CROI 2024 Report Back: Treatment Updates

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Last Updated: 18 March 2024

Disclosures

No conflicts of interest or relationships to disclose.

Outline

- LA CAB-RPV Updates
- Lenacapavir Updates

LA CAB-RPV Updates

Key LA CAB-RPV Abstracts

1. CARES Study
2. LATITUDE Interim Data
3. Real world experiences
    a. Ward 86 Week 48 Data
    b. Virologic Failures at a Chicago Clinic

Background: LA CAB-RPV

- ATLAS, FLAIR, and ATLAS-2M studies demonstrated efficacy of LAI CAB-RPV and led to FDA approval for those with viral suppression[1,2]
  - Virologic failures in ATLAS-2M have occurred at a rate of 2.3% q8w vs 0.4% q4w[2]

- Clinical trials to date had not included persons with adherence challenges[3]

- Clinical trials to date had little representation from Africa[4], among people who are
  - mostly Black African women
  - have different subtypes of HIV-1
  - have high exposure to NNRTI and pre-treatment resistance and
  - have varied treatment strategies with infrequent lab monitoring

1-Orkin C et al, NEJM, 2020. 2-Overton ET et al, CID, 2023. 3-Rana AI et al, CROI 2024 #212. 4-Kityo CM et al, CROI 2024 #122.

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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
- Resistance analysis performed at 48 weeks due to their public health approach to enrollment, so proviral DNA was performed for archived resistance on stored PBMCs
- Study sites in Uganda, Kenya, and Tanzania

Kityo CM et al, CROI 2024 #122.

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CARES: Baseline Characteristics

Characteristic	CAB + RPV LA (n=255)	Oral ART (SOC) (n=257)	Overall (N=512)
Female sex, n (%)	146 (57.2)	149 (58.0)	295 (57.6)
Age, median (IQR), years	43 (36-51)	42 (35-49)	42 (35-51)
BMI≥30 kg/m^2, n (%)	57 (22.4)	51 (19.8)	108 (21.1)
Black race, n (%)	254 (99.6)	256 (99.6)	510 (99.6)
Time on first-line ART, median (IQR), years	8 (4-13)	7 (4-13)	8 (4-13)
Prior exposure to NNRTI, n (%)	189 (73.7)	191 (74.3)	380 (74.2)
INSTI regimen at screening	231 (90.6)	240 (93.4)	471 (92.0)
NNRTI regimen at screening	24 (9.4)	17 (6.6)	41 (8.0)
Archived DNA analysis * †			
Viral subtype A1, n/n (%)	119/213 (55.9)	115/201 (57.2)	234/414 (56.5)
RPV resistance mutations, n/n (%)	25/200 (12.5)	26/177 (14.7)	51/377 (13.5)
RPV intermediate/high-level resistance, n/n (%)	17/200 (8.5)	21/177 (11.9)	38/377 (10.1)
CAB resistance mutations, n/n (%)	15/95 (15.8)	14/85 (16.5)	29/180 (16.1)
CAB intermediate/high-level resistance, n/n (%)	10/95 (10.5)	5/85 (5.9)	15/180 (8.3)

Kityo CM et al, CROI 2024 #122.

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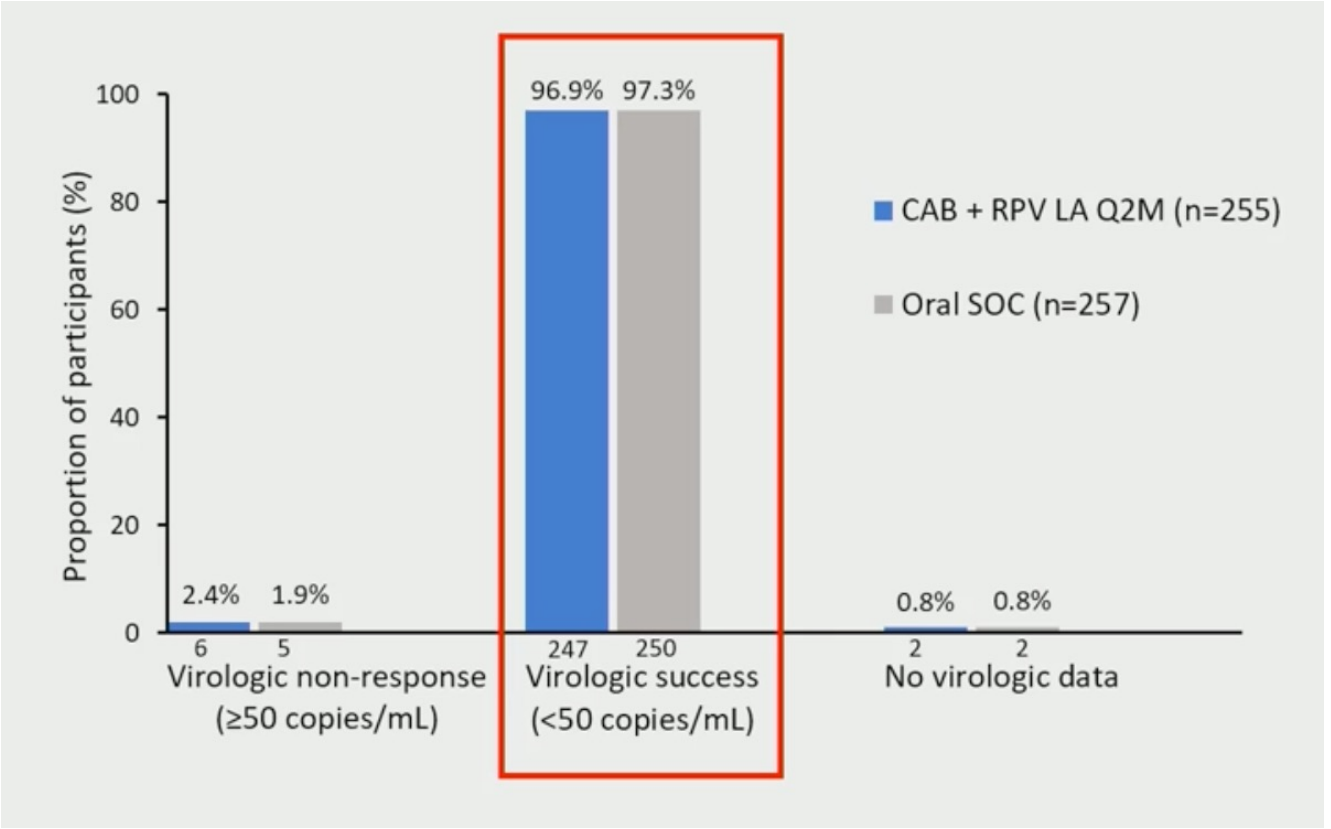
CARES: Week 48 Results

- LA CAB-RPV demonstrated noninferior virologic efficacy as compared to oral standard of care ART
- 73% had an injection site reaction (ISR)
- Satisfaction increased for those who switched to LA CAB-RPV
- 96% of scheduled injections occurred within the 7-day target injection date
- 2 cases of virologic failure (0.4%)



Kityo CM et al, CROI 2024 #122.

CARES: Virologic Failures at Week 48

Outcome	LA CAB + RPV (n = 255)	Oral ART (SoC) (n = 257)	Difference (95% CI)
Confirmed virologic failure, n (%)	1 (0.4)*	0	0.4 (-0.4 to 1.2)

*1 additional virologic failure (unconfirmed) in LA CAB + RPV arm.

Confirmed Virologic Failure: Patient Characteristics

- HIV-1 RNA 8608 copies/mL
- No delayed injections
- Sex and location: female from Uganda
- Baseline BMI 25.9 kg/m^2
- Subtype A1
  - Resistance mutations at baseline: no NNRTI or INSTI
  - Failure mutations: V108I, E138K, V179L (RPV high); E92E/V, N155H, L74M (CAB intermediate; DTG nil)
- Resuppressed on TDF/3TC/DTG once daily

Unconfirmed Virologic Failure: Patient Characteristics

- HIV-1 RNA 44,984 copies/mL
- No delayed injections
- Sex and location: male from Uganda
- Baseline BMI 22.0 kg/m^2
- Subtype D
  - Resistance mutations at baseline: K103N/S, E138A (RPV low); no INSTI mutations
  - Failure mutations: K103N/S, V106V/A, E138A (RPV low), G118R (CAB high; DTG intermediate)

Slide credit: clinicaloptions.com

Kityo CM et al, CROI 2024 #122.

CARES: Conclusions

- At Week 48, LA CAB-RPV q 8 weeks administered in sub-Saharan Africa in public health settings was non-inferior in virologic efficacy to oral standard of care, had a good safety profile, and was well tolerated

- Only 2 cases of VF occurred in the LA CAB-RPV arm, both with emergence of INSTI and NNRTI resistance

- In demonstrating safety and efficacy of LA CAB-RPV in sub-Saharan Africa using their public health approach, CARES 48-week results are a key first step in implementation in this patient population

Kityo CM et al, CROI 2024 #122.

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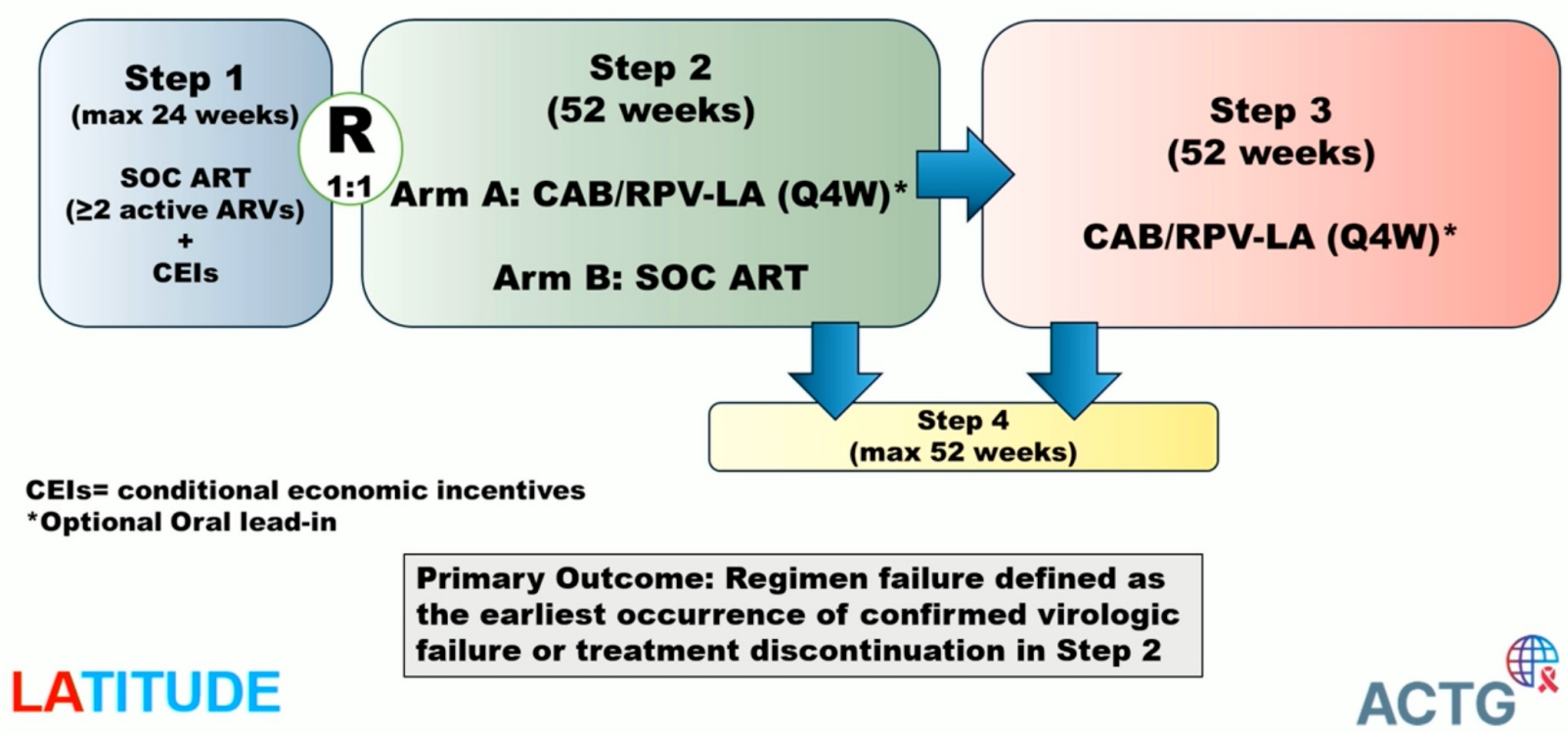
LATITUDE: Study Design

- Phase 3 prospective, randomized, open-label trial

- PWH who have barriers to adherence:
  - Poor viral response despite oral ART for ≥ 6m
  - Loss to follow up with ART non-adherence ≥ 6m
- No Hepatitis B
- No INSTI or RPV RAM historically or by screening



LATITUDE: Baseline Characteristics

Study population (Step 1 and Step 2)

Characteristic		Total (N=434)
Age, years	Median (Q1, Q3)	40 (32, 51)
	≤30	88(20%)
	31-50	232(53%)
	51+	114 (26%)
Sex at birth	Female	129 (30%)
Gender Identity	Transgender Spectrum	21 (5%)
Race	Black/African American	277 (64%)
	White	117 (27%)
	Other/multiple/unknown	40 (9%)
Ethnicity	Hispanic/Latino	75 (17%)
History of IDU	Currently + Previous	61 (14%)
Non-Adherence criteria	Lost to follow-up	87 (20%)
	Poor response	283 (65%)
	Both	64 (15%)
Time since HIV Dx, years	Median (Q1, Q3)	13 (7, 21)

Characteristic		Step 1 Total (N=434)
Baseline HIV-1 RNA (c/mL)	<200	141 (32%)
	201-10,000	110 (25%)
	10,001-100,000	121 (28%)
	>100,000	62 (14%)
Baseline CD4⁺ T (cells/mm³)	Median (Q1, Q3)	270 (116, 498)

Characteristic		Step 2 Treatment Arm: CAB/RPV-LA (n=146)	Step 2 Treatment Arm: SOC (n=148)
Step 2 Baseline HIV-1 RNA (c/ml)	>200*	24 (17%)	10 (7%)
Baseline CD4+ T (cells/mm3)	Median (Q1, Q3)	417 (198, 688)	374 (198, 605)

* including 8 participants with HIV-1 RNA >10,000 c/ml in the CAB/RPV-LA arm

LATITUDE

ACTG

Rana AI et al, CROI 2024 #212.

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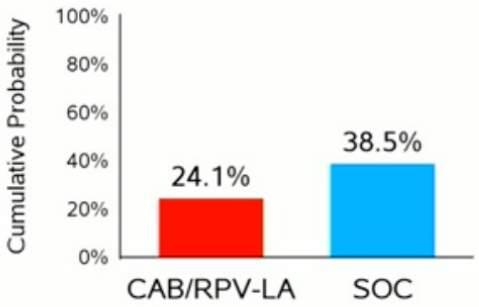
LATITUDE: Interim Data

Primary Outcome

Regimen Failure

Difference	Nominal 98.75% CI
-14.5%	(-29.8%, 0.8%)



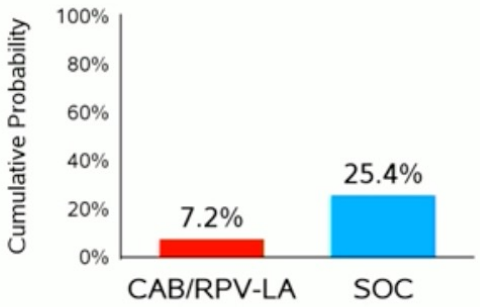
Number of participants

Regimen Failure	28	47
VF	6	28
TRT-DISC	23	19

Secondary Outcomes

Virologic Failure

Difference	Nominal 98.75% CI
-18.2%	**(-31.1%, -5.4%)**

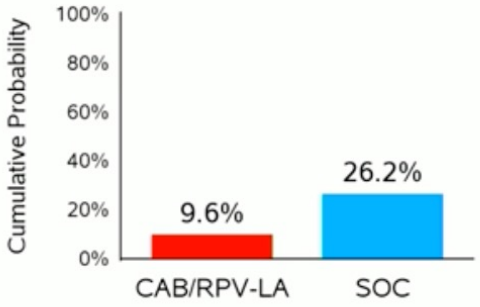


Number of participants

Virologic Failure	6	28

Treatment-related Failure

Difference	Nominal 98.75% CI
-16.6%	**(-29.9%, -3.3%)**

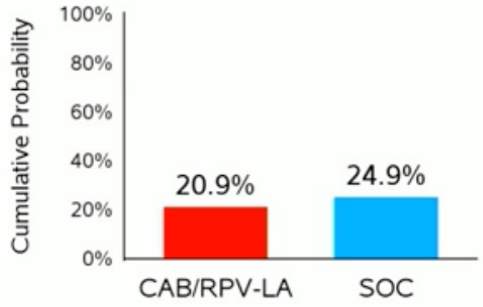


Number of participants

Treatment-related Failure	9	29
VF	6	28
TRT-DISC (AE)	3	1

Permanent Treatment Discontinuation

Difference	Nominal 98.75% CI
-4.1%	(-18.0%, 9.8%)



Number of participants

Permanent TRT-DISC	25	30

LATITUDE

ACTG

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Rana AI et al, CROI 2024 #212.

LATITUDE: Interim Data

- Injection Site Reactions
  - Occurred in 57% of individuals

- Timing
  - 93% on time (21 to <36 days)
  - 3% missed

Patient	Week	LA CAB-RPV RAMs
1	18	E138K, G140GS, Q148K, K103R
2	49	E138K, Q148K, K20R, M230L

- Confirmed Virologic Failures
  - 6 in LA CAB-RPV arm: 2 with RAMs
  - 28 in SOC arm: 2 with RAMs

Rana AI et al, CROI 2024 #212.

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LATITUDE: Conclusions

- In PWH with adherence challenges, LA CAB-RPV q4w showed superior efficacy to oral SOC in secondary outcomes; there were fewer:
  - Virologic failures
  - Treatment-related failures

- On February 12, 2024, given these key secondary endpoints met stringent stoppage criteria, DSMB recommended halting randomization and offering all eligible participants switch to CAB/RPV

- Data supports the use of LA CAB-RPV in populations with adherence challenges

Rana AI et al, CROI 2024 #212.

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Ward 86 LA CAB-RPV: Week 48 Results

- CROI 2023: 55/57 without VS achieved VS at median of 33 days[1]
  - VF rate of 1.5% with INSTI RAMs
- At Ward 86, 286 patients on LA CAB-RPV[2]
  - 101 with baseline VL ≥ 50 copies/mL
  - 185 with VL < 50 copies/mL
- 59 included in Week 48 analysis
  - Viral suppression
    - 81% (48/59) remained on LA-CAB-RPV and were VS
    - 93% (55/59) VS on LA-CAB-RPV + alternative ART
  - Virologic failure
    - 3 with VF (5%)
      - 2 within 8 weeks of initiation despite on-time injections
      - 1 following self-discontinuation of ART

Patient	Pretreatment VL and mutations	Treatment-emergent RAMs
1	137K; T97A	E138K (NNRTI) R263K
2	215K; V179I, N348I	L100I, Y181I
3	67K; none	K101E, E138K, Y181FIN, M230L

1-Gandhi M et al, CROI 2023, #OA518. 2-Hickey MD et al, CROI 2024, #628.

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Virologic Failures at a Chicago HIV Clinic

- 75 virally suppressed PWH switched to LA CAB-RPV
  - 10 received at independent infusion center
  - 65 received at clinic
- 3 VFs occurred (4%)
  - 2 at infusion center, 1 at clinic
  - VF occurred at 8, 10, and 16 months
  - All used a 1.5-inch needle
  - All 3 switched to a PI-based regimen and achieved VS

Demographics		Patient 1	Patient 2	Patient 3
Age at VF		24	44	47
Gender		F	M	M
Race/ethnicity		Other/Latinx	African American/Non Latinx	African American/Non Latinx
Years since HIV diagnosis		23	18	1
No. of prior ART regimens		>3	2	1
Smoker		N	N	N
BMI		27	35	28
Injection delivery site				
	Clinic	Y		
	Infusion center		Y	Y
UD on INI at time of switch		Y	Y	Y
Prior Rilpivirine exposure		Y	N	N
Prior known resistance mutations		M184V	K103N	N/A
Resistance mutations at VF		L74L/M, T97T/A, **G140S, Q148H** **K101P, E138K,** I178L, Q207E	L74I, T97T/A, S147S/G, **N155H**	**G140G/S, Q148Q/R**

Shankaran S et al, CROI 2024 #686.

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Lenacapavir Updates

Background: Lenacapavir

- Lenacapavir (LEN) is a capsid inhibitor administered subcutaneously every 6 months
- FDA approved in December 2022 for MDR HIV, informed by the CAPELLA Study
- CAPELLA: When combined with an optimized background regimen (OBR) in individuals with MDR HIV, LEN every 6 months led to viral suppression at week 104 in 82% of PWH by missing=excluded analysis
- LEN has a low barrier to resistance with M66I as the signature capsid mutation
  - LEN-R is associated with inadequate OBR adherence and OBRs lacking fully active agents

Segal-Maurer S et al, NEJM, 2022.

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LEN efficacy with no fully active agents in OBR

- Aim: Assess LEN efficacy through week 104 in CAPELLA participants whose OBR had no fully active ARVs
- Calculated OBR overall susceptibility score (OSS)
  - 12 of 72 had no fully active ARVs
    - 5/12 had an OSS of zero
    - 6/12 had an OSS of 0.5
    - 1/12 had an OSS of 1 (two partially active ARVs)
  - Note: CAPELLA median OSS was 2.0
- Heavily treatment experienced cohort
  - Median of 4 agents in the OBR
  - Baseline mean HIV-1 RNA 4.02 $\log_{10}$ copies/mL
  - Baseline mean CD4 175 cells/mm^3

Ogbuagu O et al, CROI 2024 #630.

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LEN efficacy with no fully active agents in OBR

Table 2. Resistance Mutations at Baseline

Participant	Baseline Resistance Mutations			
	INSTIs	NNRTIs	NRTIs	PIs
1	M50I, T97A, S119R, E138K, G140S, Q148H	Y181I, Y188L	M41M/L, M184V, T215F	V32I, I54M, Q58E, I84V, L90M
2	L74I/M, S119P, E138E/K, S147S/G, S153S/A/C/G, N155H, E157E/Q	V106M, V108I, Y181V	D67N, K70R, M184V, T215F, K219E	V32I, M46I, I54L, L76V, I84V, L90M
3	M50I, T97A, S119P, E138K, G140S, Q148H	L100I/V, G190Q	M41L, D67N, L74I/V, M184V, L210W, T215Y, K219R	V32I, M46I, I47V, I54L, I84V
4	T97A, E138K, G140S, Q148H	L100I, K103N, V108V/I	M41L, D67N, L74I, M184V, L210W, T215Y, K219N	M46I, I47V, I50V, L76V, V82T
5	E138K, G140A, S147G, Q148R, E157Q	K101H, Y181C, G190A	M41L, D67N, K70K/R, M184V, T215F, K219Q	V32I, M46L, I54L, N83D, I84V
6	M50I/T, L74M, T97A, S119T, Y143C, S147G, N155H, E157Q	L100I/M, K103S, H221Y	T69(del), V75I, F77L, Y115F, F116Y, Q151M, M184V, K219Q	V32I, M46L, I54L, T74P, V82T, I84V, L90M
7	N155N/H	K101E, Y181I	M41L, M184V, T215F	V32V/I, I47I/V, I54I/M, Q58Q/E, I84I/V, L90M
8	M50M/I, T97A, S119R, S147G, N155H, E157Q	L100I, K103N	M41L, D67N, L74V, L210W, K219D/N	V32I, M46I, Q58E, I84V, L90M
9	M50I, G140S, Q148H, N155H	E138Q, Y181V, H221Y, M230L	M41L, M184V, T215F	V32I, M46I, I47V, I54L, Q58E, I84V, L90M
10	E138A, G140A, S147G, Q148R, N155H, E157Q	V106I/M, Y181C	M41L, V75I, F77L, F116Y, Q151M	V32I, I54L, Q58E, T74P, V82L, I84V, L90M
11	E138E/A, G140A, Q148R	K103N, E138Q	K70R, T215F, K219E	V32I, M46I, I54L, L76V, I84V
12	G140S, Q148H	K103N	M41L, D67N, L210W, T215Y, K219R	V32I, M46L, I54V, T74P, V82A, I84V, L90M

Ogbuagu O et al, CROI 2024 #630.

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Results: LEN efficacy with no fully active agents in OBR

- 8/12 suppressed at all 3 visits; of the 4 not suppressed at all 3 visits:
  - 3/4 developed an M66I/M at weeks 4, 4, and 10, respectively
  - 1/4 never achieved viral suppression
  - Lack of viral suppression prompted changes to their OBR
- Mean increase in CD4 cell count was 105 cells/mm^3
- None developed treatment emergent resistance to their OBR through week 104
- When considering LEN use, I recommend looking at Tables 1-3 and Figure 2

Ogbuagu O et al, CROI 2024 #630.

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Lenacapavir + LA Cabotegravir

- Case series of 34 patients from 4 clinics using off-label LEN and CAB with or without RPV for selected patients with adherence challenges
  - UCSF Ward 96, UCSD Owen Clinic, MetroHealth's HIV Clinic, UPenn Clinic
- Patient Characteristics
  - 76% male, 24% cis/trans female; 41% Black, 38% Latino/a
  - 29% and 71% on CAB every 4 or 8 weeks, respectively
- Reasons for using LEN + LA CAB with or without LA RPV
  - Documented or suspected NNRTI-R (59%), INSTI-RAMs (15%), high VL (18%) or continued viremia on CAB-RPV alone (12%)
  - Look at their table for patient details!
- Results
  - ISR in 44% of patients
  - 94% viral suppression (median 8w after starting LEN), up from 47% suppressed at baseline

Gandhi M et al, CROI 2024, #629.

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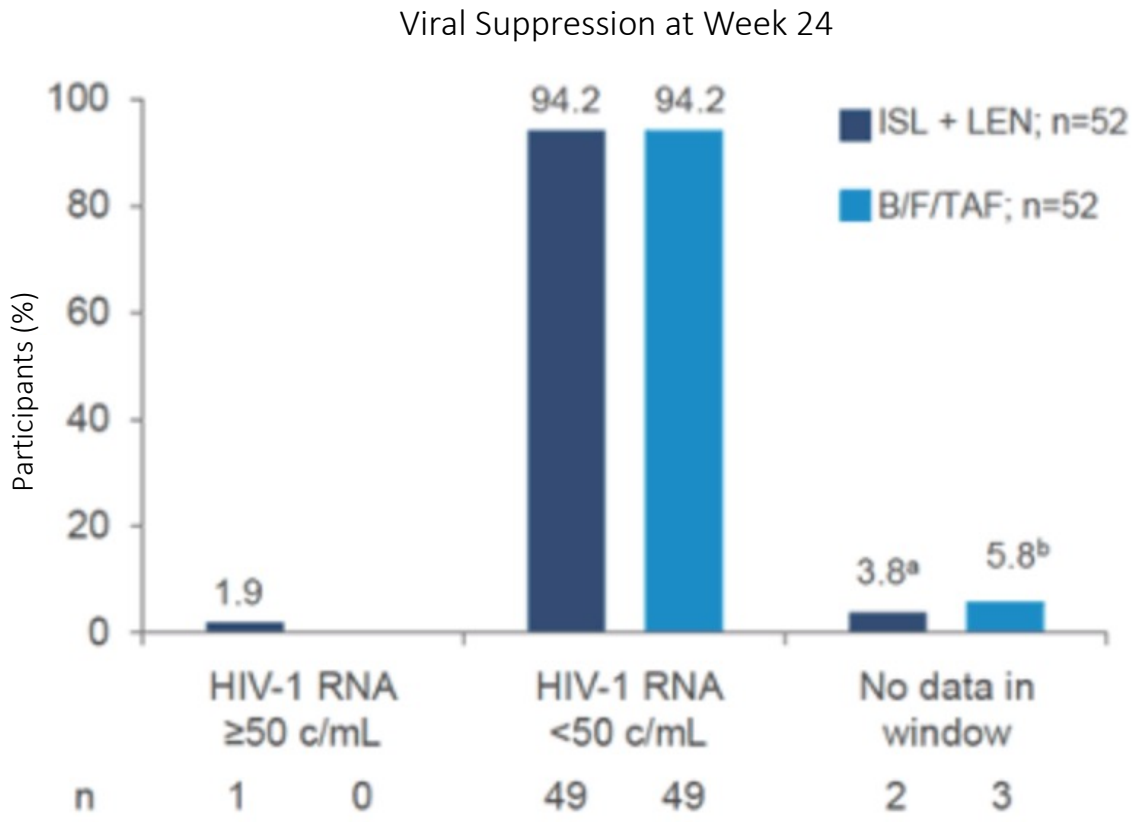
Weekly Oral Islatravir + Lenacapavir

- Phase II trial of once weekly oral Islatravir 2mg (NRTTI) + oral Lenacapavir 300mg compared to BIC/TAF/FTC in PWH who are virologically suppressed
- Viral suppression was achieved in 94% of participants at 24 weeks and was well tolerated
- No significant differences in changes in CD4 cell count or absolute lymphocyte count with ISL + LEN vs BIC/TAF/FTC



Colson A et al, CROI 2024 #208.

Conclusions

1. Week 48 CARES data demonstrated that LA CAB-RPV was non-inferior to oral SOC in sub-Saharan Africa.
2. LA CAB-RPV is superior to oral SOC in key secondary outcomes in the LATITUDE study, leading the DSMB to stop randomization and offer CAB-RPV to all eligible participants.
3. LA CAB-RPV appears durable, but real world virologic failures are ~4-5%.
4. Lenacapavir, even when combined with no fully active agents in the OBR, was efficacious in 8/12 participants from the CAPELLA study.
5. The combination of LEN + LA CAB +/- LA RPV proved efficacious in 34 patients, and we will likely see more data about this in the coming years.
6. Still in phase II, weekly oral islatravir plus lenacapavir has the potential to become a long-acting option for PWH.

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