CROI 2025 Report Back: Treatment Updates

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Disclaimer

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AETC AIDS Education & Training Center Program Mountain West

Outline

- LA CAB-RPV
  - CARES 96 Week Data
  - More Observational Data
  - Outcomes in PWH with Viremia
  - CAB-RPV in Pregnancy
  - Stopping CAB-RPV

- DOR-ISL

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LA CAB-RPV Updates

CARES: Study Design

- Phase 3b, Randomized, Open-Label, Active-Controlled, Non-Inferiority Study

  - ≥ 18 years of age
  - On stable oral TDF + XTC + DTG or NVP or EFV
  - HIV-1 RNA < 50 copies/mL at ≥4-12 prior to and at screening
  - No history of renal failure
  - No HBV infection

  → Oral ART Standard of Care (SOC) n = 256

  → CAB-RPV q 8 weeks +/- 4-week oral lead-in n = 256

- HIV-1 RNA checked every 24 weeks
- Due to a public health approach to enrollment, resistance analysis performed during therapy and proviral DNA was performed for archived resistance on stored PBMCs
- Study sites in Uganda, Kenya, and Tanzania

Kityo CM et al, CROI 2025 #202.

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CARES: Key Baseline Characteristics

Characteristic	CAB + RPV LA (n=255)	Oral ART (SOC) (n=257)	Overall (n=512)
BMI ≥ 30 kg/m^2, n (%)	57 (22)	52 (20)	108 (21)
Time on 1st line ART regimen, median (IQR), years	8 (4-13)	7 (4-13)	8 (4-13)
Prior exposure to NNRTI, n (%)	189 (74)	191 (74)	380 (74)
INSTI regimen at screening	231 (91)	240 (93)	471 (92)
Archived DNA analysis*+			
Viral subtype A1, n/n (%)	116/218 (53)	120/215 (56)	236/433 (55)
RPV resistance mutations, n/n (%)	14/208 (7)	16/193 (8)	30/401 (7)
CAB resistance mutations, n/n (%)	8/99 (8)	12/103 (12)	20/202 (10)

*Retrospective, batched sequencing performed on archived viral DNA extracted from PBMCs stored at baseline
+Viral subtype, RAMs, and drug susceptibility determined using the Los Alamos National Laboratory Panel, IAS-USA 2022 mutations list, and Stanford algorithm respectively. APOBEC-related mutations were excluded.

Kityo CM et al, CROI 2025 #202.

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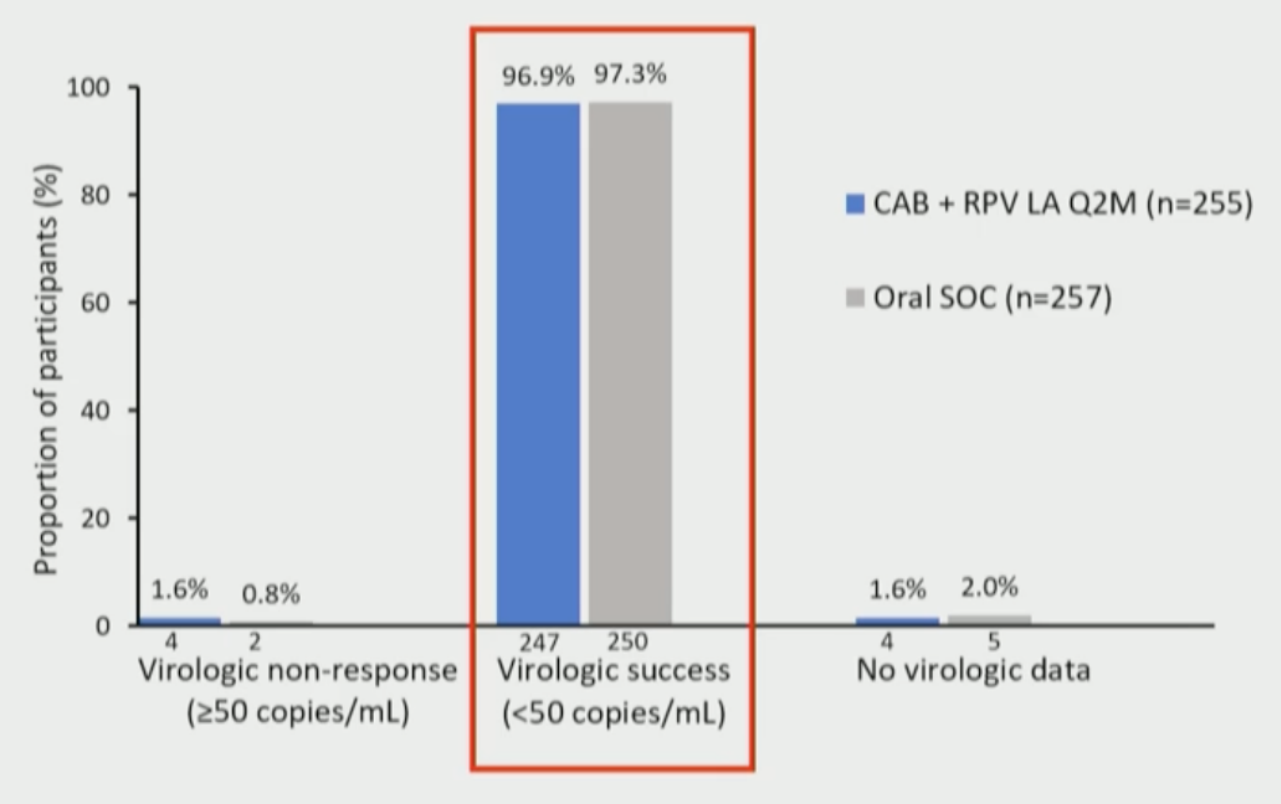
CARES: Week 96 Results

- LA CAB-RPV demonstrated noninferior virologic efficacy as compared to oral standard of care ART
- 77% had an injection site reaction (ISR)
- Over 99% on LA CAB-RPV preferred injectable to daily oral therapy
- 81% of participants received injections within the 7-day target window
- 4 cases of virologic failure (1.6%)



Kityo CM et al, CROI 2025 #202.

CARES: Virologic Failures at Week 96

Confirmed virological failure (VL ≥ 200 copies/ml x 2)	CAB + RPV LA 4 (1.6%)	Oral ART 0	Difference (95% CI) 1.6% (0.4 to 4.2)

	Participant 1	Participant 2	Participant 3	Participant 4
At confirmed virological failure				
Week of failure	48	48	**72**	**72**
Viral load, copies/ml	8,608 and 1612	44,984, no repeat	798 and 563	259 and 16,161
RPV mutations (level) ††	V108I, E138K (intermediate)	K103N/S, V106V/A, E138A, M230M/L (high)	Test Failed	E138A (low)
CAB mutations (level CAB, DTG) ††*	E92E/V, N155H, L74M (intermed., potential low)	G118R (high, high)	Test Failed	Q148R (M50I) (high, low)
At baseline				
RPV mutations (level) †	Nil	K103N/S, E138A (low)	E138K (low)	Nil
CAB mutations (level) †	L74M (low)	Nil	Test Failed	Nil
Viral subtype †	A1	D	A1	C
BMI, kg/m^2	25.9	22.0	22.2	19.9

Kityo CM et al, CROI 2025 #202.

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CARES: Conclusions

- At Week 96, LA CAB-RPV q 8 weeks administered in public health settings in sub-Saharan Africa was non-inferior in virologic efficacy to oral standard of care, had a good safety profile, and was well tolerated

- 4 cases of VF occurred in the LA CAB-RPV arm, with emergence of INSTI-R and NNRTI-R

- This remains an important contribution not only regarding broad implementation in sub-Saharan Africa using a public health approach, but also in individuals with high exposure to NNRTIs and pre-treatment resistance, and different subtypes of HIV-1

Kityo CM et al, CROI 2025 #202.

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Key Highlights from CAB-RPV Observational Data

1. Viral Suppression (VS) in the OPERA Cohort
2. VS in Women in the OPERA Cohort
3. VS in the TRIO Cohort

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Key Highlights from CAB-RPV Observational Data

- VS in OPERA Cohort[1]
  - Of 2,618 PWH who started CAB-RPV, 83% were on CAB-RPV at end of study period
  - With a median follow up of 11 months, 95% had VS
  - After a median of 7 months, 21 (1%) had confirmed virologic failure (CVF)
- VS in Women in the OPERA Cohort[2]
  - Of 532 women who started CAB-RPV, 78% were on CAB-RPV at end of study period
  - With a median follow up of 12 months, 94% had VS, and 5 (≤ 1.3%) had CVF
- VS in the TRIO Cohort[3]
  - Of 1198 virally suppressed PWH, 79% were on CAB-RPV at the end of the study period
  - With a median follow up of 12 months, 95% had VS, and 15 (1.6%) had CVF
    - 5/15 CVF had genotypic data
      - 3 had RPV-R (Y181C+G190S; K101E; Y181C), 1 of whom had CAB-R (S147G+N155H)

1-Sension M et al, CROI 2025 #674. 2-Altamirano JA et al, CROI 2025 #676. 3-Sax PE et al, CROI 2025 #675.

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Outcomes Among PWH Initiating CAB-RPV with Viremia

1. **Ward 86:** 370 PWH on CAB-RPV – 129 (35%) initiated with HIV RNA > 30 copies/mL[1]
   - 97.9% achieved and maintained VS at 48 weeks
   - No statistically significant difference in VS between those VS or with viremia at baseline

2. **Ponce Clinic:** 361 PWH on CAB-RPV – 81 (22%) initiated with HIV RNA > 50 copies/mL[2]
   - 69% on CAB-RPV only, 28% on CAB and/or RPV + LEN, 2% on CAB/RPV + LEN + IBA
   - 92% (72/79) achieved VS
   - Of the 6 who did not achieve VS:
     - 2 had VF with NNRTI and INSTI resistance associated mutations (RAMs)
     - 2 had persistent low-level viremia
     - 2 had HIV RNA levels 1000-3000 without RAMs

1-Gistand NL et al, CROI 2025 #689. 2-Colasanti JA et al, CROI 2025 #690.

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CAB-RPV in Pregnancy

- Little is known about the safety, efficacy, and outcomes of CAB-RPV use in pregnancy

- Multicenter retrospective chart review of pregnant women prescribed LA CAB-RPV
  - 23 women received LA CAB-RPV during pregnancy (11 q4w, 12 q8w)
    - 73% initiated prior to pregnancy, 27% switched to it during pregnancy
  - Viral suppression at delivery
    - Among those who stayed on CAB-RPV, 20/21 had HIV RNA < 200 copies/mL
    - One person had a HIV RNA > 1000 copies/mL
  - Neonatal outcomes
    - 81% of newborns received zidovudine only post-delivery
    - No cases of vertical transmission

Short WR et al, CROI 2025 #1015

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Why do people stop CAB-RPV?

- Ward 86 retrospective chart review of 437 PWH starting CAB-RPV
  - Median time on treatment 553 days
  - 69 (16%) discontinued treatment
    - 30% were on q8w dosing
  - Among those who started with VS, most common reason for discontinuation was pain
  - Among those who started viremic, lateness [of injections] and virologic failure drove discontinuation

Table 1. Reasons for Discontinuation, Stratified by HIV VL at LA-CAB/RPV Initiation

Reason for Discontinuation	Overall (n=69)	HIV VL <50 copies/mL (n=47)	HIV VL ≥50 copies/mL (n=22)
Injection site pain	14	10	4
Injection site pain with other side effect/concern*	11	9	2
Other side effect/concern*	14	11	3
Residential treatment for mental health/substance use or incarceration	5	5	-
Need to come to clinic for injections	2	2	-
Allergic reaction	1	1	-
Relocation	2	2	-
Lateness leading to provider discontinuation	8	2	6
Provider discontinuation for HIV RNA blip	1	1	-
Loss to follow up	3	3	-
Virologic failure	7	1	6
Declined ART but remained in care	1	-	1

*Other side effect/concern (not mutually exclusive): flu-like symptoms (7), weight gain (2), fatigue (2), patient concern about efficacy (3), mistrust/misunderstanding (2), muscle spasms (1) injection site abscesses (1), bloating (1), sleep/appetite concern (1), patient desire for control of HIV treatment (1), feeling "stuck in a jar" (1), wanted to "take a break" (1), feeling like "too much medicine" in body (1), discomfort with subcutaneous lenacapavir injections given for intensification of treatment regimen

Christopolous KA et al, CROI 2025 #683.

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Why do people stop CAB-RPV?

- UCSD Owen Clinic retrospective chart review of 465 PWH starting CAB-RPV
  - Median time on treatment 164d
  - 92 (19.7%) discontinued treatment
    - >90% of those who restarted oral ART had VS
  - 1 person developed NNRTI-R during PK tail
    - Baseline HIV RNA 44 copies/mL, no RAMs
    - After 2 injections, lost to follow up
    - Re-established care after 9 months
      - HIV RNA: 36,300 copies/mL
      - Genotype: Y181C
      - Concurrent proviral DNA: A98G, E138Q, V179I, Y181C, M230L

Reason for stopping LAI CAB/RPV	n (%)
Injection site reaction (ISR)	26 (28.3)
Side effect other than ISR	11 (12.0)
Difficulty coming in for injections	8 (8.7)
Lost to follow-up but returned to care*	7 (7.6)
Lost to follow-up and did not return	5 (5.4)
Insurance challenges	10 (10.9)
Virologic Failure	6 (6.5)
Concern about HBV reactivation	2 (2.2)
Deceased	5 (5.4)
Pregnancy	2 (2.2)
Other/Not documented	10 (10.9)

Faggiano T et al, CROI 2025 # 685.

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DOR-ISL

ISL-DOR

- Islatravir (ISL) is a nucleoside reverse transcriptase translocation inhibitor (NRTTI)
  - Prior studies with higher doses ISL had declines in CD4 T-cell and total lymphocyte count (TLC)
  - Studies being repeated with lower dose ISL (0.25mg) with DOR

- Among 513 VS PWH on B/F/TAF randomized 2:1 to DOR/ISL QD (342) vs. continued B/F/TAF (171), VS was high and DOR/ISL was non-inferior at 48w[1]
  - 2 PWH in ISL-DOR had HIV RNA > 200 copies/mL but no treatment emergent resistance
  - 2 PWH on ISL-DOR and 1 on B/F/TAF discontinued due to decrease in CD4 T-cell or TLC

- Among 551 VS PWH on baseline ART (bART) randomized 2:1 to DOR/ISL QD (366) vs. continued bART (185), VS was high and DOR/ISL was non-inferior at 48w[2]
  - 5 PWH in ISL-DOR arm had VF but no treatment emergent resistance

1-Colson A et al, CROI 2025 #204A. 2-Orkin C et al, CROI 2025 #204B.

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Conclusions

1. Week 96 CARES data demonstrated that LA CAB-RPV was non-inferior to oral SOC in sub-Saharan Africa.
2. In observational cohorts of individuals on CAB-RPV, VS remains high, including in people starting viremic.
3. LA CAB-RPV may be a viable option in pregnancy, but more studies are needed.
4. In clinics with large numbers on CAB-RPV, approximately 15-20% of PWH have discontinued injections, mostly due to pain/injection site reactions.
5. DOR-ISL appears efficacious and safe at a dose of 100mg/0.25mg in phase 3 trials.

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