First Case of HIV Seroconversion With Emergence of InSTI Resistance on CAB-LA PrEP in Routine Care

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Catherine A. Koss,[1] Monica Gandhi,[1] Elias K. Halvas,[2] Hideaki Okochi,[1] Carolyn Chu,[1] David V. Glidden,[1] Lisa Georgetti Gomez,[1] Amy L. Heaps,[2] Amy A. Conroy,[1] Michael Tran,[3] Bhavna Chohan,[4] James Ayieko,[5] John W. Mellors,[2] Urvi M. Parikh,[2] for the SeroPrEP Study Team

[1]Univ. of California San Francisco, CA, USA, [2]Univ. of Pittsburgh, PA, USA, [3]Men's Health Foundation, Los Angeles, CA, USA, [4]Univ. of Washington, WA, USA, [5]Kenya Medical Research Institute, Nairobi, Kenya

BACKGROUND

- Long-acting cabotegravir (CAB-LA) is highly effective for HIV prevention but delayed diagnoses and integrase strand transfer inhibitor (InSTI) resistance were observed with incident infections in registrational trials.
- We report the first case outside of trials, to our knowledge, of HIV infection with emergence of InSTI resistance on CAB-LA.

CASE REPORT

- A 23-year old gender-nonbinary person, assigned male at birth, started CAB-LA at a clinic in California. HIV-1 RNA was not detected (TND) on the date of each injection. After 5th injection, CAB-LA was stopped due to loss of insurance.
- 6 months later, the patient presented to a second clinic to restart CAB-LA.
- 20 days before CAB-LA restart (Day -20), HIV Ag/Ab was non-reactive (NR) and HIV-1 RNA TND. (**Figure 1**). BMI was 18 kg/m^2.
- On the day of CAB-LA injection (Day 0), point-of-care HIV Ab was negative.
- On Day 28, the patient received a 2nd CAB-LA injection. Labs later returned with HIV Ag/Ab reactive (index value 1.24; threshold 1.0), HIV-1 RNA 451 copy (c)/mL.
- On Day 30, repeat HIV-1 RNA was 410 c/mL; commercial genotype failed to amplify.
- On Day 34, ART was started with single-table combination DRV/c/FTC/TAF.

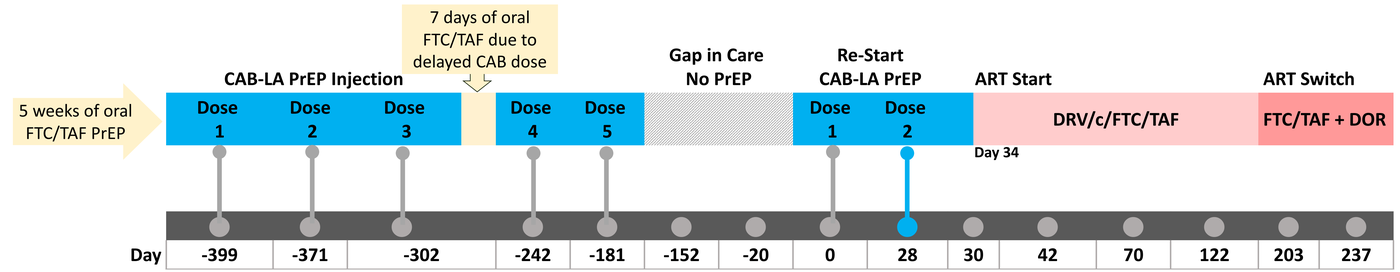
METHODS

- The patient enrolled in **SeroPrEP** (seroprep.ucsf.edu), a study of breakthrough infections on PrEP modalities across the U.S. Blood and hair samples were collected for sensitive diagnostic, PK, and resistance assays.
- RNA below routine thresholds was quantified via single copy assay (SCA), which detects HIV-1 RNA down to 1 c/mL.
- Single genome sequencing (SGS) of full-length integrase was done to identify InSTI mutations, which were compared to the partner's viral genotype.
- For pharmacokinetic testing, cabotegravir concentrations were quantified in plasma and segmented hair samples via LC-MS/MS using validated methods.

RESULTS

- Genotypic testing by SGS of HIV-1 RNA was performed on plasma collected 2 days after diagnosis and the 2nd CAB-LA injection (Day 30). SGS identified InSTI mutations Q148R in 2/24 and A128T in 1/24 sequences, while the commercial genotype failed to amplify (HIV-1 RNA 410 c/mL). (**Table 1**)
- The partner's plasma viral genotype had no INSTI mutations, suggesting that CAB resistant variants arose after HIV infection and were selected by CAB-LA.
- Cabotegravir concentrations in hair were 0.19 ng/mg (reflecting ~2 weeks before diagnosis) and 0.95 ng/mg (reflecting ~3 weeks post-diagnosis and 2nd injection); plasma cabotegravir was 3.37 µg/mL 14 days post-diagnosis and 2nd injection.
- HIV-1 RNA was TND one month post-ART (DRV/c/FTC/TAF) start.
- On Day 203, ART was switched to DOR + FTC/TAF due to ongoing nausea requiring oral antiemetics; subsequent HIV-1 RNA was 1.88 c/mL (SCA) on Day 237.

Figure 1. Case of Seroconversion on CAB-LA: Timeline of ARV Administration and Research and Clinical Testing for HIV Infection



		-399	-371	-302	-242	-181	-152	-20	0	28	30	42	70	122	203	237
Clinical Records	Point-of-Care Rapid	NEG	-	NEG	NEG	-	NEG	NEG	NEG	-	-	-	-	-	-	-
	4th Gen Ag/Ab (Reactive: S/CO ≥1.00)[1]	-	-	-	-	-	-	NR	-	R (1.25)	-	-	-	-	-	-
	Viral Load HIV-1 RNA c/mL[2]	TND	TND	TND	TND	TND	-	TND	-	451	410	-	TND	-	-	-
Research Assays	BioPlex 5th Gen 2200 HIV Ag-Ab Multiplex Flow Assay	-	-	-	-	-	-	-	-	-	-	Ab equiv p24-	-	Ab equiv p24-	-	Ab + p24-
	Single Copy Assay HIV-1 RNA c/mL	-	-	-	-	-	-	-	-	-	-	22.9	-	2.59	-	1.88
	InSTI Resistance by SGS	-	-	-	-	-	-	-	-	-	YES	Not detected[3]	-	-	-	-
PK	Plasma CAB Levels (µg/mL)[4]	-	-	-	-	-	-	-	-	-	-	3.37	-	-	-	-
	Hair CAB Levels (ng CAB/mg hair)								(Day 14 – Day 28) 0.19		(Day 28 – Day 52) 0.95					

1. ARCHITECT HIV Ag/Ab Combo; signal to cutoff (S/CO) value ≥1.00 considered reactive. 2. Clinic #1: Hologic Aptima HIV Quant Dx Assay, LOQ 30 c/mL; Clinic #2: COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test, v2.0; LOQ 20 c/mL
3. Day 42 SGS limited in sensitivity to detect resistance due to HIV-1 RNA 22.9 c/ml and only 3 genomes sequenced (See Table 1). 4. Plasma CAB concentration on Day 42 (14 days after 2nd injection) was ~20x PA-IC_{90} (well above 8x PA-IC_{90})
CAB-LA: long-acting cabotegravir; TND: target not detected; Ag/Ab: antigen/antibody; NR: non-reactive; R: Reactive; equiv: equivocal; ART: antiretroviral therapy; DRV/c/FTC/TAF: Darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DOR: Doravirine

First case of HIV infection with InSTI resistance on CAB-LA for prevention in routine clinical care. InSTI resistance emerged rapidly and required a sensitive assay for detection.

Table 1. Plasma Genotype by Single-Genome Sequencing (SGS)

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%.

CONCLUSIONS

- In this first case in routine care of HIV infection on CAB-LA with emergence of InSTI resistance, HIV infection was identified four weeks after CAB-LA restart.
- Cabotegravir resistance emerged rapidly and required a sensitive research assay for detection. Commercial genotyping failed, likely due to HIV-1 RNA <500 c/mL.
- Seroconversion was delayed, with HIV antibody remaining equivocal for 3 months following HIV detection by RNA and ART start.
- Optimal testing strategies are needed to detect acute HIV infection prior to CAB-LA start and during ongoing injections to mitigate the risk of InSTI resistance. Moreover, accelerated pathways are needed to minimize the time between HIV testing and initial CAB-LA injection.
- As this highly effective long-acting prevention method is scaled up, continued vigilance is needed to monitor for cases of HIV acquisition, and evaluate pharmacokinetics, resistance, and subsequent outcomes on ART.

Contact information: Catherine A. Koss, MD, catherine.koss@ucsf.edu
For more on the SeroPrEP study and information on participant referrals:
seroprep.ucsf.edu; +1 (415) 539-5688; seroprep@ucsf.edu; @seroprep

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