

Supplementary Appendix

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This appendix has been provided by the authors to give readers additional information about the work.

SUPPLEMENTARY APPENDIX

- List of investigators**2
- Characteristics and clinical implications of LEVI**3
 - Key features of LEVI3
 - Time window for LEVI in the setting of CAB-LA PrEP3
 - Use of HIV RNA screening to detect HIV infections in the setting of CAB-LA PrEP..3
 - Clinical management of possible HIV infection in the setting of CAB-LA PrEP.....4
- LEVI cases identified in HPTN 083 and HPTN 084**4
 - Table S1. LEVI cases grouped by clinical and laboratory criteria.....5
 - Figure S1: Key events and laboratory data for LEVI cases.....6
- Examples of LEVI cases with assay reversion**12
 - Figure S2. Laboratory results from cases with assay reversion12
- References**15

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Characteristics and clinical implications of LEVI

Long-acting early viral inhibition (LEVI) is a new presentation of early HIV infection that is observed when HIV infection occurs in the setting of a potent, long-acting pre-exposure prophylaxis (PrEP) agent. To date, LEVI has only been observed in the setting of long-acting injectable cabotegravir (CAB-LA). Going forward, it is reasonable to anticipate that LEVI will occur with other long-acting, potent PrEP agents, including small molecules and immune-based agents.

Key features of LEVI

LEVI can occur when a long-acting PrEP agent is started in persons with undiagnosed acute HIV infection (AHI) or when HIV infection occurs after initiation of the PrEP agent. In contrast to AHI, LEVI is characterized by “smoldering” viral replication with very low viral loads. Viral RNA may be undetectable for long periods, even after drug administration stops and drug levels decline. In some cases, RNA levels may be too low to detect even using a single copy RNA assay. Antibody production is also profoundly diminished/delayed. In some cases, antibody levels remain below the level of detection for months after drug administration stops. Transient increases in antibody levels may occur prior to breakthrough, but are usually too low to yield a positive confirmatory/discriminatory assay result. HIV infections are usually clinically silent with LEVI and levels of HIV antigen, antibody, RNA, and DNA are often below or near the level of detection of available assays. Results from different types of HIV tests may revert from reactive, indeterminate, or positive to non-reactive or negative and may alternate between these categories, making it challenging to detect and confirm HIV infection. The very low viral loads seen in LEVI are likely to be associated with a low risk of sexual HIV transmission. However, transmission through other routes (e.g., injection drug use or blood product transfusion) remains biologically plausible. Integrase strand transfer inhibitor (INSTI) resistance often emerges early in LEVI when the viral load is very low. LEVI can persist for months, even after CAB-LA injections are discontinued, likely reflecting the long terminal half-life or “tail phase” of the drug. LEVI usually resolves when antiretroviral drug concentrations decline sufficiently or resistance mutations are selected to allow for viral breakthrough. It is not known whether there are differences in HIV disease progression in AHI¹ vs. LEVI.

Time window for LEVI in the setting of CAB-LA PrEP

In the HIV Prevention Trials Network (HPTN) 083 trial, LEVI was only observed in participants who acquired HIV infection within 6 months of their last cabotegravir (CAB) dose; INSTI resistance was also only observed when infections occurred in this time window. The time window for diagnostic delays and emergence of resistance with CAB-LA PrEP may be longer in persons assigned female at birth since these persons have a longer terminal CAB elimination half-life than those assigned male at birth.²

Use of HIV RNA screening to detect HIV infections in the setting of CAB-LA PrEP

Findings from HPTN 083 and 084 demonstrate that HIV RNA screening detects infections earlier than Ag/Ab testing in the setting of CAB-LA PrEP.^{3,4} Our research also shows that HIV RNA screening would have detected some infections before INSTI resistance emerged.⁵ The United States (US) Food and Drug Administration prescribing information for CAB-LA includes use of an RNA test to screen for HIV infection prior to initiation of CAB-LA PrEP and with each CAB-LA injection.⁶ The US Centers for Disease Control recommends HIV RNA screening within 1 week before CAB-LA PrEP initiation, at each injection visit, and every three months for a year after

stopping injections.⁷ In contrast, the current World Health Organization guidelines do not include HIV RNA screening in this setting.⁸ While RNA testing will detect infections earlier in LEVI, decisions to include HIV RNA screening with CAB-LA PrEP must balance the ability to detect infections earlier and avoidance of resistance against the low number of anticipated infections, against the cost and availability of testing, and the possibility of false-positive test results which could complicate clinical management and cause significant emotional distress. HPTN 083 and 084 are continuing as open-label extension studies; in this phase of the studies, HIV RNA testing is included as part of prospective HIV screening algorithms. Analysis of data from these studies will help assess the utility of prospective RNA screening in this setting.

Clinical management of possible HIV infection in the setting of CAB-LA PrEP

The impact of LEVI on the clinical presentation of HIV infection and HIV diagnostic test results should be kept in mind in the setting of CAB-LA PrEP. Providers should have a heightened suspicion for infection if reactive or positive HIV test results are obtained, even in the absence of clinical symptoms. When interpreting test results, providers should recognize that levels of HIV antigen, antibodies, RNA, and DNA may all be low; that test results can revert to non-reactive/negative in true infections; that a prolonged period of observation with frequent retesting may be needed in some cases before infection can be confirmed which may complicate clinical care; and that delays in diagnosis and antiretroviral therapy (ART) initiation may be associated with emergence of INSTI resistance, including cross-resistance to dolutegravir and bictegravir.^{3,4,9} Such cross-resistance is especially important given the role of dolutegravir- and bictegravir-based ART regimens globally.¹⁰ Expert consultation is advised to assist in management of ambiguous cases. Development of new highly-sensitive HIV diagnostic tests, including those that provide point-of-care results, that are inexpensive and are robust to supply chain fragility would help optimize clinical care in persons receiving both current and future long-acting PrEP agents.

LEVI cases identified in HPTN 083 and HPTN 084

Methods for determining HIV status in HPTN 083 and 084 are described previously.^{3,4} HIV screening was performed at study sites using HIV rapid tests and a laboratory-based antigen/antibody (Ag/Ab) test. Additional testing was performed at study sites using HIV antibody and HIV RNA tests; HIV DNA testing was performed in selected cases. Additional HIV testing was performed retrospectively at the HPTN Laboratory Center for cases with one or more reactive/positive test; in selected cases, a single copy HIV RNA test was performed at the University of Pittsburgh (Pittsburgh, PA). An independent Endpoint Adjudication Committee determined the final HIV status and timing of HIV infection in each case based on all available HIV test results.

HIV infections are rare in the setting of CAB-LA PrEP. In HPTN 083, only 34 infections were identified among 2,282 persons randomized to CAB^{3,9,11,12} (four prior to enrollment, three during the oral lead-in, six with on-time injections, three with one or more delayed injections, three near the time of CAB re-initiation, and 16 with no CAB administration in the prior six months). In HPTN 084, only seven infections were identified among 1,164 persons randomized to CAB^{4,13,14} (one prior to enrollment, one during the oral lead-in, one with delayed injection, four with no CAB administration in the prior six months). In nearly half of these cases, detection of infection was delayed when HIV rapid tests and an Ag/Ab test were used for HIV screening according to a pre-specified testing algorithm.

This file shows key events and laboratory results for the 14 participants identified to date who acquired HIV infection in the HPTN 083 and 084 trials and had characteristics of early HIV infection consistent with LEVI. The following criteria were used for case selection: (1) delayed detection of HIV infection at study sites using HIV rapid and antigen/antibody tests; (2) at least one CAB injection; last CAB injection <6 months prior to the first HIV-positive visit. These infections occurred in the blinded phase of the trials and up to one year after each trial was unblinded. This supplementary file presents the cases from both trials in a single document and presentation format. Additional data for these cases, including data from the period prior to infection and results of testing performed at study sites, are presented in prior reports.^{3,4,9}

In both trials, the first HIV-positive visit was determined based on laboratory results from site testing and retrospective testing. In seven of the 14 cases, the participants acquired HIV infection before their first CAB injection (Figure S1, Panel A, pre-injection cases: five from HPTN 083, two from HPTN 084); in the other seven cases, the participants acquired HIV infection after their first CAB injection (Figure S1, Panel B, post-injection cases: all from HPTN 083). The pre-injection cases included participants who acquired HIV infection prior to enrollment (A cases) and participants who acquired HIV infection during the oral CAB lead-in phase (C cases). The post-injection cases included participants who acquired HIV infection while receiving on-time CAB injections (D cases) and a participant who acquired HIV infection at the time of CAB re-initiation more than 6 months after the last CAB injection (BR case). Each case had one or more of the features associated with LEVI. Table S1 below groups the cases according to clinical and laboratory criteria (timing of HIV infection relative to CAB-LA initiation; assay reversion; drug levels at the timing of viral breakthrough; INSTI resistance; initiation of ART).

Table S1. LEVI cases grouped by clinical and laboratory criteria

	HPTN 083	HPTN 084
Pre-injection cases	A2, A3, A4, C1, C3	A1, C1
Post-injection cases	D1, D2, D3, D4, D5, D6, BR1	
Assay reversion (retrospective testing)	A3, A4, C1, C3, D2, D3	A1, C1
Viral breakthrough ^a		
On-time injections with expected drug levels	D3, D4	
After injections stopped with declining drug levels	A3, D5	
No breakthrough	A4, D1, D2	A1, C1
INSTI resistance	A2, C1, C3, D1, D2, D3, D4, D5, D6, BR1	
ART started ^b	A4, C3, D1, D3, D4, D5, D6, BR1	

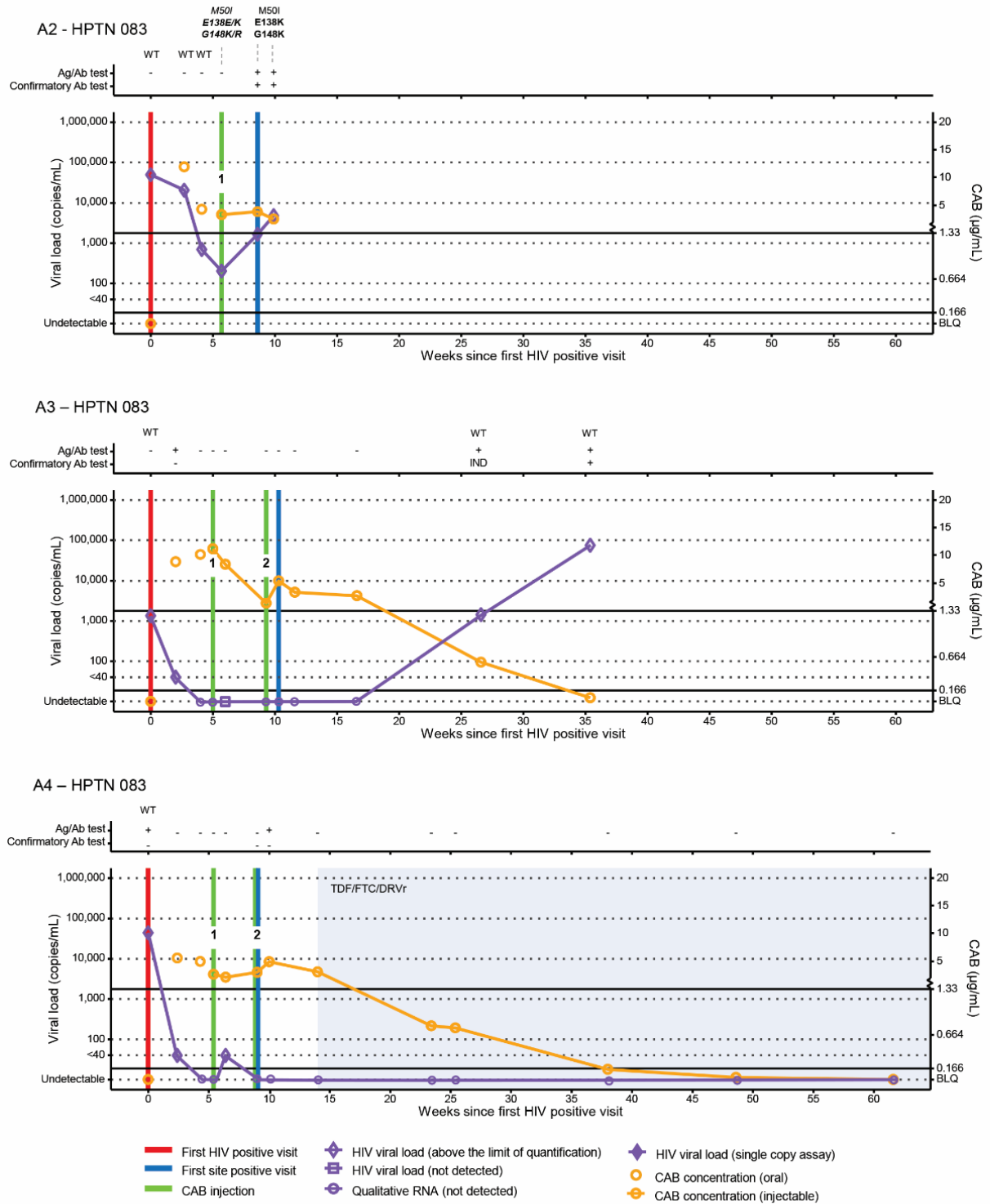
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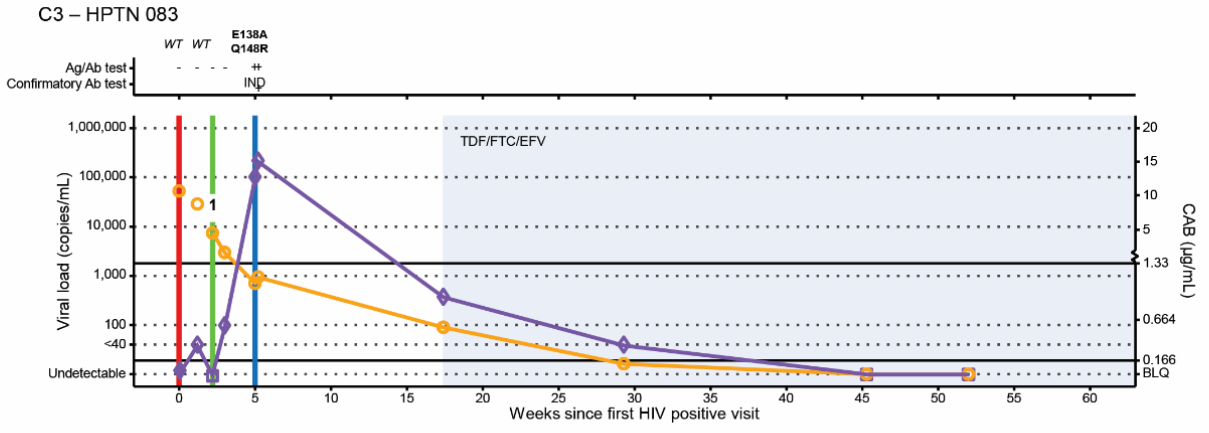
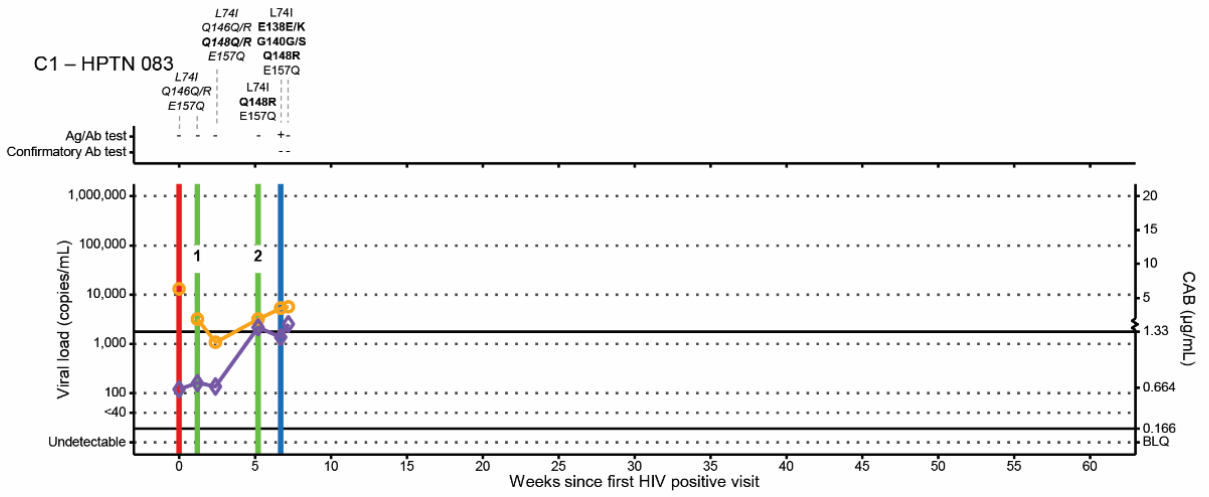
^a Cases are listed in the table if the participant was virally suppressed and had viral breakthrough after one or more CAB-LA injections.

^b Four participants received a darunavir-based regimen; four received an efavirenz-based regimen. All eight participants achieved viral suppression. In addition, one participant received a short course of post-exposure prophylaxis (PEP) with a darunavir-based regimen (HPTN 083 Case D2).

Figure S1: Key events and laboratory data for LEVI cases

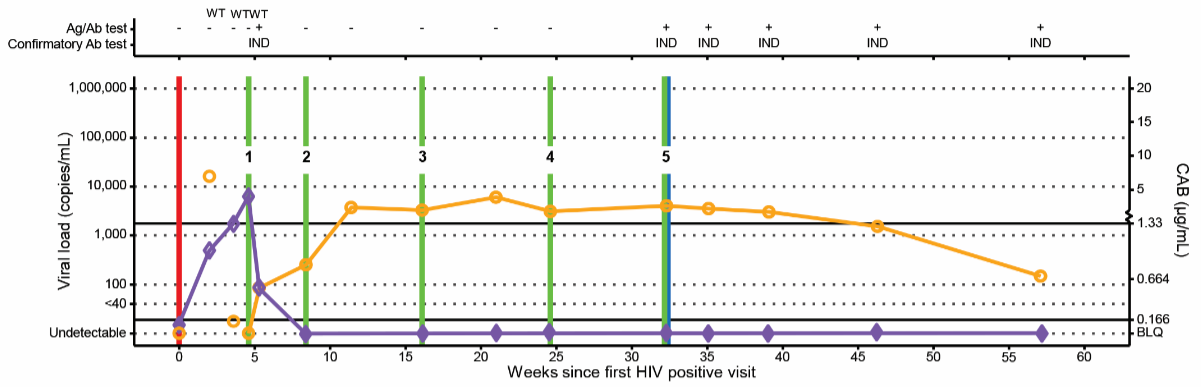
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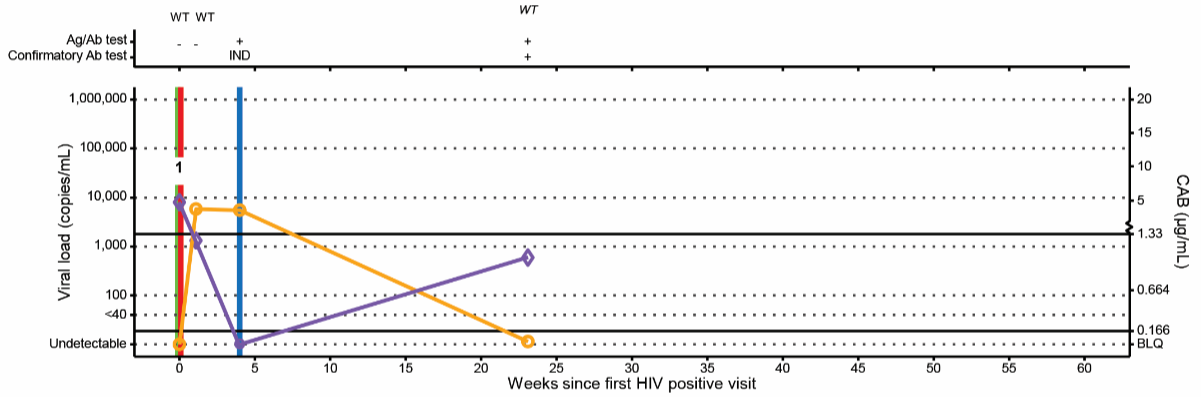


- First HIV positive visit
- First site positive visit
- CAB injection
- ◆ HIV viral load (above the limit of quantification)
- HIV viral load (not detected)
- ◆ HIV viral load (single copy assay)
- CAB concentration (oral)
- ◐ CAB concentration (injectable)
- Qualitative RNA (not detected)

A1 – HPTN 084

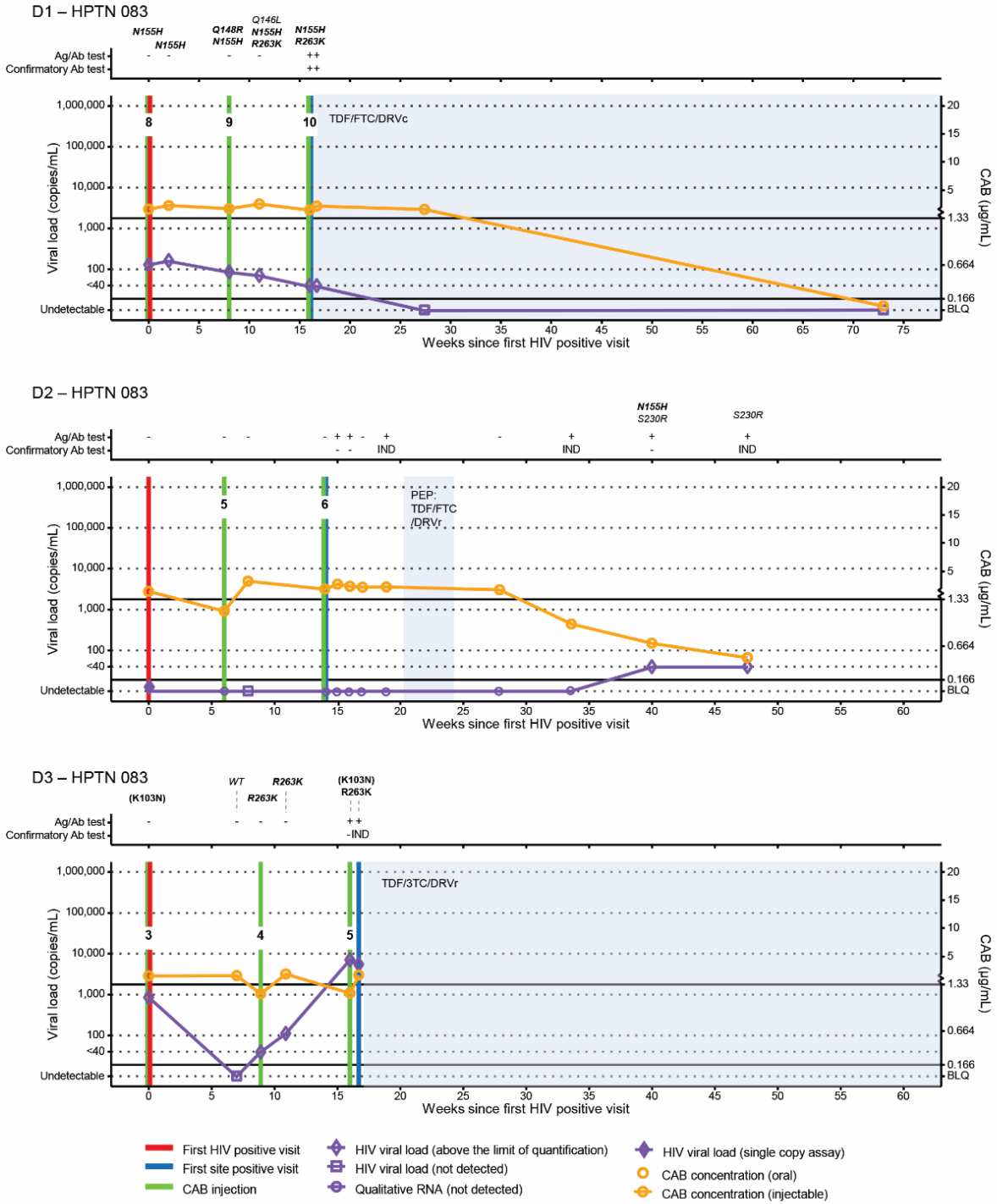


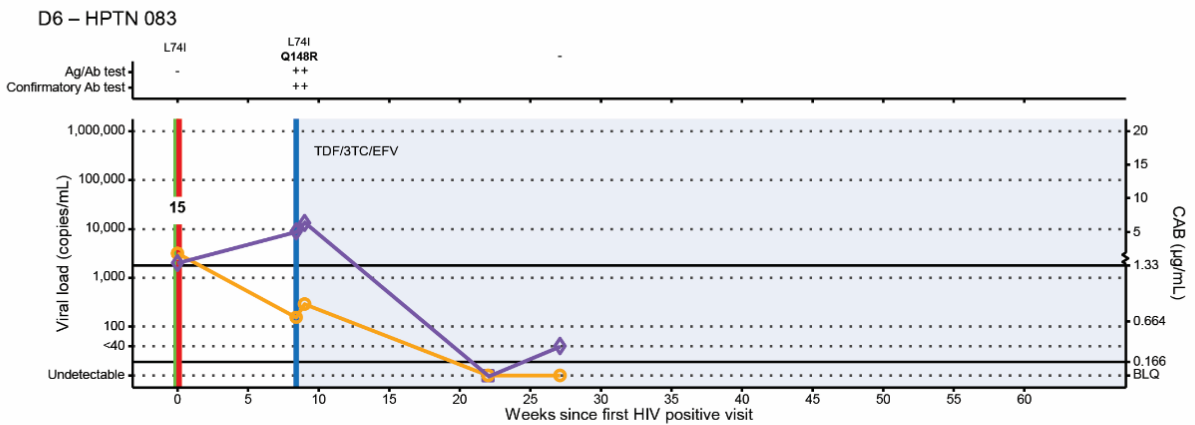
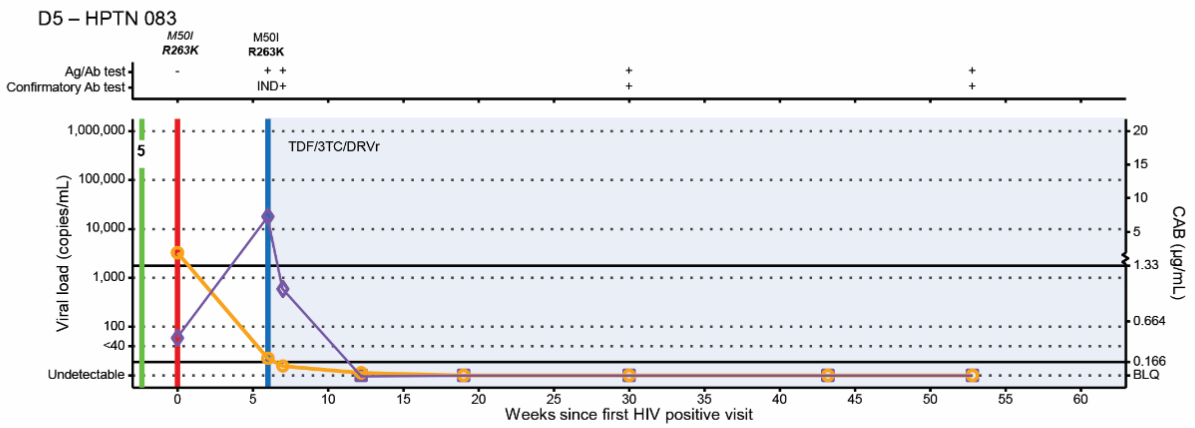
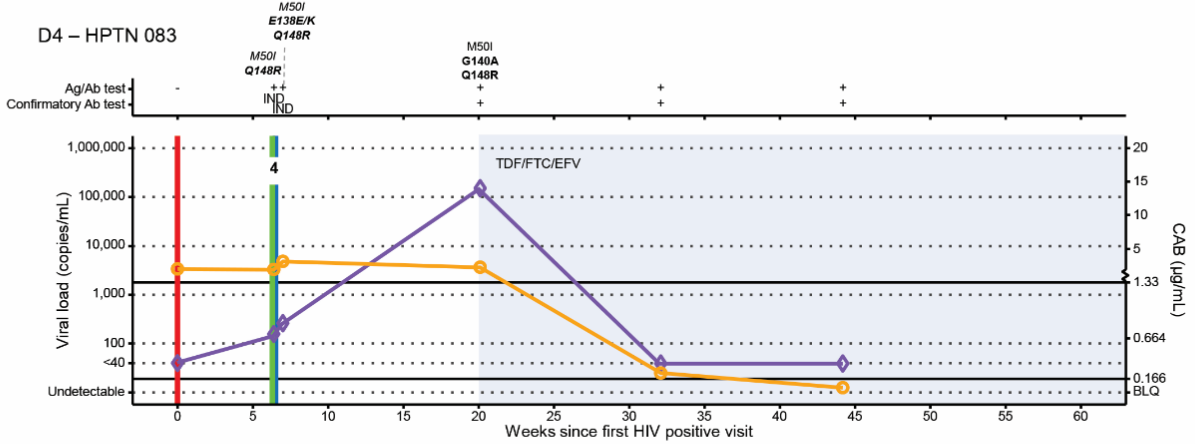
C1 – HPTN 084



- █ 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)

B





- 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)

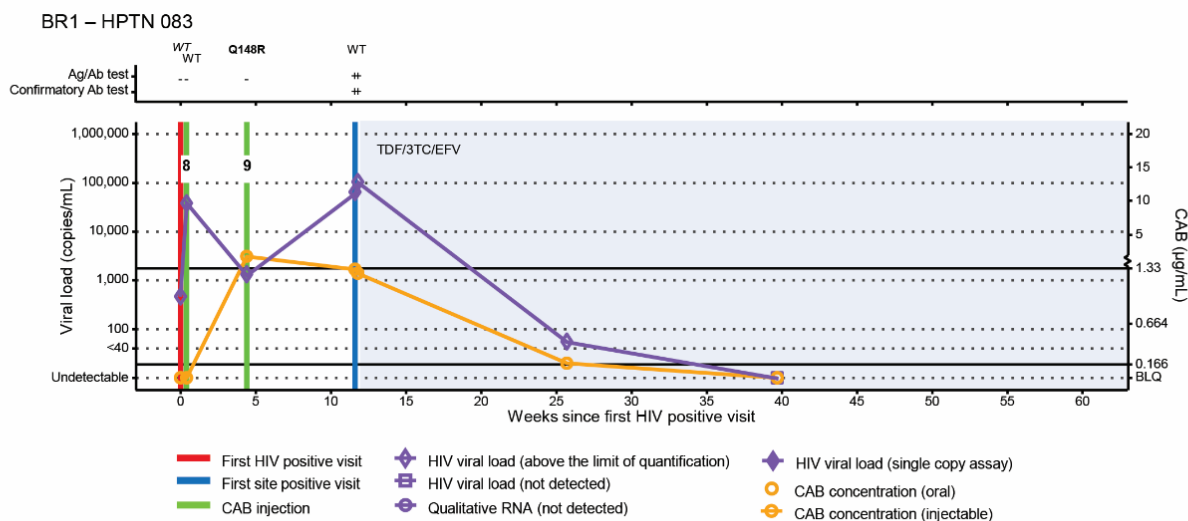


Figure S1 legend

The plots show key events and laboratory data for each case (Panel A: pre-injection cases, Panel B: post-injection cases). The X axis shows the number of weeks after the first HIV-positive visit (Week 0, red line); the left Y axis indicates viral load, and the right Y axis indicates CAB concentration. The first site-positive visit (blue line) is the first visit near the time of infection where the site obtained a reactive HIV test result. Green lines indicate CAB injections; numbers overlying these lines indicate the injection number (e.g., 1 = first CAB injection). Orange symbols show CAB concentrations. Horizontal lines indicate CAB cutoffs (1.33 µg/mL = 8x PA-IC₉₀; 0.664 µg/mL = 4x PA-IC₉₀; 0.166 µg/mL = 1x PA-IC₉₀; BLQ <0.025 µg/mL); PA-IC₉₀ refers to the *in vitro* protein-adjusted 90% CAB inhibitory concentration. A target concentration >8x PA-IC₉₀ was used to interpret drug concentrations. Symbols are defined in the figure legends. The assays used for analysis are described in prior reports.¹⁻³ Purple symbols show data from three different HIV RNA assays (a quantitative viral load assay with a lower limit of quantification of 40 copies/mL, VL); a qualitative assay with a lower limit of quantification of 30 copies/mL, Qualitative RNA); and a single copy RNA assay performed at the University of Pittsburgh. Results from retrospective antigen/antibody (Ag/Ab) and discriminatory antibody (Ab) testing performed at the HPTN Laboratory Center are shown above each graph. A plus sign (+) indicates a reactive or positive test result; a minus sign (-) indicates a non-reactive or negative test result. HIV genotyping results are shown above table. All INSTI resistance associated mutations (RAMs) are shown; major INSTI RAMs are bolded. HIV genotyping was performed using the GenoSure PRIME assay (Monogram Biosciences, South San Francisco, CA) for samples with viral loads >500 copies/mL; this assay detects RAMs in HIV protease, reverse transcriptase, and integrase. HIV genotyping was performed at the University of Pittsburgh for samples with lower viral loads using a low viral load INSTI genotyping assay (*italics*). Major RAMs that confer resistance to other drug classes are shown in parentheses. Blue shading indicates that the participant was on ART; ART regimens are noted for these cases.

Abbreviations: Ag/Ab: antigen/antibody test; Ab: antibody; BLQ: below the limit of quantification; CAB: cabotegravir; IND: indeterminate; mL: milliliter; PA-IC₉₀: *in vitro* protein-adjusted 90% CAB inhibitory concentration; PEP: post-exposure prophylaxis; µg: microgram; WT: wild type (no RAMs detected).

Examples of LEVI cases with assay reversion

Figure S2 below shows laboratory results for two participants who acquired HIV infection in the setting of CAB-LA PrEP. In these two representative cases, test results from several assays reverted over time (e.g., from positive or indeterminate to negative; from reactive to non-reactive; from detected to not detected; or from quantified to not detected).

Additional assay information for these cases is provided in above and in prior reports.^{3,4,9} The table for each case shows laboratory results from HIV-positive visits.

Figure S2. Laboratory results from cases with assay reversion

(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	

(B) HPTN 084 – Case A1

	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
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	

Figure S2 Legend

Each panel shows results from real-time testing that was performed at the study site (Site testing); the results of real-time HIV DNA testing that was performed at the Cure Laboratory at Johns Hopkins University using an ultrasensitive assay is also shown under Site testing. Test results are also shown for assays performed retrospectively at the HPTN Laboratory Center or other designated reference laboratories (Retrospective testing). Reactive and positive site test results are shown in blue font; reactive, indeterminate and positive retrospective test results are shown in red font. The red shaded row indicates the first HIV positive visit. The blue shaded row indicates the visit where the site first detected the possibility of infection. The purple shaded row indicates the first visit where the site confirmed the infection using locally-available testing.

Panel A: HPTN 083 Case D2

This participant acquired HIV infection 26 weeks after enrollment, after receiving oral CAB and four on-time CAB-LA injections. The participant received two additional CAB-LA injections before the site detected the infection 3.3 months later. It took about 6 months before the site was able to confirm the infection using locally available tests. During that time, the participant received a 4-week course of 3-drug post-exposure prophylaxis, since the participant did not believe his HIV status. The participant later started antiretroviral therapy (ART) with a protease inhibitor-based regimen and was virally suppressed on that initial regimen.

Retrospective testing showed that the viral load (VL) was 6.1 c/mL at the first HIV-positive visit. The highest VL result obtained over >9 months of follow-up was <40 c/mL. The discriminatory antibody test was not positive at any study visit. HIV DNA was detected at low levels at three visits. Assay reversion was noted for six different tests. HIV genotyping indicated that the participant likely had subtype B infection; major integrase strand transfer inhibitor resistance mutations (N155H and S230R) were detected at the visit when the site confirmed the infection. These mutations are predicted to confer high-level resistance to elvitegravir and raltegravir, intermediate-level resistance to cabotegravir and dolutegravir; and low-level/potential resistance to bictegravir.¹⁵

Panel B: HPTN 084 Case A1

This cisgender woman had early acute HIV infection at study enrollment that was not detected by the study site. CAB concentrations during the oral lead-in phase indicated suboptimal adherence. Five on-time CAB-LA injections were administered before the site detected the infection 7.5 months later. It took an additional 5.8 months before the site was able to confirm the infection using a locally available test. ART was started 6 weeks after the site confirmed the infection; information is not available about the ART regimen or treatment outcome.

Retrospective testing showed that the viral load was 21.4 copies/mL at the first HIV-positive visit. The VL rose to 6,300 c/mL during the oral lead-in phase, then declined to 87 c/mL after the first CAB-LA injection. The VL then fell below the level of detection using a single copy RNA assay (SCA) and remained undetectable with this assay for all subsequent visits (6 months while the participant received CAB-LA injections and 5 months after the last injection). The discriminatory antibody test was indeterminate throughout study follow-up. HIV DNA was detected at low levels at three visits (range: <4.09 to 4.4 copies/million cells). HIV genotyping revealed that the participant was infected with subtype A1 HIV with no INSTI mutations. Assay reversion was observed for five different tests in this case.

Abbreviations:

1st HIV POS: first HIV positive visit; Rapid 1, Rapid 2: HIV rapid test; Ag/Ab: antigen/antibody test; DNA: HIV DNA test; VL: HIV viral load test; Qual RNA: qualitative RNA test; Discrim: discriminatory antibody test; LLOQ: lower limit of quantification; LLOD: lower limit of detection; SCA: single copy RNA test; genotype: HIV genotyping test; NR: non-reactive; R: reactive; POS: positive; NEG: negative; INDET: indeterminate; ND: not detected; WT: wild type (no INSTI resistance mutations detected).

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