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‘Best of CROI’ Feedback 2024

ART: Injectable CAB/RPV

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GILEAD Creating Possible
MSD
ViiV Healthcare

With thanks to those presenting research for permission to use slides for ‘Best of CROI’

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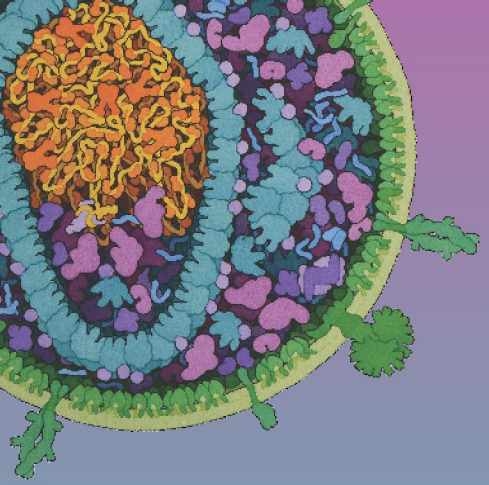
Conflicts of Interest

I have received conference support, speaker fees, and advisory board honoraria from Gilead, Janssen, MSD, and ViiV (GSK)

I am a PI on the ILANA Study

Speakers are required by the Federation of the Royal Colleges of Physicians to disclose conflicts of interest at the beginning of their presentation, with sufficient time for the information to be read by the audience. They should disclose financial relationships with manufacturers of any commercial product and/or providers of commercial services used on or produced for patients relating to the 36 months prior to the event. These include speaker fees, research grants, fees for other educational activities such as training of health professionals and consultation fees. Where a speaker owns shares or stocks directly in a company producing products or services for healthcare this should also be declared.



Oral Abstract: 00122

Monday, March 4, 2024

Randomized trial of Cabotegravir and Rilpivirine Long-acting in Africa (CARES):Week 48 Results

Cissy Kityo Mutuluuza, Ivan K. Mambule, Simiso Sokhela, Henry Mugerwa, Reena Shah, Caroline Otike, Joseph Musaazi, Kimton Opiyo, Fiona Cresswell, Gilbert Ategeka, Charity Wambui, Josphat Kosgei, Logashvari Naidoo, Fafa A. Boateng, **Nicholas Paton**

on behalf of the CARES Study Team

Nicholas Paton received research funding from Janssen

CARES

- Additional evidence required to determine role of LA therapy in treatment programs in Africa:
  - Most of the population affected by HIV-1 are Black African women
  - HIV-1 subtypes are different (majority A1)
  - High levels of NNRTI exposure and pre-treatment resistance
  - Care and treatment strategies are different, with infrequent viral load and safety monitoring

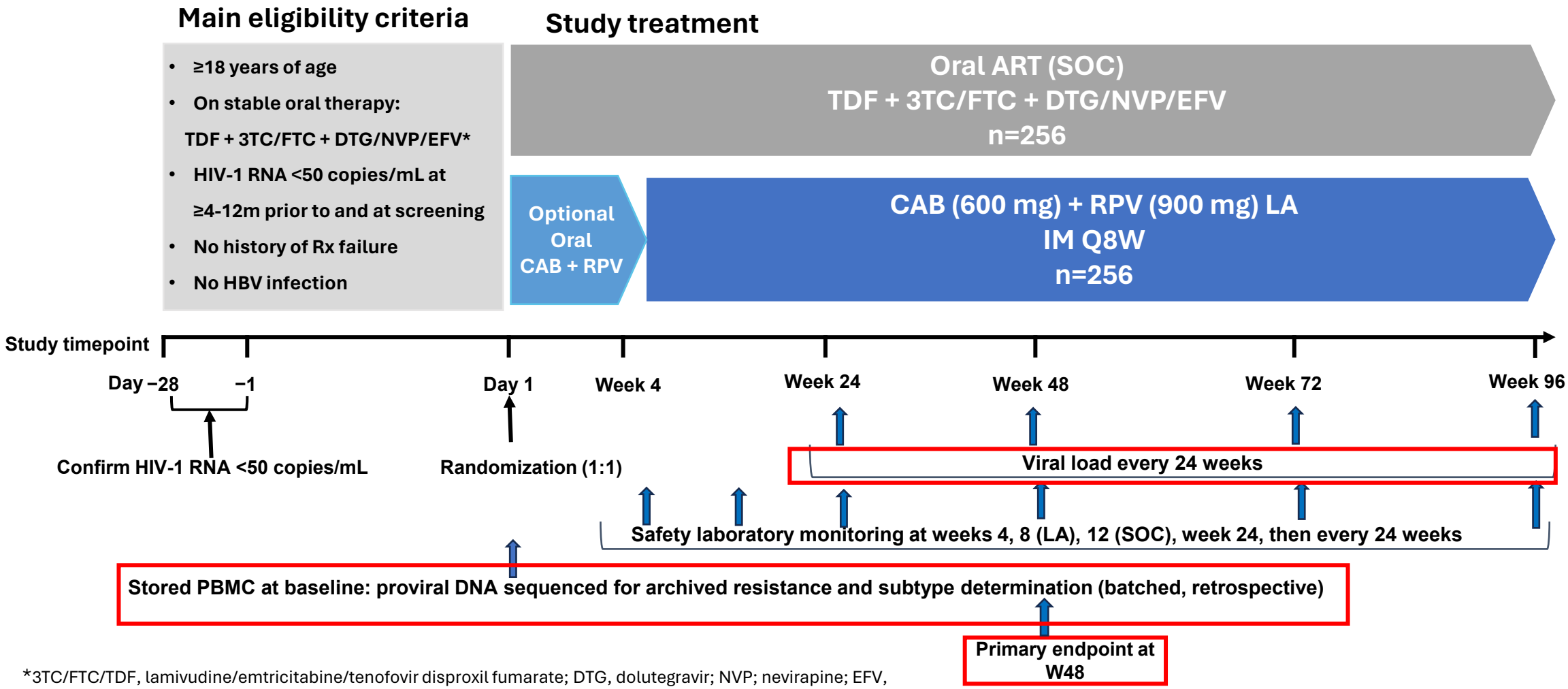
- **Aim:**

To assess non-inferiority of switching virologically-suppressed adults to CAB + RPV LA every 8 weeks vs. continuing maintenance therapy with oral standard of care (SOC) in a sub-Saharan African population managed using a Public Health Approach

Kityo et al. CROI 2024; Virtual and Denver, CO.

Study Design

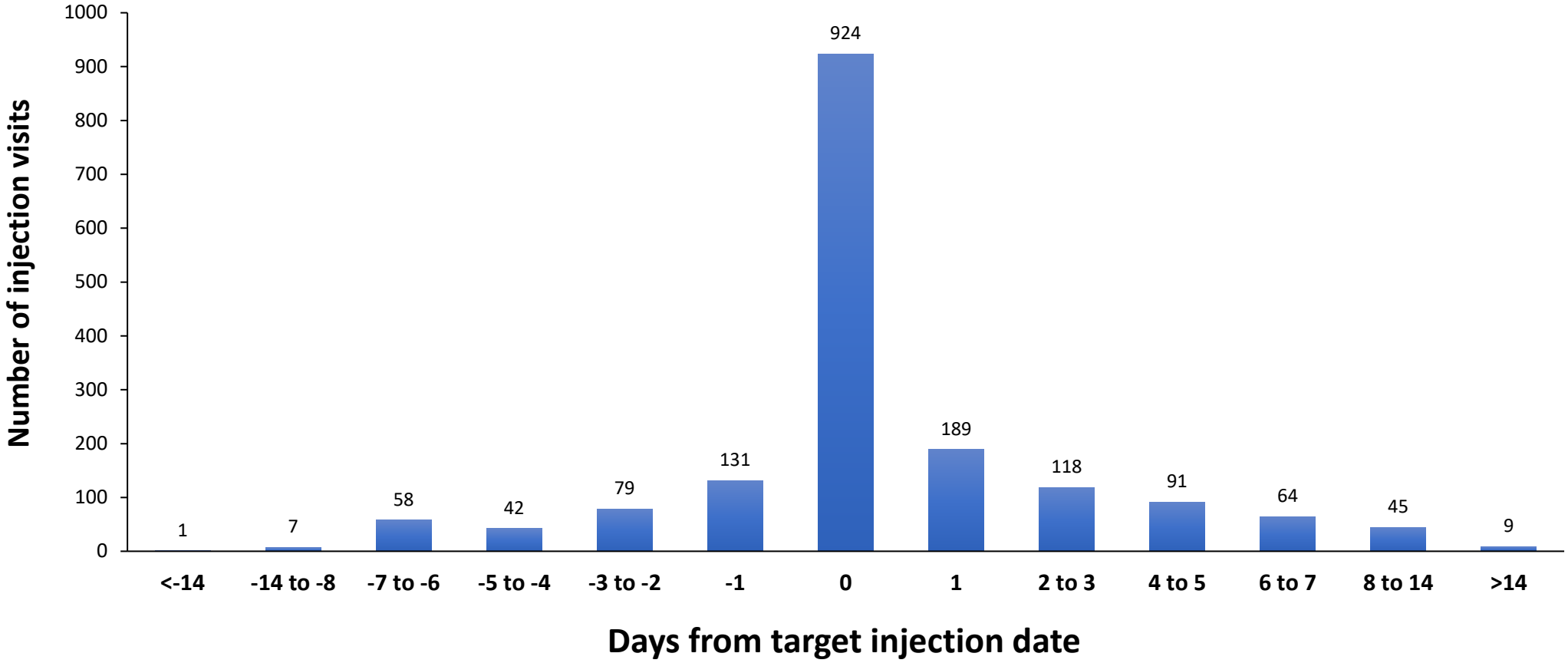
Phase 3b, Randomized (1:1), Open-Label, Active-Controlled, Multi-Centre, Parallel-Group, Noninferiority Study



*3TC/FTC/TDF, lamivudine/emtricitabine/tenofovir disproxil fumarate; DTG, dolutegravir; NVP; nevirapine; EFV, efavirenz; CAB, cabotegravir; LA, long-acting; Q8W, every 8 weeks; RPV, rilpivirine; SOC, standard of care

Kityo et al. CROI 2024; Virtual and Denver, CO.

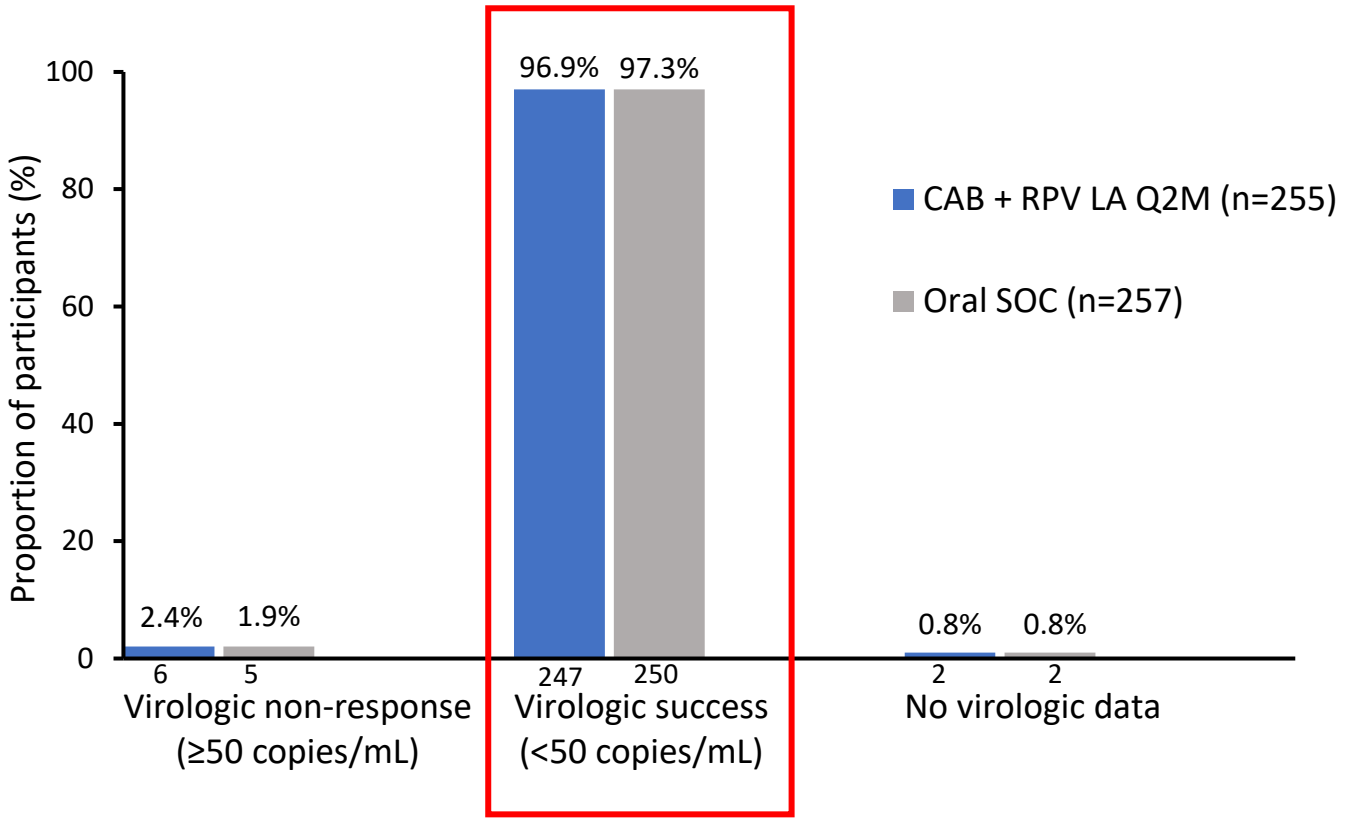
Adherence and Timing of Injections

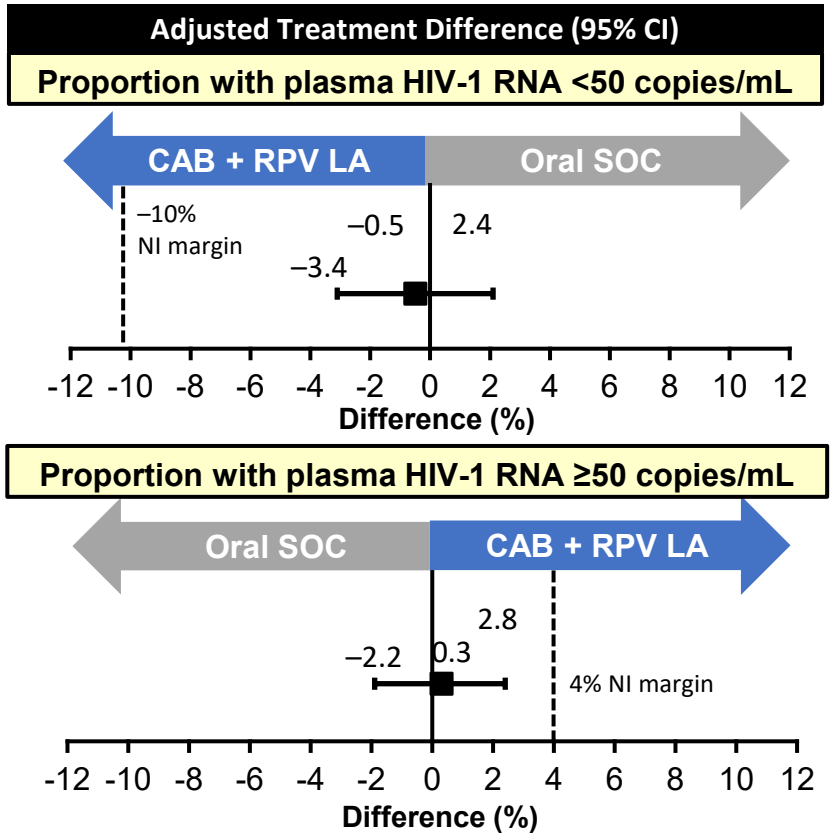


- 211 (82.7%) participants received all scheduled injections within the protocol-mandated 7-day window
- 96% of 1758 scheduled injections were within the protocol-mandated 7-day window
- Well tolerated overall; side effects as predicted including ISRs

Kityo et al. CROI 2024; Virtual and Denver, CO.

Virologic Outcomes at Week 48 (ITT)





Primary outcome - proportion with plasma HIV-1 RNA <50 copies/ml:

- Main analysis (ITT): adjusted difference -0.5% (95% CI, −3.4 to 2.4), **meeting the non-inferiority criterion**
- Sensitivity analysis (per-protocol): adjusted difference -0.3% (95% CI, -3.0 to 2.3) **confirming non-inferiority**

Kityo et al. CROI 2024; Virtual and Denver, CO.

Participants with virological failure

	CAB + RPV LA	Oral ART	Difference (95% CI)
Confirmed virological failure (VL ≥ 200 copies/ml x 2)	1 (0.4%)	0	0.4 (-0.4 to 1.2)

+ One additional virological failure (unconfirmed) in CAB + RPV LA arm (died before retest; HIV-unrelated cause)

Participant with confirmed virological failure

- Failure at week 48 (VL = 8,608 copies/ml)
- No delayed injections
- Female, Uganda
- Baseline BMI: 25.9 kg/m^2
- Subtype A1
- Resistance mutations [Stanford resistance level]:

  Baseline*: No NNRTI or INSTI mutations

  Failure:

  V108I, E138K, V179L [RPV high]

  E92E/V, N155H, L74M [CAB intermediate; DTG nil]
- Re-suppressed on TDF/3TC/DTG once daily

Participant with virological failure (unconfirmed)

- Failure at week 48 (VL = 44,984 copies/ml)
- No delayed injections
- Male, Uganda
- Baseline BMI: 22.0 kg/m^2
- Subtype D
- Resistance mutations [Stanford resistance level]:

  Baseline*: K103N/S, E138A [RPV low]; no INSTI mutations

  Failure:

  K103N/S, V106V/A, E138A [RPV low]

  G118R [CAB high; DTG intermediate]

* Retrospective, batched sequencing performed on archived viral DNA extracted from PBMCs stored at baseline

Conclusions

Summary: at week 48, CAB + RPV LA every 8 weeks:

Had high efficacy:

- 97% had VL suppression < 50 copies/ml; non-inferior to oral ART (SOC)
- 0.4% had CVF (1 participant); resuppressed on DTG, once daily
- This was achieved in the public health approach with sparse viral load monitoring; and despite population with high rates of obesity; prior NNRTI exposure and RPV resistance mutations; different subtypes (majority A1)

Had a good safety profile and was well tolerated:

- 1.2% had severe (≥ grade 3) AE related to study medication; 1.2% serious AEs
- Injection site reactions were mainly Grade 1-2; only 1 leading to discontinuation

Increased treatment satisfaction:

- Greater increase from baseline in satisfaction score in participants who switched to CAB + RPV LA versus those continuing oral SOC

Overall conclusion

This demonstration of safety and efficacy of CAB + RPV LA is the essential first step to discussing a potential role for LA in treatment programs in sub-Saharan Africa using the public health approach.

Kityo et al. CROI 2024; Virtual and Denver, CO.

Long-Acting Injectable CAB/RPV is Superior to Oral ART in PWH With Adherence Challenges: ACTG A5359

Aadia I. Rana

University of Alabama at Birmingham, Birmingham, AL, USA

Disclosure: Dr Rana reported no relevant financial relationships with ineligible companies.

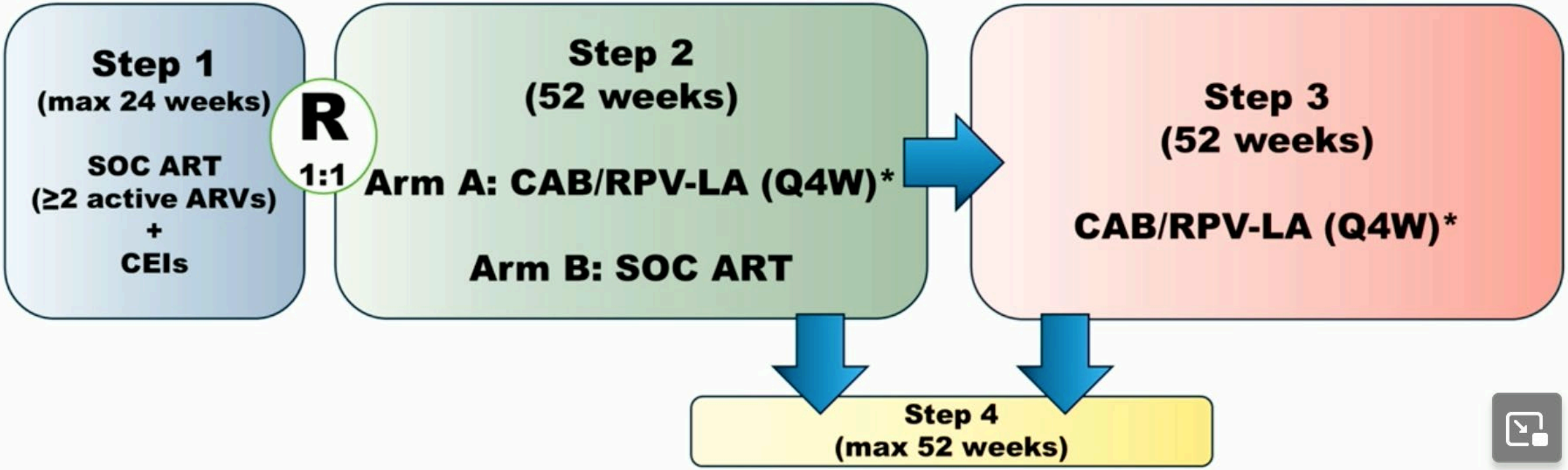
Study Design and Study Population

- A5359-**L**ong-**A**cting **T**herapy to **I**mprove **T**reatment success in **D**aily lif**E**
- Phase III prospective, randomized, open-label trial
- Monthly IM CAB/RPV-LA vs. oral Standard of Care (SOC) ART
- PWH who have barriers to adherence:
  a) Poor viral response despite oral ART for ≥6 months.
  b) Loss to clinical follow-up with ART non-adherence ≥6 months.
- No Hepatitis B
- No INSTI or RPV RAM historically or by screening.
- No exclusion based on $CD4^+$ T-cell, HIV VL, active substance/alcohol use or unstable housing.

LATITUDE

ACTG

Study design



CEIs= conditional economic incentives
*Optional Oral lead-in

Primary Outcome: Regimen failure defined as the earliest occurrence of confirmed virologic failure or treatment discontinuation in Step 2

LATITUDE

ACTG

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/mm^3)	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

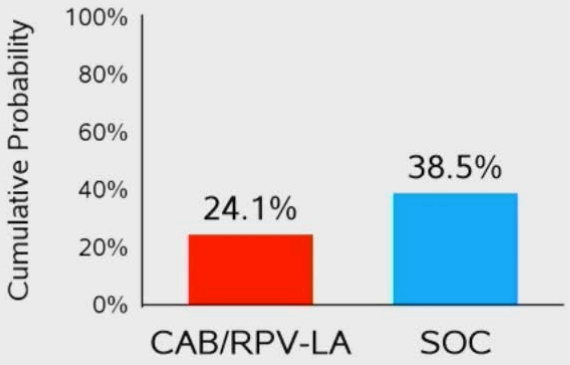
ACTG

Results-All Outcomes

Primary Outcome

Regimen Failure

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



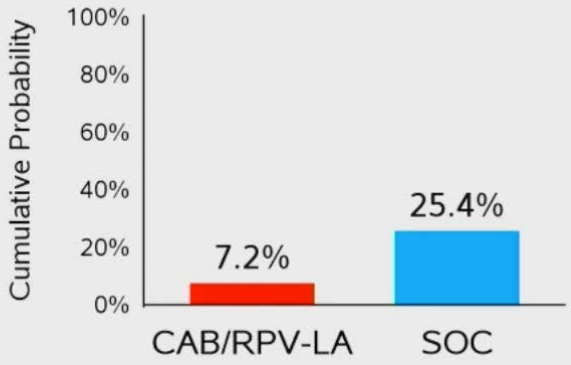
Number of participants

Regimen Failure	28	47
VF	5	28
TRT-DISC	23	19

Secondary Outcomes

Virologic Failure

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

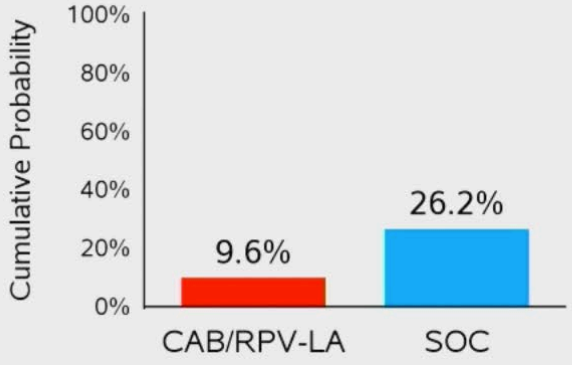


Number of participants

Virologic Failure	6	28

Treatment-related Failure

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

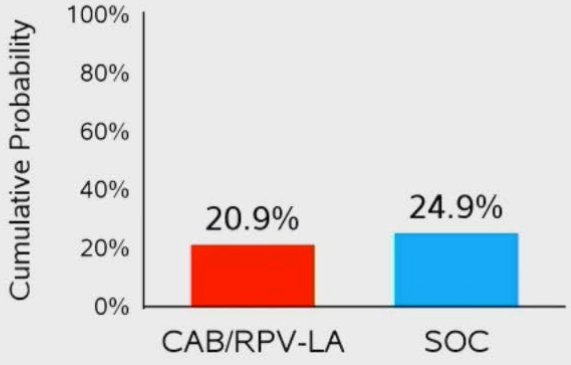


Number of participants

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

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Participants with confirmed VF in Step 2

RAM Evaluation	CAB/RPV-LA (n=6)	Oral SOC ART (n=28)	Total (n=34)
With new RAM, n	2 Week 18 E138EK; G140GS; Q148K; K103R Week 49 E138K; Q148K; K20KR; M230ML	2 Week 37 A71V; V77I; V106I Week 48 M184I	4
Without new RAM, n	3	19	22
D/c without confirmation sample, n	0	2	2
HIV-1 RNA <400 c/mL, n	1	3	4
Sample not collected, n	0	2	2

Conclusions

- Considering all endpoints together, CAB/RPV-LA demonstrated superiority when compared to daily oral SOC ART in PWH in the US who face barriers to adherence and have a prior history of virologic non-response or loss to follow-up.
- Clinical trials in this important population are feasible.
- These data support the use of LAI in this population. Future clinical trials should assess use of CAB/RPV in actively viremic patients.

LATITUDE

ACTG

Conclusions

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- Clinical trials in this important population are feasible.
- These data support the use of LAI in this population. Future clinical trials should assess use of CAB/RPV in actively viremic patients.

LATITUDE

ACTG

Long-Acting Cabotegravir Plus Rilpivirine In Adolescents With HIV: Week 24 IMPAACT 2017(MOCHA) Study

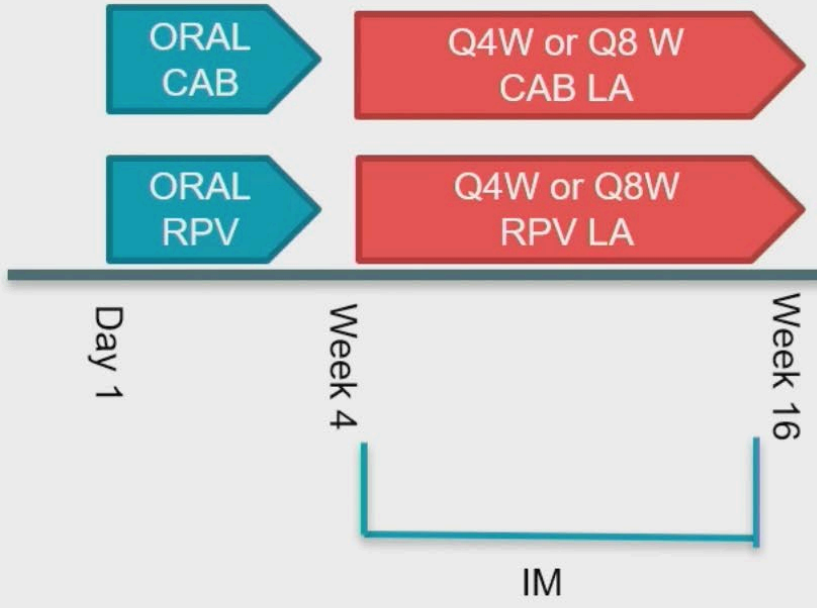
Aditya Gaur

St Jude Children's Research Hospital, Memphis, TN, USA

Disclosure: Dr Gaur reported Institution: Grants/grants (Gilead Sciences, Inc, ViiV Healthcare).

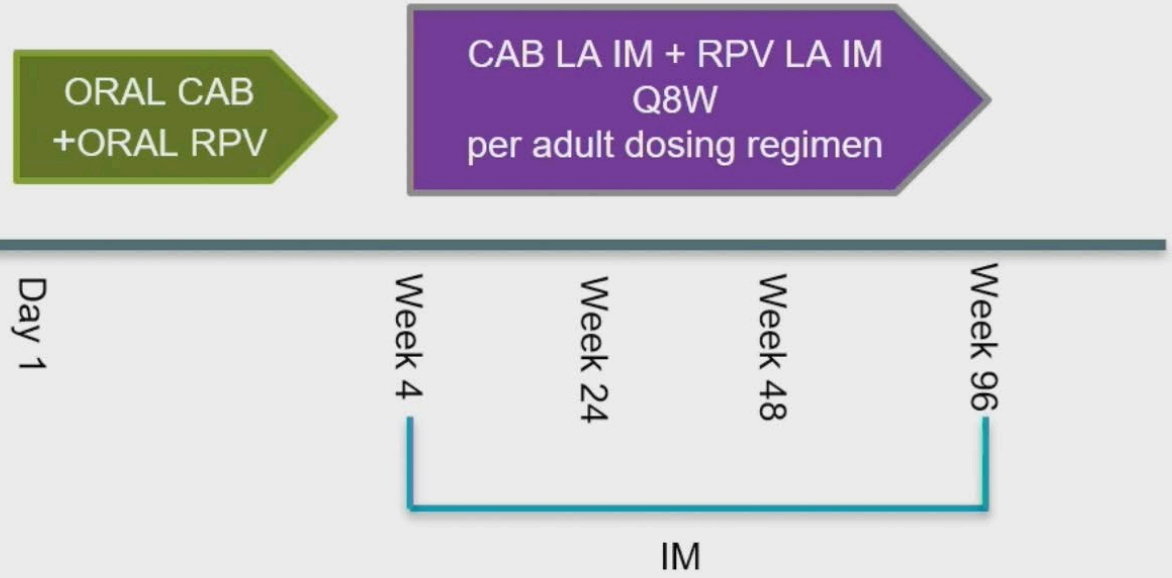
Study Design

Cohort 1
(retain background cART)
Total n = 55:
30 (CAB) + 25 (RPV)



Cohort 2
(switch from background cART)
Total n = 144: 44 (roll over) + 100 (Cohort 1 naïve)

Primary Objective: To assess the safety of CAB LA + RPV LA through Week 24 in virologically suppressed adolescents living with HIV.



In this first group of virologically suppressed adolescents switched to long-acting CAB + RPV every 2 months

- There were no unexpected safety events
- Week 24 CAB and RPV troughs were similar to those in adults
- Virologic suppression was maintained.
- Overwhelming preference for long-acting injections over oral medications.

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

CAB 4 monthly

- Phase 1, 38 participants
- Evaluation of the approved CAB 200 mg/mL (CAB200) formulation SC with recombinant human hyaluronidase PH20 (rHuPH20) and a new CAB 400 mg/mL (CAB400) formulation administered SC or IM without rHuPH20
- Safety and PK results indicate low potential to achieve less frequent dosing with CAB200 and rHuPH20
- The new CAB400 formulation (SC and IM) exhibits favourable safety and PK commensurate with dose intervals of ≥4 months and is in ongoing clinical development

Han et al. CROI 2024; Virtual and Denver, CO.

Implementing LA CAB+RPV therapy in six UK clinics & in the community - ILANA *(poster 621)*

- Implementation study
- ILANA cohort of PWHs who switched to CAB+RPV LA Q2M.
- First 6 months in the clinic with an option to receive the drug in the clinic or community from M6-M12.
- M4 analysis evaluated PWHs perspectives on feasibility and acceptability of CAB+RPV LA, and on potential community delivery through validated implementation questionnaires at baseline and 4 months.

Table 1. Baseline demographics

Participant demographics	N=114 (%)
Age (years)	
≥ 50	46 (40.4)
Gender	
Cis-Woman	60 (52.6)
Cis-Man	52 (45.6)
Transgender woman	2 (1.8)
Sexual orientation	
Heterosexual	77 (67.6)
Ethnicity	
White	34 (29.8)
Asian / Asian British	6 (5.3)
Black African / Caribbean / British	58 (50.9)
Mixed / Other	16 (14.0)
Highest education level	
Higher Education Qualifications	61 (53.5)
Occupation	
Employed	92 (80.7)
Enough money to cover basic needs	
Most / all of the time	82 (71.9)
Disability	
No	101 (88.6)

Implementing LA CAB+RPV therapy in six UK clinics & in the community - ILANA *(poster 621)*

- By month 4, ILANA patient participants found injectable CAB+RPV increasingly feasible and appropriate, and treatment satisfaction increased.
- In contrast, perceptions of receiving injections in the community in the future did not change.
- Black participants were less likely to find the injection and the community setting appropriate compared to white participants

24-Week Viral Suppression in Patients Starting LA CAB/RPV Without HIV Viral Suppression *(poster 628)*

- Retrospective cohort study of PWH who initiated LA-CAB/RPV (publicly funded HIV clinic in San Francisco).
- Start all unsuppressed patients on Q4W dosing, with option to change to Q8W dosing after 3-6 months suppression.
- Primary outcomes: VS and LA-CAB/RPV persistence (not discontinued or late by >14 days at 48 weeks)

Table 1. Baseline characteristics (n=59)

Gender	Female	5 (8.5%)
	Male	53 (89.8%)
	Gender minority	1 (1.7%)
Age	18-29	2 (3.4%)
	30-49	29 (49.2%)
	50+	28 (47.5%)
Race/ Ethnicity	White	24 (40.7%)
	Black/AA	14 (23.7%)
	Latino	17 (28.8%)
	Other	4 (6.8%)
Housing status	Stable	28 (47.5%)
	Unstable	26 (44.1%)
	Homeless	5 (8.5%)
Substance use	Methamphetamine/cocaine	36 (61.0%)
	Opioids	6 (10.2%)
CD4 count	<50	9 (15.3%)
	50-199	20 (33.9%)
	200-349	13 (22.0%)
	350-499	7 (11.9%)
	>=500	10 (16.9%)
HIV viral load	50 to <200	3 (5.1%)
	200 to <1,000	5 (8.5%)
	1,000 to <10,000	10 (16.9%)
	10,000 to <100,000	22 (37.3%)
	>=100,000	19 (32.2%)

24-Week Viral Suppression in Patients Starting LA CAB/RPV Without HIV Viral Suppression *(poster 628)*

- 286 PWH received ≥1 dose of LA-ART (101 with baseline VL ≥50, and 185 with baseline VL <50).
- 48 week VS:
  - 81% (48/59) remained on LA-CAB/RPV and were virally suppressed (VL <50)
  - 93% (55/59) were virally suppressed (VL <50) (LA-CAB/RPV + alternative ART)
  - 95% (56/59) were virally suppressed (VL <200) (LA-CAB/RPV + alternative ART).

Figure 1. HIV Viral Suppression at 48 weeks following initiation of LA-CAB/RPV with baseline HIV RNA ≥50 copies/mL (n=59)

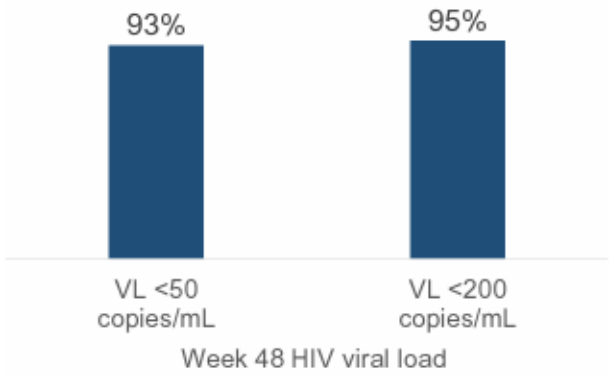


Table 2. Status at week 48*	VL <50 (N=55)	VL ≥50 (N=4)	Overall (N=59)
Remained on LA-CAB/RPV	48	1†	49 (83%)
Discontinued LA-CAB/RPV and resumed oral ART	5	-	5 (8%)
Failure with resistance			
• On-time injections	2	-	3 (5%)
• Lost to follow-up and off oral ART, later determined to have resistance	-	1	
Lost to follow up and off oral ART	-	2	2 (3%)

* Four VLs missing at week 48. Three categorized as VL ≥50 due to VL ≥50 before/after window and/or evidence off ART. One categorized as VL <50 due to VL <50 before & after window and on ART throughout.

† Intensified to LA-CAB/RPV + Lenacapavir for low-level viremia. Week 48 VL <200 copies/mL.

Reasons for discontinuation and switching to oral ART: side effects (n=3), provider-initiated switch due to viremia associated with incorrect needle length in patient with BMI ≥30 kg/m^2 (no resistance; n=1), transfer to another clinic that did not have LA-CAB/RPV available (n=1).

Reasons for discontinuation/loss to follow-up and not taking oral ART: fixed belief that cured from HIV (n=1), psychosis (n=1), depression (n=1)

Model-Based Comparison of Cabotegravir Pharmacokinetics Following Thigh and Gluteal Injections

617

Kelong Han,[1] Ronald D'Amico,[2] William Spreen,[2] Susan L. Ford[3]
[1]GSK, Collegeville, PA, USA; [2]ViiV Healthcare, Durham, NC, USA; [3]GSK, Durham, NC, USA

- Fourteen participants who were living without HIV and received a 600 mg single thigh injection in the Phase 1 study 208832 and 118 participants who were living with HIV and received thigh injections (400 mg QM × 4 or 600 mg Q2M × 2) after ≥3 years of gluteal injections in the Phase 3b ATLAS-2M study provided CAB concentrations for the analysis
- The absorption rate of thigh injection was lower in females than males and decreased with increasing BMI
- The bioavailability of thigh injection was estimated to be 89.9% of gluteal injection
- Simulations demonstrate the potential for chronic thigh injections QM and intermittent thigh injections both QM and Q2M of up to two consecutive thigh injections, **but not for chronic Q2M thigh injections**
- CAB + RPV LA thigh administration has not been approved by regulatory agencies, as long-term safety and efficacy are unknown

Han et al. CROI 2024; Denver, CO. Poster 617.

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Population PK simulations demonstrate the potential for chronic thigh injections QM and intermittent thigh injections both QM and Q2M of up to 2 consecutive thigh injections but not for chronic Q2M thigh injections

Han et al. CROI 2024; Denver, CO. Poster 617.

Take Home Points

- In the CARES Study in Africa, LA CAB+RPV was non inferior to SoC oral ART using a public health approach
- In the LATITUDE Study, in people with HIV with adherence challenges, LA CAB+RPV was superior to SoC oral ART
- Data from the MOCHA Study support safety and efficacy of switch to LA CAB+RPV among adolescents with HIV
- In people with HIV who were viraemic at initiation, LA CAB+RPV was effective through to 48w

Thank You!

Thank You!

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