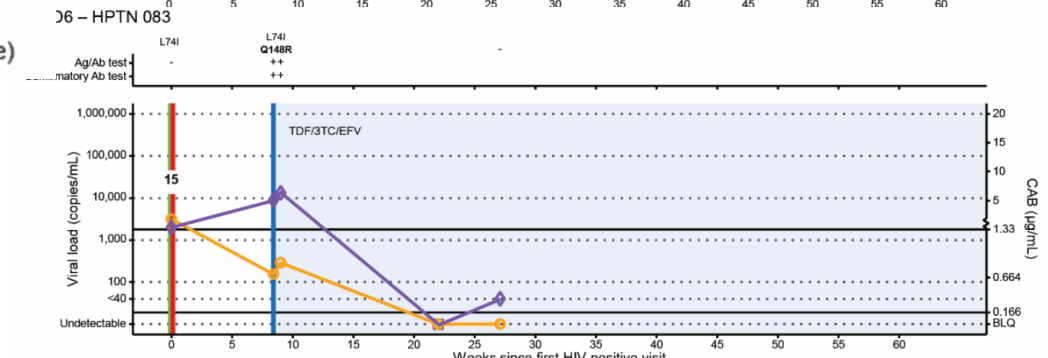
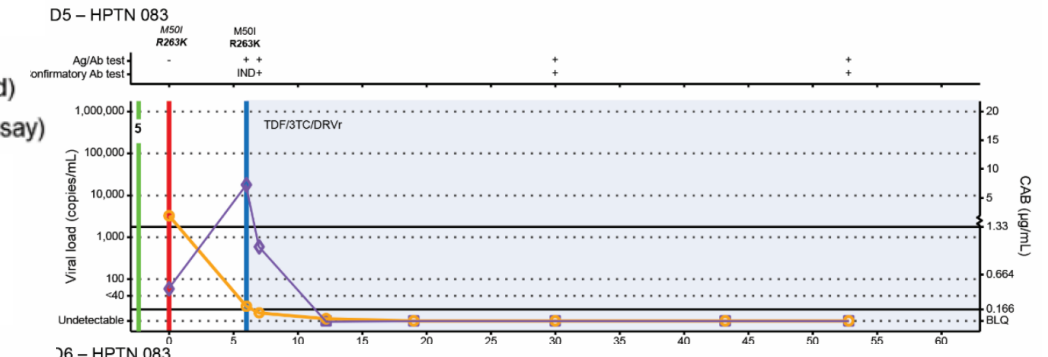
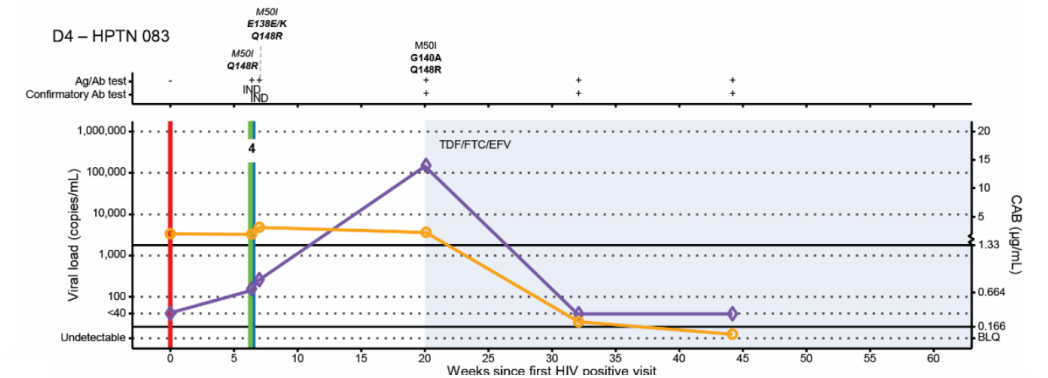
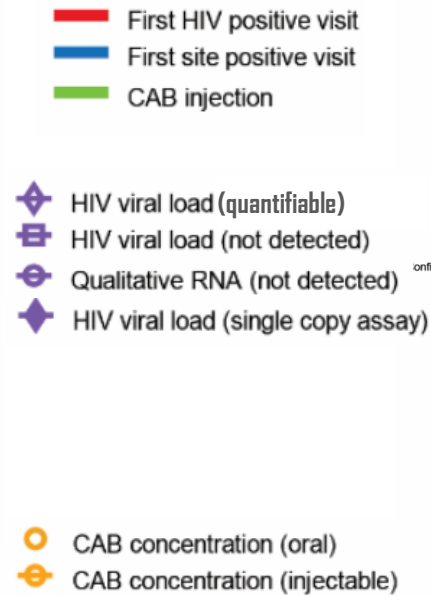
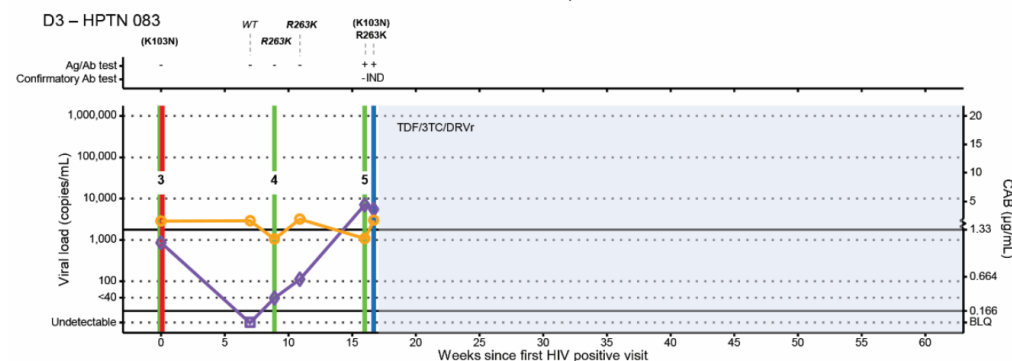
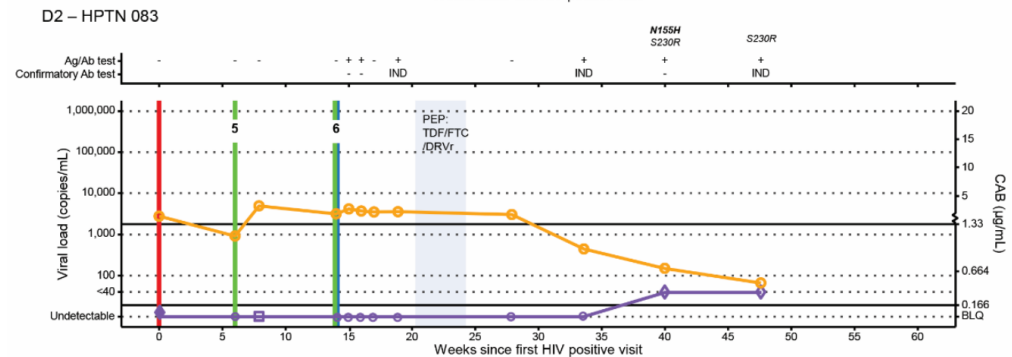
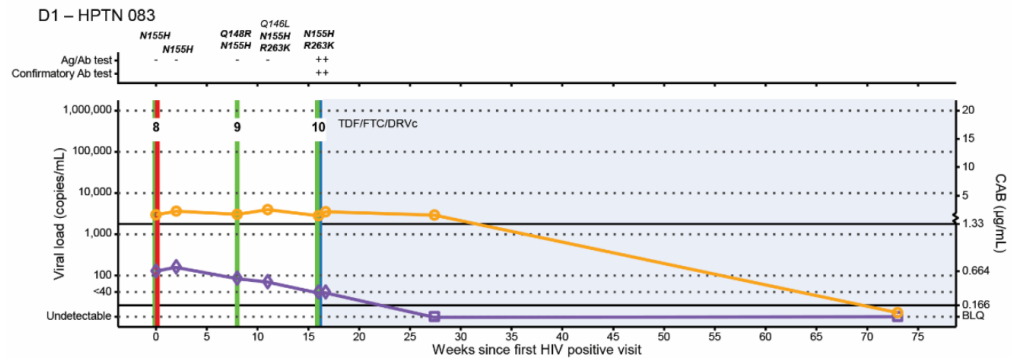
HPTN 083: HIV Infections in Cabotegravir Arm

Case C3



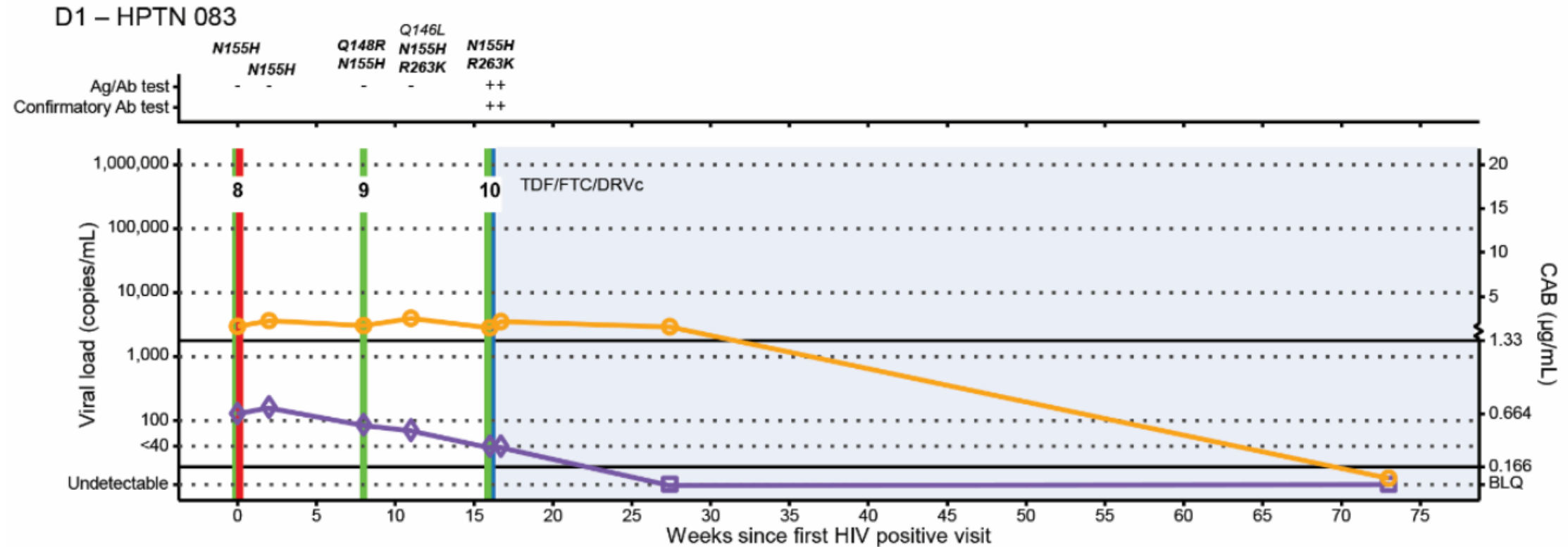
HPTN 083: HIV Infections in Cabotegravir Arm

Cases D1-D6



HPTN 083: HIV Infections in Cabotegravir Arm

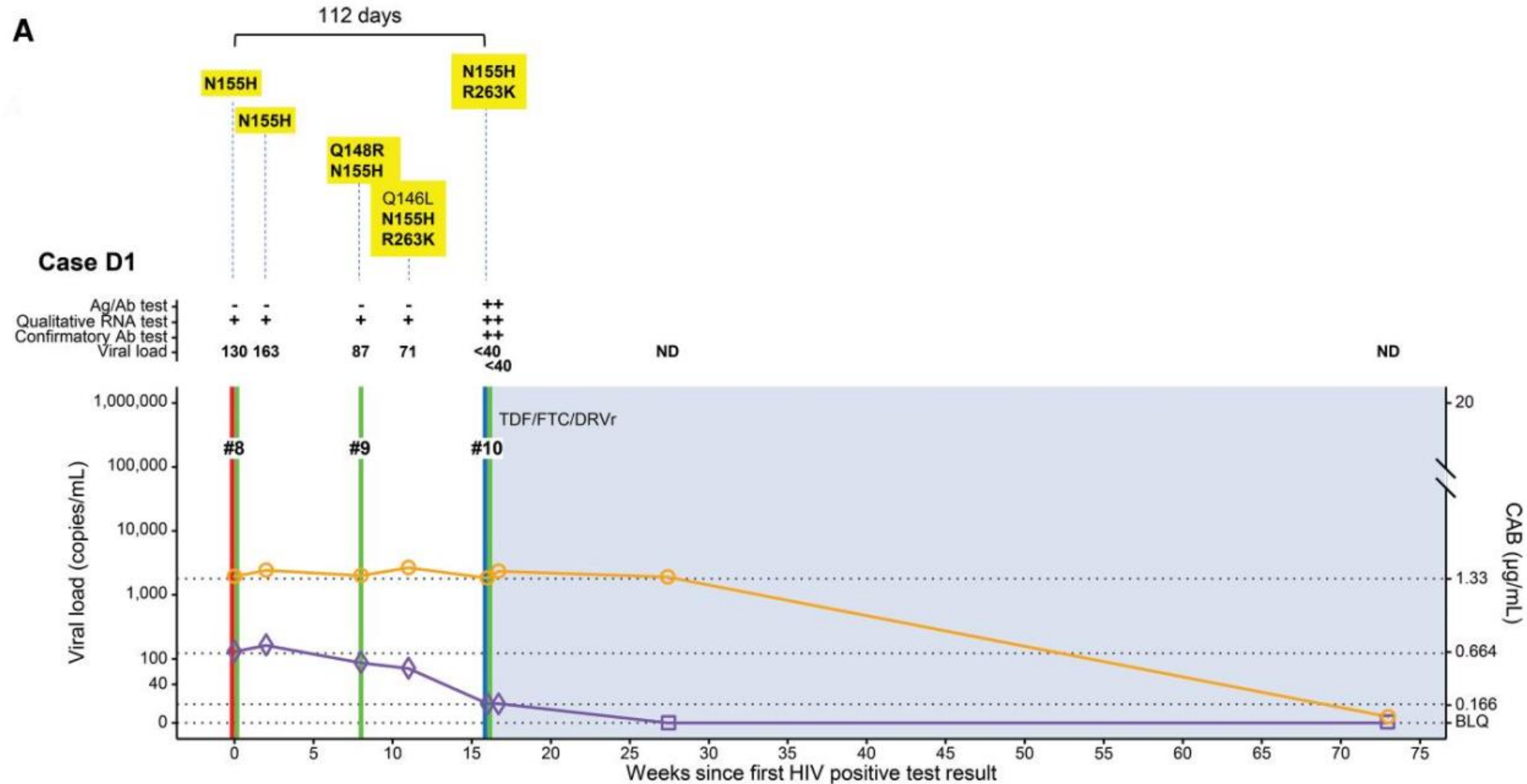
Case D1



- First HIV positive visit
- First site positive visit
- CAB injection
- HIV viral load (above the limit of quantification)
- HIV viral load (not detected)
- Qualitative RNA (not detected)
- HIV viral load (single copy assay)
- CAB concentration (oral)
- CAB concentration (injectable)

HPTN 083: HIV Infections in Cabotegravir Arm

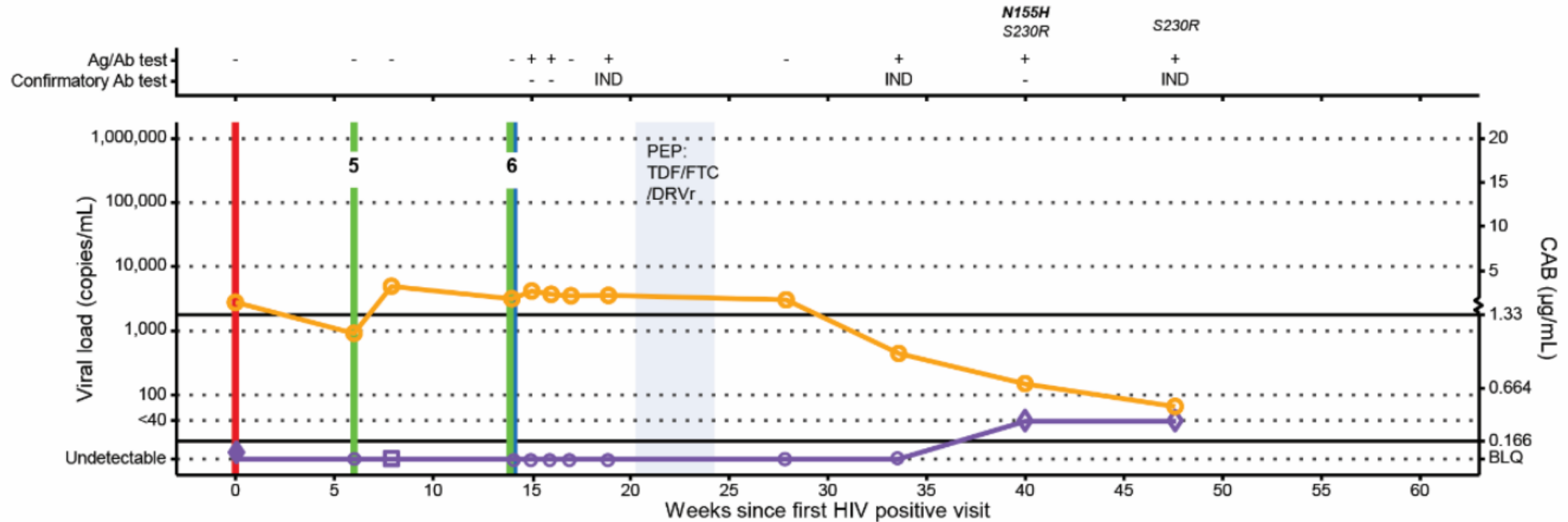
Case D1



HPTN 083: HIV Infections in Cabotegravir Arm

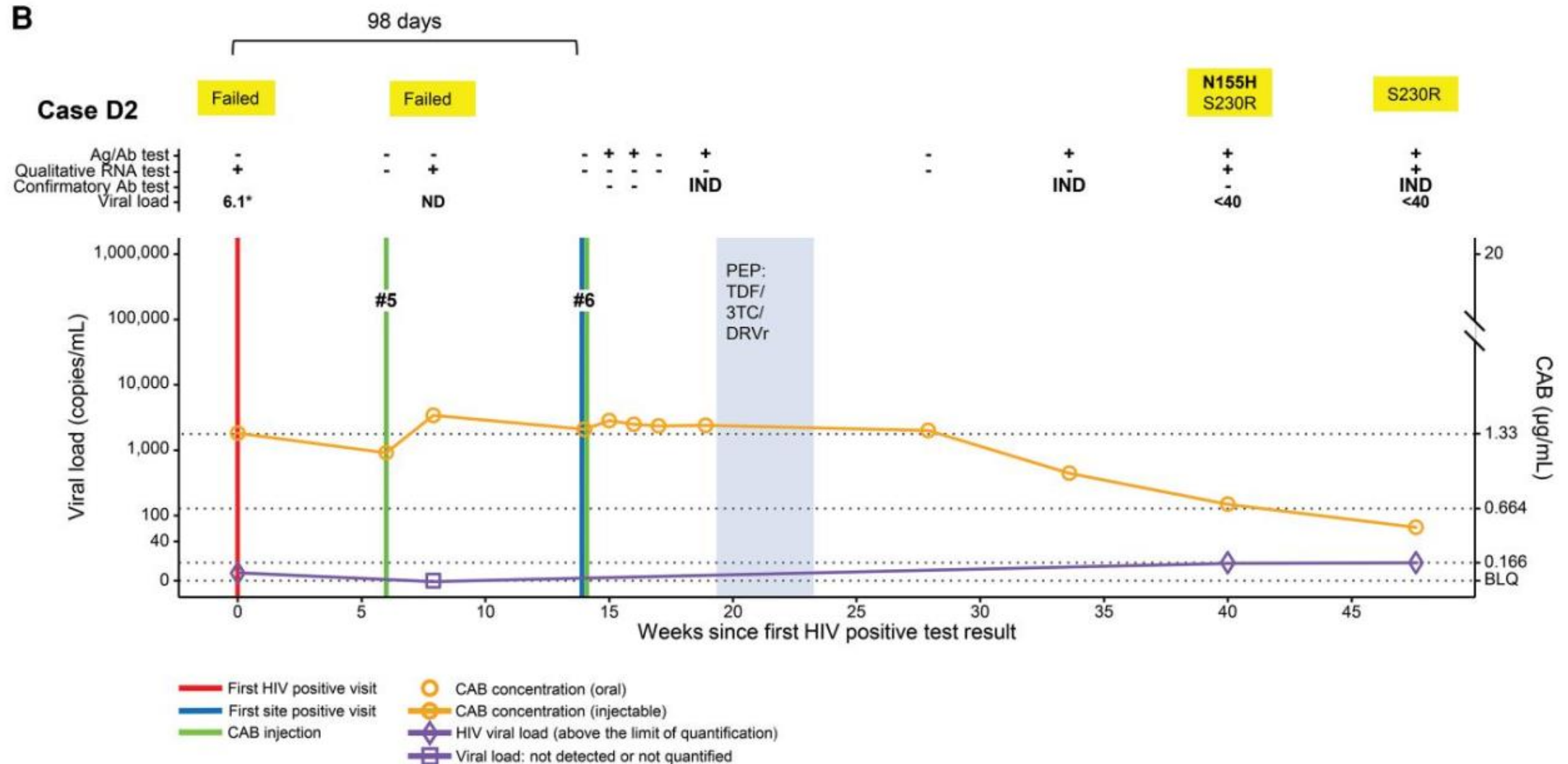
Case D2

D2 – HPTN 083



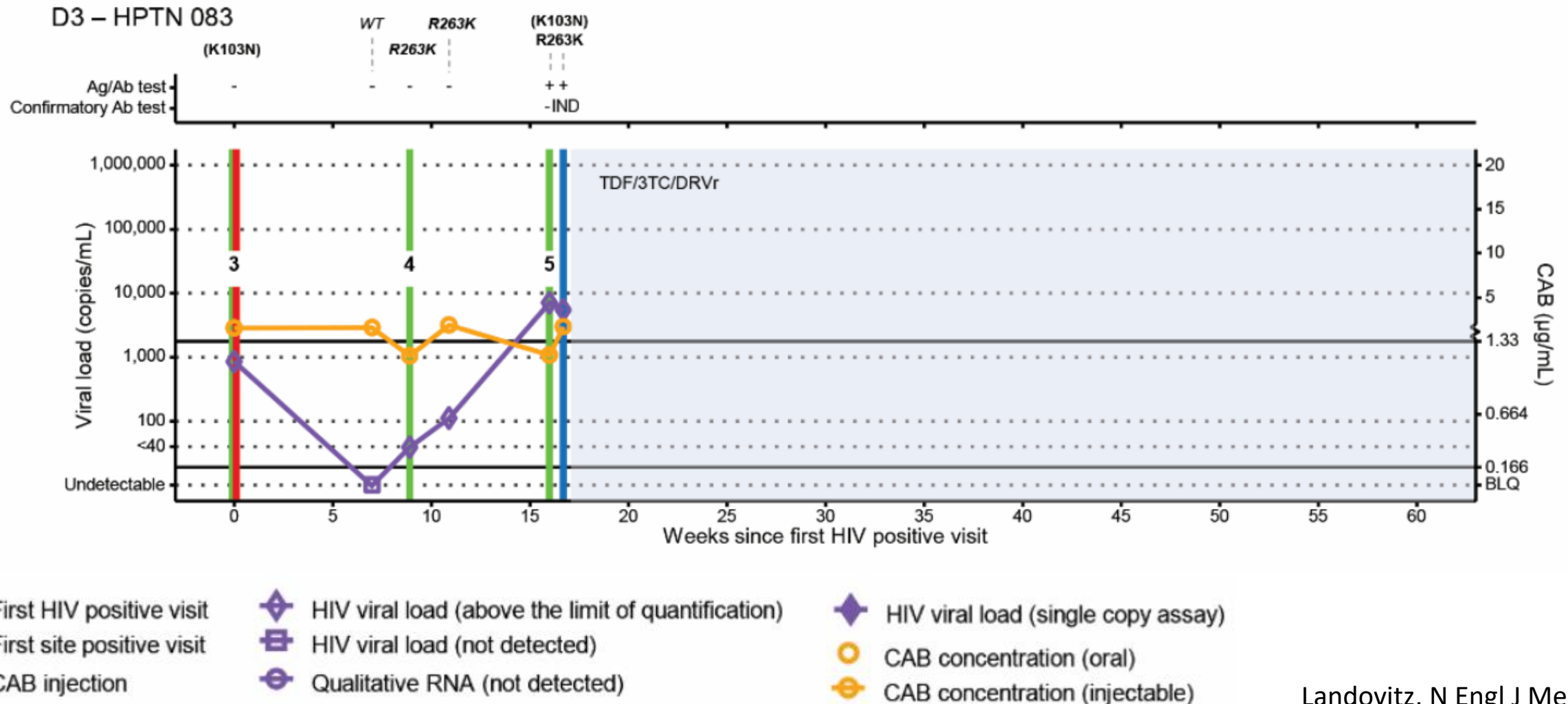
HPTN 083: HIV Infections in Cabotegravir Arm

Case D2



HPTN 083: HIV Infections in Cabotegravir Arm

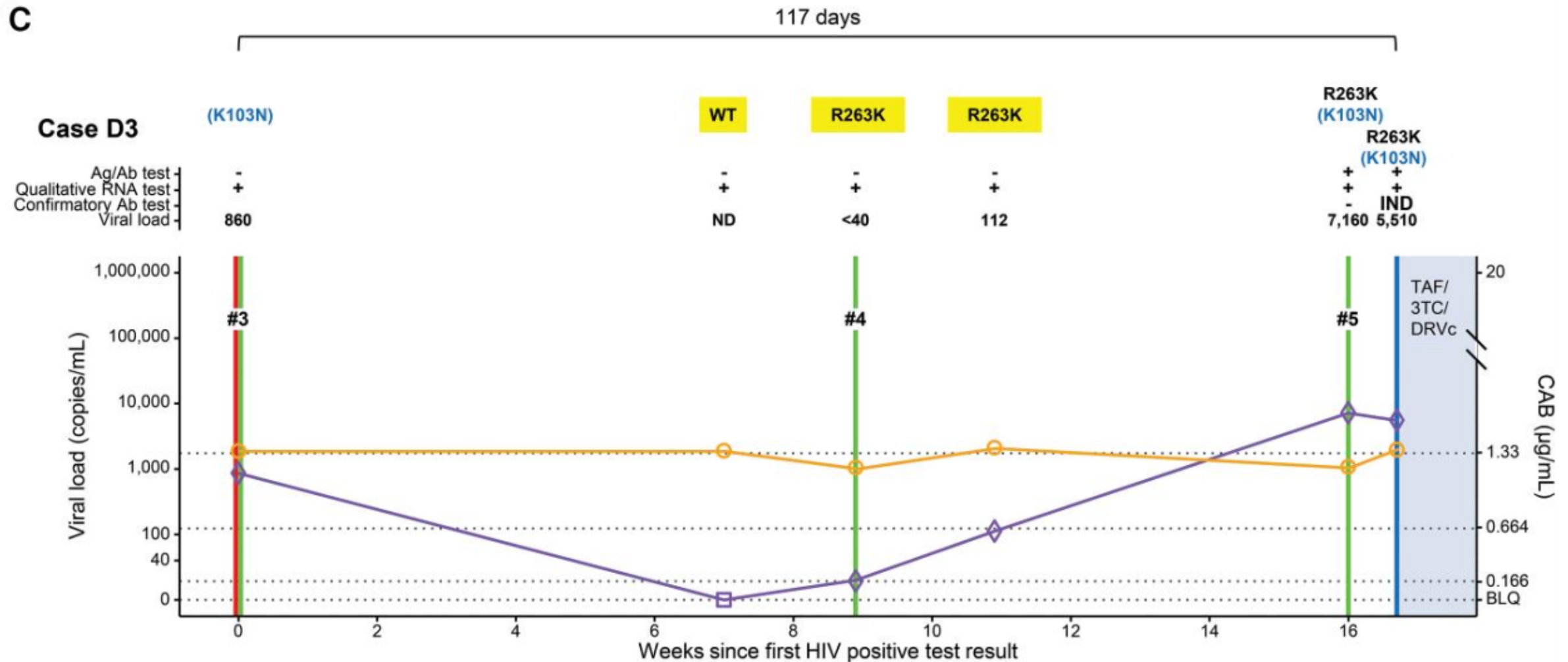
Case D3



HPTN 083: HIV Infections in Cabotegravir Arm

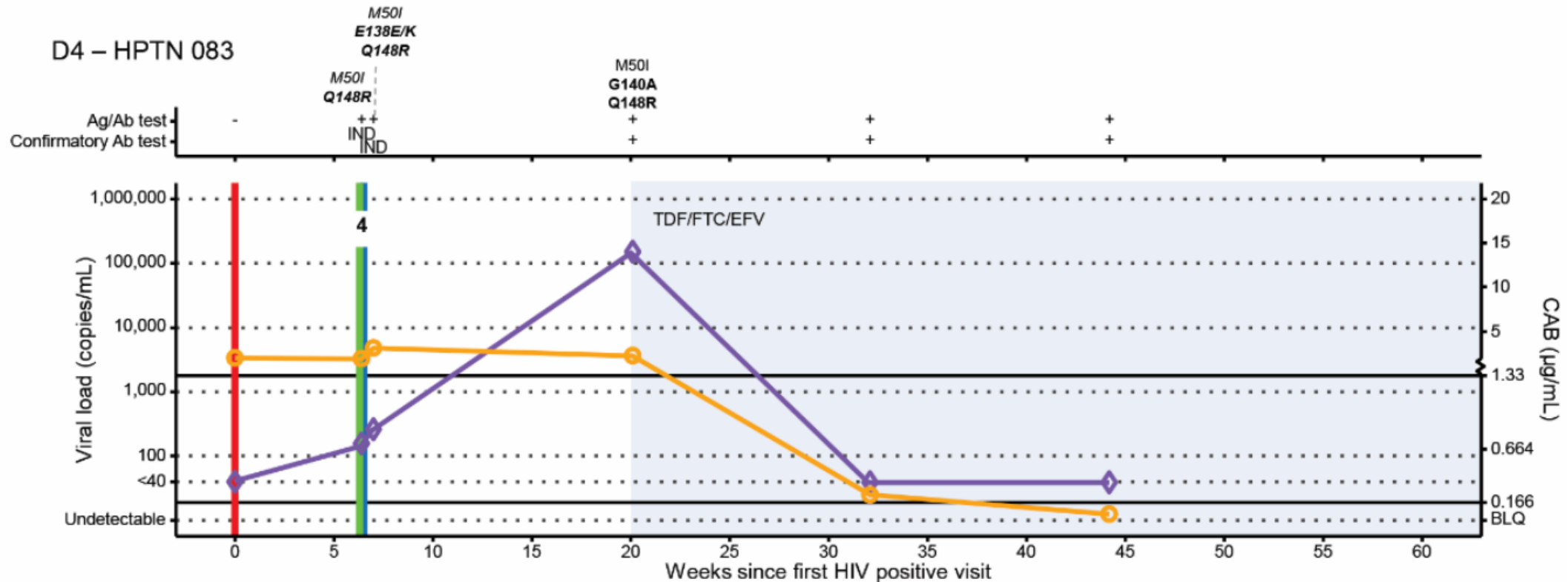
Case D3

C



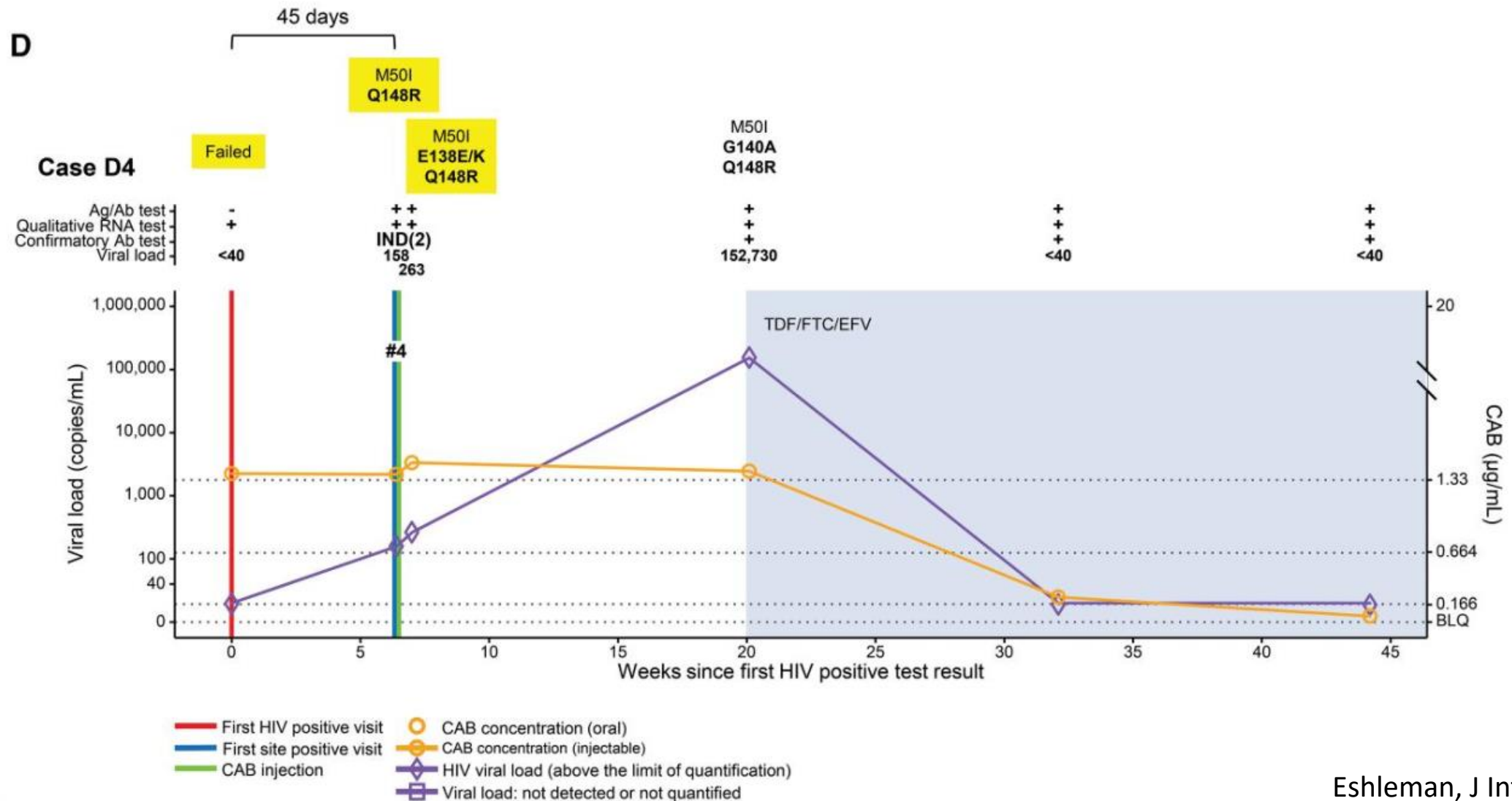
HPTN 083: HIV Infections in Cabotegravir Arm

Case D₄



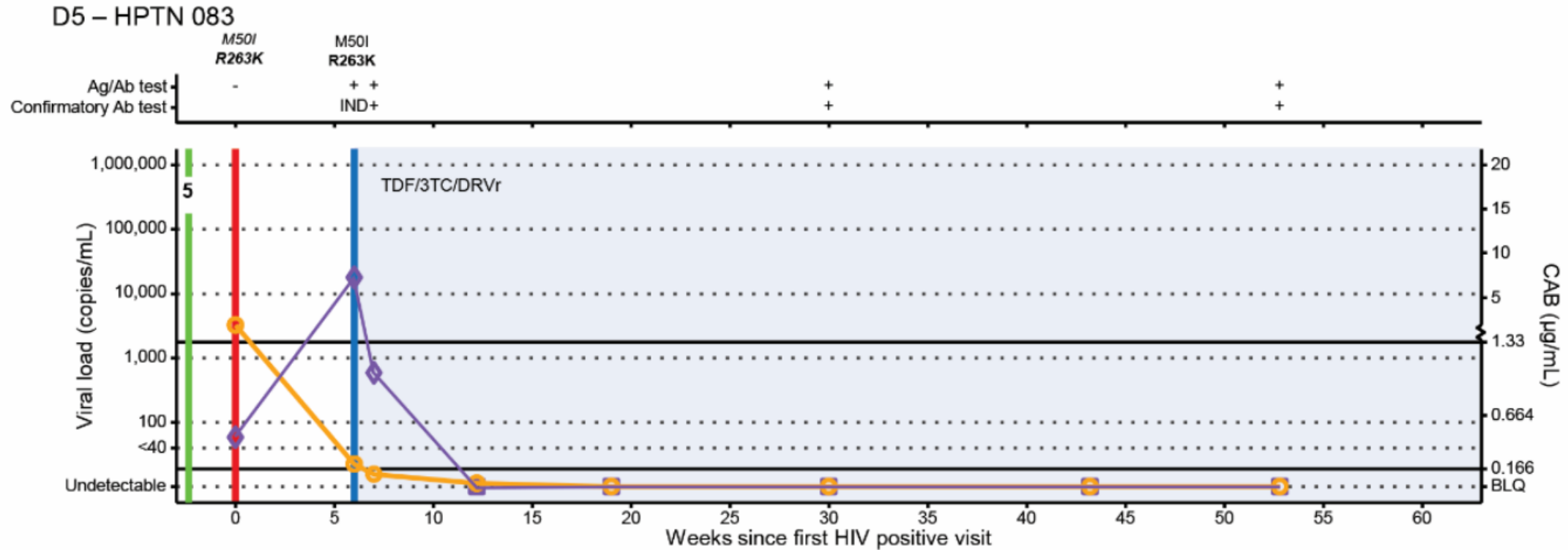
HPTN 083: HIV Infections in Cabotegravir Arm

Case D4



HPTN 083: HIV Infections in Cabotegravir Arm

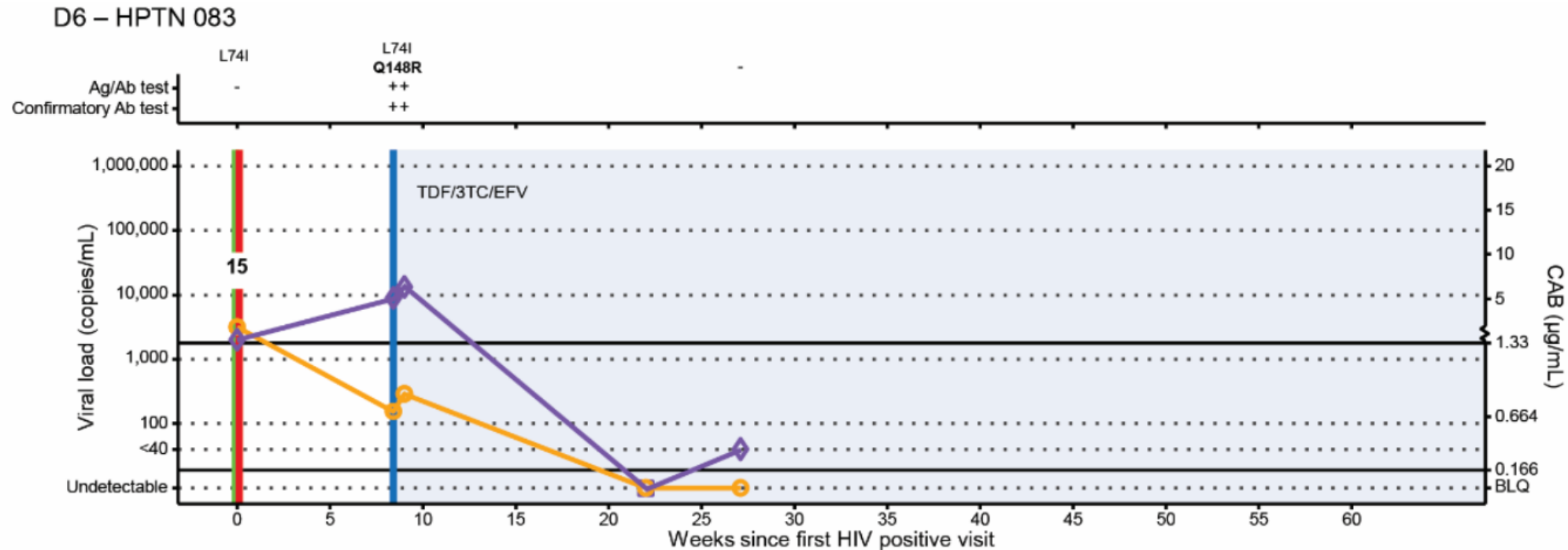
Case D5



- First HIV positive visit
- First site positive visit
- CAB injection
- HIV viral load (above the limit of quantification)
- HIV viral load (not detected)
- Qualitative RNA (not detected)
- HIV viral load (single copy assay)
- CAB concentration (oral)
- CAB concentration (injectable)

HPTN 083: HIV Infections in Cabotegravir Arm

Case D6



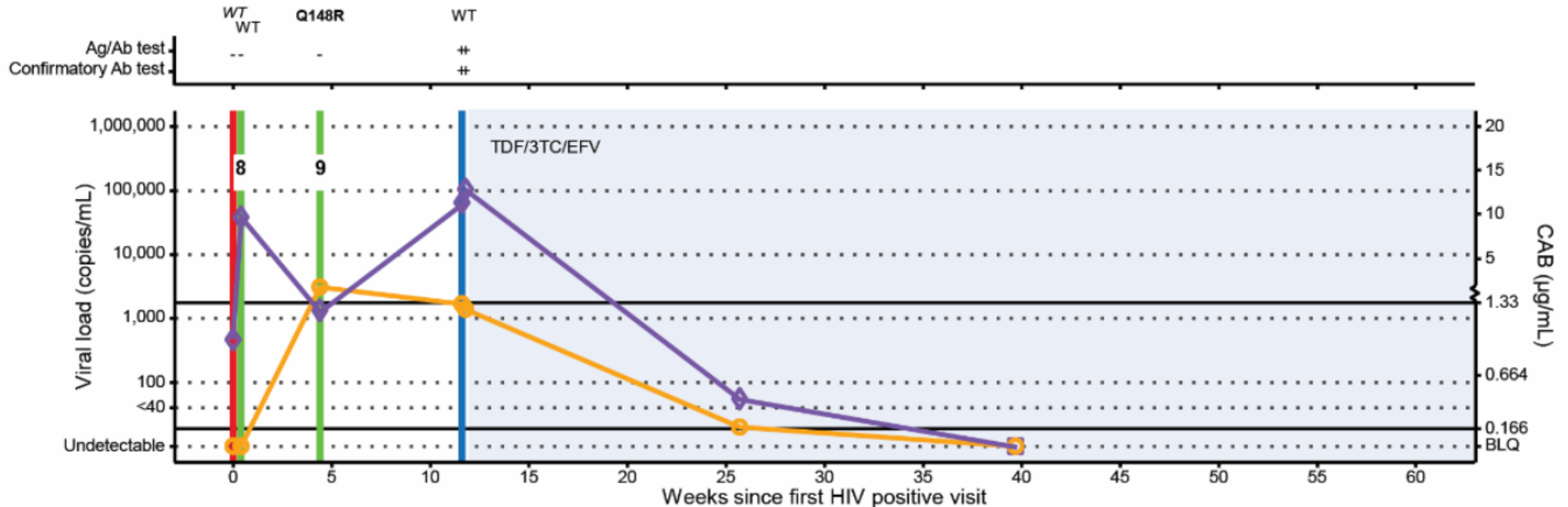
- First HIV positive visit
- First site positive visit
- CAB injection
- HIV viral load (above the limit of quantification)
- HIV viral load (not detected)
- Qualitative RNA (not detected)
- HIV viral load (single copy assay)
- CAB concentration (oral)
- CAB concentration (injectable)

- First HIV positive visit
- First site positive visit
- CAB injection
- HIV viral load (above the limit of quantification)
- HIV viral load (not detected)
- Qualitative RNA (not detected)
- HIV viral load (single copy assay)
- CAB concentration (oral)
- CAB concentration (injectable)

HPTN 083: HIV Infections in Cabotegravir Arm

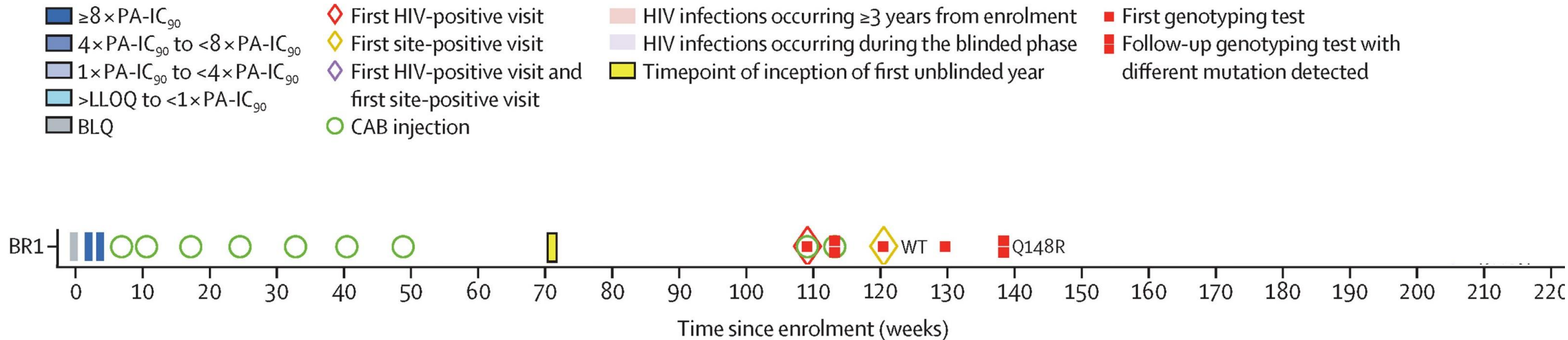
Case BR1

BR1 – HPTN 083



HPTN 083: HIV Infections in Cabotegravir Arm

Case BR1



CAB LA tail phase was technically defined as >10 to <66.6 weeks after a cabotegravir injection, and for which post-hoc pharmacological assessment suggested that the infection was likely to have been acquired while cabotegravir was quantifiable in plasma; this excludes participants re-exposed to injectable cabotegravir subsequent to infection

HPTN 083: classification of HIV-1 infections (blinded phase)

Infection Type and Study Arm	Infections, No.	Classification Group	Breakthrough Infections, No. ^b
Baseline			
CAB arm	4 (A1–A4)	HIV positive at study enrollment	...
TDF/FTC arm	3 (E40–42)	HIV positive at study enrollment	...
Incident			
CAB arm	5 (B1–B5)	No recent CAB exposure ^c	0
	3 (C1–C3)	Infected during the CAB oral lead-in period	0
	4 (D1–D4)	Infected in the setting of on-time CAB-LA injections	4 ^d
	39 (E1–E39)	Infected after enrollment	2 ^e

^bIn the TDF/FTC arm, breakthrough infections were defined as having plasma and dried blood spot drug concentrations consistent with good adherence to daily oral dosing at the time of the first HIV-positive visit and at key earlier visits. In the CAB arm, breakthrough infections were defined as having target drug concentration (>8 times the 90% inhibitory concentration) at the first HIV-positive visit.

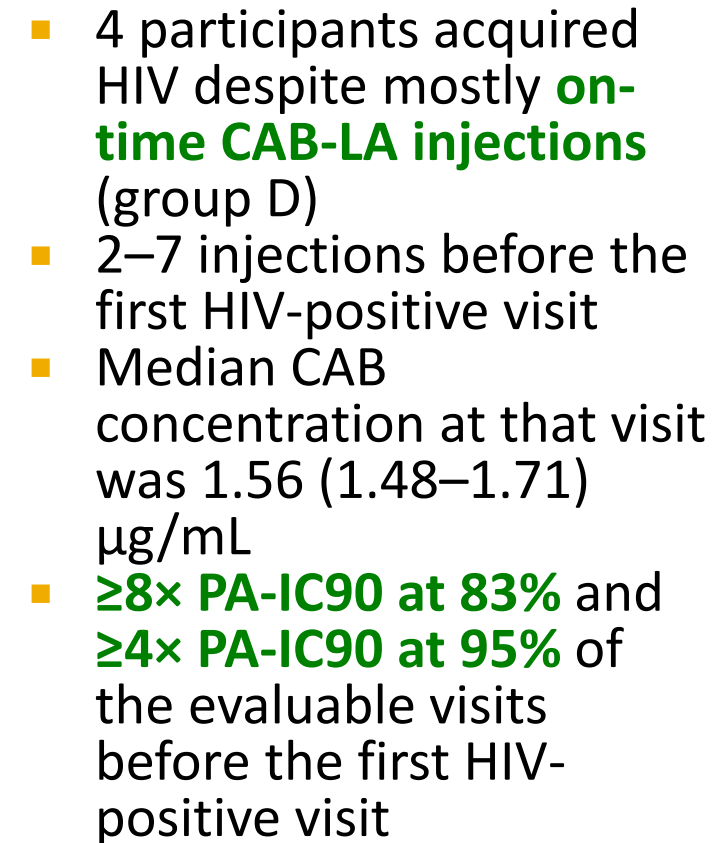
^cGroup B included participants who had no CAB injections or had their last injection ≥6 months before their first HIV-positive visit.

^dThese 4 participants had expected drug concentrations at the first HIV-positive visit (D1–D4).

^eThese 2 participants had drug concentrations consistent with good adherence to oral TDF/FTC (cases E16 and E34); exposure to HIV resistant to TDF/FTC may have contributed to infection in 1 case (E16).

^fCase E16 only.

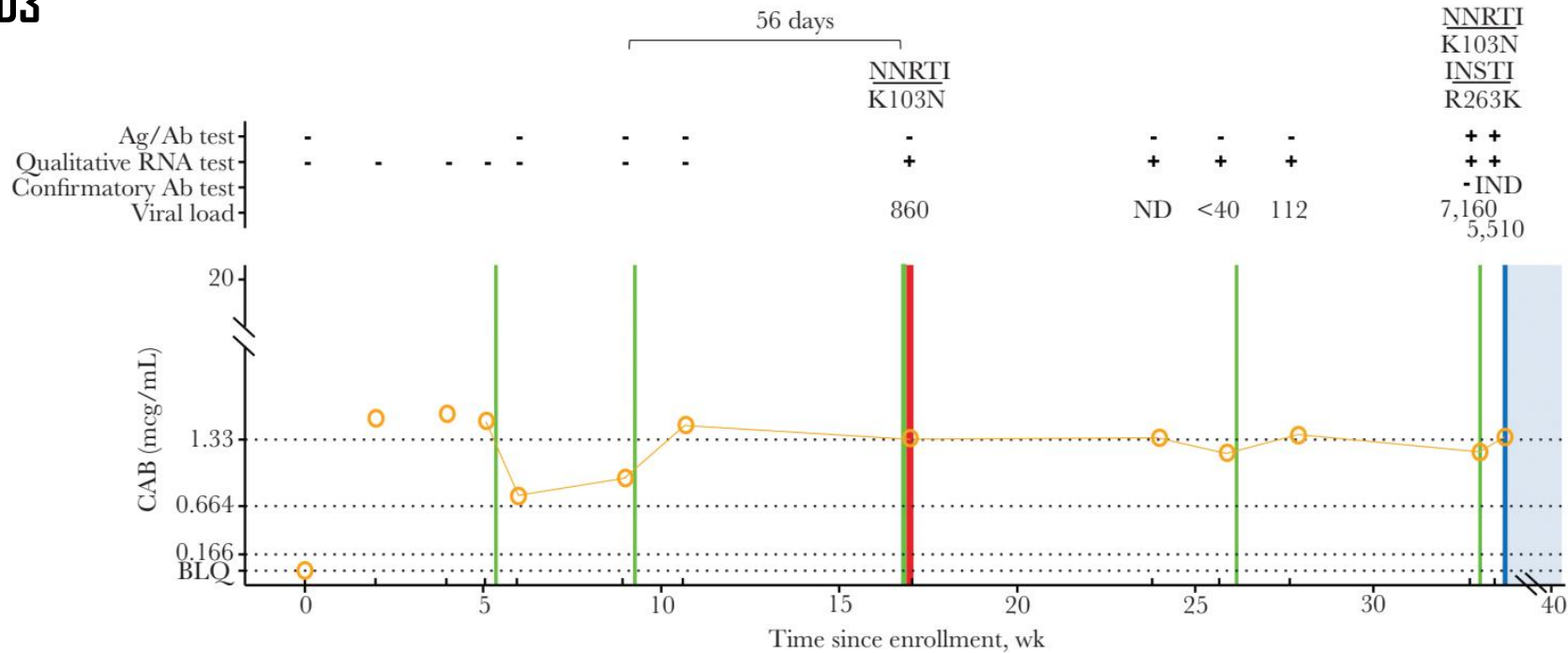
HPTN 083: breakthrough HIV Infections in CAB Arm

[illegible]

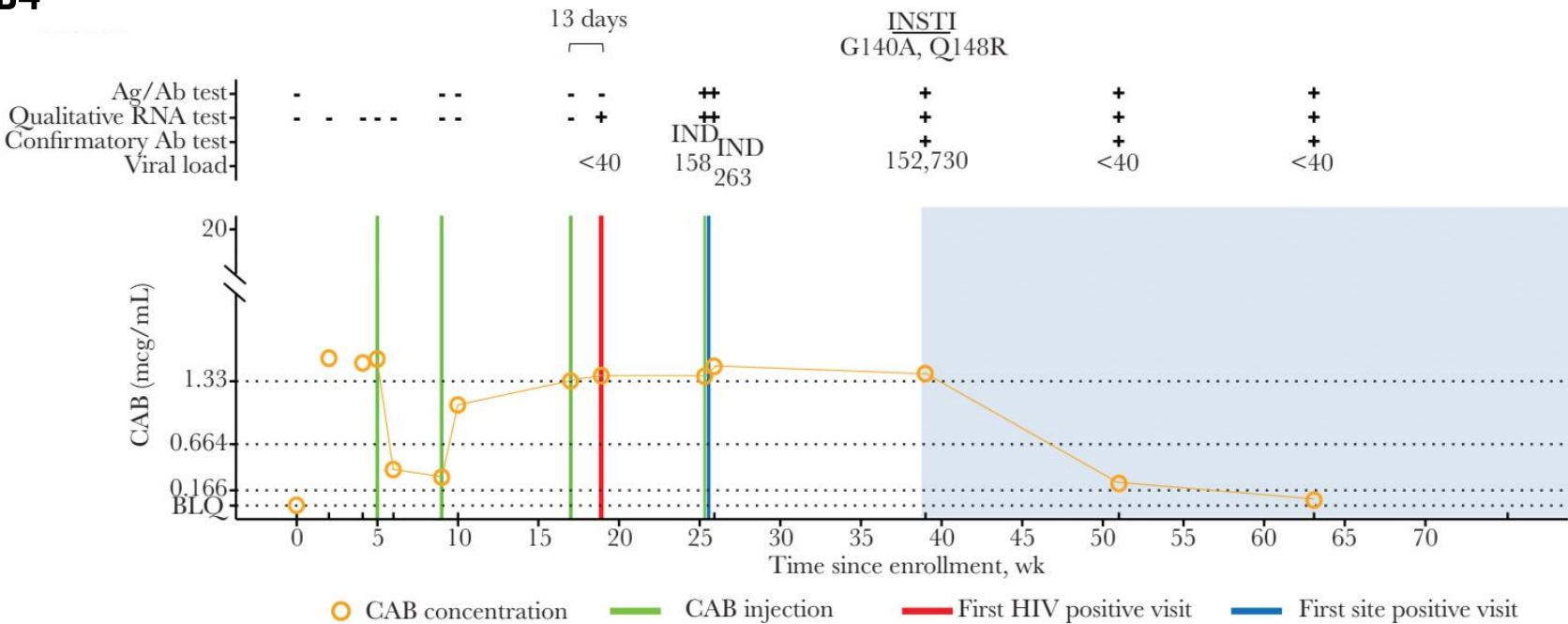
HPTN 083: breakthrough HIV Infections in CAB Arm

- 4 participants acquired HIV despite mostly **on-time CAB-LA injections** (group D)
- 2–7 injections before the first HIV-positive visit
- Median CAB concentration at that visit was 1.56 (1.48–1.71) µg/mL
- ≥8× PA-IC90 at 83%** and **≥4× PA-IC90 at 95%** of the evaluable visits before the first HIV-positive visit

D3



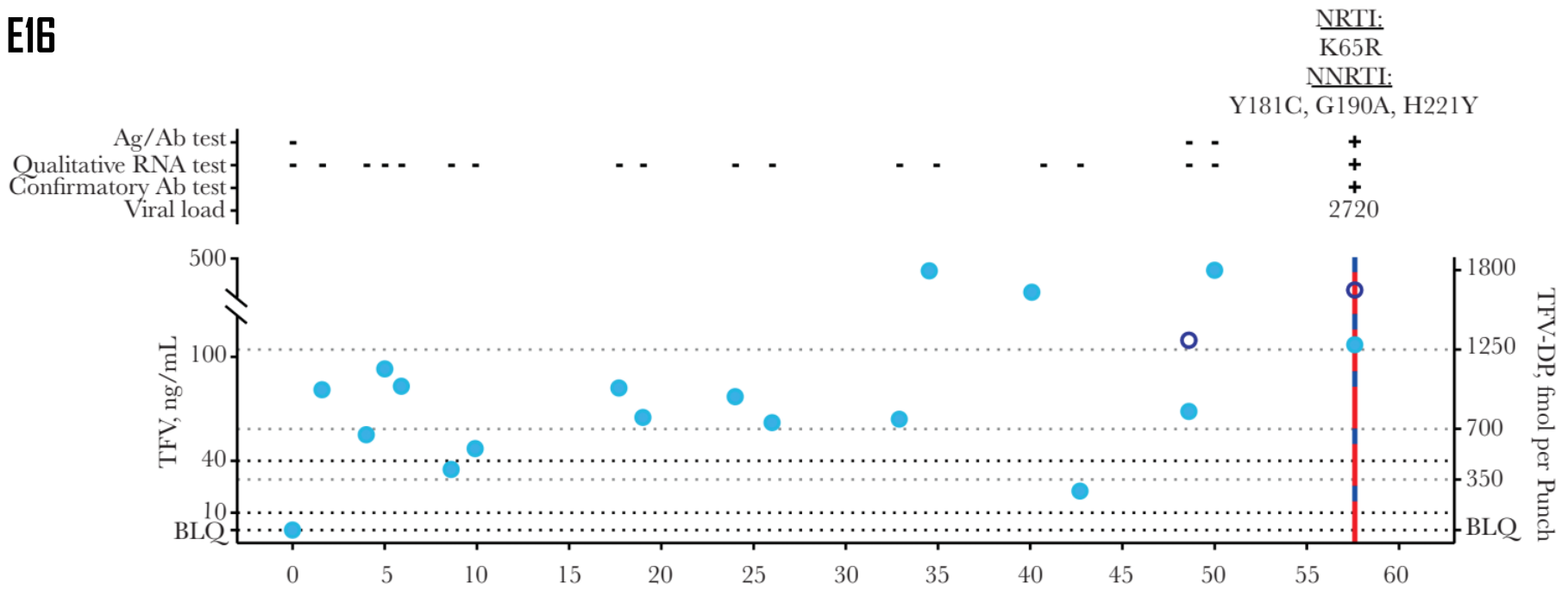
D4



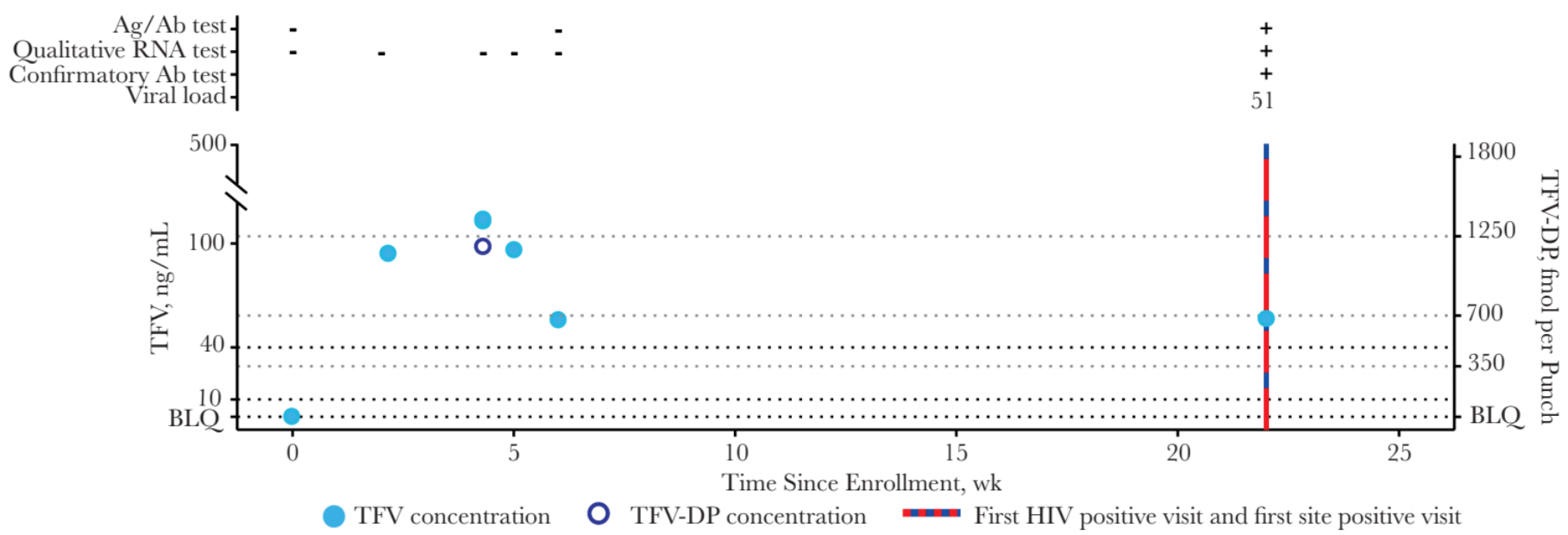
HPTN 083: breakthrough HIV Infections in TDF/FTC Arm

- The half-lives of TFV and TFV-DP are 17 hours and 17 days, respectively
- Plasma and dried blood spots provide detection windows of 1–2 weeks and 2–3 months after TDF/FTC cessation, respectively
- Two of 39 participants with incident infection had TFV and TFV-DP concentrations consistent with daily TDF/FTC adherence

E16

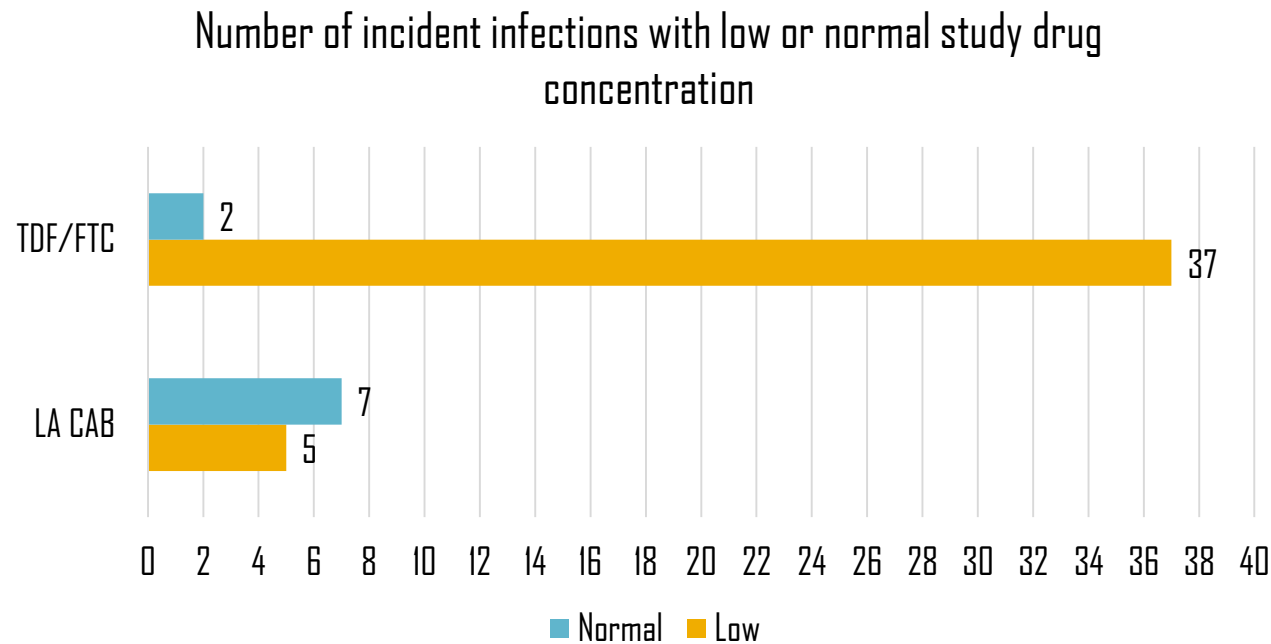


E34



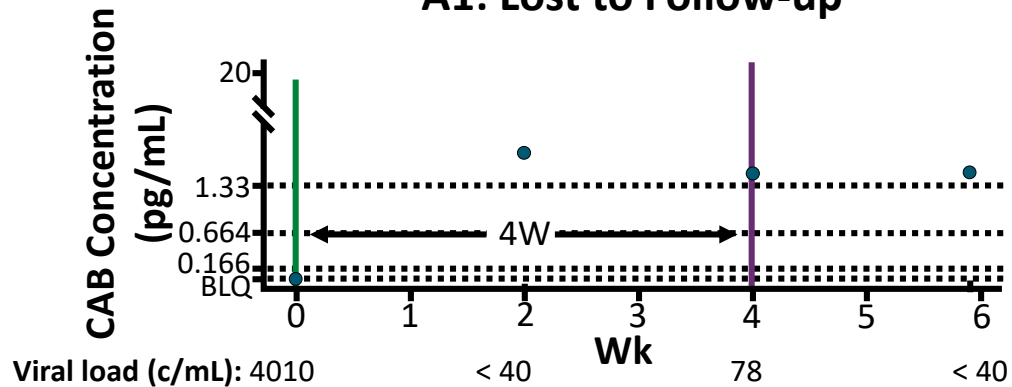
HPTN 083: study drug concentration in incident HIV-1 infections

- Blinded phase of HPTN 083
- 51 incident infections (12 in CAB arm and 39 in TDF/FTC arm)



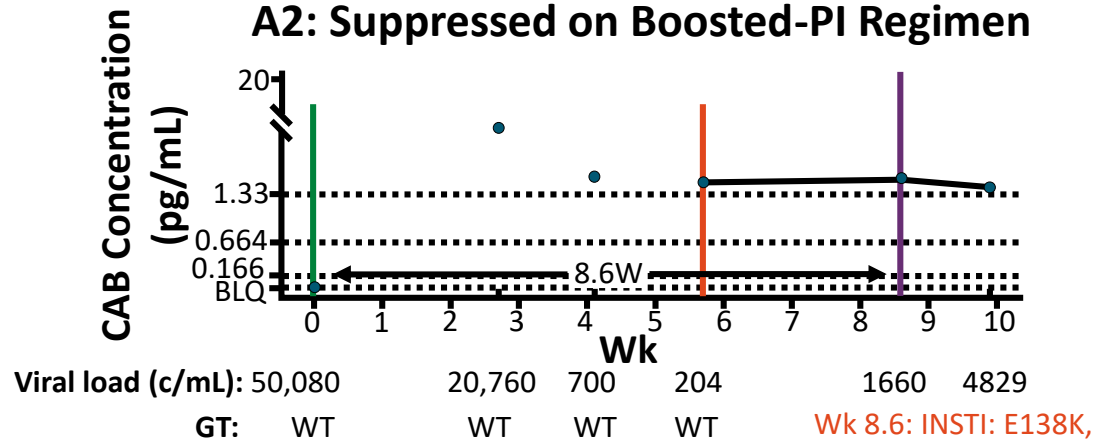
HPTN 083: Laboratory Analysis of Group A in CAB Arm (HIV-Positive Test at Study Enrollment)

A1: Lost to Follow-up



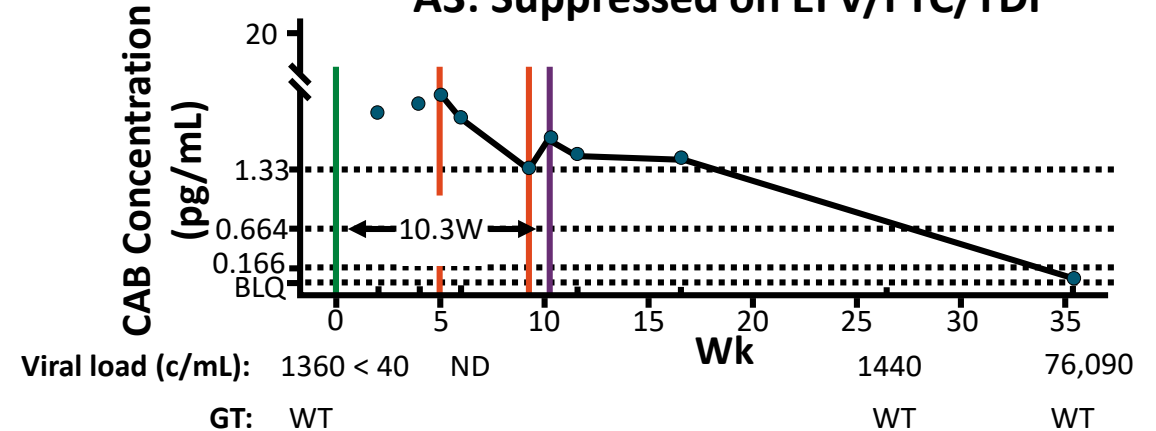
GT at Wk 0: NRTI: K65R, M184V; NNRTI: L100I, K103N, P225H

A2: Suppressed on Boosted-PI Regimen

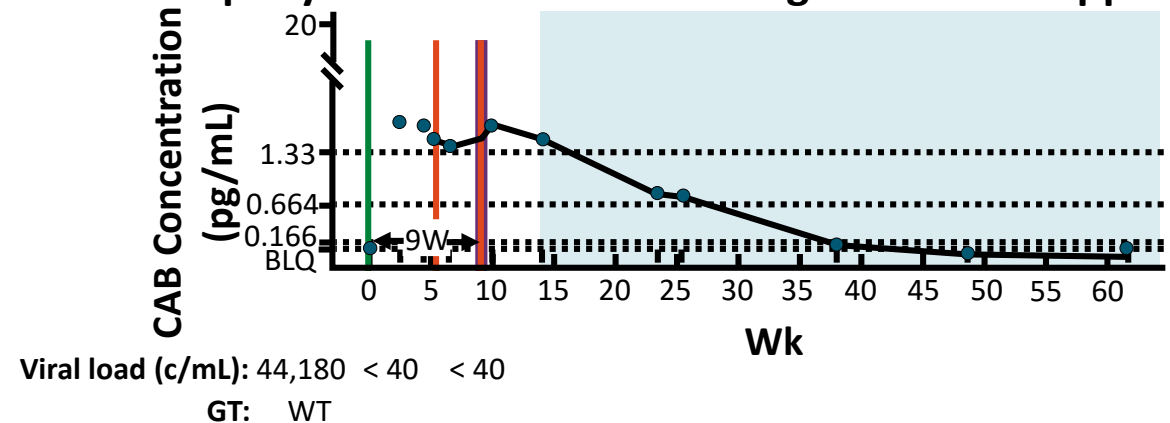


Wk 8.6: INSTI: E138K, Q148K

A3: Suppressed on EFV/FTC/TDF

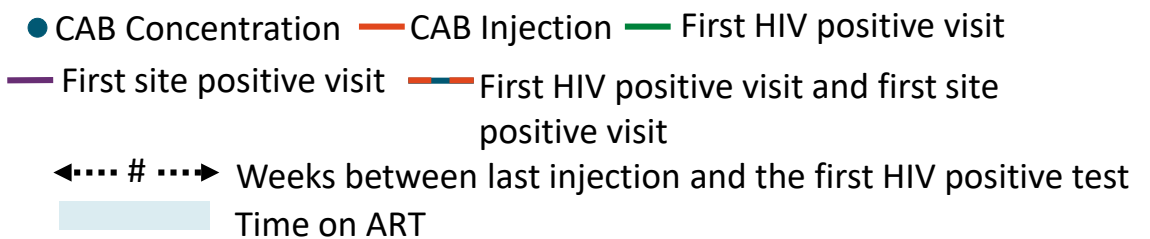
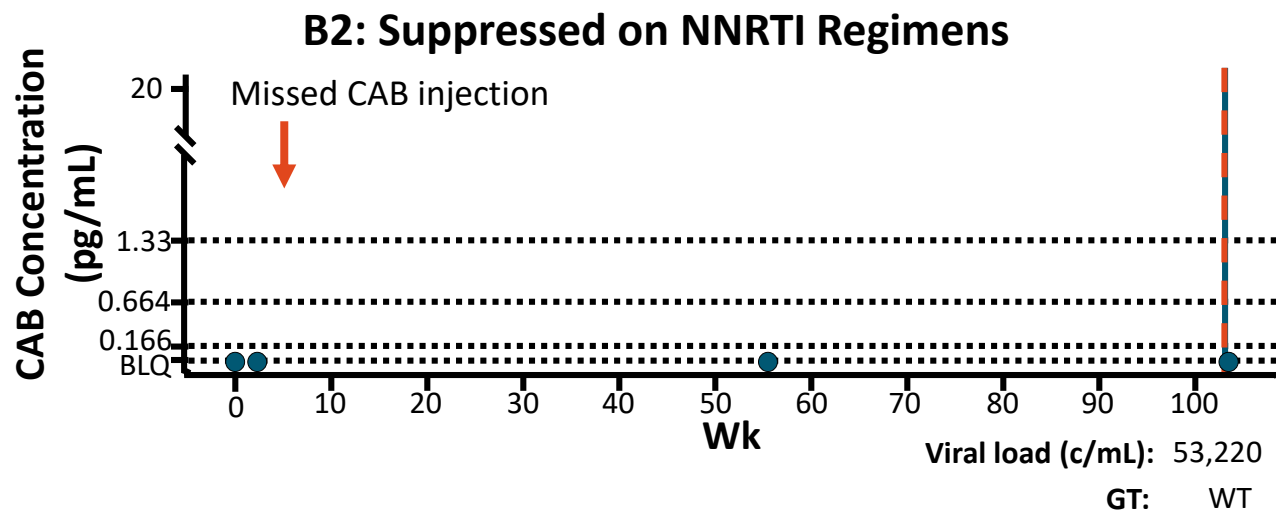
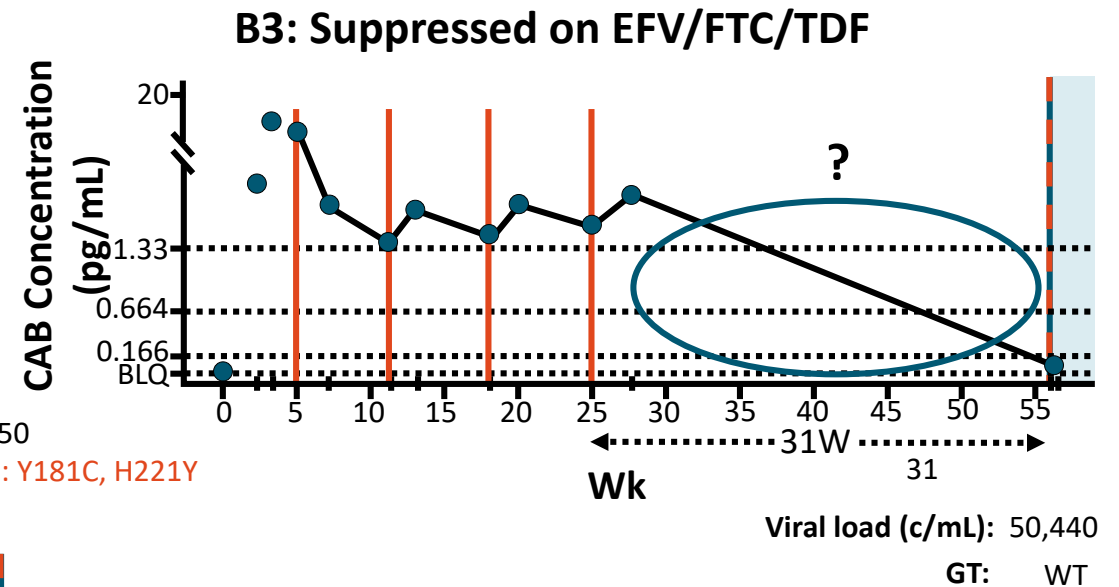
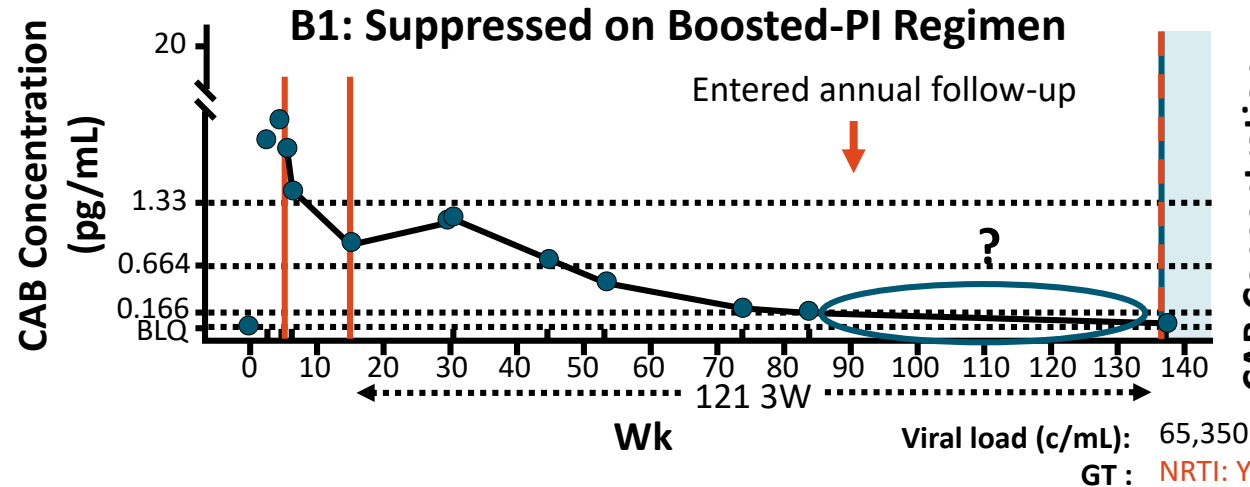


A4: Rapidly Initiated Boosted-PI Regimen With Suppression

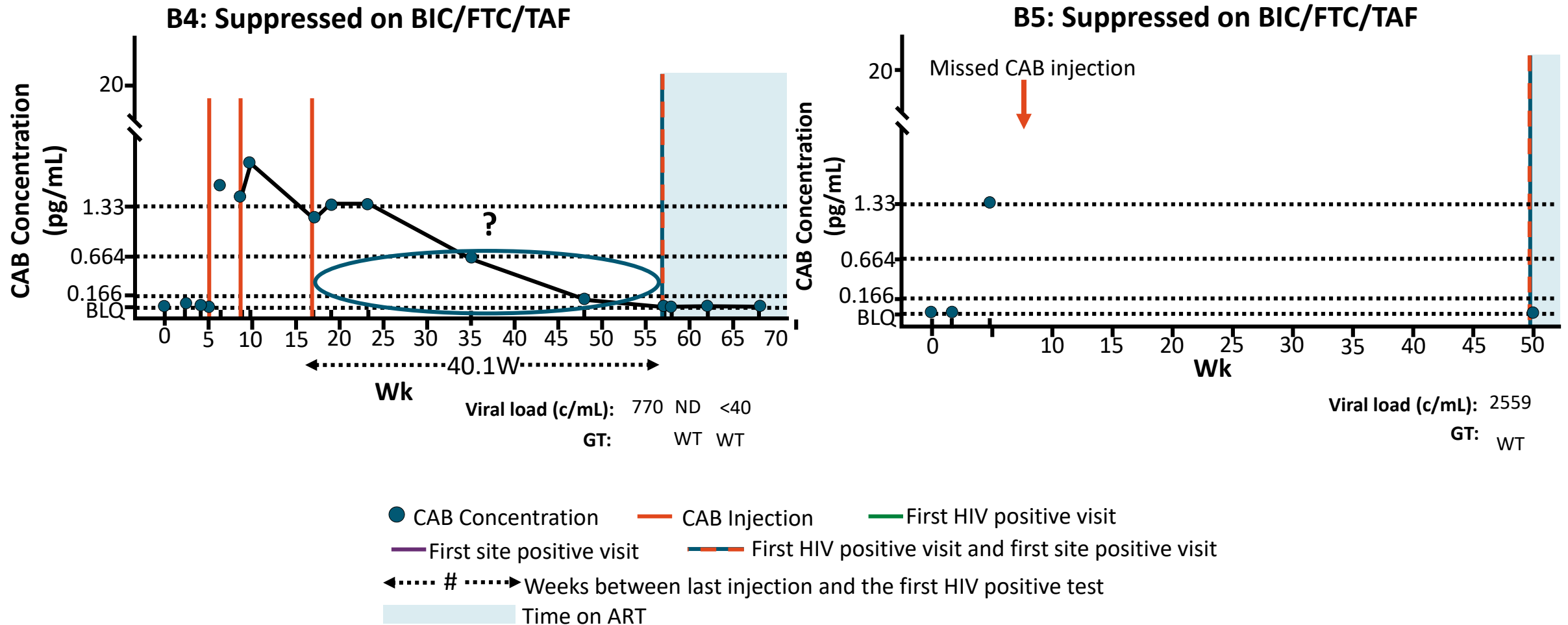


● CAB concentration — CAB injection — First HIV positive visit — First site positive visit Time on ART
 ← # → Weeks between first HIV positive visit and the first site positive test

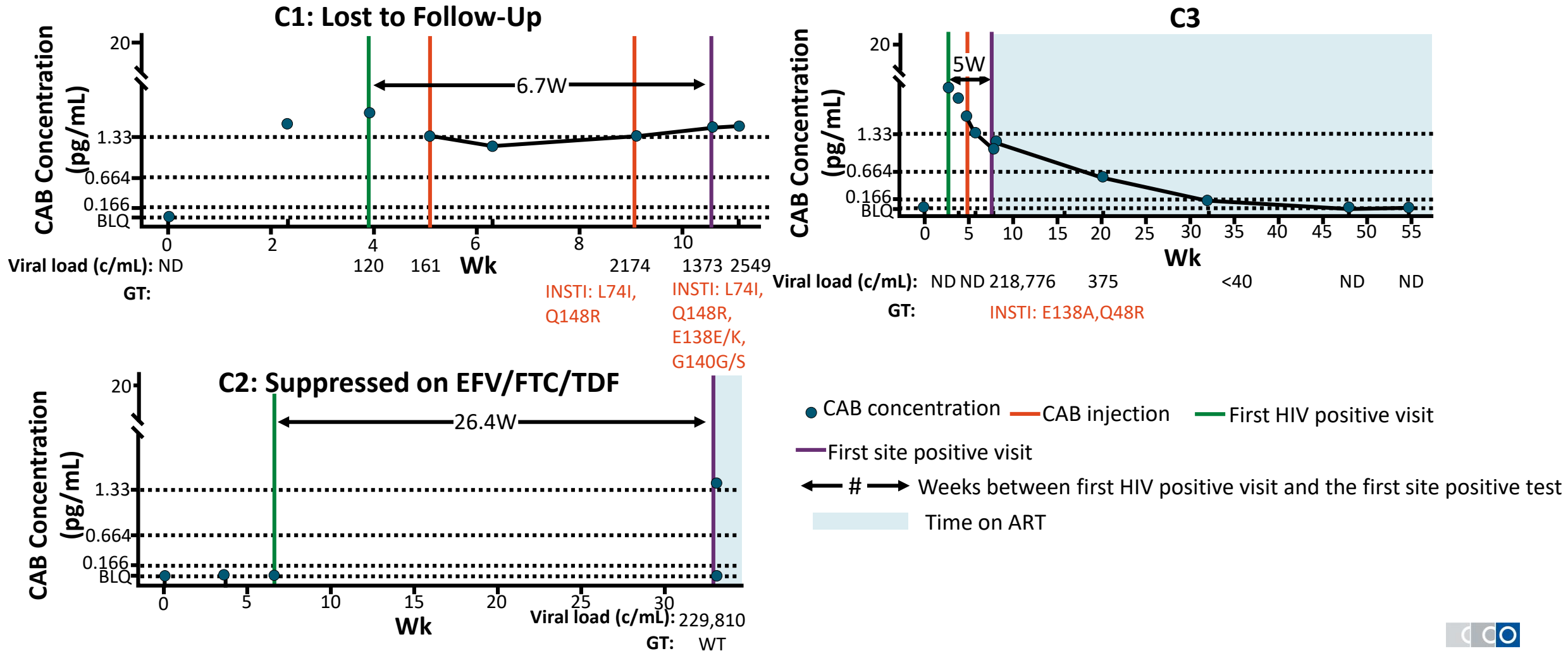
HPTN 083: Laboratory Analysis of Group B in CAB Arm (No Recent CAB Exposure)



HPTN 083: Laboratory Analysis of Group B in CAB Arm (No Recent CAB Exposure)

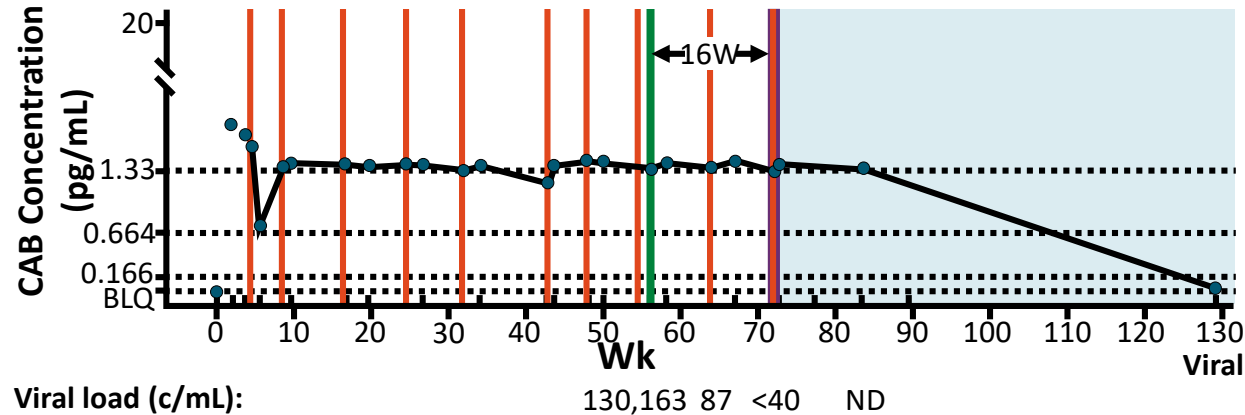


HPTN 083: Laboratory Analysis of Group C in CAB Arm (Infected During CAB Oral Lead-in)

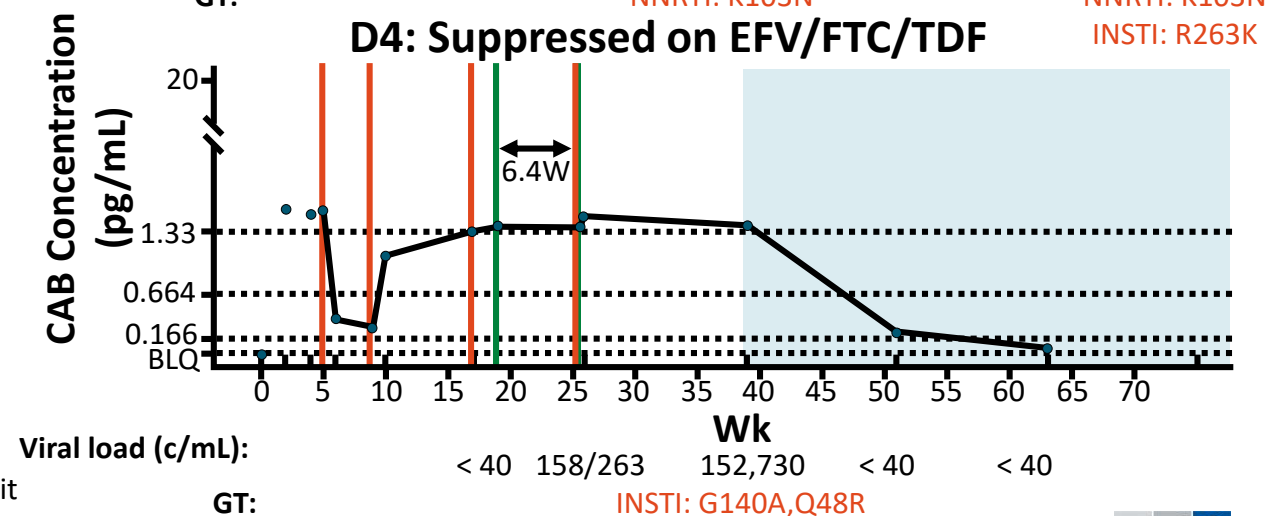
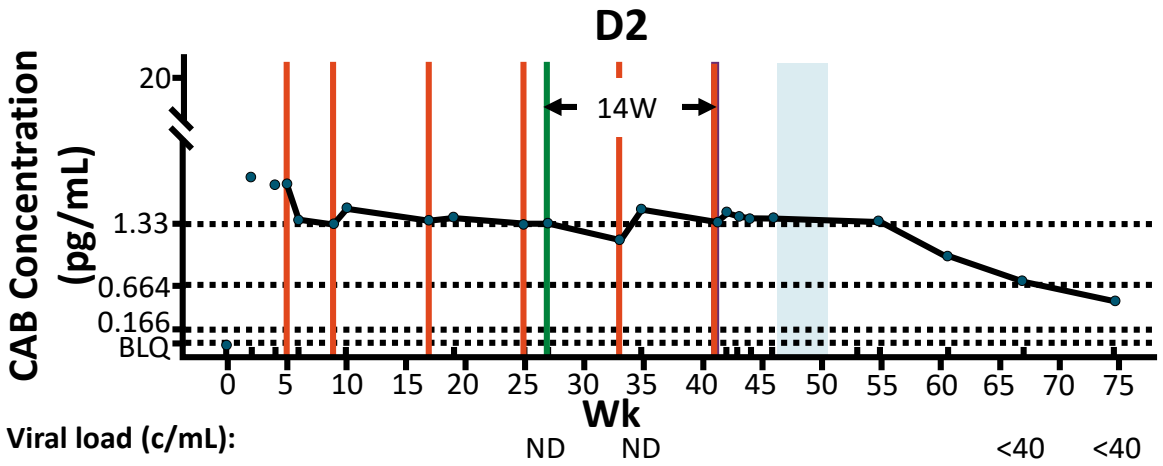
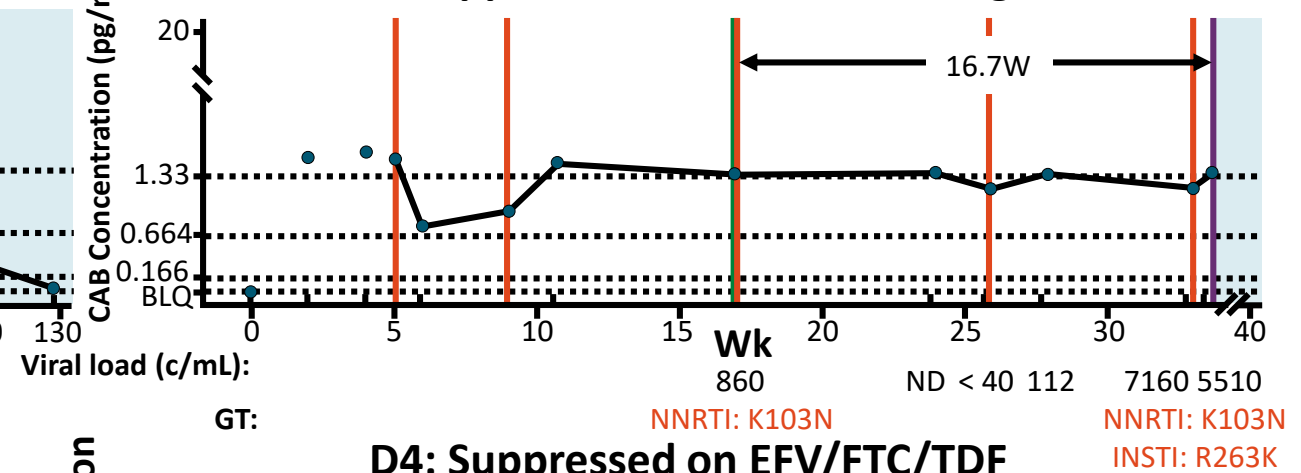


HPTN 083: Laboratory Analysis of Group D in CAB Arm (Infected During On-Time CAB Injections)

D1: Suppressed on Boosted-PI Regimen



D3: Suppressed on Boosted-PI Regimen



● CAB concentration — CAB Injection — First HIV positive visit — First site positive visit
 ← # → Weeks between first HIV positive visit and the first site positive test Time on ART

Case	Sample Type ^a	Visit Type	Subtype	Drug Resistance Mutations ^b				INSTI Phenotype ^{c, d}
				NRTI	NNRTI	PI	INSTI	
A1	1st Viremic	Enrollment	B	K65R , M184V	L100I , K103N , P225H	L10V, I62V	...	NA (assay failure)
A2	1st Viremic	Enrollment	C	...	...	M36I, L89M	...	Sensitive to all INSTIs; RC, 101% (95% CI, 64%–160%)
	Follow-up (60 d later)	wk 6	...	...	...	M36I, L89M	<i>E138K</i> , Q148K	NA (assay failure)
	Follow-up (69 d later)	wk 6	...	...	...	M36I, L89M	<i>E138K</i> , Q148K	NA (assay failure)
B1	1st Viremic	Yearly 1	B	...	V179T, Y181C , H221Y	I62V	...	NA (assay failure)
C1 ^e	1st Viremic	wk 9	B	...	...	L10I, M36I	Q148R	NA (assay failure)
	Follow-up (10 d later)	wk 10	...	...	...	L10I, M36I	<i>E138E/K</i> , <i>G140G/S</i> , Q148R	NA (assay failure)
	Follow-up (14 d later)	wk 10	...	...	...	L10I, M36I	<i>E138E/K</i> , <i>G140G/S</i> , Q148R	NA (assay failure)
C3	1st Viremic	wk 9	B	...	...	M36I, I62V, A71T	<i>E138A</i> , Q148R	CAB (FC, 5.92), EVG (FC above max), RAL (FC, 17), DTG (FC, 1.69), BIC (FC, 1.2); RC, 1.3% (95% CI, .82%–2.1%)
	Follow-up (1 d later)	Interim visit	...	...	...	M36I, I62V, A71T	<i>E138A</i> , Q148R	CAB (FC, 7.42), EVG (FC above max), RAL (FC, 35), DTG (FC, 2.39), BIC (FC, 1.48); RC, 5.2% (95% CI, 3.3–8.3%)
D3	1st Viremic	wk 17	BF	...	K103N	L10V, M36I	...	Sensitive to all INSTIs; RC, 47% (95% CI, 30%–47%)
	Follow-up (112 d later)	wk 33	...	...	K103N	L10V, M36I	R263K	NA (assay failure)
	Follow-up (117 d later)	wk 33	...	...	K103N	L10V, M36I	R263K	CAB (FC, 2.32), EVG (FC, 4.14), RAL (FC, 1.38), DTG (FC, 2.29), BIC ^f (FC, 2.89); RC, 24% (95% CI, 15%–38%)
D4	1st Viremic	Follow-up wk 12	C	...	...	K20R, M36I, L89M	<i>G140A</i> , Q148R	CAB (FC, 13), EVG (FC, 107), RAL (FC, 43), DTG (FC, 2.09), BIC ^f (FC, 2.77); RC, 25% (95% CI, 16%–40%)

RAMs in the CAB arm in HPTN-083

- HIV genotyping performed at the first viremic visit (>500 cps/mL) and at subsequent visits before initiation of ART
- Phenotypic resistance testing was performed for participants in the CAB arm
- Genotyping results were obtained at the first viremic visit for
- Genotype obtained for 13/16 cases in the CAB arm (1 failed analysis; 2 had no viremic visits) and 40/42 in the TDF/FTC arm (2 had no viremic visit)

HIV RNA Screening Reduces INSTI Resistance Risk in Persons Receiving LA CAB for HIV Prevention (HPTN-o83)

Clinical presentation	Case	HIV ST	Number of injections		Detection delay (days)	Viral load (copies/mL)		INSTI RAMs		
			Total	After infection		1 st HIV pos visit	1 st visit with major INSTI RAMs	1 st HIV pos visit	1 st site pos visit	Subsequent visits ^a
Infected before CAB	A2	C	1	1	60	50,080	204	None	M50I, E138K, Q148K	M50I, E138K, Q148K
Infected while receiving oral CAB	C1	B	2	2	47	120	137	L74I, Q146Q/R, E157Q	L74I, E138E/K, G140G/S, Q148R , E157Q	L74I, E138E/K, G140G/S, Q148R , E157Q
	C3	B	1	1	35	15.3 ^b	102,329	None	E138A, Q148R	Not tested/ on ART
Infected while receiving CAB injections	D1	B ^c	10	3	112	130	130	N155H	N155H, R263K^d	Not tested/ on ART
	D2	B ^c	6	2	98	6.1 ^b	<40	N/A	N/A	N155H, S230R
	D3	B/F	5	3	117	860	<40	None ^e	R263K	Not tested/ on ART
	D4	C	4	1	45	<40	158	N/A	M50I, Q148R	M50I, E138E/K, G140A, Q148R

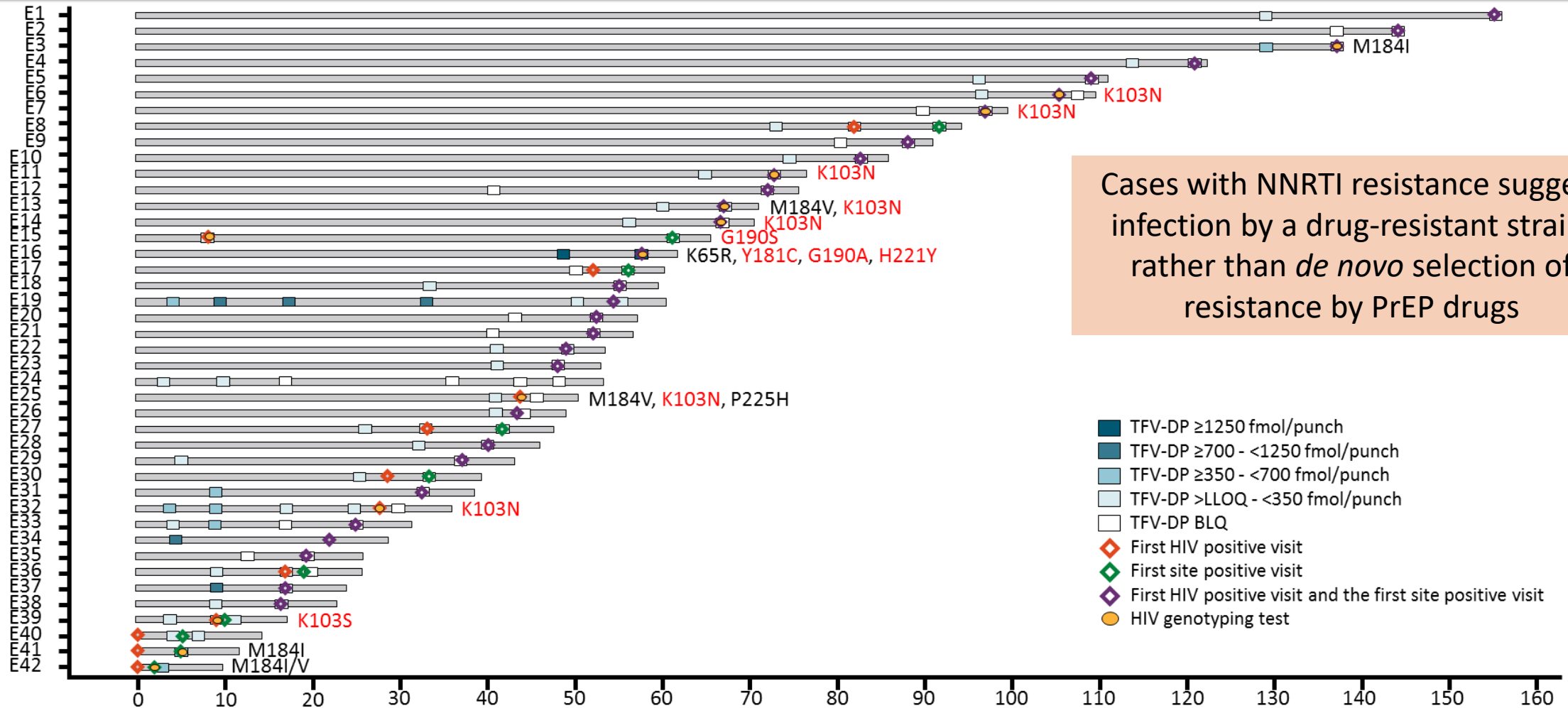
HIV RNA Screening Reduces INSTI Resistance Risk in Persons Receiving LA CAB for HIV Prevention (HPTN-083)

Table 2. Characteristics of the first visit with a major INSTI RAM detected.

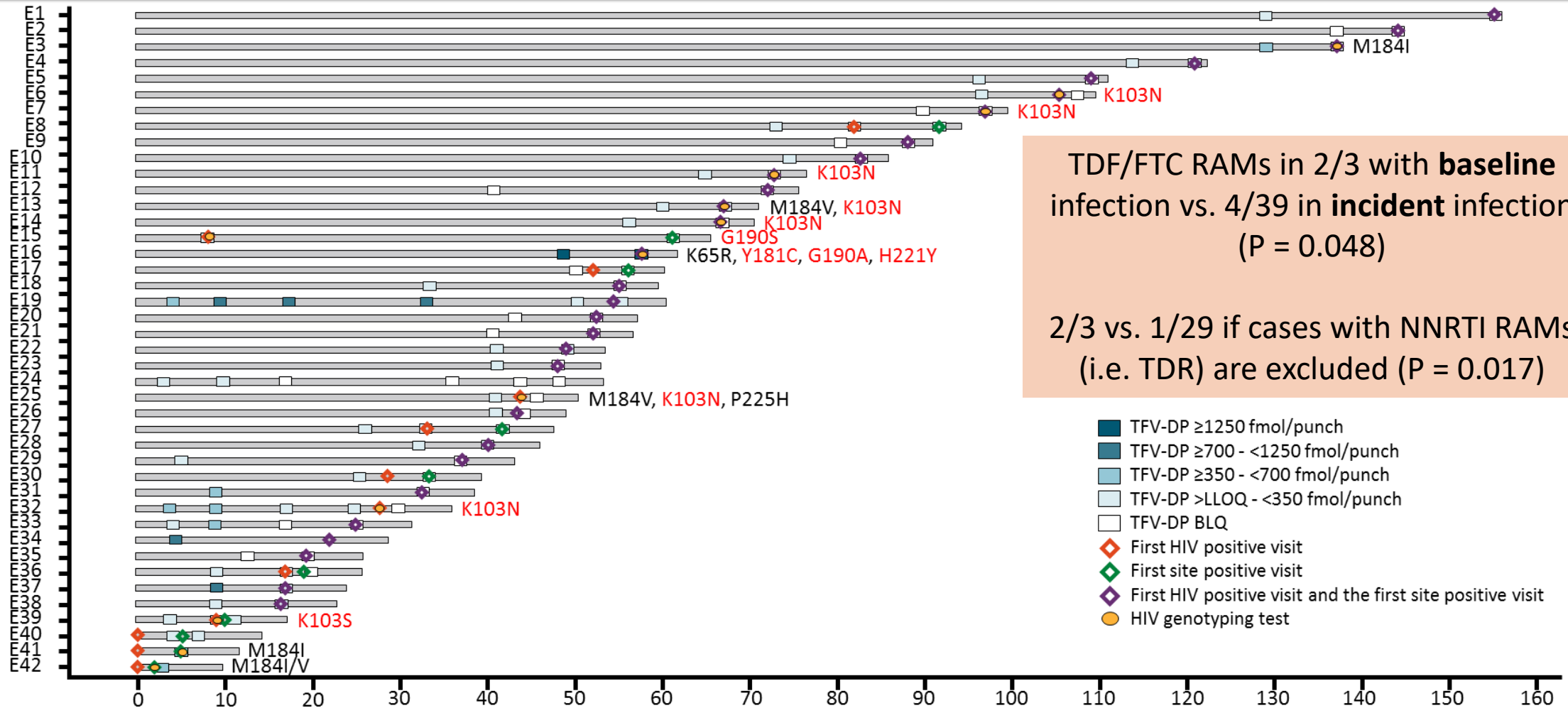
Timing of infection	Case	Viral load (copies/mL)	Major INSTI RAMs detected	Timing			CAB concentration (µg/mL) ^a
				Relative to injections	Relative to the 1 st site pos visit	Days since the 1 st HIV pos visit	
Enrollment	A2	204	E138E/K, Q148K/R	1 st injection visit	Before	40	3.318
While receiving oral CAB	C1	137	Q148Q/R	8 days after the 1 st injection	Before	17	1.219
	C3	102,329	E138A, Q148R	20 days after the 1 st injection	Same visit	35	1.108
While receiving CAB injections	D1	130	N155H	8 th injection visit	Before	0	1.613
	D2	<40	N155H	182 days after the 6 th injection	After ^b	280 ^b	0.703
	D3	<40	R263K	4 th injection visit	Before	62	1.213
	D4	158	Q148R	4 th injection visit	Same visit ^c	45	1.930

^aThe concentration of cabotegravir associated with protection against HIV infection (PAIC90) is 1.330 µg/mL.

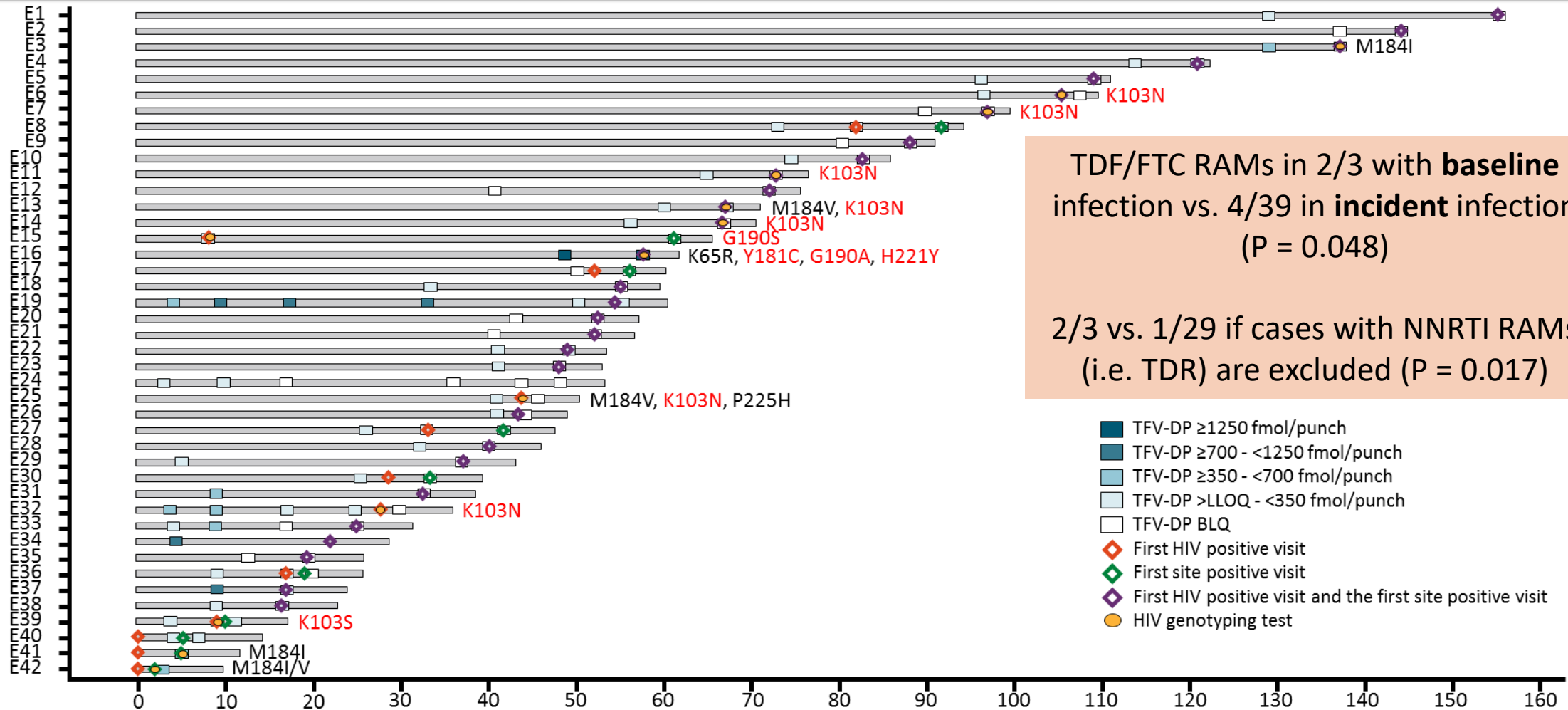
HPTN 083: HIV Infections in FTC/TDF Arm



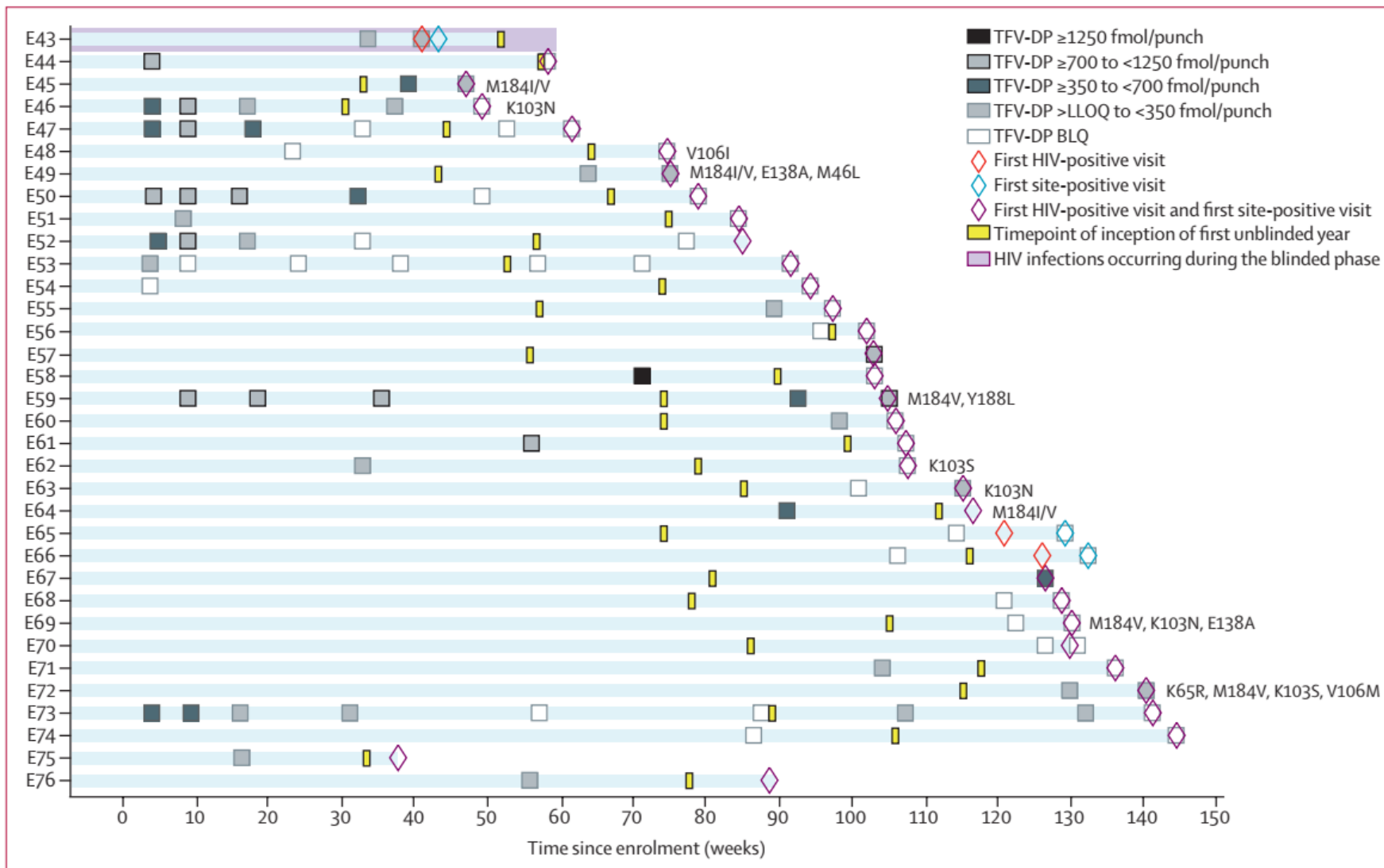
HPTN 083: HIV Infections in FTC/TDF Arm



HPTN 083: HIV Infections in FTC/TDF Arm



HPTN 083 one year after study unblinding



Pharmacological and virological data for HIV infections in the oral tenofovir disoproxil fumarate plus emtricitabine group that were identified in the extended analysis.

HIV genotyping results are shown for the first visit with a viral load greater than 500 copies per mL.

INSTI Resistance Occurring During PrEP With LA CAB

- In HPTN 083, INSTI resistance occurred in 10/18 cases within 6 mo of first HIV+ visit
 - INSTI resistance was not observed if first HIV+ visit >6 mo after LA CAB injection
 - Most infections detected by retrospective sensitive HIV-1 RNA assay before INSTI resistance emerged
- HIV-1 RNA screening being considered in ongoing HPTN 083 and HPTN 084 studies

HPTN 083: Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women

- Marzinke CROI 2021
- INSTI resistance
 - Observed upon viremic “escape” at higher CAB concentrations
 - Not observed in 3 tail-phase infections or 1 tail “escape” case
- Therefore, prompt diagnosis and initiation of ART are important to avoid resistance with CAB LA

HPTN 083: Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women

- In HPTN 083, 4 incident infections were observed despite on-time injections and expected cabotegravir concentrations in plasma
- The risk of PrEP failure may be influenced by
 - low plasma cabotegravir concentrations between initial injections
 - low cabotegravir concentrations in rectal tissue
 - rectal inflammation related to sexually transmitted infection

HPTN 083 one year after study unblinding

- One year after unblinding data from 3290 of the 4488 participants who contributed person-time to the blinded analysis (of 4566 ITT participants)
- Updated HIV incidence per 100 PYFU in the blinded phase: 0.41 for LA CAB PrEP vs. 1.29 for daily oral TDF/FTC PrEP (HR 0.31 [0.17–0.58], $p=0.0003$)
- HIV incidence per 100 PYFU in the first unblinded year: 0.82 for LA CAB PrEP vs. 2.27 for daily oral PrEP (HR 0.35 [0.18–0.69], $p=0.002$)

HPTN 083 one year after study unblinding

- 3 additional incident infections later found to have occurred within the blinded period (1 CAB, 2 TDF/FTC), updating incident infections during the blinded phase to 13 and 41
- 22 additional infections in the long-acting PrEP group included 2 with on-time injections; 3 with one or more delayed injections; 2 detected with long-acting PrEP reinitiation; and 11 more than 6 months after their last injection
- Infection within 6 months of cabotegravir exposure was associated with diagnostic delays and INSTI resistance
- 6 cabotegravir infections identified to date that occurred despite on-time injections, including the two cases described in this report; major INSTI RAMs were identified in all six cases
- LA PrEP correlates or thresholds of protection might be distinct for rectal, vaginal, penile, and parenteral exposures
- HIV infections that occurred more than 6 months after the last cabotegravir injection did not result in INSTI resistance and were usually detected without delay using standard testing algorithms

HPTN 083 one year after study unblinding

- Almost all of the infections observed in the daily oral PrEP group of HPTN 083 occurred in participants with poor adherence or no evidence of drug dosing
- Because the active forms of tenofovir and emtricitabine have relatively short plasma half-lives, infections in people taking daily oral PrEP can usually be detected with little or no delay using routine testing algorithms, apart from in the window or eclipse phase of early acute HIV infection
- In fact, all detection delays in participants in the daily oral PrEP group of HPTN 083 were due to detection of the infection during the acute phase (ie, Fiebig Stage I14), which reflected frequent study visits

HPTN 083 one year after study unblinding

Fifty-two additional HIV infections are described in this report (18 CAB arm, 34 TDF/FTC arm). Three of these cases occurred in the blinded phase of the study (1 CAB 2 TDF/FTC arm) and 49 occurred in the first unblinded year (17 CAB arm, 32 TDF/FTC arm). The table below summarizes the timing of HIV infections and the number of cases included in the assessment of HIV incidence.

	Total # cases	# incident cases	# cases included in the HIV incidence assessment [†]
Blinded phase (updated)			
CAB arm	17	13 [¶]	13 [¶]
TDF/FTC arm	44	41	41
First unblinded year			
CAB arm	17	17	12 [‡]
TDF/FTC arm	32	32	32
Total (updated analysis)			
CAB arm	34	30	25 [‡]
TDF/FTC arm	73	73	73

[†] This group is limited to incident infections that occurred <3 years after study initiation.

[‡] Excludes five infections that occurred >3 years after study initiation.

[¶] One prevalent (baseline) infection in the CAB arm was initially characterized as an incident infection and was included in the HIV incidence assessment in the primary study report; that case is not included here.

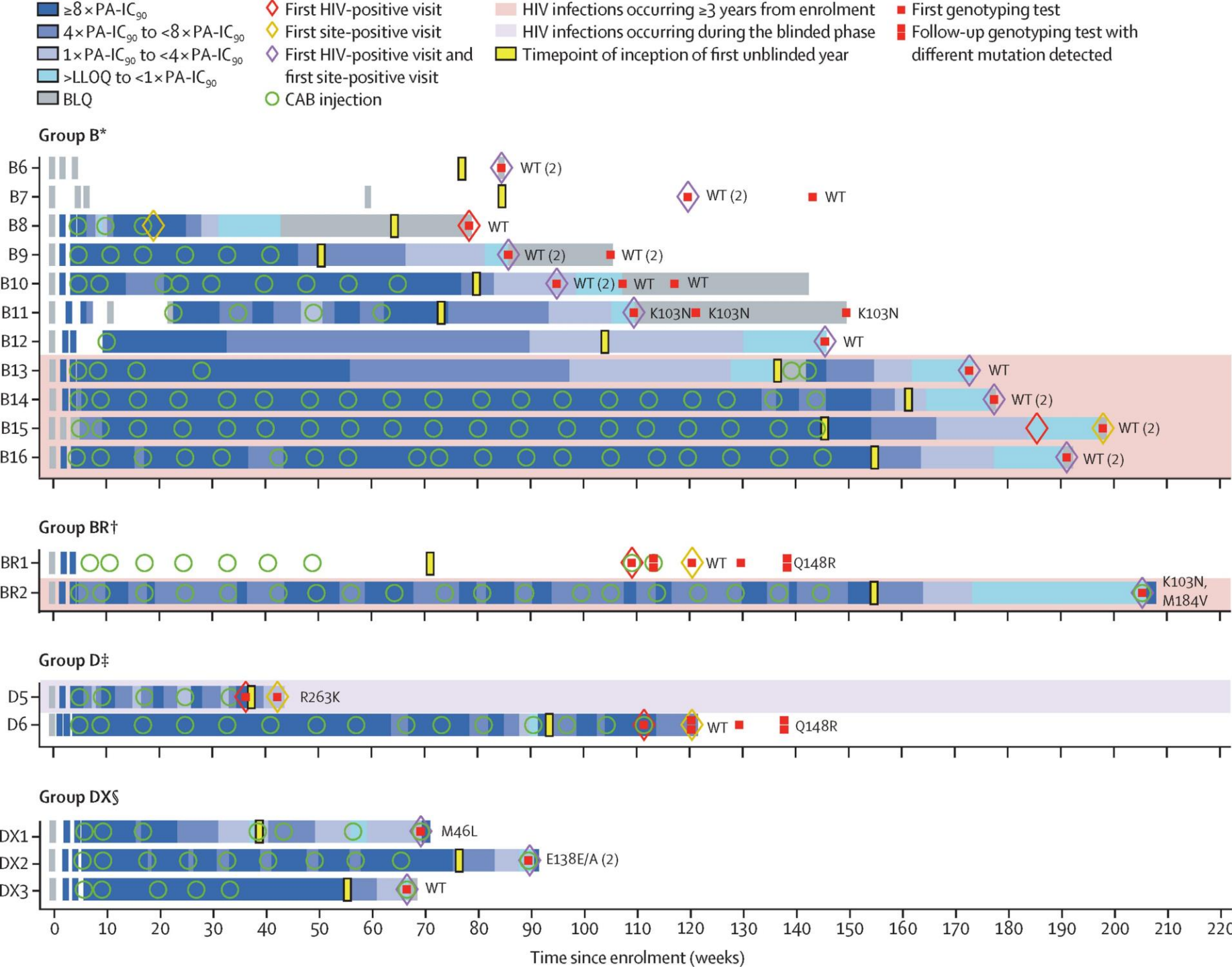
HPTN 083 one year after study unblinding

	Long-acting cabotegravir group	Daily oral tenofovir disoproxil fumarate plus emtricitabine group	HR (95% CI)	p value
Blinded phase (updated analysis)	..	..	0.31 (0.17–0.58)	0.0003
Number of participants	2241	2247	..	..
Median (IQR) time on study, days	511 (314–700)	511 (307–700)	..	..
Infections/person-years	13/3204	41/3186	..	..
Incidence rate per 100 person-years (95% CI)	0.41 (0.22–0.69)	1.29 (0.92–1.75)	..	..
First unblinded year analysis	..	..	0.35 (0.18–0.69)	0.0021
Number of participants	1663	1627	..	..
Median (IQR) time on study, days	344 (275–380)	342 (279–378)	..	..
Infections/person-years	12/1456	32/1410	..	..
Incidence rate per 100 person-years (95% CI)	0.82 (0.43–1.44)	2.27 (1.55–3.20)	..	..
Combined period	..	..	0.34 (0.22–0.53)	<0.0001
Number of participants	2244	2248	..	..
Median (IQR) time on study, days	823 (596–1026)	808 (577–1015)	..	..
Infections/person-years	25/4660	73/4596	..	..
Incidence rate per 100 person-years (95% CI)	0.54 (0.35–0.79)	1.59 (1.25–2.00)	..	..

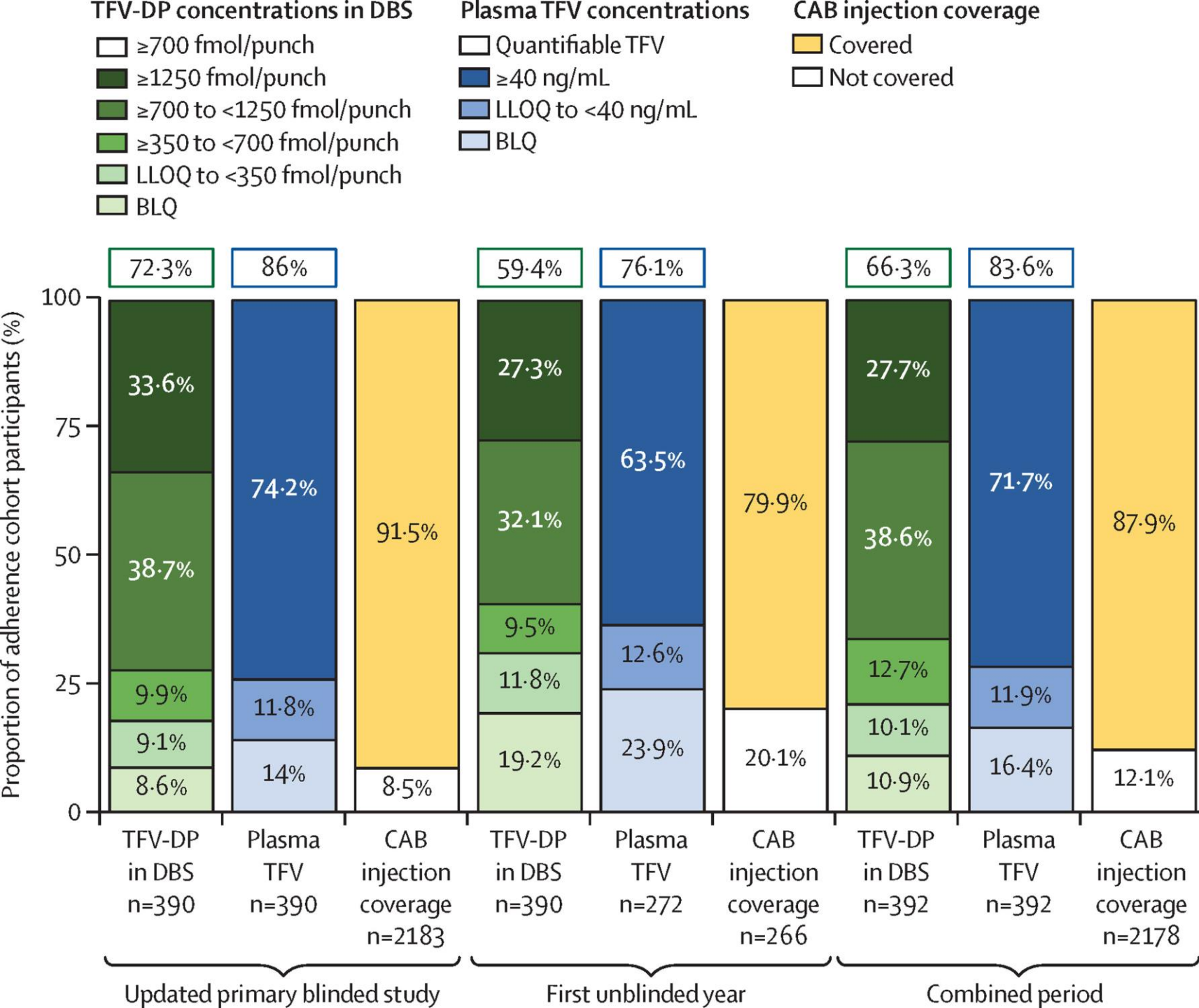
HR=hazard ratio.

Table 1: HIV incidence overall, by treatment group, and by analysis period

HPTN 083 one year after study unblinding



- group A, infection present at study entry
- group B, infections detected more than 6 months after the last cabotegravir injection
- group C, infections detected during the oral lead-in phase
- group D, infections in the setting of on-time injections
- group DX, infections in the setting of at least one inter-injection delay of 10 weeks or more but not meeting group B criteria
- group BR, infections detected more than 6 months after the last injection that were identified when long-acting PrEP was restarted in the open-label study



HPTN 083 one year after study unblinding

- Study product adherence during the blinded phase, first unblinded year, and combined period
- Adherence to both study products decreased after study unblinding
- CAB coverage was defined by an initial injection providing 6 weeks of anticipated protective coverage and subsequent injections providing 10 weeks of anticipated coverage

HPTN 083 one year after study unblinding

TABLE 1 Classification of HIV infections in the CAB arm of HPTN 083^a

Case type	Case description	Infection description	Classification		
			Previous report	Current report	No. of cases
A	Baseline infection	HIV positive at study enrollment	A1–A4		4
B	No recent CAB administration	No CAB administration in the 6 mo before the 1st HIV-positive visit	B1–B5	B6–B16	16
C	Oral-phase infection	Infected during the 5-wk oral CAB lead-in phase	C1–C3		3
D	Infected despite on-time injections	Infected <6 mo after the last injection with on-time injections	D1–D4 ^b	D5–D6	6
DX	Delayed injection	Infected <6 mo after the last injection with at least 1 delayed injection (>70 days after the last injection)		DX1–DX3	3
BR	CAB restarted after infection	No CAB administration in the 6 mo before the 1st HIV-positive visit; CAB restarted at or after the 1st HIV-positive visit		BR1–BR2	2
Total no. of cases			16	18	34

^aThe approach used to classify infections in the cabotegravir (CAB) arm of HPTN 083 is shown. Sixteen cases were described in a previous report (3); 18 additional cases are included in this report. HIV testing performed at study sites and the HPTN Laboratory Center was used to determine HIV infection status and identify the first HIV-positive visit. Injections were classified as delayed if they were administered >2 weeks after the planned injection date (>44 days after the 1st injection or >70 days after subsequent injections).

^bOne case that was classified as a D case in the previous report had a single late injection (D1) (75 days after the previous injection); that case would have been classified as a DX case according to the updated classification system used in this report.

HPTN 083 one year after study unblinding

- HIV infections in CAB arm in current analysis included 3 cases with INSTI mutations
- In FTC/TDF arm, 2 of 34 infections in current analysis not explained by adherence

Category of Infections in CAB Arm in Current Analysis, n	HIV Infections in CAB Arm (n = 18)
≥6 mo after last CAB exposure	7
≥6 mo after last CAB exposure and >3 yr from enrollment	4
≥1 injection delayed by ≥10 wk	3
≥6 mos after last CAB exposure, reinitiated CAB	2
With on-time injections	2

Overall Summary Major INSTI RAMS in CAB Arm of HPTN 083			
Category of HIV Infection	HIV Infections, n	INSTI RAMs, n (%)	INSTI RAMs
CAB initiated/reinitiated with occult HIV infection	4 (before drug administration)	1 (25)	E138E/K, Q148K/R
	2 (≥6 mos after last CAB exposure, reinitiated CAB)	1 (50)	Q148R
Acquired during oral lead-in	3	2 (66)	E138A/E/K, G140G/S, Q148R
Breakthrough infection with on-time injections	6	6 (100)	E138K, G140A, Q148R, N155H, R263K
Breakthrough infection with ≥1 injection delayed ≥10 wk	3	0 (0)	-
Infection 6+ mo from last injection	16	0 (0)	-

Delayed detection of HIV infection under CAB shield



Minimal or no
symptoms



Very low viral load



Decreased/delayed
antibody

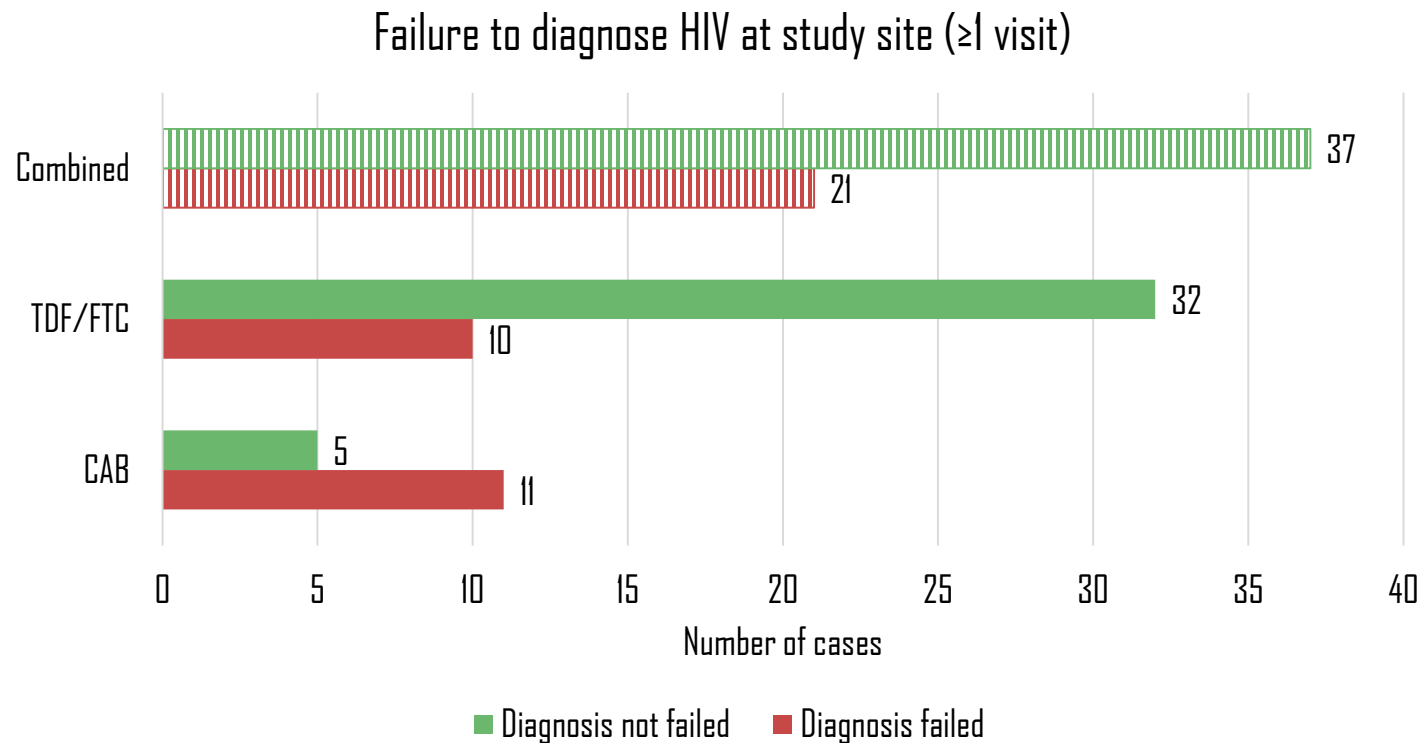
Long-acting early viral inhibition syndrome (LEVI)

HIV Monitoring on PrEP

- 2021 CDC guidelines recommend **HIV-1 RNA assays** for monitoring people receiving **both oral and LA injectable PrEP**¹
 - Every 3 mo with oral PrEP; every 2 mo with LA CAB
- In HPTN 083, HIV detection with antigen/antibody testing was delayed compared with qualitative HIV-1 RNA testing for both arms²

Delays in Diagnosis, Median Days ^{3,4}	Baseline Infections	Incident Infections
CAB	62	98
FTC/TDF	34	31

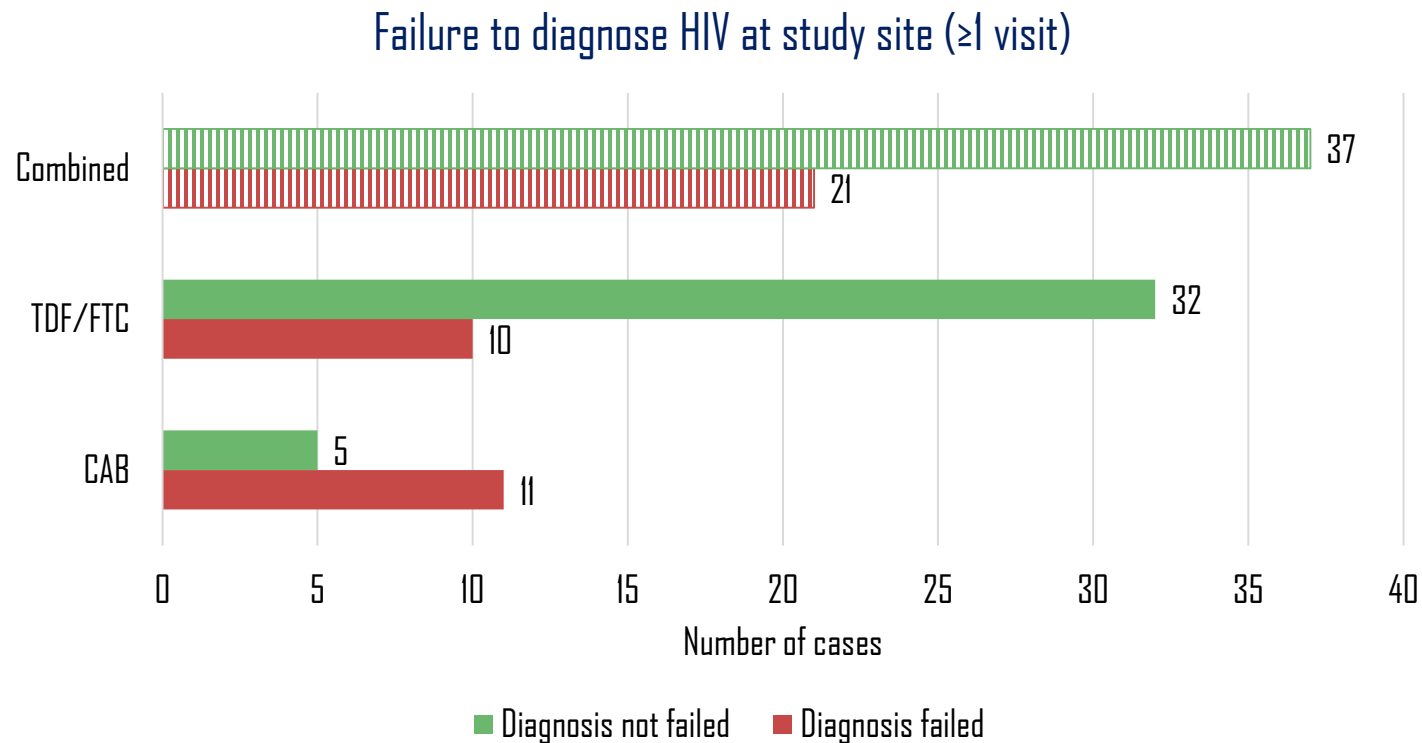
Delayed detection of HIV infection in HPTN 083



Provision/administration of study drug after infection in 5/10 and 11/11 undiagnosed participants in TDF/FTC and CAB arm, respectively

- 16 HIV-1 infection cases in CAB arm (4 baseline and 12 incident cases)
- 42 HIV-1 infection cases in TDF/FTC arm (3 baseline and 39 incident cases)
- HIV testing based on rapid test plus Ab/Ag combo at study site, Ab/Ag combo plus qualitative HIV-1 RNA at HPTN lab

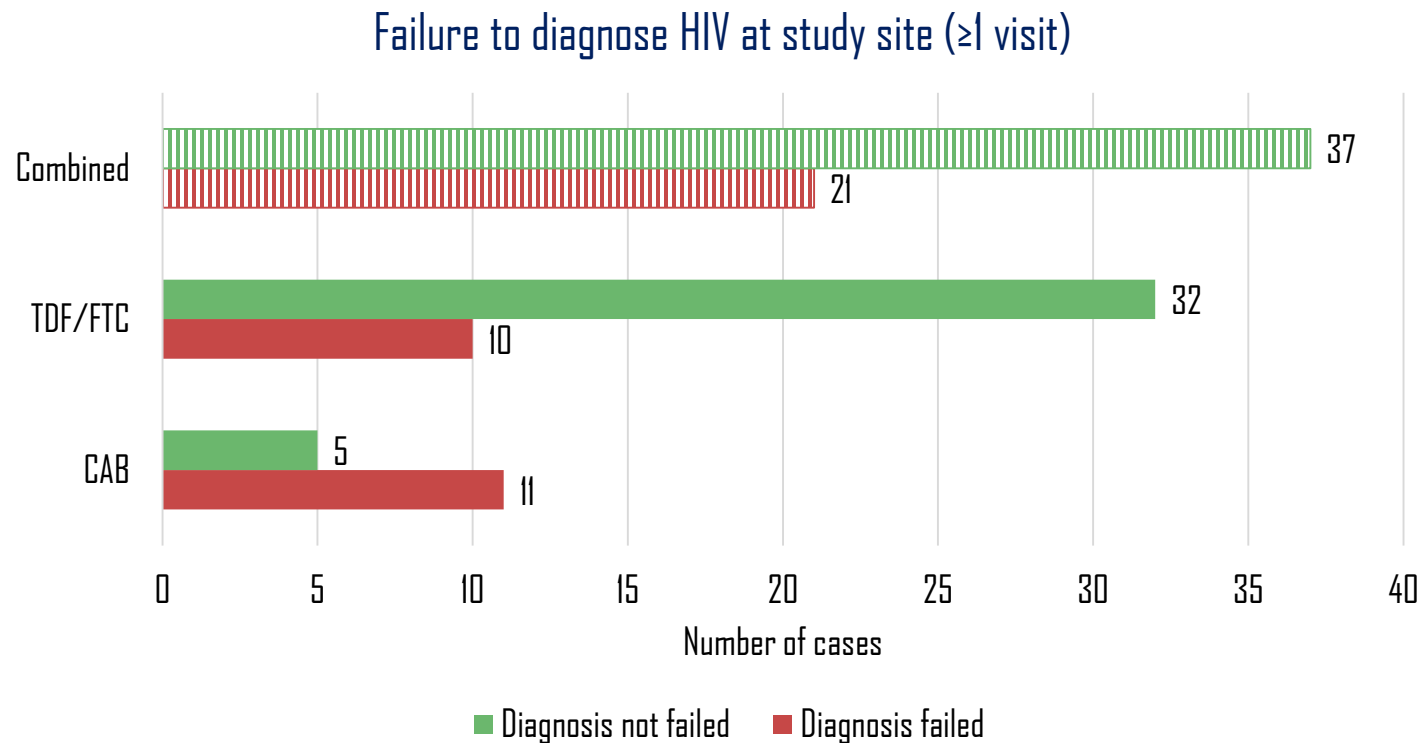
Delayed detection of HIV infection in HPTN 083



Provision/administration of study drug after infection in 5/10 and 11/11 undiagnosed participants in TDF/FTC and CAB arm, respectively

- 11/16 CAB cases with **delayed diagnosis**
 - 4/4 with baseline infection, median VL 24095 cps/mL
 - 7/12 with incident infection, median VL 130 cps/mL
- **VL testing** would have detected infection at first HIV-positive visit in 4/4 baseline infections and 5/7 incident infections

Delayed detection of HIV infection in HPTN 083



Provision/administration of study drug after infection in 5/10 and 11/11 undiagnosed participants in TDF/FTC and CAB arm, respectively

- 10/42 TDF/FTC cases with **delayed diagnosis**
 - 3/3 with baseline infection, median VL 1930 cps/mL
 - 7/39 with incident infection, median VL 13230 cps/mL
- **VL testing** would have detected infection at first HIV-positive visit in 3/3 baseline infections and 6/7 incident infections

Delayed detection of HIV infection in HPTN 083

Feature	CAB arm	TDF/FTC arm
Cases with delayed diagnosis*	4/4 with baseline infection 7/12 with incident infection 11/16 (69%) overall	3/3 with baseline infection 7/39 with incident infection 10/42 (24%) overall
Median delay (days)	62 [28–72] for baseline cases 98 [35–185] for incident cases	34 [14–36] for baseline cases 31 [7–68] for incident cases
Median VL at first positive visit (cps/mL)	24095 (1360–50080) for baseline cases 130 (<40 to 860) for incident cases	1930 (124–10000) for baseline cases 13230 (<40 to 22 070) for incident cases
Infections which would have been detected by HIV-1 RNA testing at study site	4/4 with baseline infection 5/7 with incident infection	3/3 with baseline infection 6/7 with incident infection
Prolonged viral suppression	2/4 with baseline infection 6/12 incident cases	0/3 with baseline infection 0/39 incident cases

*Defined as failure to detect infection at ≥ 1 study visits at study site

Adapted from Marzinke, J Infect Dis 2021

Delayed detection of HIV infection in HPTN 083

Feature	CAB arm	TDF/FTC arm
Cases with delayed diagnosis*	4/4 with baseline infection 7/12 with incident infection 11/16 (69%) overall	3/3 with baseline infection 7/39 with incident infection 10/42 (24%) overall
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*Defined as failure to detect infection at ≥ 1 study visits at study site

Adapted from Marzinke, J Infect Dis 2021

Delayed detection of HIV infection in HPTN 083

	CAB Arm			TDF/FTC Arm	
	Baseline: Group A (n = 4)	Incident: Group B (n = 5)	Incident: Groups C and D (n = 7)	Baseline (n = 3)	Incident (n = 39)
Delay between 1st reactive qualitative RNA test and 1st reactive Ag/Ab test					
Participants, no. (%)	3 (75)	0	7 (100)	3 (100)	8 (21)
Duration of delay, range, d (among those with delayed Ag/Ab test result)	14-60 ^b	NA	35-185	14-36	7-68 ^c
Delay between 1st reactive qualitative RNA test and 1st positive confirmatory Ab test					
Participants, no. (%)	4 (100) ^d	1 (20)	7 (100) ^e	3 (100)	18 (46) ^f
Duration of delay, d (among those with delayed confirmatory Ab test result)	60-248 ^d	3	36-185 ^e	21-49	4-68 ^{c,f}
Participants with assay reversion, no. (%)					
Ag/Ab test (from reactive to nonreactive)	2 (50) ^b	0	2 (29)	0	0
Confirmatory Ab test (from indeterminate to negative)	0	0	1 (14) ^g	0	0
Qualitative RNA test (from reactive to nonreactive)	2 (50)	0	2 (29)	0	0

^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. ^dTwo cases did not achieve a positive confirmatory Ab test (longest pre-ART follow-up, 98 days). ^eThree cases did not achieve a positive confirmatory Ab test (longest pre-ART follow-up, 333 days). ^fEight cases did not achieve a positive confirmatory Ab test (longest pre-ART follow-up, 14 days). ^gThis participant did not achieve a positive confirmatory Ab test after 333 days of follow-up.

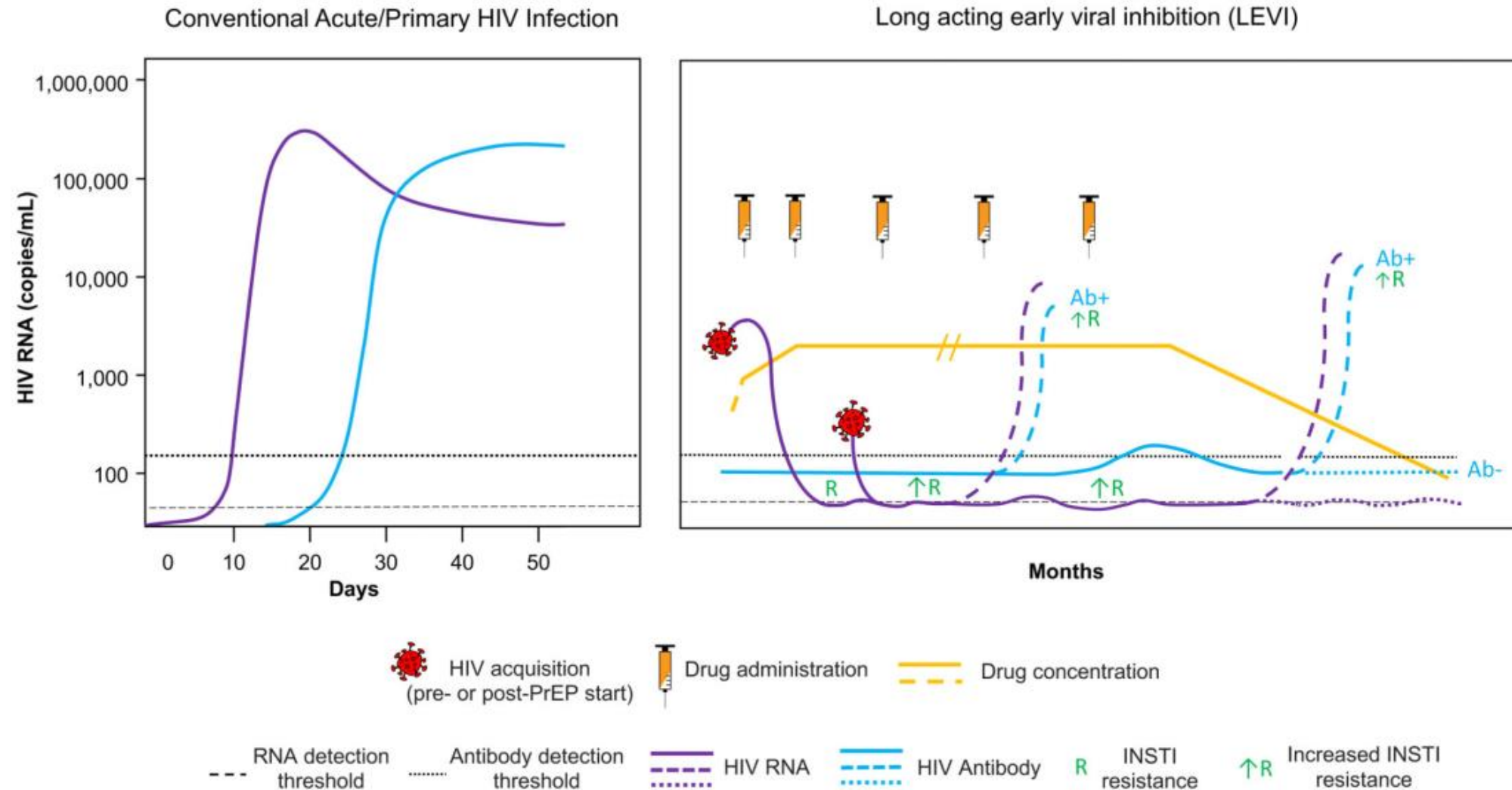
AHI vs LEVI Syndrome With LA CAB PrEP

Feature	AHI	LEVI
Cause	Phase of natural HIV infection	LA ARV for PrEP
Onset	New infection	Infection during PrEP; initiation of PrEP 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, RNA (including point-of-care and pooled tests), DNA, and total nucleic acid assays	Ultrasensitive RNA assay (often low/undetectable HIV-1 RNA and HIV-1 DNA, diminished/delayed Ab production)
Assay reversion	Rare	Common for many test types
Duration	1-2 wk (until Ab detection)	Mo (until viral breakthrough, drug clearance, or ART start); can persist mo after ARV is discontinued
Transmission	Very likely	Unlikely (except possibly via blood transfusion)
Drug resistance	No (unless transmitted)	Yes (can emerge early when HIV-1 RNA is low)

The long acting early viral inhibition (LEVI) syndrome

	AHI	LEVI
Setting	• No antiretroviral drugs	• Long-acting anti-viral PrEP agent (prototype: CAB-LA)
Onset	• New infection	• Infection during PrEP • Initiation of PrEP agent during acute/early infection
Symptoms	• Fever, chills, rash, night sweats, muscle aches, sore throat, fatigue, swollen glands	• Minimal, variable, often no symptoms reported
Viral replication	• Explosive	• Smoldering
Viral load	• Very high	• Low or undetectable
Detection	• Ag/Ab assay, RNA assays (including less sensitive POC 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 antibody detection)	• Months (until viral breakthrough, drug clearance, or ART start); can persist for months after the antiviral agent is discontinued
Drug resistance	• No (unless transmitted)	• Yes (can emerge early when the viral load is low)

The long acting early viral inhibition (LEVI) syndrome

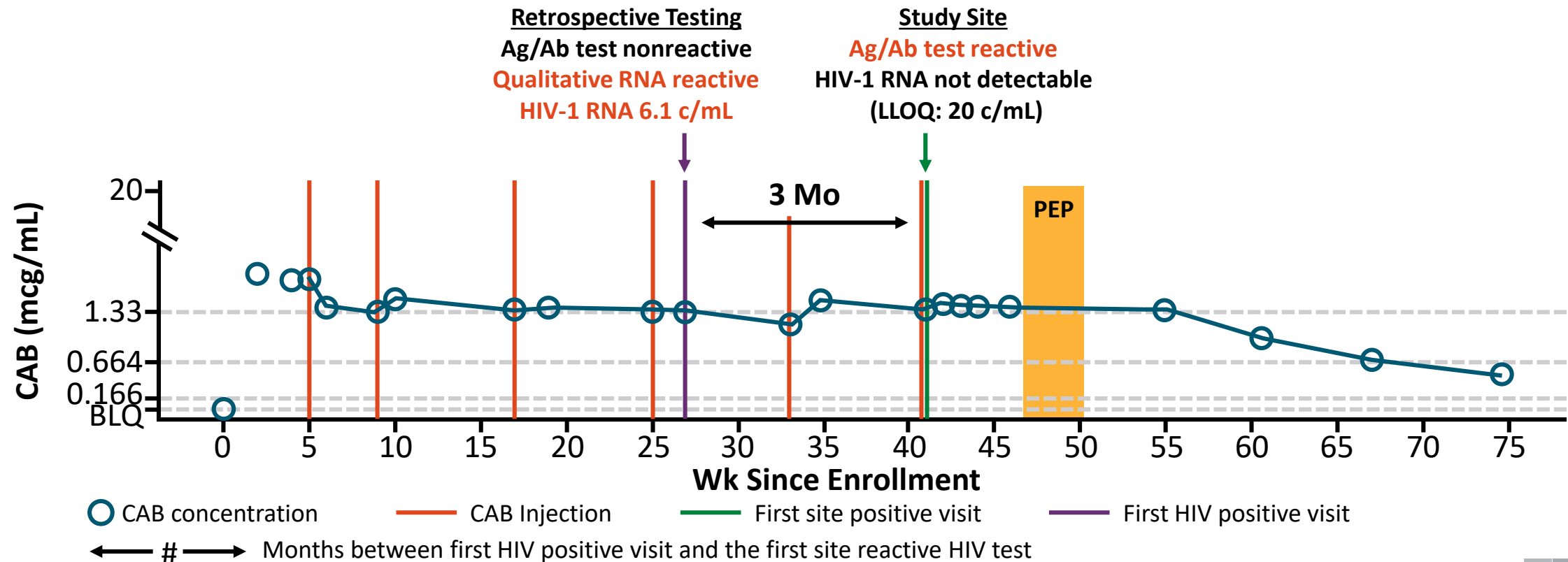


LEVI Syndrome: Background

- For HIV PrEP, LA CAB efficacy superior to oral FTC/TDF in HPTN 083 (cisgender MSM and TGW) and HPTN 084 (cisgender women)¹
- In HPTN 083, 6 cases of HIV infection occurred despite on-time LA CAB injections
 - Rapid and Ag/Ab tests often fail to detect HIV infection due to viral suppression and delayed/diminished Ab expression that can persist for months after infection, even after injection discontinuation
- Delayed detection of HIV infection may result in delayed ART start, ongoing HIV transmission, and emergence of INSTI resistance
- Current report describes case from HPTN 083 of patient who received LA CAB PrEP with LEVI syndrome²
 - Report also examined retrospective lab testing and genotyping

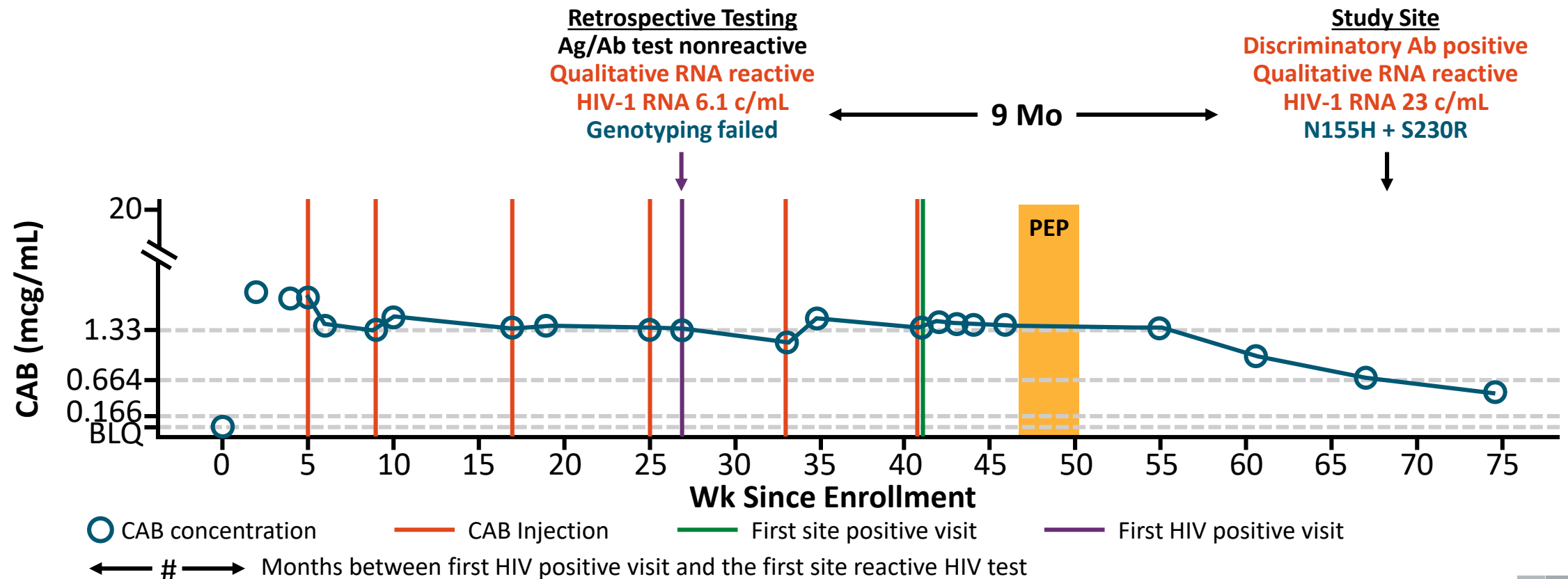
LEVI Syndrome Patient Case: Detection of Infection

- Retrospective sensitive HIV-1 RNA testing detected HIV infection 3 mo earlier than study site



LEVI Syndrome Patient Case: Confirmation of Infection

- HIV infection not confirmed by study site until after 9 mo from first HIV+ visit
- Retrospective genotyping failed at first HIV+ visit (HIV-1 RNA 6.1 c/mL) and detected INSTI resistance at study site HIV+ visit (HIV-1 RNA 23 c/mL)



LEVI Syndrome Patient Case: Assay Reversion

11 mos	Days since 1 st HIV+ visit	Rapid test	Ag/Ab test	Qualitative RNA test, LLOD 30 c/mL	Confirmatory Ab test	HIV-1 RNA (c/mL) LLOD 40 c/mL or single copy	HIV-1 DNA (c/mL) LLOD 4.09 c/10 ⁶ cells
	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	

Laboratory results from LEVI cases

(A) HPTN 083 – Case D2

	Days since 1st HIV POS	Site Results					Retrospective testing					Genotype
		Rapid 1	Rapid 2	Ag/Ab	DNA	VL	Discrim	Ag/Ab	Qual RNA LLOD 30	Discrim	VL LLOQ 40 or SCA	
9.3 months	0	NR		NR				NR	POS		6.1	
	42	NR		NR				NR	ND			
	55	NR		NR				NR	POS		ND	
	98	NR		R		ND		NR	ND			
	105	R		R	<LLOD	ND		R	ND	NEG		
	112	NR		R				R	ND	NEG		
	119	NR		R				NR	ND			
	202	NR		R	ND	ND		R	ND	INDET		
	195	R	R	R	<LLOD	ND		NR	ND			
	235	NR		R				R	ND	INDET		
	280	NR		R	5.8	23	POS	R	POS	NEG	<40	N155H, S230R
	333	R		R		23		R	POS	INDET	<40	

Laboratory results from LEVI cases

(B) HPTN 084 – Case A1

		Site Results						Retrospective testing					
		Days since 1st HIV POS	Rapid 1	Rapid 2	Ag/Ab	DNA	VL	Discrim	Ag/Ab	Qual RNA LLOD 30	Discrim	VL LLOQ 40 or SCA	Genotype
13.3 months	0	NR		NR					NR	POS		21.4	
	14	NR		NR					NR	POS		500	WT
	25	NR		NR					NR	POS		1,740	WT
	32	NR		NR					NR	POS		6,300	WT
	37	NR		NR					R	POS	INDET	87	
	59	NR		NR					NR	ND		SCA NEG	
	80	NR		NR					NR	ND		SCA NEG	
	113	NR		NR					NR	ND		SCA NEG	
	147	NR		NR					NR	ND		SCA NEG	
	172	NR		NR					NR	ND		SCA NEG	
	226	NR		R		ND			R	ND	INDET	SCA NEG	
	246	NR		NR	<LLOD	ND			R	ND	INDET	SCA NEG	
	274	NR		R	4.6	ND			R	ND	INDET	SCA NEG	
324	NR	R	NR	4.4	ND			R	ND	INDET	SCA NEG		
400	NR	NR	NR		33			R	ND	INDET	SCA NEG		

13.3
months

HPTN 083: HIV-1 RNA Screening in Cisgender Men and Transgender Women Receiving LA CAB for PrEP

- In original HPTN083 PrEP study, in both LA CAB and FTC/TDF arms, HIV detection with antigen/antibody testing was delayed vs with qualitative HIV-1 RNA testing²⁻³

Delays in Diagnosis, Median Days ³	Baseline Infections	Incident Infections
LA CAB for PrEP	62	98
Oral FTC/TDF for PrEP	34	31

- Based on these results, 2021 CDC guidelines recommend HIV-1 RNA assays to monitor people on oral or LA injectable PrEP⁴
- Current analysis of OLE participants (LA CAB only) through November 30, 2023, calculated positive predictive value and false positive rates of isolated positive RNA results and assessed screening sensitivity¹

1. Landovitz. AIDS 2024. Abstr OAE0406LB. 2. Marzinke. CROI 2021. Abstr 153. 3. Marzinke. J Infect Dis. 2021;224:1581.

4. [cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf](https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf).

HPTN 083: HIV-1 RNA Testing Results

- Out of 26,528 HIV-1 RNA tests, 22 were false positives
 - Of these, 7 resulted in subsequent LA CAB administration delays
- A single, isolated positive HIV-1 RNA test result was uncommon, but when it occurred, was frequently a false positive
- Repeat HIV-1 RNA testing can clarify whether the initial positive result is indeed an HIV infection

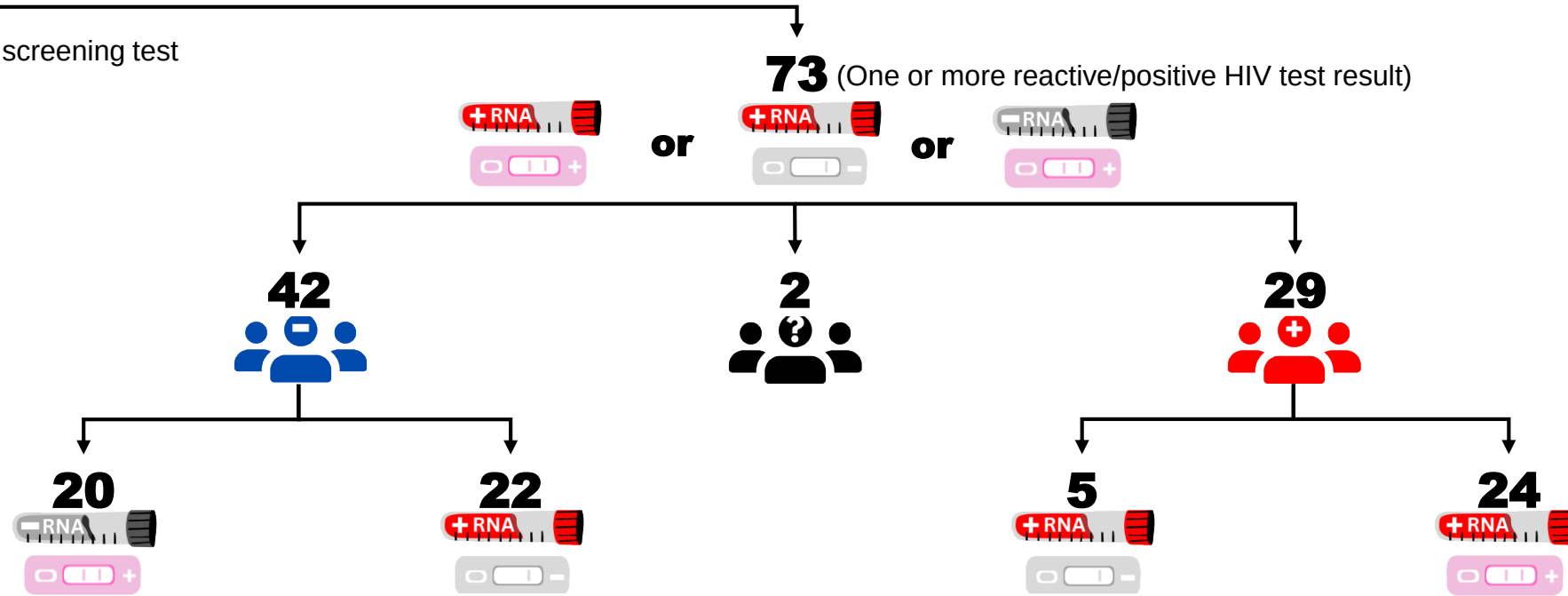
Results From Isolated Positive HIV-1 RNA Tests

Patient Group	PPV, % (95% CI)	FPR, % (95% CI)
Overall	18.5 (7.0-38.7)	0.08 (0.05-0.13)
No LA CAB in last 6 mo	60 (17-92.7)	0.06 (0.01-0.25)
LA CAB in last 6 mo	9.1 (1.6-30.6)	0.09 (0.05-0.14)

- HIV-1 RNA assay performed better in those who had not received LA CAB in the past 6 mo

26,528

Visits with an RNA screening test



Landovitz, IAC 2024



ADJUDICATED
NEGATIVE



ADJUDICATED
POSITIVE



ADJUDICATION STATUS
NOT DETERMINED



POSITIVE HIV
RNA TEST



NEGATIVE HIV
RNA TEST



POSITIVE NON-RNA
HIV TEST



NEGATIVE NON-RNA
HIV TEST



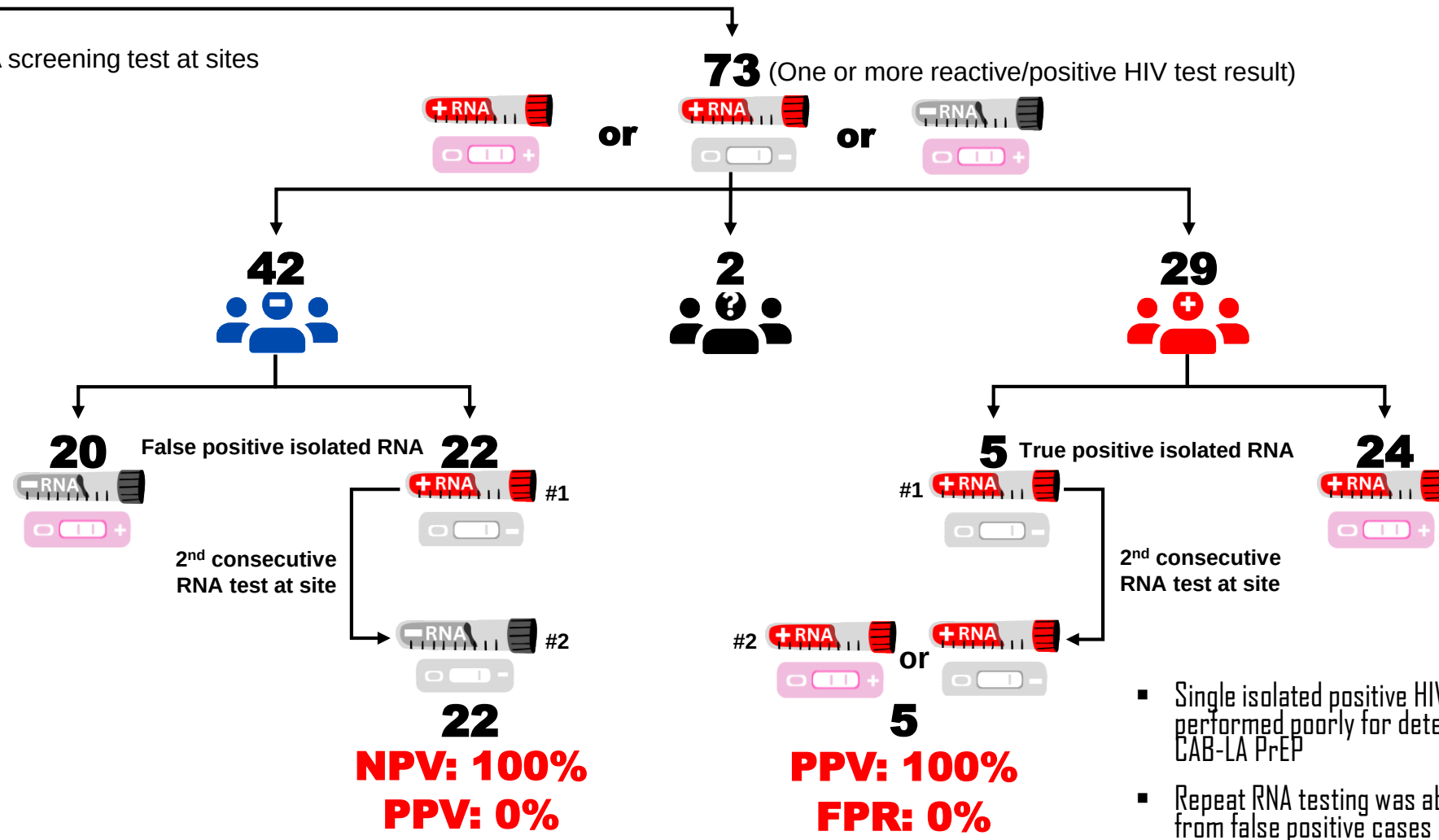
NO CAB-LA W/ IN
THE LAST 6 MONTHS



CAB-LA W/ IN
THE LAST 6 MONTHS

26,528

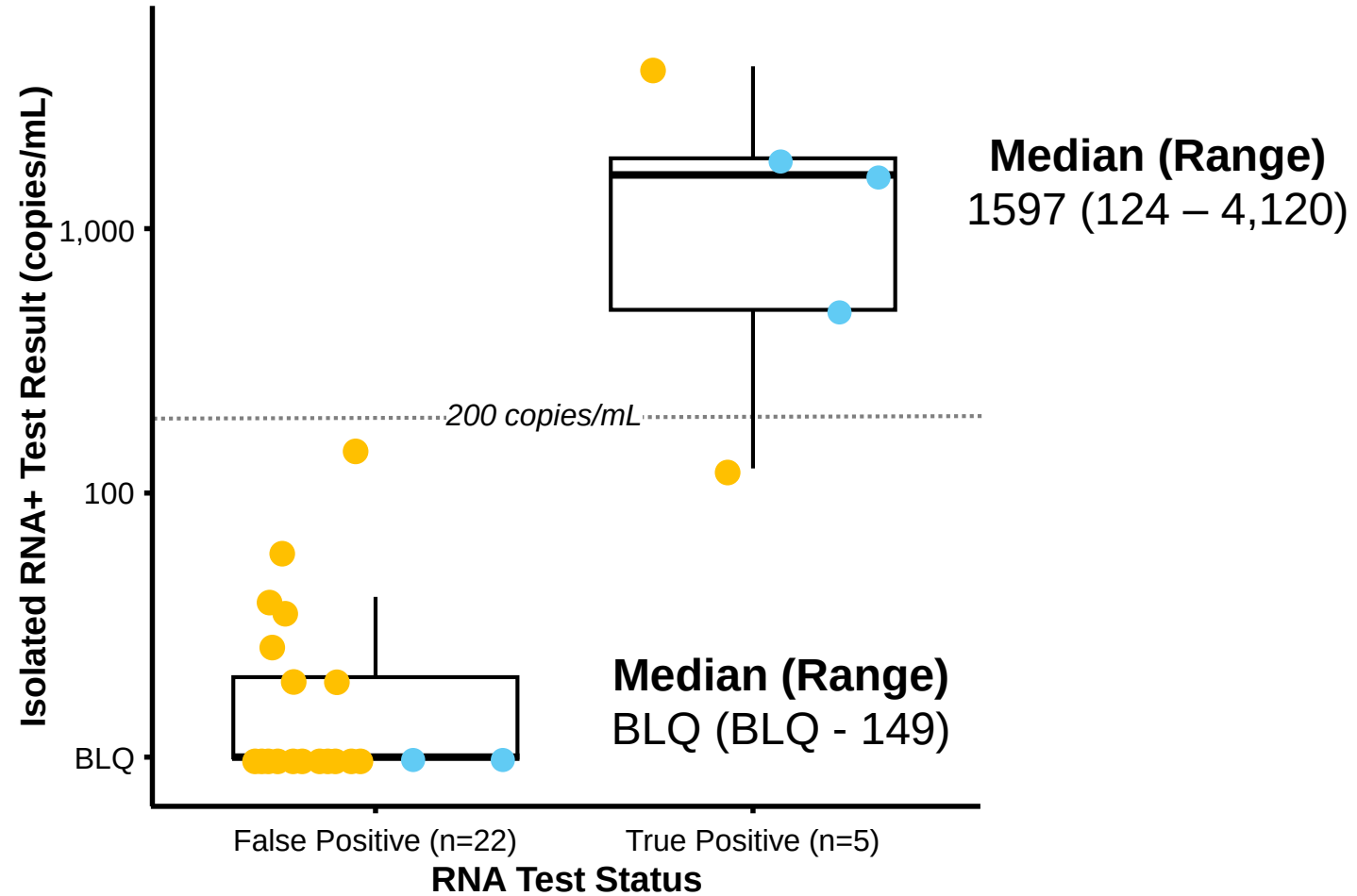
Visits with an RNA screening test at sites



- Single isolated positive HIV RNA result at sites performed poorly for detecting HIV infection with CAB-LA PrEP
- Repeat RNA testing was able to discriminate true from false positive cases

Landovitz, IAC 2024

HIV viral load at isolated RNA-positive visits



Landovitz, IAC 2024



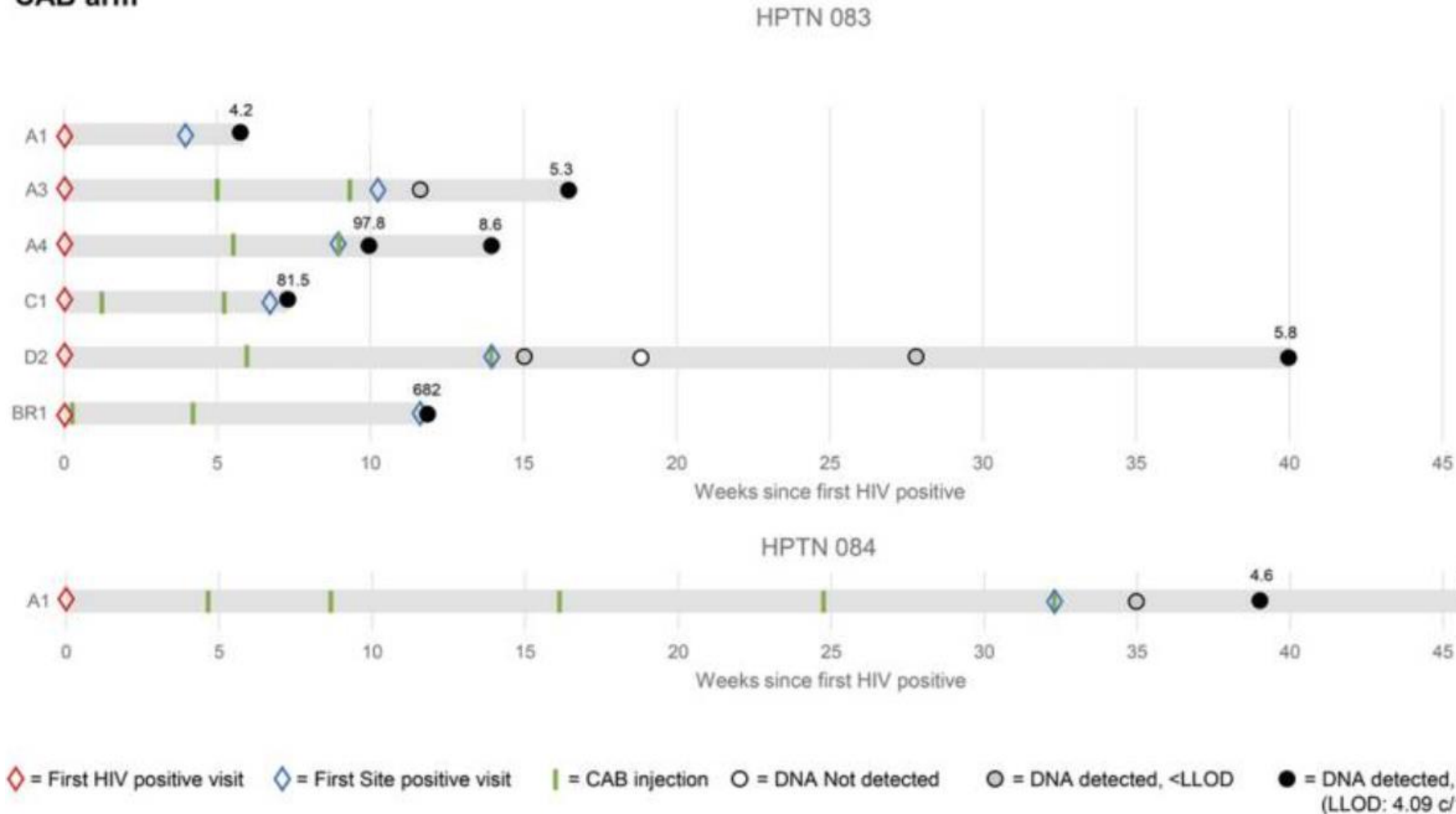
No CAB-LA w/ in
the last 6 months



CAB-LA w/ in
the last 6 months

HIV DNA Levels in Persons Who Acquired HIV in the Setting of LA CAB for HIV Prevention: Analysis of Cases from HPTN 083 and 084

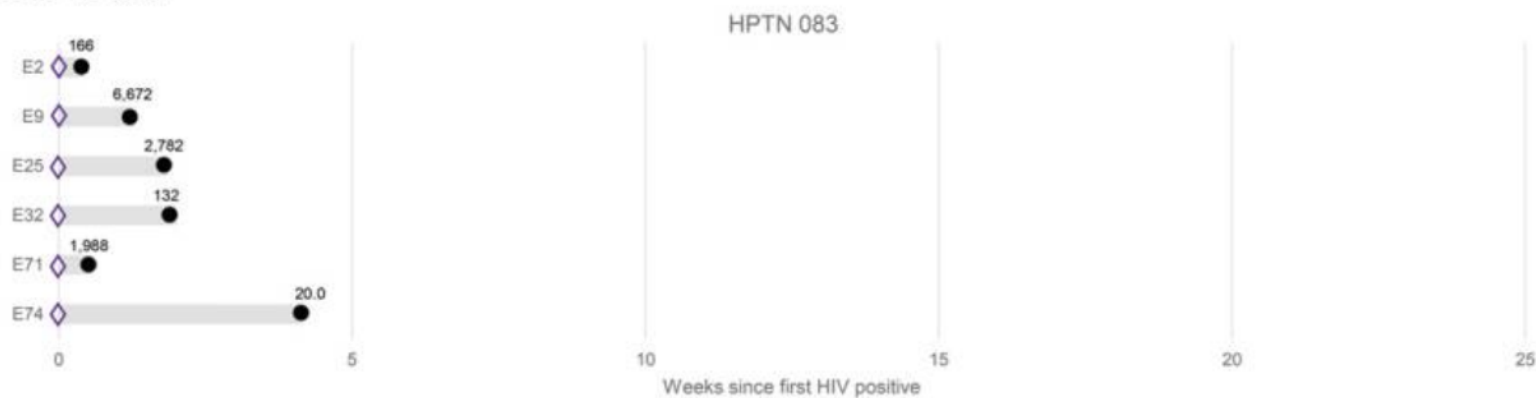
CAB arm



- HIV DNA quantification by dPCR in samples from 7 CAB and 14 TDF/FTC infections in HPTN 083 and 084
- **4/7** CAB cases had a low initial DNA result and in 2/4 cases, the DNA level was still <10 copies/million PBMCs >40 weeks after the first HIV-positive visit
- Only **3/14** of the TDF/FTC cases had a low or negative initial DNA test result
- **CAB-LA exposure may limit seeding of the HIV reservoir in early infection**

HIV DNA Levels in Persons Who Acquired HIV in the Setting of LA CAB for HIV Prevention: Analysis of Cases from HPTN 083 and 084

TDF/FTC arm



- HIV DNA quantification by dPCR in samples from 7 CAB and 14 TDF/FTC infections in HPTN 083 and 084
- **4/7** CAB cases had a low initial DNA result and in 2/4 cases, the DNA level was still <10 copies/million PBMCs >40 weeks after the first HIV-positive visit
- Only **3/14** of the TDF/FTC cases had a low or negative initial DNA test result
- **CAB-LA exposure may limit seeding of the HIV reservoir in early infection**

◆ = First HIV positive visit ◆ = First Site positive visit ◆ = First HIV positive/First Site positive visit ○ = DNA Not detected ○ = DNA detected, <LLOD ● = DNA detected, >LLOD (LLOD: 4.09 c/10⁶ PBMCs)

HIV DNA Levels in Persons Who Acquired HIV in the Setting of LA CAB for HIV Prevention: Analysis of Cases from HPTN 083 and 084

TABLE 2. CHARACTERISTICS OF PERSONS WITH HIV WITH ONE OR MORE DNA TEST RESULT^a

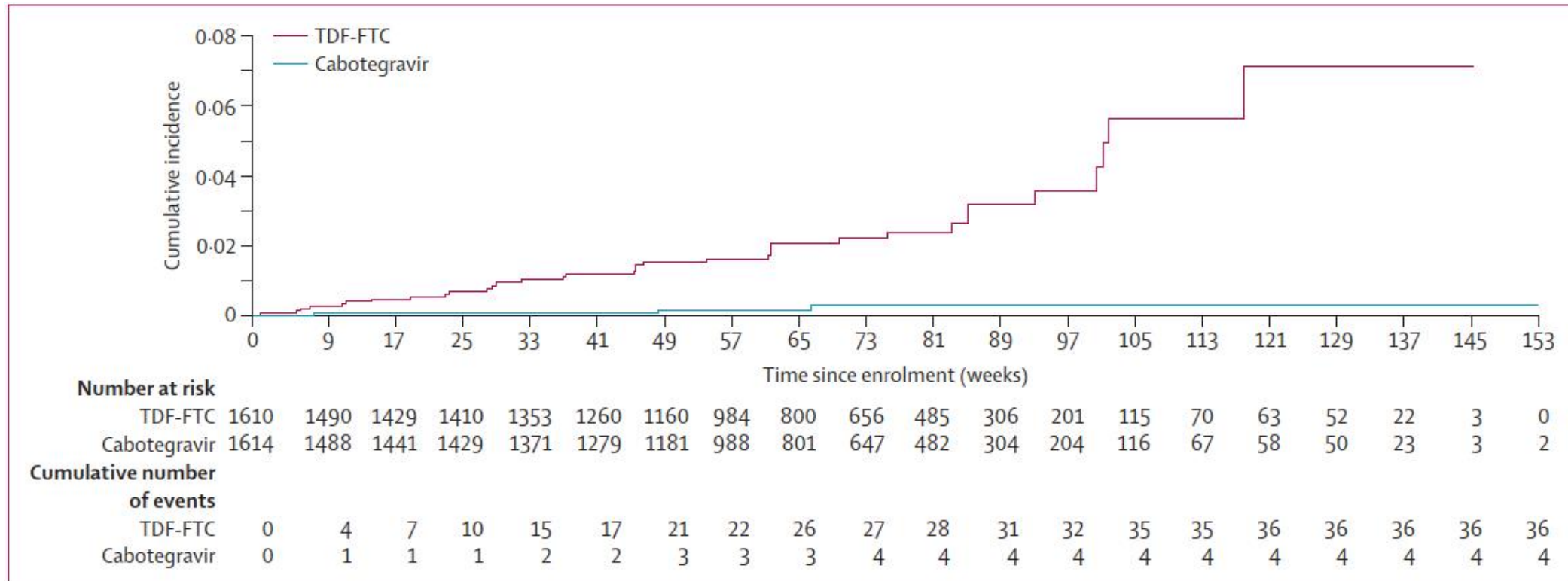
Study arm	Study	Case ^b	Detection delay ^c	VL at 1 st HIV pos visit (c/mL)	TDF/FTC adherent at 1 st HIV pos visit ^d	First visit with DNA results ^e			
						Days since 1 st HIV pos visit	HIV RNA ^f	DNA (c/10 ⁶ PBMC)	ARV drug concentration ^g
CAB (7 cases)	083	A1	Yes	4,010	—	41	Detected <40	4.2	3.68
		A3	Yes	1,360	—	81	NR	Detected <LLOD	3.37
		A4	Yes	44,180	—	70	NR	97.8	4.90
		C1	Yes	120	—	51	2,549	81.5	3.65
		D2	Yes	6.1	—	105	NR	Detected <LLOD	2.67
		BR1	Yes	450	—	83	100,260	682	1.29
		A1	Yes	21.4	—	246	SCA negative	Detected <LLOD	2.16
TDF/FTC (14 cases)	083	E2	No	34,180	No	3	50,050	166	BLQ (3 days prior)
		E9	No	505,690	No	9	82,397,780	6672	BLQ (9 days prior)
		E25	No	36,976,550	No	13	13,150,570	2,782	BLQ
		E32	No	11,310	No	14	14,360	132	BLQ
		E71	No	711,390	No	4	674,200	1,988	BLQ (4 days prior)
		E74	No	358	No	29	Not detected	20.0	BLQ (29 days prior)
		E17	No	2,706,990	No	3	2,144,273	3,906	BLQ
	084	E21	No	15,800	No	11	7,400	2,978	36.6
		E27	No	1,005,760	No	5	11,600	12.1	BLQ
		E31	Yes	71	Inconsistent	84	SCA 0.8	Not detected	432
		E36	No	Not detected	Partial	11	SCA negative	6.9	541
		E37	Yes	9,160	No	127	NR	99.0	1,051
		E42	No	Not detected	No	115	SCA negative	7.0	BLQ
		E47	No	113,080	No	4	33,165	101	BLQ

HPTN 084: HIV Incidence

Characteristic	CAB (n = 1614)	FTC/TDF (n = 1610)	Pooled (n = 3224)
HIV infections, n	4	36	40
PYFU	1953	1939	3892
HIV incidence per 100 PY (95% CI)	0.2 (0.06-0.52)	1.86 (1.30-2.57)	1.03 (0.73-1.4)

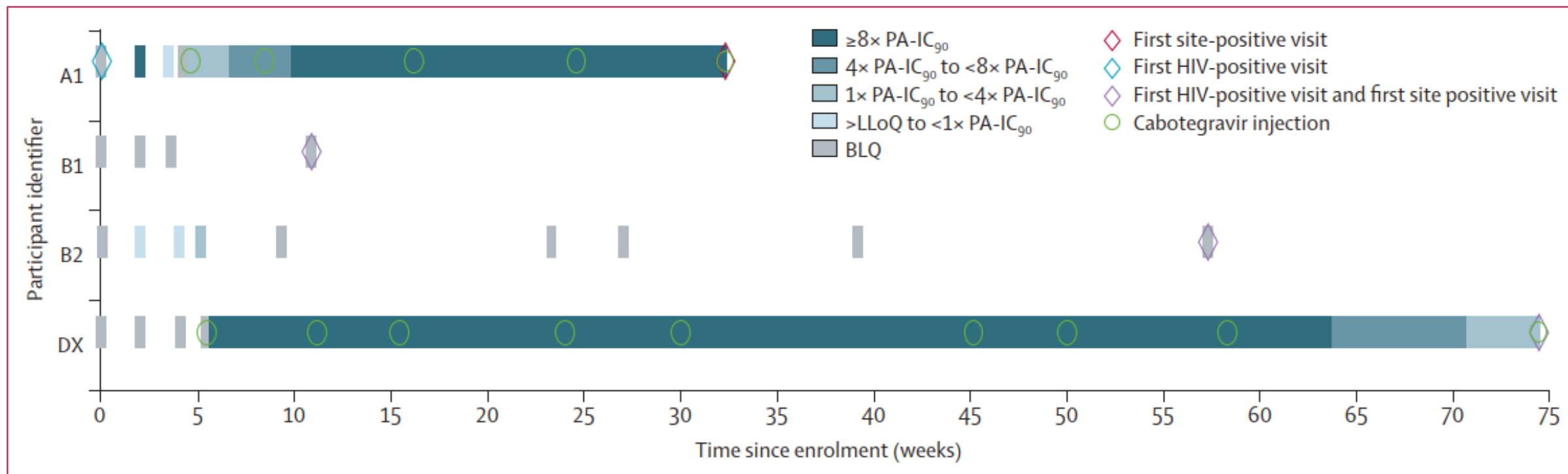
- 89% lower risk of HIV infection with CAB vs FTC/TDF ($P = .000027$)
 - **Met criteria for superiority of CAB in HIV prevention**
- Among 4 incident HIV infections in CAB arm, 2 occurred despite CAB injections

Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial



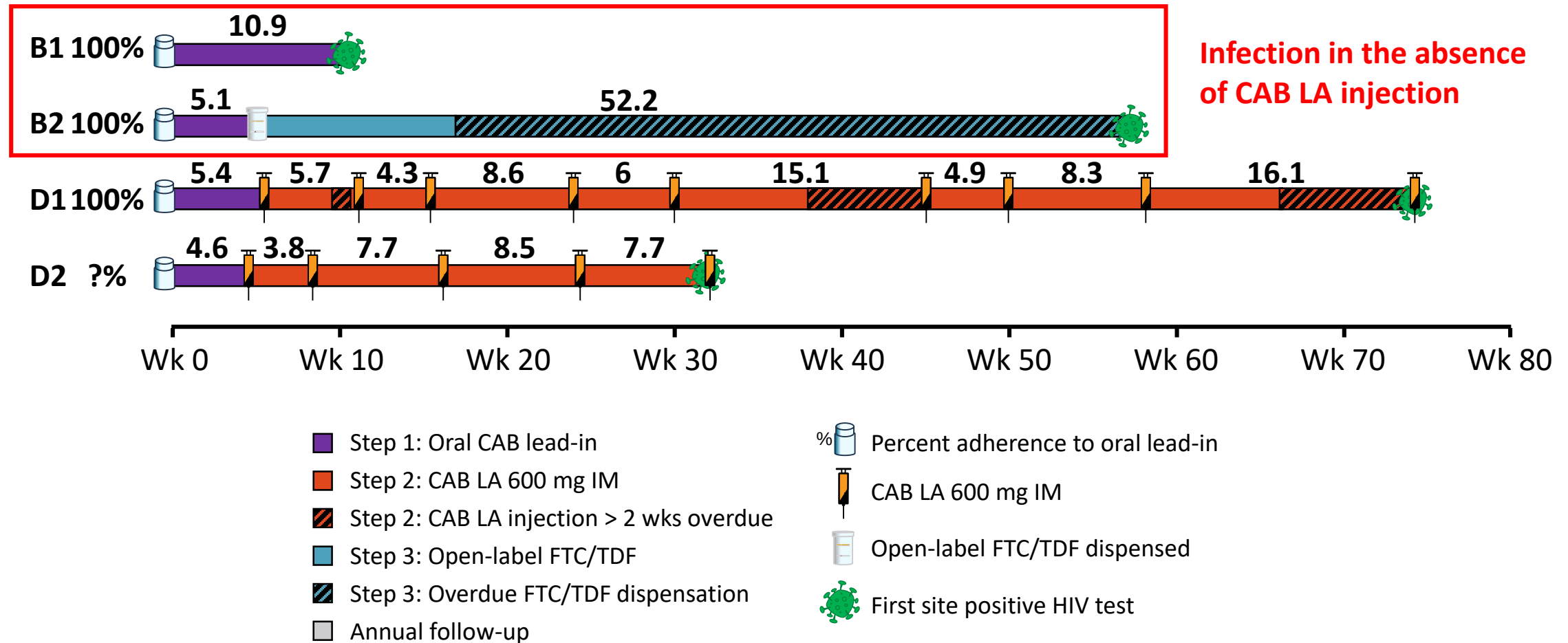
Four HIV infections were observed in the cabotegravir group (HIV incidence **0.20** per 100 person-years [95% CI 0.06–0.52]) and 36 in the TDF-FTC group (**1.85** per 100 person-years [1.3–2.57]). Participants in the cabotegravir group had an **88% lower risk** of HIV infection than those in the TDF-FTC group (hazard ratio 0.12 [0.05–0.31]; $p < 0.0001$).

Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial



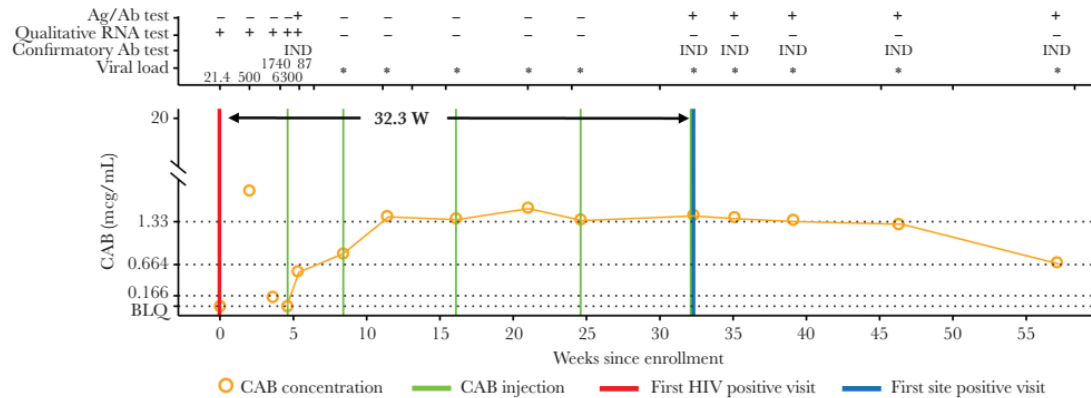
Group A includes infections that occurred before enrolment; **group B** includes infections that occurred with no recent exposure to cabotegravir; and **group D** includes infections that occurred in participants with appropriately timed cabotegravir injections. Participant **DX** acquired the infection during the step 2 injection phase but is called DX because three of nine injections were delayed.

HPTN 084: Incident HIV Infections With Cabotegravir

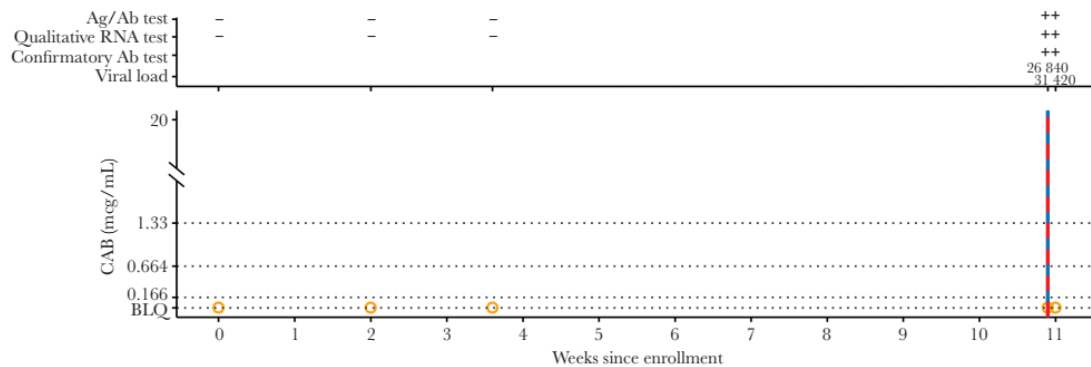


HPTN 084: HIV Infections in CAB Arm

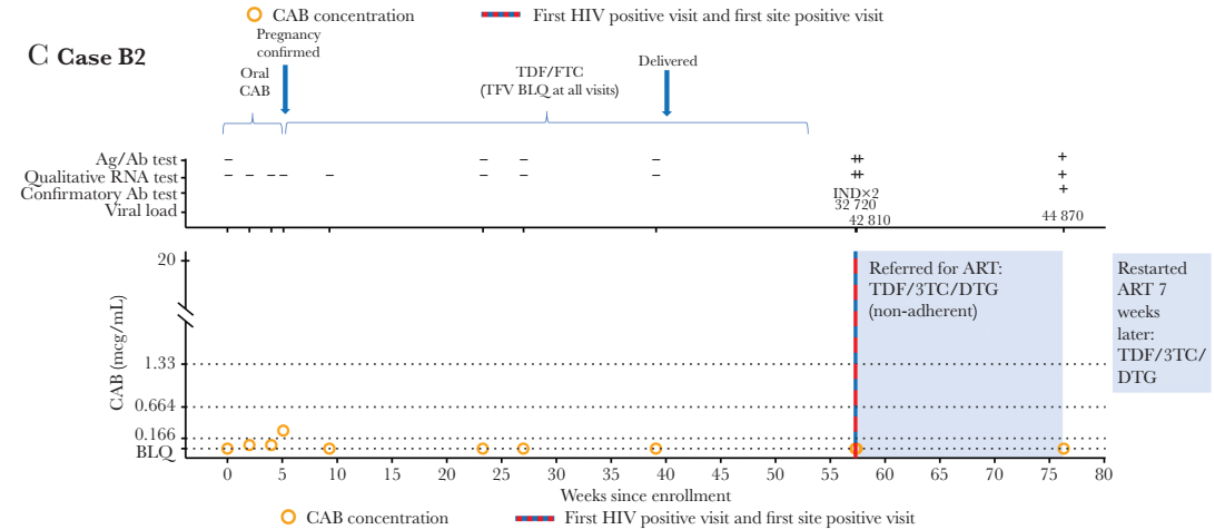
A Case A1



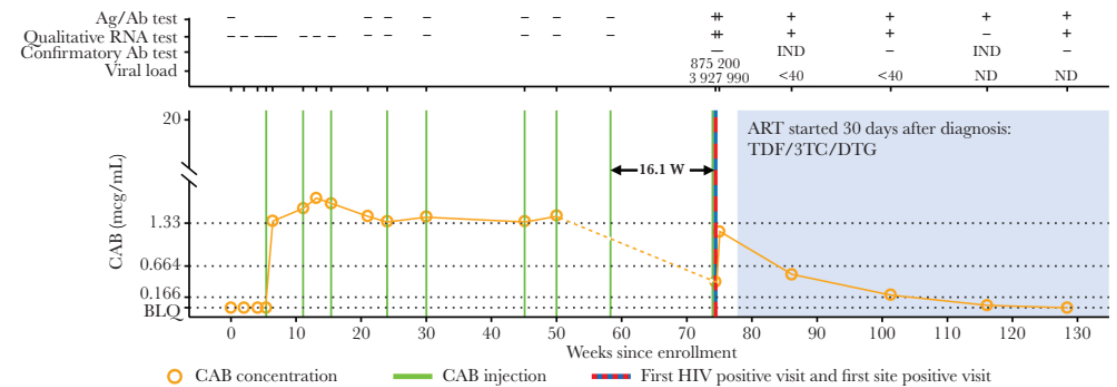
B Case B1



C Case B2



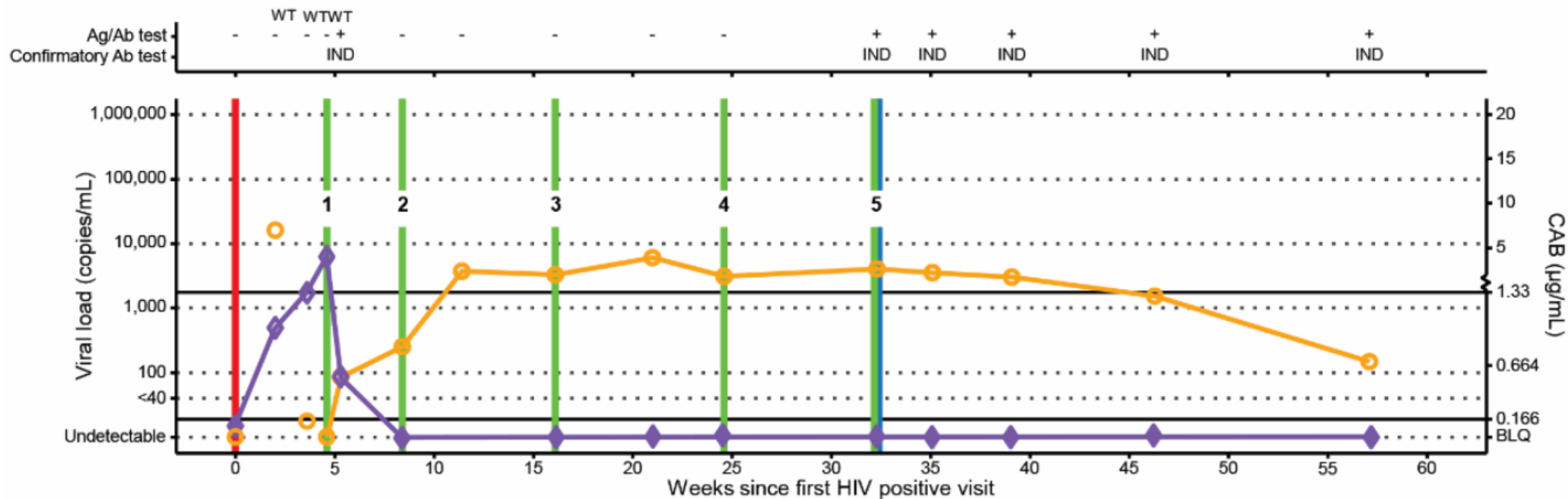
D Case DX



HPTN 084: HIV Infections in CAB Arm

Case A1

A1 – HPTN 084

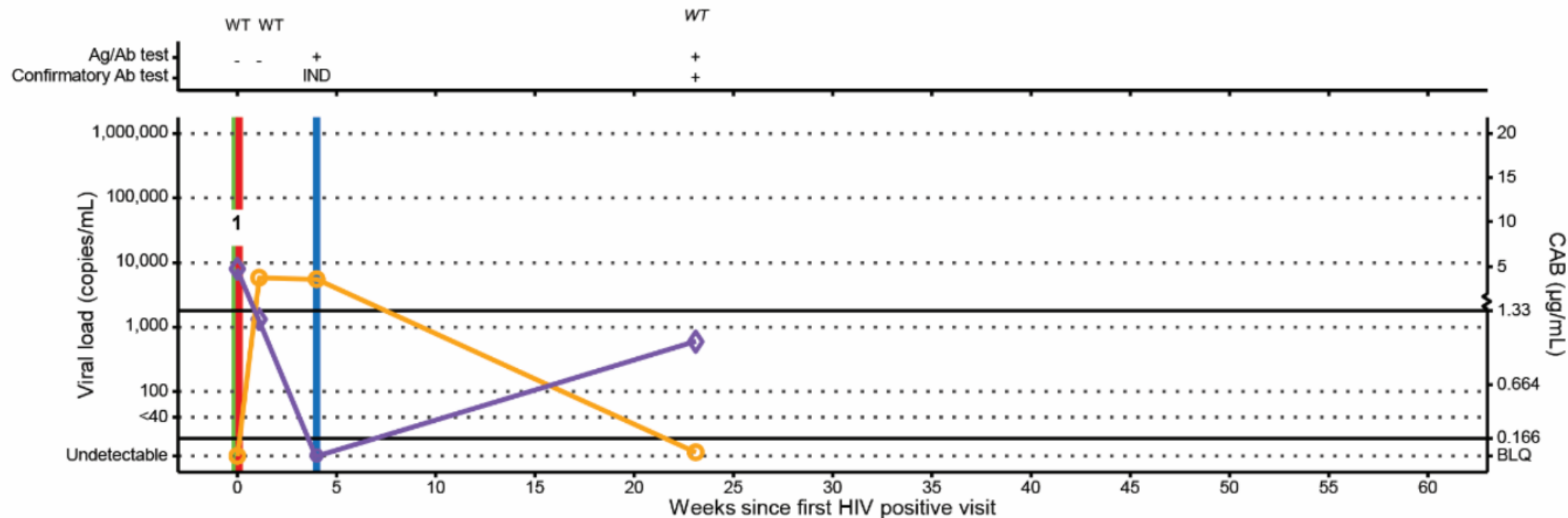


- First HIV positive visit
- First site positive visit
- CAB injection
- HIV viral load (above the limit of quantification)
- HIV viral load (not detected)
- Qualitative RNA (not detected)
- HIV viral load (single copy assay)
- CAB concentration (oral)
- CAB concentration (injectable)

HPTN 084: HIV Infections in CAB Arm

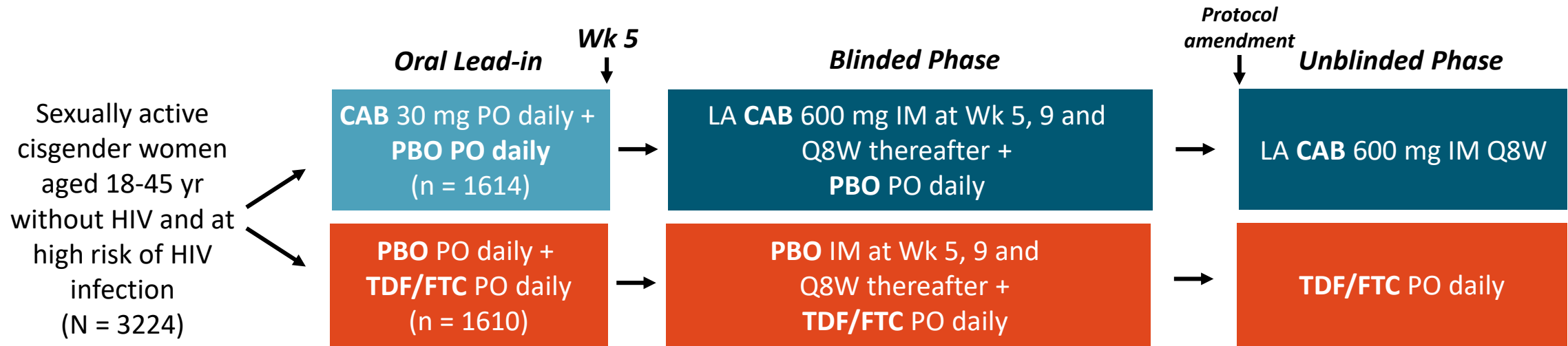
Case C1

C1 – HPTN 084



HPTN 084 Update: Study Design

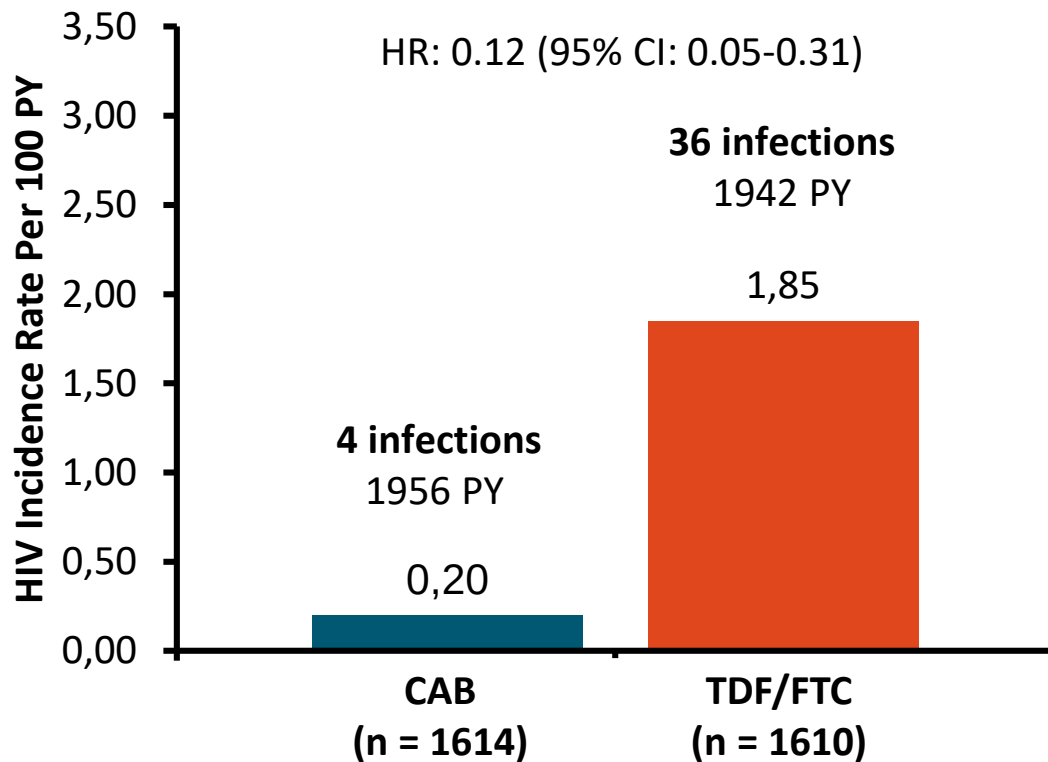
- International, randomized, double-blind phase III trial^{1,2}



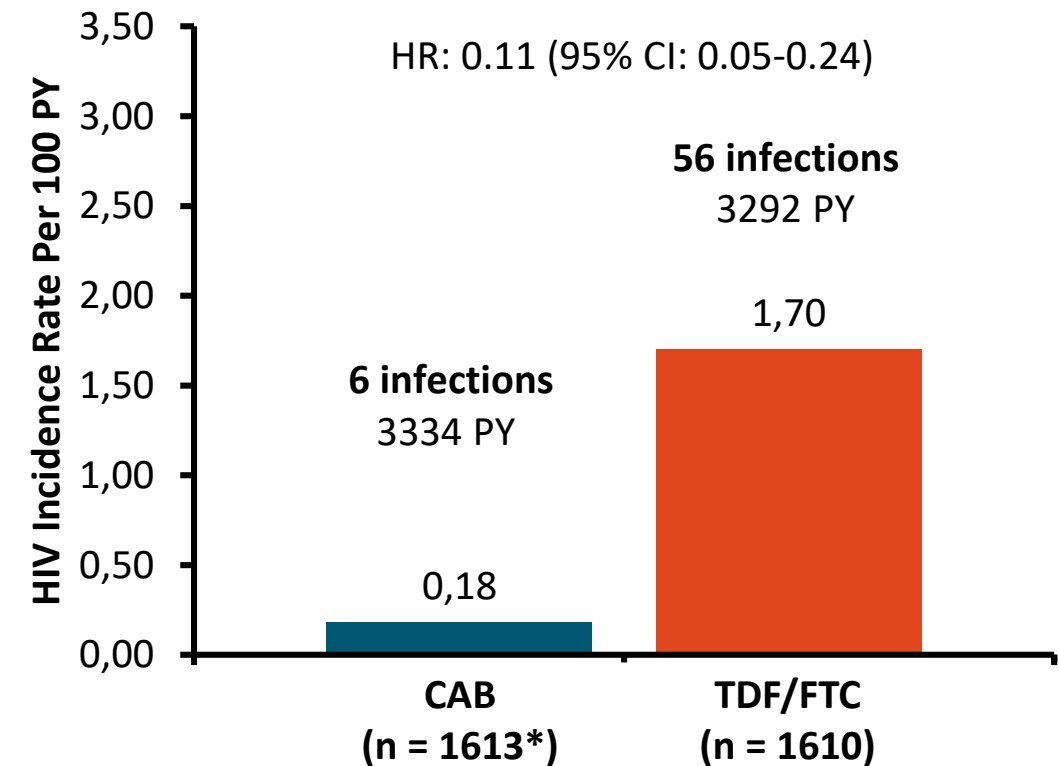
- Primary endpoints (blinded study): incident HIV infections (ITT), grade ≥ 2 AEs¹
- Current analysis: incident HIV infections during 12-mo period following unblinding (11/5/2020 - 11/5/2021, detected through 12/31/2021); grade ≥ 2 AEs, ISRs, pregnancy incidence/outcomes during 12-mo unblinded phase; cumulative HIV incidence for primary blinded and 12-mo unblinded follow-up²

HPTN 084 Update: HIV Incidence

**Primary Blinded Period
Through Nov 2020¹**

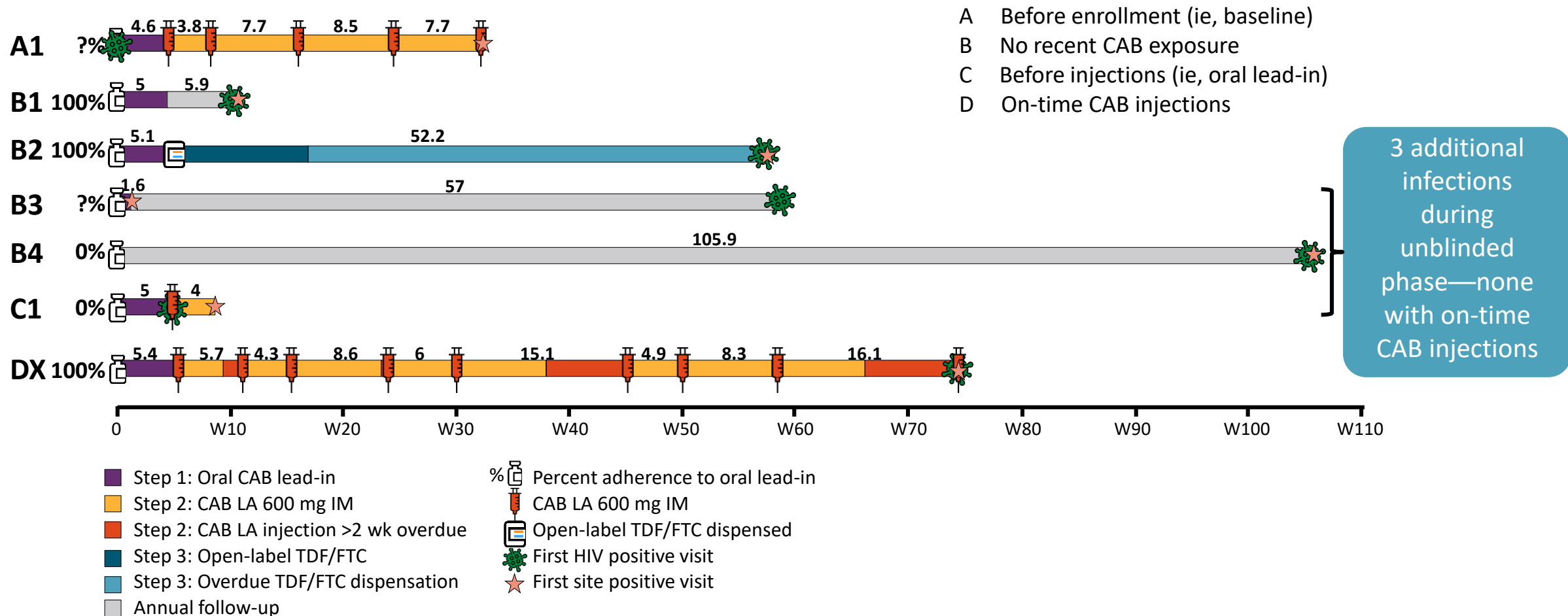


**Combined Blinded and Unblinded Period
Through Dec 2021²**



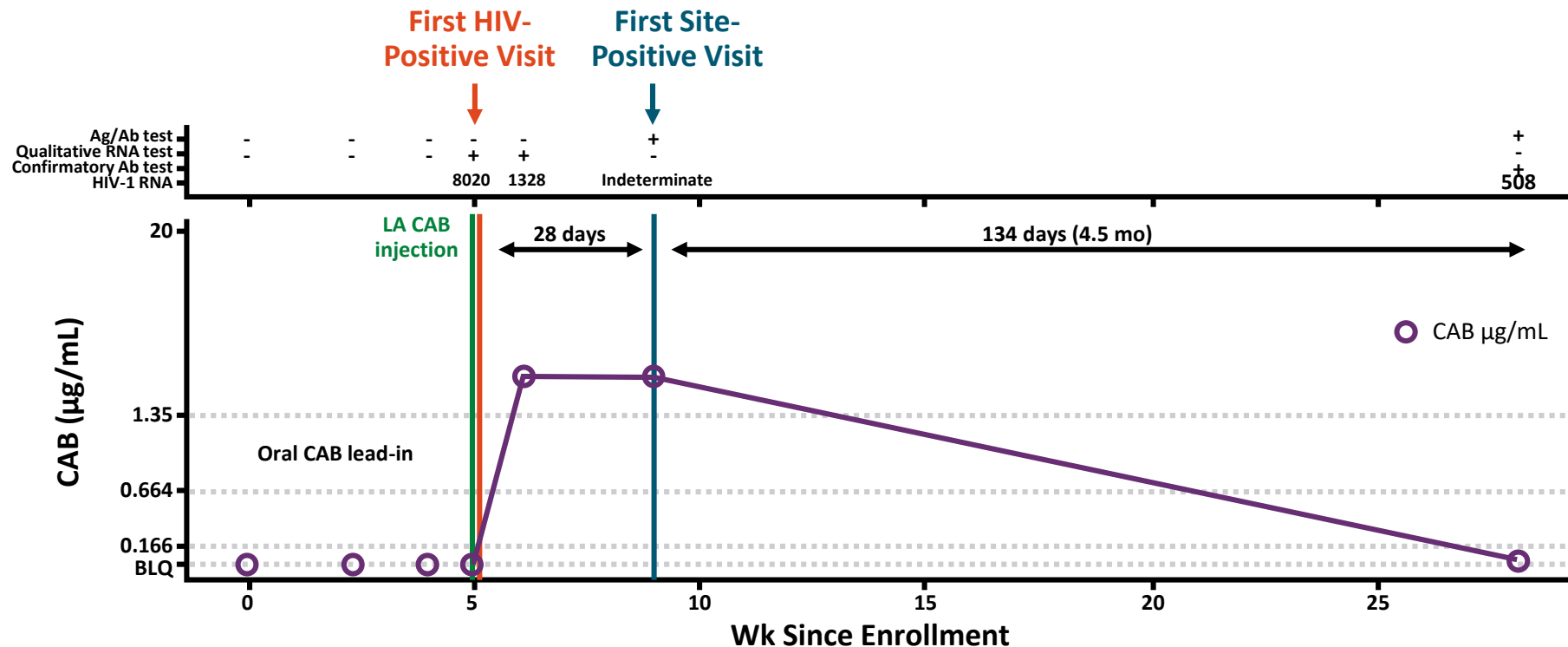
*Excludes 1 baseline infection from the blinded period.

HPTN 084 Update: Cumulative HIV Infections



HPTN 084 Update: C1 Case

- Infection occurred prior to injections during oral lead-in
 - CAB not quantifiable during oral lead-in
- First CAB injection given at first HIV-positive visit
- Site-based Ag/Ab testing not detected at first visit, but 28 days later when CAB was held
- Infection confirmed 4.5 mo later



HPTN 084: drug resistance in HIV infections in TDF/FTC Arm

Table 2. Human Immunodeficiency Virus Drug Resistance (Tenofovir Disoproxil Fumarate/Emtricitabine Arm)

Case	Week of Visit	DRMs ^a	Drug Resistance ^b
E7	89	NNRTI: K103N , P225H ; PI: K20R, M36I, L89M	EFV, NVP, (DOR)
E9	81	NNRTI: K103N , P225H ; PI: K20R, M36I, I62V, <u>I85V</u>	EFV, NVP, (DOR)
E11	65	NNRTI: E138A ; PI: K20R, M36I, I62I/V, L89M	RPV
E12	65	NNRTI: V90I, K103N , E138A ; PI: K20R, M36I, L89M	EFV, NVP, RPV
E17	49	NNRTI: K101E ; PI: M36I, D60E, L89M	RPV, (EFV), (NVP)
E18	49	NNRTI: K103K/N ; PI: M36I	EFV, NVP
E24	33	NNRTI: K103N ; PI: M36I, L89M	EFV, NVP
E32	17	NRTI: M184V ; NNRTI: K103N ; PI: M36I, L89M	EFV, NVP, FTC, 3TC, (ddI)
E33	9	NNRTI: K103N ; PI: M36I, I62V, L89M	EFV, NVP

aResults from human immunodeficiency virus (HIV) genotyping for cases in the tenofovir disoproxil fumarate/FTC arm with ≥1 major DRM noted in the 2019 IAS drug resistance mutations update [8]. HIV genotyping was performed at the first study visit with a viral load >500 copies/mL; this was the first HIV-positive visit for 8 of the 9 cases (in case E32, the first sample with a viral load >500 copies/mL was collected 33 days after the first HIV-positive visit). All 9 cases had subtype C infection. Major protease inhibitor mutations were not detected. Major DRMs associated with resistance to integrase strand transfer inhibitors were not detected. Bold text indicates major DRMs and italics, drugs that affect susceptibility to study drugs (M184V only); underlined mutations are recommended for surveillance of transmitted drug resistance [12].

bDrugs noted as having reduced susceptibility (resistant) on reports from Monogram Biosciences; those in parentheses are noted as having partial susceptibility (resistance possible). HIV genotyping results were obtained at follow-up visits for cases E7 and E33 (7 and 39 days later respectively); no change in mutations was detected in these cases. Three additional cases that had no drug resistance at the first viremic visit had genotyping results at follow-up visits (cases E23, E26, and E35; 16–57 days later); no change in mutations was detected in these case.

HPTN 084: drug resistance in HIV infections in TDF/FTC Arm

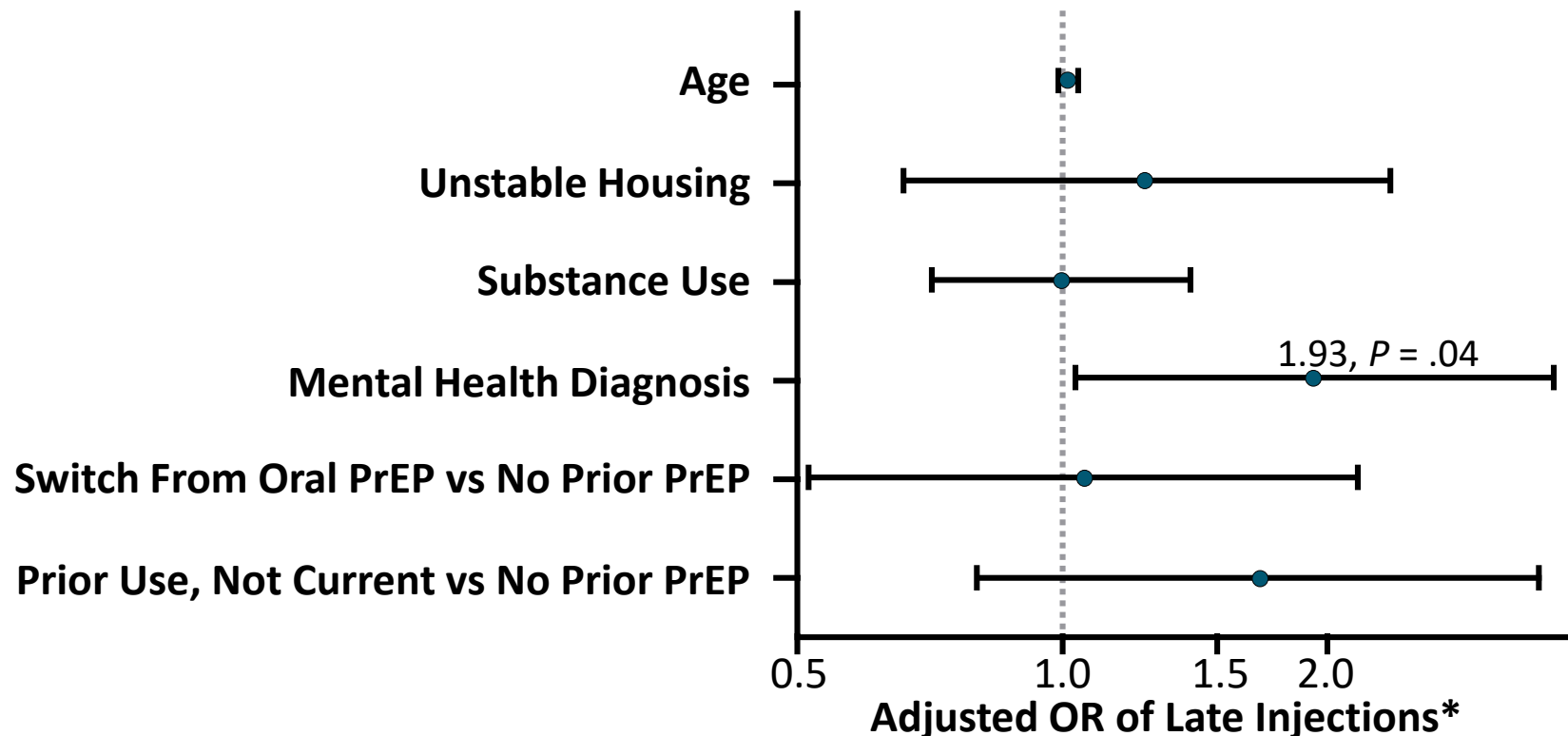
- We did not identify any cases with INSTI resistance in HPTN 084. The high frequency of transmitted NNRTI drug resistance observed in this cohort is concerning and emphasizes the importance of drug resistance testing and use of protease inhibitor– or INSTI-based treatment regimens where appropriate. Emergence of NRTI resistance in participants in the TDF/FTC arms of both trials was rare, most likely because most participants who acquired HIV infection in the TDF/FTC arms had poor adherence to the TDF/FTC regimen.
- Data from HPTN 084 and HPTN 083 show that these delays were more frequent and longer in persons receiving CAB than in those receiving TDF/FTC. These delays resulted in drug administration to persons with undetected HIV infection in almost all cases; INSTI resistance emerged in some of these cases.

HPTN 084: VL in HIV Infections in TDF/FTC Arm

- See
Eshleman_JID_2022_HIV_infections_in_HPTN084_CAB_PREP_supplementary
- Indicates viral breakthrough with VL typical of acute infection, i.e. the drugs do not work at all? Is it due to resistant strains?

LA CAB PrEP in Primary Care Clinics: Late Injections

- 85% of injections (n = 507) were on time
- Mental health diagnosis associated with late injections; other factors were not

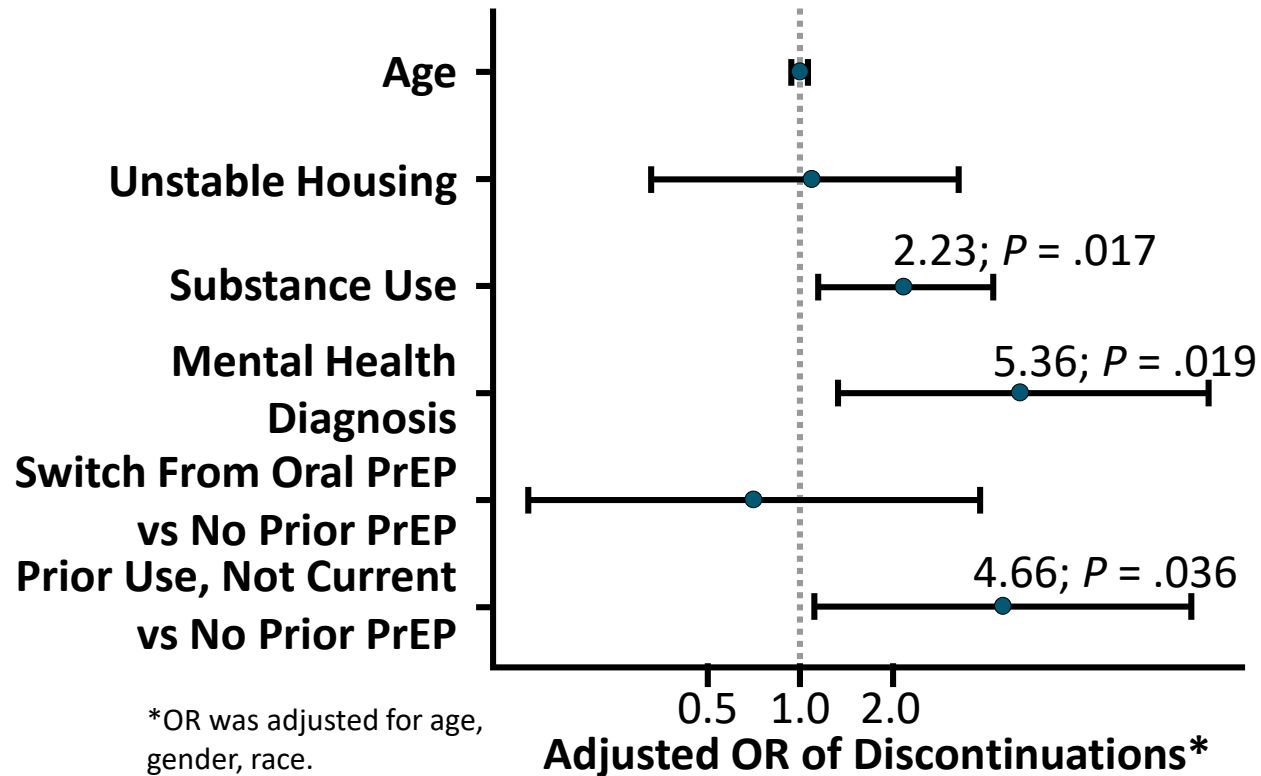


*OR was adjusted for age, gender, race.

Heise. HIVR4P 2024. Abstr OA0503.

Slide credit: clinicaloptions.com

LA CAB PrEP in Primary Care Clinics: Discontinuations



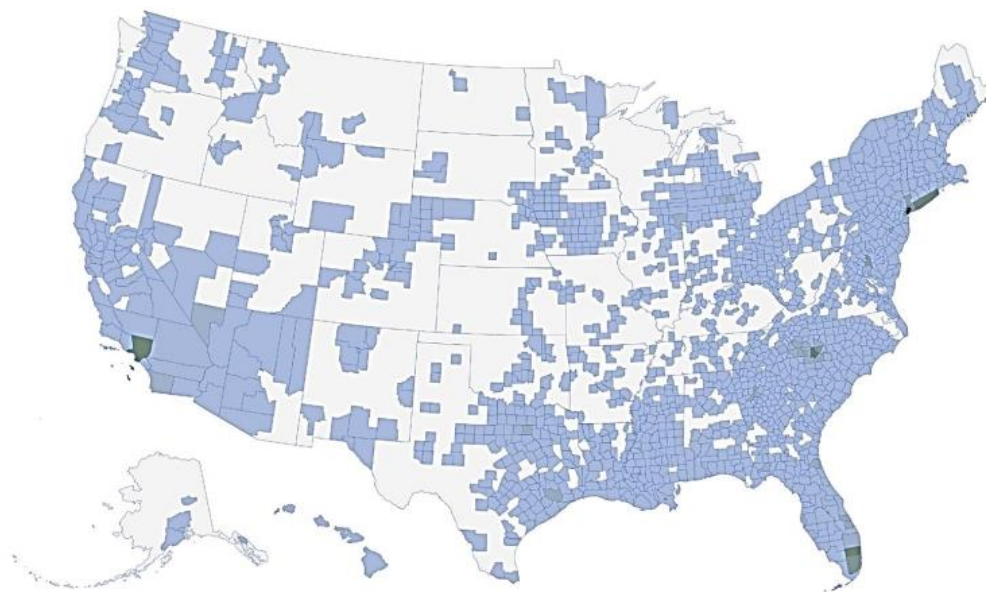
Reason for Discontinuation, n	Patient Population (N = 111)
Low self-perceived risk	6
Adverse events	4
Lost to follow-up	6

- Ward 86 saw lowest discontinuation rate (aHR: 0.18; 95% CI: 0.03-0.95; $P = .043$)
- No discontinuation difference among stable vs unstable housing groups (aHR: 1.06; 95% CI: 0.33-3.36; $P = .924$)
- Of 19 patients who discontinued LA CAB:
 - 4 transitioned to oral PrEP
 - 15 did not restart any PrEP
- No seroconversions**
 - 3 false-positive viral loads (<30 copies/mL detected)**

LA CAB PrEP: Real World Data on On-Time Dosing, HIV Testing and HIV Acquisition from the OPERA Cohort



OPERA[®]
The Longitudinal Cohort



**Observational Pharmaco-Epidemiology
Research & Analysis**

> 849,000 people without HIV

> 53,000 people ever received PrEP

LA CAB PrEP: Real World Data on On-Time Dosing, HIV Testing and HIV Acquisition from the OPERA Cohort



Study population



CAB LA PrEP users

- ≥ 1 CAB LA PrEP injection between 21DEC2021 and 30JUN2023
- ≥ 18 years old at first CAB LA injection
- Follow-up through study end (31DEC2023), loss to follow-up, death, or HIV acquisition



Oral PrEP users

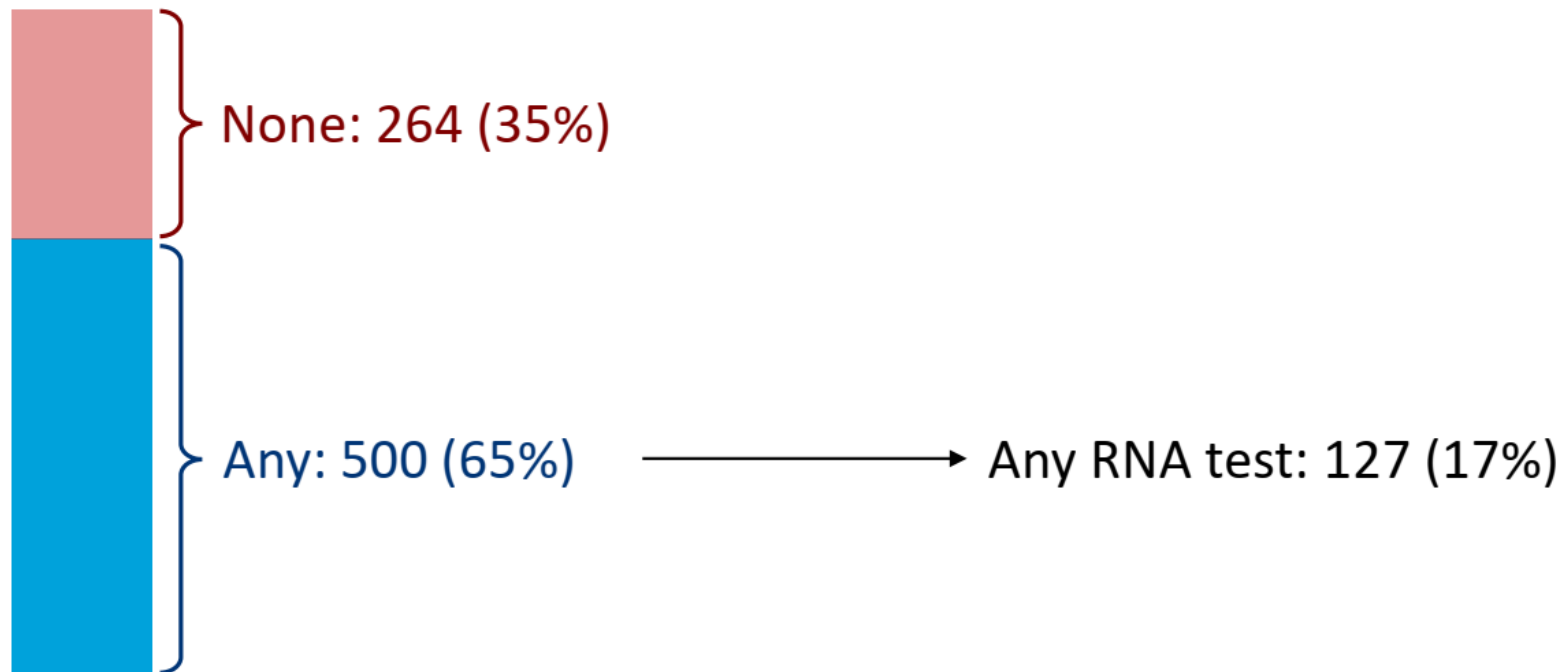
- New oral PrEP regimen (TDF/FTC or TAF/FTC) between 21DEC2021 and 30JUN2023
- ≥ 18 years old at start of new oral PrEP regimen
- No CAB LA injection during the study period

OPERA: HIV Testing Outcomes

Testing Within 1 Wk of Injection, n (%)	LA CAB PrEP
First LA CAB injection (n = 764)	
▪ No test	264 (35)
▪ Any test	500 (65)
▪ HIV-1 RNA test	127 (17)
Subsequent LA CAB injection (n = 646)	
▪ Always	320 (50)
▪ ≥50% of injections	165 (26)
▪ <50% of injections	92 (14)
▪ Never	69 (11)
▪ HIV-1 RNA test	187 (29)

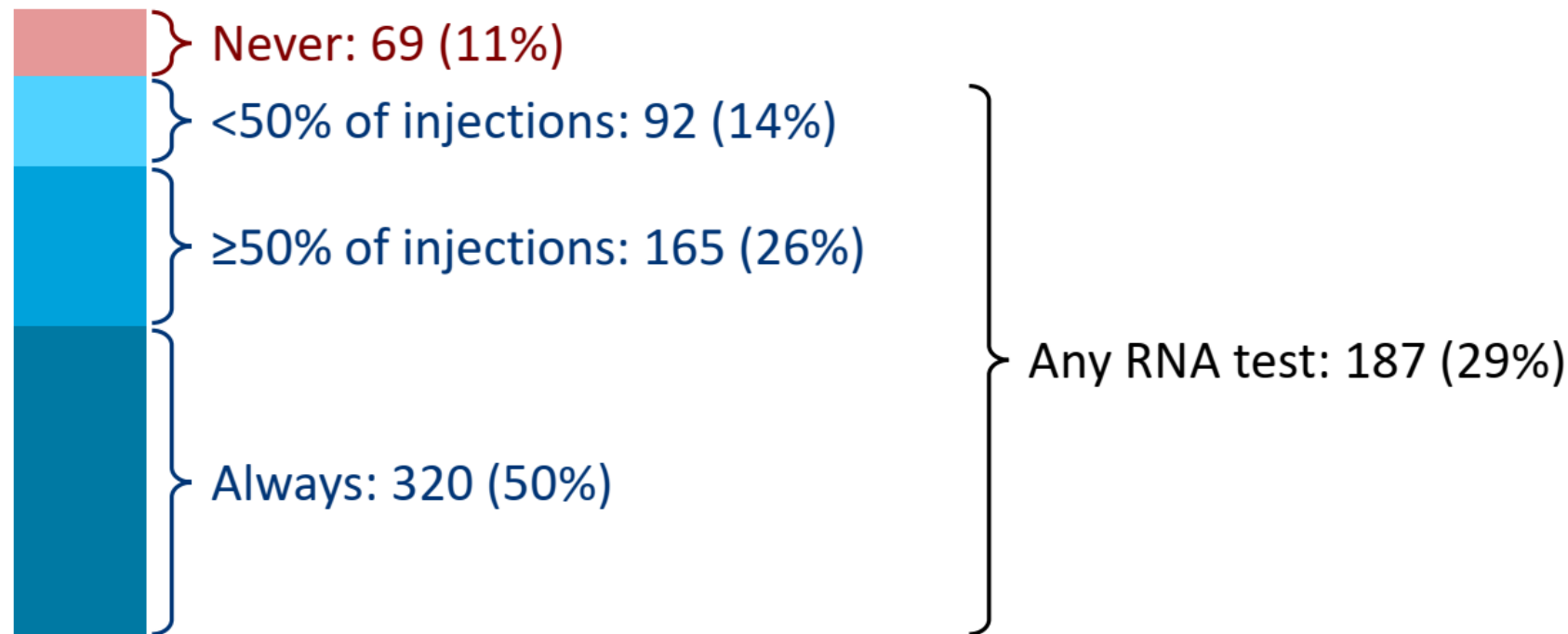
LA CAB PrEP: Real World Data on On-Time Dosing, HIV Testing and HIV Acquisition from the OPERA Cohort

HIV testing within 1 week before/at
1st CAB LA PrEP injection (N = 764)



LA CAB PrEP: Real World Data on On-Time Dosing, HIV Testing and HIV Acquisition from the OPERA Cohort

HIV testing within 1 week before/at subsequent
CAB LA PrEP injection (N = 646)

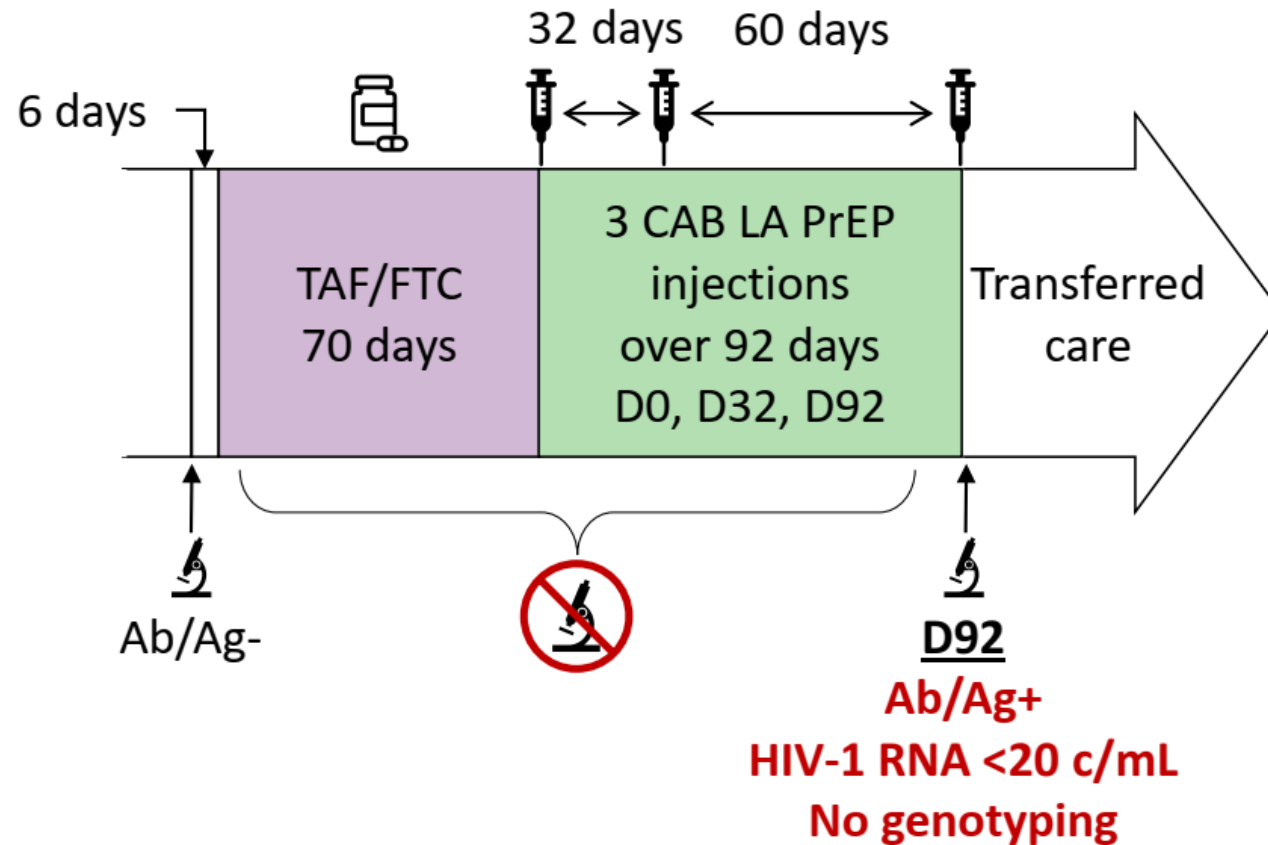


OPERA: HIV Seroconversions

- 2 HIV seroconversions (0.3%) among 764 participants receiving LA CAB PrEP
- **Case 1:** FTC/TAF for 70 days, then received 3 LA CAB injections (Day 0, 32, and 92)
 - No HIV testing at time of LA CAB initiation
 - Day 92: HIV Ab/Ag positive; HIV-1 RNA <20 c/mL; no genotyping performed
- **Case 2:** FTC/TAF for 65 days, then received 4 LA CAB injections (Days 0, 93, 212, and 272)
 - Tested and remained HIV negative over course of LA CAB PrEP
 - **No PrEP for 130 d after LA CAB**, then restarted on FTC/TAF after negative HIV Ag/Ab test
 - HIV-1 RNA >100,000 c/mL after 9 days of FTC/TAF; retained susceptibility to all ARVs

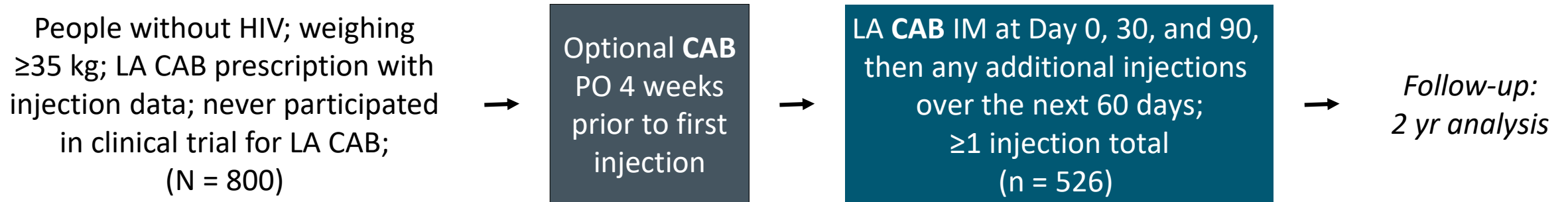
LA CAB PrEP: Real World Data on On-Time Dosing, HIV Testing and HIV Acquisition from the OPERA Cohort

Case #1*



TRIO COHORT: Real-World LA CAB for PrEP Over the First 2 Years

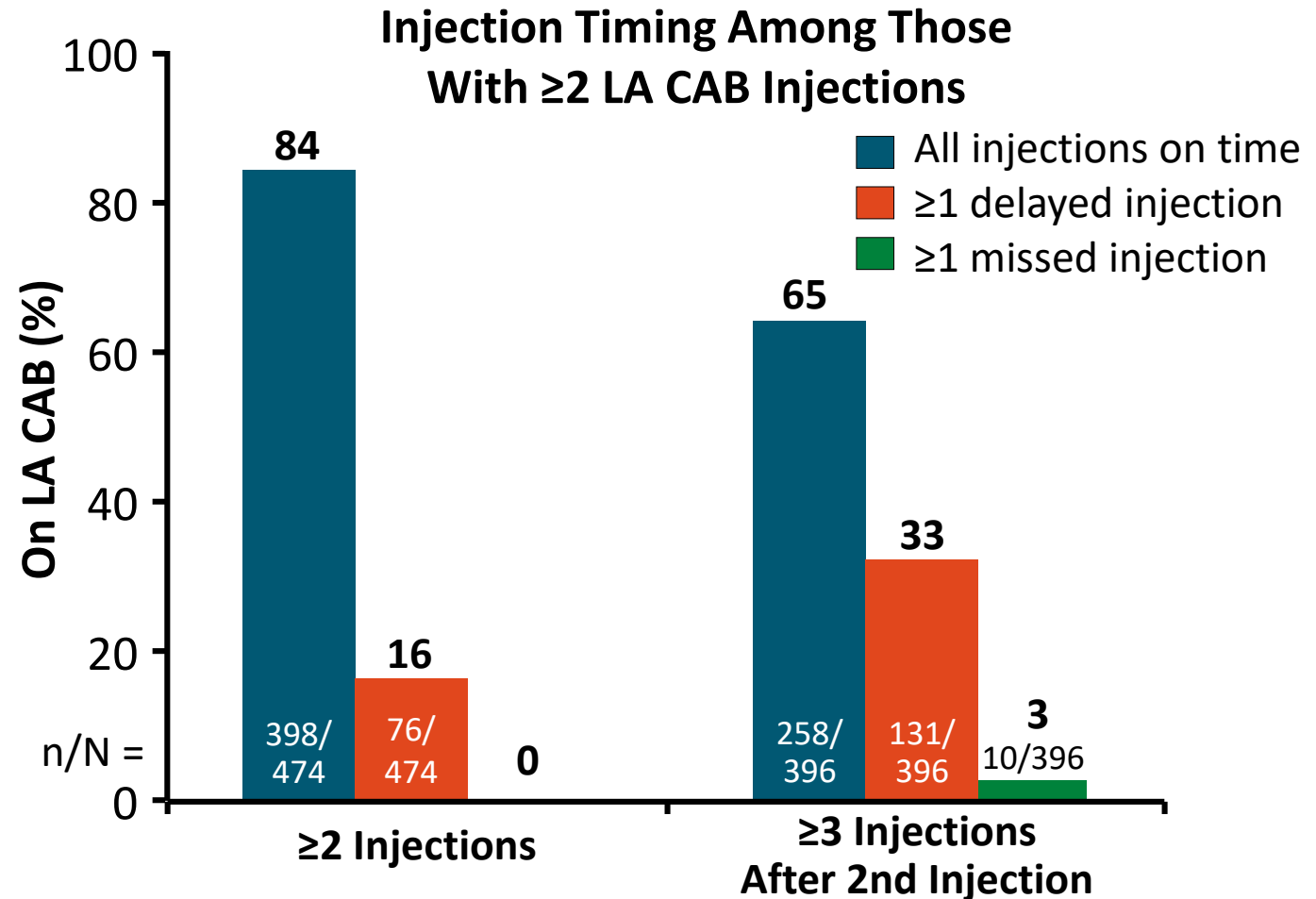
- TRIO cohort: 12 geographically distributed health clinics in US



- Median follow-up: 7 mo (IQR: 3-14 mo)
- 85 (18%) met discontinuation criteria
 - Median time to discontinuation: 7 mo
- Reinitiated LA CAB within 6 mo: 13/85 (15%)
 - Median time to reinitiation: 41 days

TRIO COHORT: Real-World LA CAB for PrEP Over the First 2 Years

- Of 16% with delayed 2nd injection:
 - Median delay = 22 days
- Of 33% with delayed 3rd or later injection:
 - Median number of delayed injections = 1
 - Median delay = 12 days
- Of 3% with ≥ 3 missed injections
 - Median number of missed injections = 1



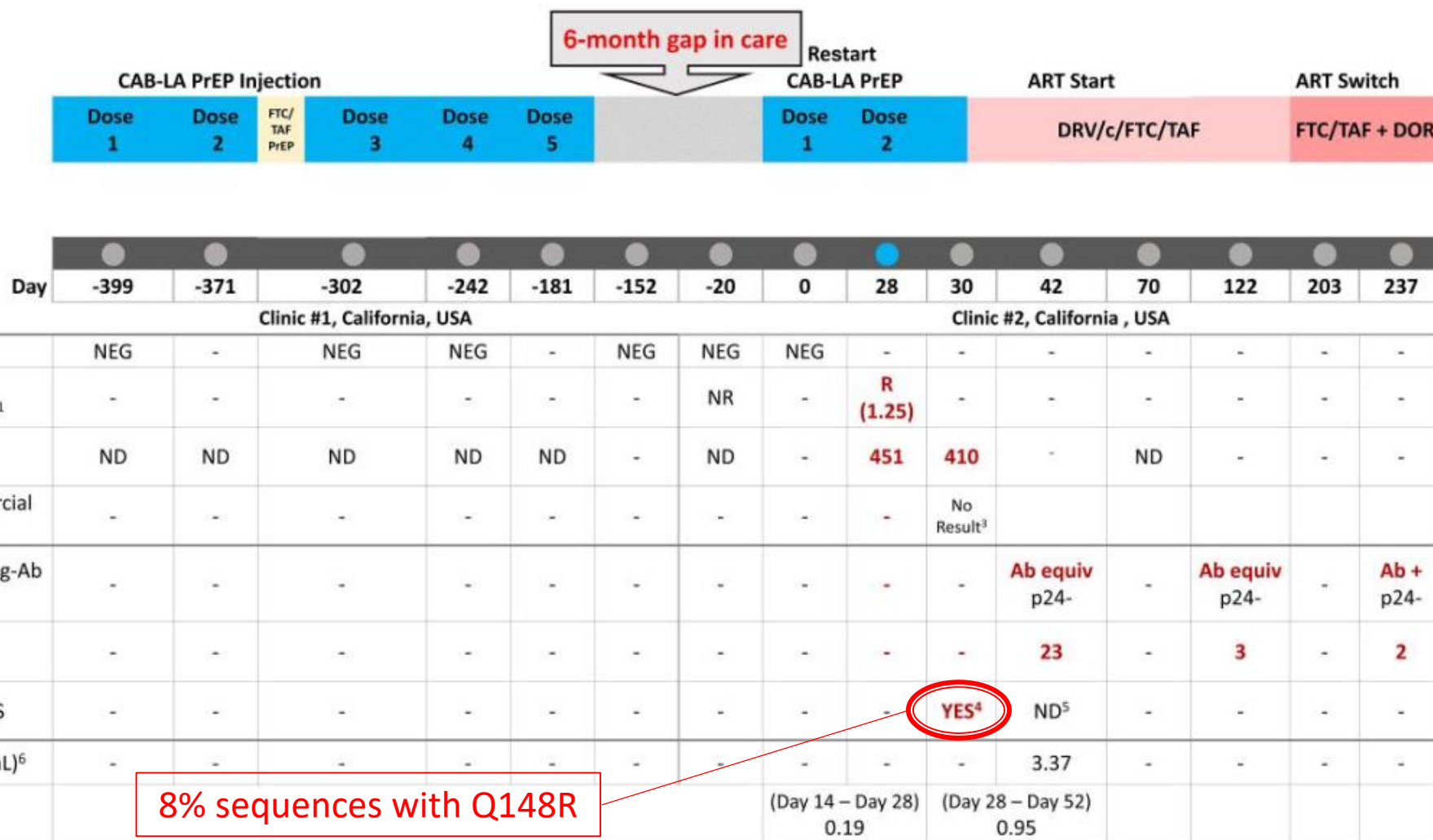
TRIO COHORT: Real-World LA CAB for PrEP Over the First 2 Years

- **No HIV seroconversion episodes**, but frequency of testing was inconsistent
- CDC guidelines recommend both HIV Ag/Ab and HIV RNA screening before each injection
 - Only 34% had both HIV Ag/Ab and HIV RNA testing

HIV Test Frequency, % (N = 526)	HIV Ag/Ab, n (%)	HIV RNA, n (%)	Both HIV Ag/Ab and HIV RNA, n (%)	Either HIV Ab/Ag or HIV RNA, n (%)	No HIV Test, n (%)
100	292 (56)	199 (38)	177 (34)	333 (63)	8 (2)
75-99	84 (16)	66 (13)	63 (12)	89 (17)	0
50-74	68 (13)	89 (17)	72 (14)	68 (13)	8 (2)
<50	82 (16)	172 (33)	214 (41)	36 (7)	510 (97)

First Case of HIV Seroconversion With Integrase Resistance Mutations on Long-Acting Cabotegravir for Prevention in Routine Care (SeroPrEP)

SeroPrEP registry and biobank of individuals who acquire HIV on PrEP in the US



First Case of HIV Seroconversion With Integrase Resistance Mutations on Long-Acting Cabotegravir for Prevention in Routine Care (SeroPrEP)

Table 1. Plasma Genotype by Single-Genome Sequencing

Mutation Frequency (%) ^a	Genotype (Full-Length Integrase) ^b	Interpretation
Plasma genotype by SGS: sample collected on day 30 (2 d after first reactive HIV test and before ART start)		
19/24 (67)	L45Q, G59E, I72V, L101I, V201I, D270N	No INSTI resistance
2/24 (8)	L45Q, G59E, I72V, L101I, Q148R , V201I, D270N	Q148R is a major INSTI resistance-associated mutation ^c
1/24 (4)	L45Q, G59E, I72V, L101I, <u>A128T</u> , V201I, D270N	A128T is a nonpolymorphic INSTI accessory mutation
1/24 (4)	L45Q, G59E, I72V, G94R, L101I, V201I, D270N	No INSTI resistance
1/24 (4)	L45Q, G59E, W61*, I72V, L101I, V201I, D270N	Contains stop codon (*); likely nonviable virus
Plasma genotype by SGS: sample collected on day 42 (14 d after first reactive HIV test and 8 d after ART start)		
3/3 (100)	L45Q, G59E, I72V, L101I, V201I, D270N	No INSTI resistance

Abbreviations: ART, antiretroviral therapy; CAB, cabotegravir; INSTI, integrase strand transfer inhibitor; RAM, resistance-associated mutation; SGS, single-genome sequencing.

^aMutation frequency calculated as number of genomes with reported genotype as a proportion of number of genomes sequenced. From the day 30 sample, 24 genomes were sequenced, yielding a 90% certainty that a mutation present at 10% frequency would be detected. From the day 42 sample, 3 genomes were sequenced, yielding a 90% certainty that a mutation present at 50% frequency would be detected.

^bMutations were defined using Stanford HIVDB, version 9.5.1, using an HXB2 subtype B reference. Major drug resistance-associated mutations are indicated in bold text, accessory mutations are indicated in underlined text, and integrase gene polymorphisms are indicated in black text.

^cQ148R confers high-level resistance to cabotegravir and low-level resistance to dolutegravir and bictegravir. Although Q148R alone may not affect response to INSTIs used for first-line HIV treatment, intermediate or high-level INSTI resistance can occur when Q148R is present in combination with other INSTI RAMs (eg, if additional INSTI RAMs accumulate in the setting of cabotegravir exposure before HIV detection).

First Case of HIV Seroconversion With Integrase Resistance Mutations on Long-Acting Cabotegravir for Prevention in Routine Care (SeroPrEP)

Mutation Frequency (%)	Genotype (Full-length Integrase) ¹	Interpretation
Day 30 Plasma Genotype by SGS (sensitivity to detect mutation at 4% due to 24 genomes sequenced)		
19/24 (67%)	L45Q, G59E, I72V, L101I, V201I, D270N	No INSTI resistance
2/24 (8%)	L45Q, G59E, I72V, L101I, Q148R , V201I, D270N	Q148R associated with CAB resistance
1/24 (4%)	L45Q, G59E, I72V, L101I, A128T , V201I, D270N	A128T is a non-polymorphic INSTI accessory mutation
1/24 (4%)	L45Q, G59E, I72V, G94R, L101I, V201I, D270N	No INSTI resistance
1/24 (4%)	L45Q, G59E, W61*, I72V, L101I, V201I, D270N	Contains stop codon (*); likely non-viable virus
Day 42 Plasma Genotype by SGS (sensitivity to detect mutation at ≥34% due to 3 genomes sequenced)		
3/3 (100%)	L45Q, G59E, I72V, L101I, V201I, D270N	No INSTI resistance

¹ Mutations defined using the Stanford HIVDB v9.5.1, using an HXB2 subtype B reference. Drug resistance-associated mutations indicated in **bolded red** text while integrase gene polymorphisms indicated in black text. Mutation sensitivity calculated as 1/number of genomes sequenced x 100%.

First Case of HIV Seroconversion With Integrase Resistance Mutations on Long-Acting Cabotegravir for Prevention in Routine Care (SeroPrEP)

- This case highlights several challenges with CAB-LA implementation in routine clinical settings that differ from trials.
 - After 7 months of CAB-LA use, the participant lost health insurance and had a lapse in injections for 6 months. After reestablishing care, as noted above, CAB-LA had to be ordered and obtained in clinic and the patient had to return to the clinic, contributing to a gap of 20 days between initial HIV RNA testing and the first CAB-LA injection.
 - Because this patient did not wish to take oral pills, this period was not covered by oral PrEP.
 - HIV RNA testing was not repeated within 7 days of restart, and fidelity to HIV testing guidelines may pose challenges in terms of logistics and costs.

SeroPrEP: Treatment Outcomes Following HIV Acquisition While on LA CAB PrEP

Characteristic	Case A	Case B	Case C
Age, yr	40	31	67
Gender identification	Cisgender male	Cisgender male	Cisgender male
BMI, kg/m ²	24	31	35.5
Sexual partners	Multiple	Multiple	Multiple
Previously on oral PrEP*	Yes	Yes	Yes
HIV-1 RNA at LA CAB initiation	Undetectable	Undetectable	Undetectable
History of injection drug use	Denies	Denies	Denies
LA CAB injections prior to HIV diagnosis, n	5	6	13
LA CAB injections received late or missed, n	0	0	0

*Cases A and B switched directly from oral TDF/FTC to LA CAB; Case C switched from oral TAF/FTC to oral CAB lead-in to LA CAB.

SeroPrEP: Treatment Outcomes Following HIV Acquisition While on LA CAB PrEP

Characteristic	Case A	Case B	Case C
Age, yr / Gender	40 / CGM	31 / CGM	67 / CGM
HIV-1 RNA at LA CAB initiation	Undetectable	Undetectable	Undetectable
LA CAB injections prior to HIV diagnosis, n	5	6	13
LA CAB injections received late or missed, n	0	0	0
HIV RNA at diagnosis, copies/mL	4880	3940	2.43 million
Ag/Ab at HIV diagnosis	POC test neg	POC test neg	Lab test reactive
[CAB] PA-IC ₉₀ multiple (sample type)	~4x (random)	~16x (random)	~6x (trough)
Days after last injection	42	21	55
INSTI RAMs, Sanger	None	None	None
INSTI RAMs, SGS (%)	Unavailable	E138K (1/56), N155K (1/43)	Q148R (10/33)

SeroPrEP: Treatment Outcomes Following HIV Acquisition While on LA CAB PrEP

Variable	Case A	Case B	Case C
HIV RNA at diagnosis, copies/mL	4880	3940	2.43 million
Ag/Ab at HIV diagnosis	POC test neg	POC test neg	Lab test reactive
[CAB], µg/mL	0.69	2.6	1.05
PA-IC ₉₀ multiple*	~4x	~16x	~6x
Days after last injection	42	21	55
Sample type	Random	Random	Trough

*LA CAB PrEP dosage Q8W targeted to achieve >4x PA-IC₉₀ (0.664 µg/mL) in 80% of individuals and >8x PA-IC₉₀ (1.33 µg/mL) in 50% of individuals.

SeroPrEP: Treatment Outcomes Following HIV Acquisition While on LA CAB PrEP

Assessment Method	Case A	Case B	Case C
Sanger genotyping			
▪ Sample collection, days post diagnosis	7	13	6
▪ INSTI mutations detected	None	None	None
Single-genome sequencing			
▪ Sample collection, days post diagnosis	Unavailable	7	10
▪ Signature INSTI mutations detected, n/N sequences	Unavailable	E138K (1/56)	Q148R (10/33)
▪ Accessory INSTI mutations detected, n/N sequences	Unavailable	N155K (1/43)	None

SeroPrEP: Treatment Outcomes Following HIV Acquisition While on LA CAB PrEP

Time Post ART Initiation	ART Regimen	HIV RNA, c/mL	
		Case A	Case B
1 mo	DRV/COBI/FTC/TAF	3*	<20
5-6 mo	DRV/COBI/FTC/TAF	Not detected	51*
10 mo	DRV/COBI/FTC/TAF	Not done	Not detected
Case C			
12 days	DRV/COBI/FTC/TAF	248,103	
26 days [†]	BIC/FTC/TAF	Not done	
2 mo	BIC/FTC/TAF	22	
4 mo	BIC/FTC/TAF	26	
6 mo	BIC/FTC/TAF	4*	

*Detected via single-copy RNA assay. [†]Switched owing to drug interactions and intolerance.

- In case C, ART switch based on commercial genotype, with no known INSTI resistance at the time
 - Presence of INSTI mutation Q148Q/R at 10 days post diagnosis in case C was not known until after ART switch was performed

SeroPrEP: Treatment Outcomes Following HIV Acquisition While on LA CAB PrEP

- Among the 3 cases who acquired HIV infection while on LA CAB PrEP
 - No INSTI mutations detected by Sanger sequencing
 - 2 had signature INSTI mutations, as detected by more sensitive assays
- All 3 achieved viral suppression on ART through ≥ 5 mo of follow-up
 - 2 started and maintained guideline-recommended DRV-based ART
 - 1 started on DRV-based ART but switched to BIC-based ART owing to drug–drug interactions and intolerance

HIV incident infections in a PrEP cohort

[ClinSex, Buenos Aires]



N=517

Individuals who started PrEP
at a sexual health clinic

Outcomes

RAMs and virologic outcomes of HIV incident cases among PrEP users



June 2018–
June 2024

Baseline Characteristics of Individuals Starting PrEP

Characteristic	N=517
Age, years, median (IQR)	31 (27, 37)
Gender, n (%)	
Cisgender MSM	512 (99)
TGW	5 (1)
ART used for PrEP, n (%)	
F/TDF	391 (76)
Q2M IM CAB	126 (24)
PrEP days, median (IQR)	545 (318, 967)

Adherence and RAMs in HIV Incident Cases Among Individuals Receiving PrEP

ART for PrEP	n/N (%)	Adherence	Major RAMs
Q2M IM CAB	2/126 (1.6%)	Good in 2/2	In 2/2 (INSTI in 2; NNRTI in 1)
F/TDF	4/391 (1.0%)	Irregular ^a in 3/4 Good in 1/4	In 1/4 (NRTI)

Although PrEP is highly effective, infrequent HIV acquisition can occur. **Major INSTI RAMs occurred in 2/2 (100%) individuals on Q2M IM CAB and NRTI RAMs in 1/4 (25%) individuals on F/TDF with incident HIV**

^aDue to missed doses and intolerance

N/A, not available; Q2M, every 2 months; TGW, transgender women

Pastor I, et al. HIV Glasgow 2024, Poster 026



HIV Incidence and Resistance Among Individuals on PrEP



N=517

Individuals who started PrEP
at a sexual health clinic

Outcomes

RAMs and virologic outcomes of HIV incident cases among PrEP users



June 2018–
June 2024

Baseline Characteristics of Individuals Starting PrEP

Characteristic	N=517
Age, years, median (IQR)	31 (27, 37)
Gender, n (%)	
Cisgender MSM	512 (99)
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Adherence and RAMs in HIV Incident Cases Among Individuals Receiving PrEP

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F/TDF	4/391 (1.0%)	Irregular ^a in 3/4 Good in 1/4	In 1/4 (NRTI)

Although PrEP is highly effective, infrequent HIV acquisition can occur. Major INSTI RAMs occurred in 2/2 (100%) individuals on Q2M IM CAB and NRTI RAMs in 1/4 (25%) individuals on F/TDF with incident HIV

^aDue to missed doses and intolerance

N/A, not available; Q2M, every 2 months; TGW, transgender women

Pastor I, et al. HIV Glasgow 2024, Poster 026



Characterization of dolutegravir drug resistance in persons diagnosed with HIV after exposure to long-acting injectable cabotegravir for preexposure prophylaxis

<i>N</i>	DRM patterns	Predicted cabotegravir resistance	Predicted dolutegravir resistance
1	E138K, Q148K	High	Intermediate
2	L74I, E138E/K, G140G/S, Q148R	High	High
3	E138A, Q148R	High	Intermediate
4	R263K	Intermediate	Intermediate
5	G140A, Q148R	High	Intermediate
6	N155H, R263K, Q148R	High	Intermediate
7	N155H, S230R	Intermediate	Intermediate

EACS guidelines 12.1 (November 2024)

Pre-exposure Prophylaxis (PrEP)

- Primary HIV Infection
 - In case of PHI in the context of LA CAB PrEP, a **DRV/b regimen should be immediately started until resistance test is available**

DHHS guidelines (September 2024)

Recommendations on CAB-LA PrEP and resistance testing

- For those with a history of CAB-LA use as PrEP, **genotype testing before starting ART** should include screening for INSTI resistance mutations [...] **regardless of the time since drug discontinuation (AIII).**
 - A regimen of **COBI or RTV-boosted DRV** with (TAF or TDF) plus (FTC or 3TC) is recommended while awaiting the results of the genotype testing **(AIII).**
 - **Use of an empiric INSTI-containing regimen is not recommended unless genotype testing shows no evidence of INSTI resistance (AIII).** This is because INSTI resistance may be present in those who acquire HIV during and possibly after the use of CAB-LA as PrEP.

DHHS guidelines (September 2024)

Recommendations on CAB-LA PrEP and resistance testing

- In an extended analysis of HPTN 083, 34 cases of HIV infection were reported in the CAB-LA arm [...]. Major resistance to an INSTI occurred in 10 of the 32 cases evaluated. All 10 participants with INSTI resistance in the CAB-LA arm received their last CAB dose within 6 months of their initial HIV-positive site visit. While the risk of acquired INSTI resistance appears to wane after 6 months, this trend is based on few observations. These data reinforce the importance of screening for INSTI-resistance mutations when acute HIV infection is diagnosed in people taking CAB-LA or with a history of prior CAB-LA PrEP use (AIII).

Recommended Initial ART When HIV Acquired While Taking PrEP

FTC/TDF or FTC/TAF PrEP

- BIC/FTC/TAF *or*
- DTG + XTC/TXF

Cabotegravir PrEP

- (DRV/RTV or DRV/COBI) + XTC/TXF

Adjust regimen once results of HIV genotype return

Transitioning From LA PrEP to HIV Treatment Regimen



General Management



- Confirm HIV status, CD4 count, and plasma HIV-1 RNA



- Connect with experienced HIV provider



- Counsel about HIV status, steps to prevent HIV transmission, how to improve their own health
 - Assist with identification of sex partners who may have been recently exposed to HIV so partners can be tested and offered PEP



Genotypic Testing and Starting Treatment



- Document genotypic HIV viral resistance test results to guide therapy
 - INSTI genotyping should be done prior to use of INSTI-based regimen



- Convert PrEP regimen to guideline-recommended HIV treatment regimen **without waiting** for test results
 - If treating **before** genotype results are available or INSTI resistance is present, use **boosted PI regimen containing DRV and XTC/TFV**



What's New in the Guidelines^{1,2}

Revisions to the Guidelines^a

PrEP

- Documented negative fourth-generation HIV test can be done a week prior to **or** on the day of PrEP initiation¹ (previously a week prior)³
 - Fourth-generation HIV test should be repeated at 1 month, then Q3M²
 - In stable long-term users on 6 monthly prescriptions, an interim fourth-generation test can be performed without a clinic visit²
- Q2M IM CAB can be considered if available as an alternative to F/TFX.^{1,b} The effectiveness of Q2M IM CAB has been evaluated in comparison to daily F/TDF in men, transgender women and cisgender women¹
- In all populations and all regimens, oral PrEP should start with 2 tablets taken together, as this achieves highly effective levels in all compartments 2 hours later¹
- For men taking on-demand PrEP, the definition of low adherence leading to PEP has been changed to noncompliance with 2-1-1 scheme¹ (previously <1 pill before and 1 pill after sexual intercourse)³

ART in TB/HIV Coinfection

- TFX/XTC + DTG BID moved to recommended regimens (previously alternative; B/F/TAF is not on the list)¹

Opportunistic Infections

- Treatment options in cryptococcal meningitis: Amphotericin B deoxycholate-based regimen has been removed, prioritizing the single-dose L-AMB-based regimen in resource-limited settings and the 2-week L-AMB + flucytosine regimen in high-resource settings²

CV and Metabolic Health

- Guidance on the primary prevention of CVD has been updated in line with the EACS “Interim Guidance on the Use of Statin Therapy for the Primary Prevention of Cardiovascular Disease in People with HIV”²
- The nomenclature of MASLD has been introduced to replace nonalcoholic fatty liver disease²
- An overarching bone health section has been introduced, incorporating the existing “Bone Disease: Screening and Diagnosis,” “Vitamin D Deficiency: Diagnosis and Management” and “Approach to Fracture Reduction” sections²

New Subsection Added to the Guidelines

- Chemsex²

^aFor an exhaustive list, please refer to EACS guidelines.² ^bPrevious guidelines stated available via compassionate release program pending EMA approval³

EACS, European AIDS Clinical Society; L-AMB, liposomal amphotericin B; MASLD, metabolic dysfunction-associated steatotic liver disease; PEP, postexposure prophylaxis; Q2M, every 2 months; Q3M, every 3 months

1. Levi L. HIV Glasgow 2024, Invited talk. 2. EACS guidelines, Version 12.1, November 2024. <https://eacs.sanfordguide.com/> (accessed November 14, 2024). 3. EACS guidelines, Version 12.0, October 2023. <https://www.eacsociety.org/media/guidelines-12.0.pdf> (accessed November 14, 2024)





IAS-USA Guideline Updates: HIV Prevention



Key Recommendations for HIV Prevention^{a,b}

Generally Recommended HIV Prevention Approach

- Adopt a serostatus-neutral approach to reduce stigma, facilitating rapid care linkage and PrEP navigation
- Offer PrEP to all sexually active individuals, those requesting it, or those with a substance use disorder, without specific risk criteria or screening tools
- Offer PrEP to sexual partners of PWH and those who share needles with individuals with HIV or unknown HIV status

Rapid PrEP Start

- Initiate PrEP in individuals with a negative HIV test result from the past 7 days
 - In individuals with no recent HIV test results, conduct testing and initiate PrEP on receipt of negative test result
- Transition to PrEP in individuals receiving PEP for substantial HIV exposure if HIV test results are negative

Laboratory Testing

- HIV screening should include an HIV RNA test and a laboratory-based antigen/antibody test after PrEP initiation or after a long hiatus
- Rapid HIV antibody and laboratory-based antigen/antibody testing is recommended at Q2M IM CAB follow-up instead of routine RNA testing
- If RNA testing is unavailable, antigen/antibody testing should be repeated at 1 month post initiation or reinitiation of TFV-based oral PrEP

Bacterial STI Prevention

- Guidance on the use of doxyPEP for men who have sex with men and transgender women has been strengthened

Long-Acting Injectable PrEP

- Key data from the PURPOSE 1 and PURPOSE 2 studies are included
- After approval by regulatory authorities and when available, LEN is recommended for prevention of HIV infection for all routes of sexual exposure^c
- The first SC injection should be overlapped with 2 daily oral doses of LEN (600 mg)
- Both Q2M IM CAB and SC LEN have been associated with ISRs, which often diminish in severity over time
- The guidelines emphasize that, with the advent of effective injectables for PrEP (e.g., Q2M IM CAB currently; LEN in the future), a global commitment to universal access is crucial for equitable implementation and scale-up

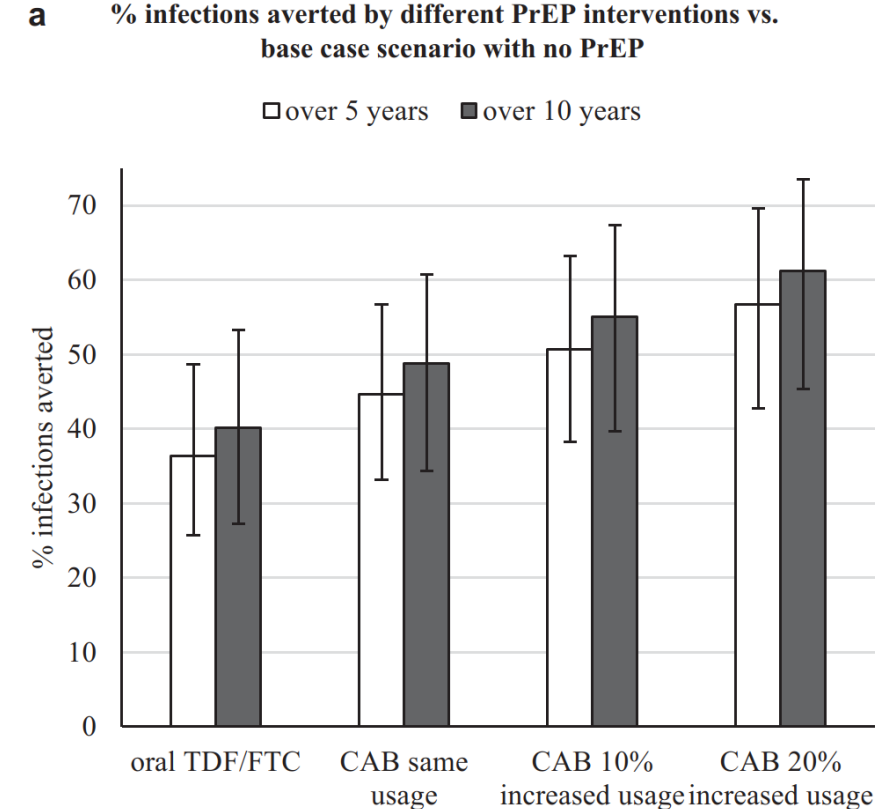
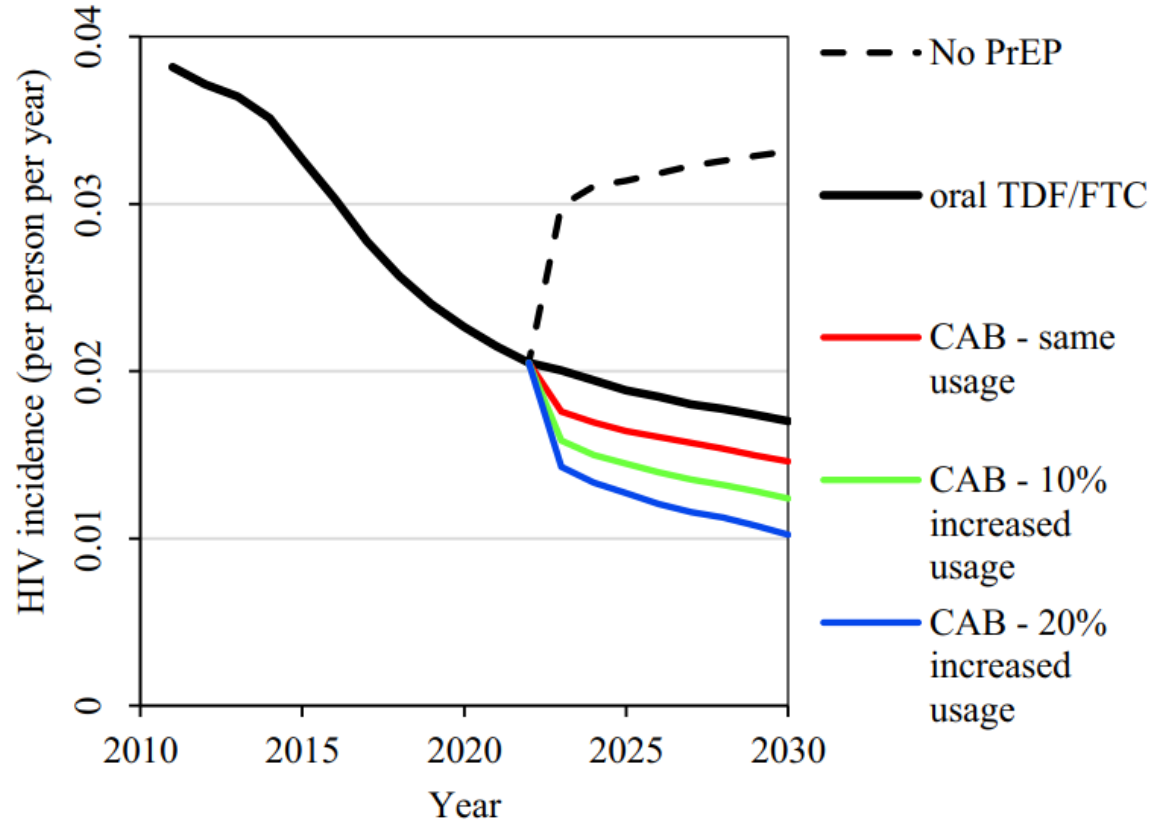
^aFor a comprehensive list of updates, please refer to the IAS-USA guidelines; ^bThe data presented on this slide were not part of the CROI 2024 program; ^cEvidence rating 1a: Strong panel support for the recommendation, with evidence from ≥1 RCT published in peer-reviewed literature

ISR, injection site reaction

Gandhi RT, et al. JAMA. December 2024 [ePub]. doi: 10.1001/jama.2024.24543

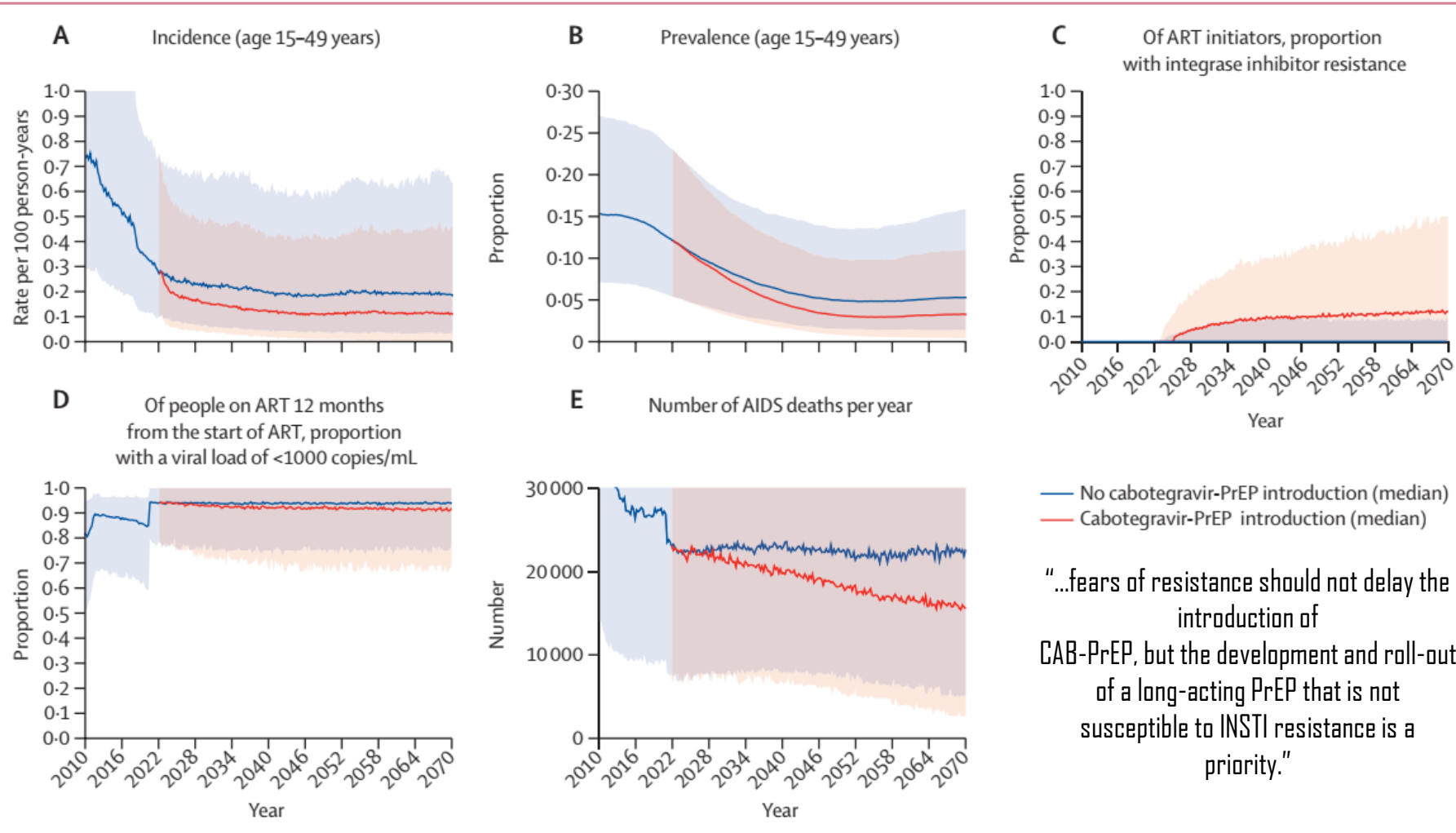


Estimating the impact of HIV PrEP regimens containing LA CAB or daily oral TDF/FTC among MSM in the US: a mathematical modelling study for HPTN 083



MSM HIV transmission model calibrated to Atlanta-specific data on HIV prevalence and PrEP usage

Predicted effects of the introduction of long-acting injectable cabotegravir pre-exposure prophylaxis in sub-Saharan Africa: a modelling study



- Predicted effects of introduction of LA CAB in SSA by HIV Synthesis modeling:
 - Increased PrEP use
 - Increased proportion of INSTI resistance
 - Small increase in PWH with VL <1000 cps/mL
 - Decreased HIV incidence and mortality
 - Little benefit from NAT over Ag/Ab assays

Key notes from Eshleman JID 2023

- Earlier detection of HIV infection may avoid or limit INSTI resistance and transmission of INSTI resistant variants
- CDC recommends HIV RNA testing using the most sensitive assay available within 1 week before starting CAB-LA PrEP, at every injection visit, and quarterly for 12 months after stopping injections (HPTN-083 tested within 14 days and 4 CAB and 4 TDF/FTC persons were enrolled with acute infection)
- The risk for emergent resistance should be put in context: in HPTN 083, only 16 HIV infections were identified among 2282 participants in the CAB arm with >3000 person-years of follow-up. Only 7 of the 16 cases identified during the blinded phase of the trial had INSTI RAMs detected; 1 of those participants would not have received CAB if the infection had been detected prior to study enrollment and 2 others were infected while receiving oral CAB, which is considered optional by the US FDA prior to starting CAB-LA PrEP.

Conclusions

- Current and upcoming PREP regimens are single class
 - They violate the paradigm of combination therapy
- Emergent resistance at failure of PREP is not new
 - But with CAB is more disturbing than with NRTI
- The risk is high with unrecognized infection when starting PREP
 - Use maximum sensitivity screening to limit the risk of ill-fated PREP start
- Resistance to CAB does develop despite on time injections and adequate plasma CAB levels, both with CAB PrEP and treatment
 - Yet, models indicate CAB PrEP benefits outweigh CAB resistance issues
- Lenacapavir sounds like another breakthrough, yet it does not seem to protect from emergent resistance at failure

TRIO Health Cohort: Efficacy and Testing

- **No HIV seroconversion episodes**, but frequency of testing was inconsistent¹
- CDC guidelines recommend both HIV Ag/Ab and HIV RNA screening before each injection²
 - Only 34% had both HIV Ag/Ab and HIV RNA testing

HIV Test Frequency, % (N = 526)	HIV Ag/Ab, n (%)	HIV RNA, n (%)	Both HIV Ag/Ab and HIV RNA, n (%)	Either HIV Ab/Ag or HIV RNA, n (%)	No HIV Test, n (%)
100	292 (56)	199 (38)	177 (34)	333 (63)	8 (2)
75-99	84 (16)	66 (13)	63 (12)	89 (17)	0
50-74	68 (13)	89 (17)	72 (14)	68 (13)	8 (2)
<50	82 (16)	172 (33)	214 (41)	36 (7)	510 (97)