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HIV: NUOVE STRATEGIE DI TRATTAMENTO CON FARMACI LONG-ACTING

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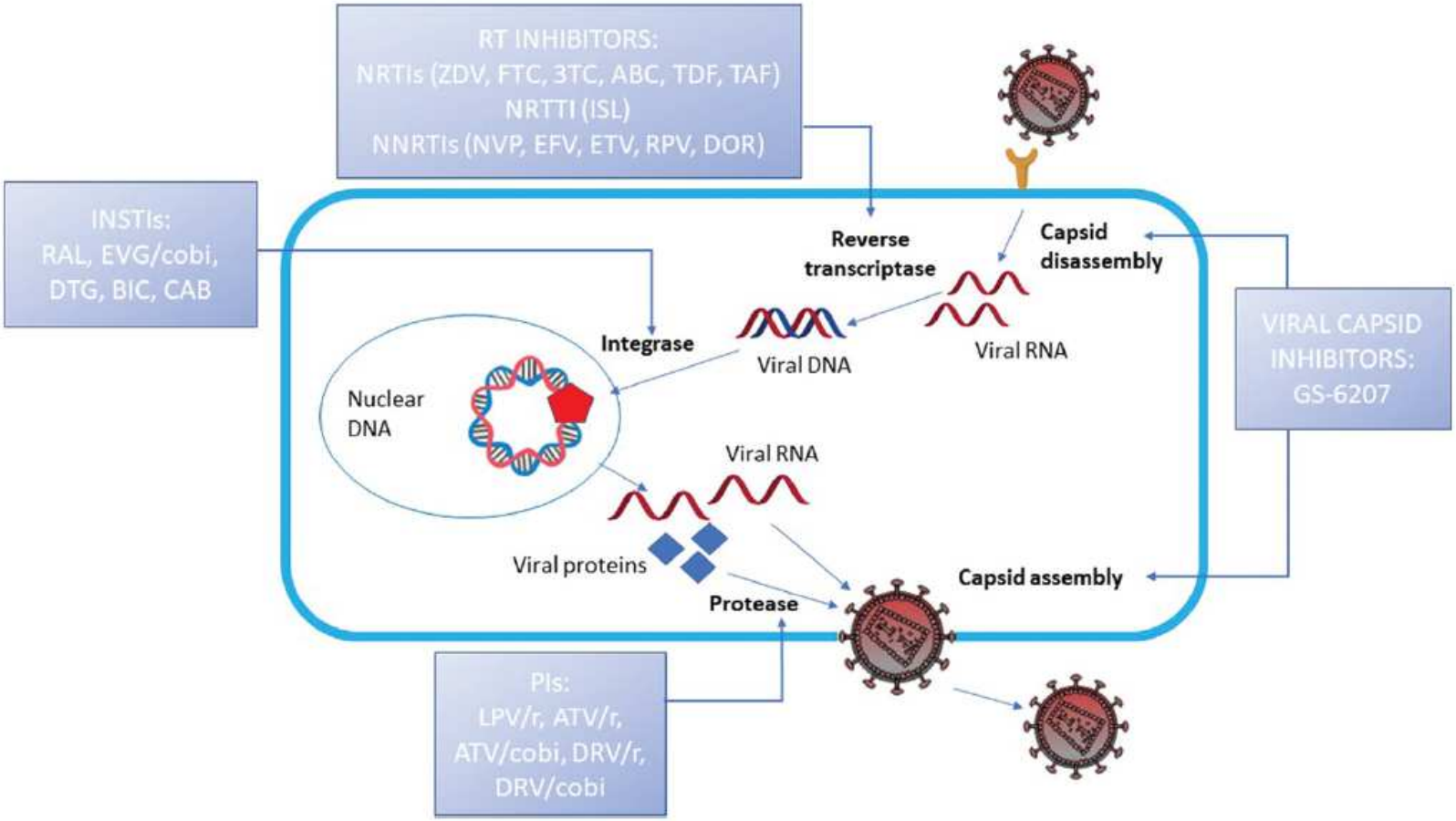
COIs

GSK, Gilead, Janssen-Cilag, MSD, ViiV

HIV-1 enzymatic steps and antiviral compounds



Andrea Giacomelli, Laura Pezzati & Stefano Rusconi.
The crosstalk between antiretrovirals pharmacology and HIV drug resistance. Expert Review of Clinical Pharmacology, 2020

PILLS vs LONG-ACTING agents

WANT

- **“I just don’t like pills”**

NEED

- **Difficulty swallowing or absorbing**
- **Risks with disclosure**
- **Internal or external stigma**
- **Difficulties with adherence**

Outline

- Efficacia e tollerabilità: dati dai trial clinici (FLAIR, ATLAS, ATLAS-2M, LATTE-2)
- Quali sono le preferenze del paziente? Analisi dei PROs dai trial clinici
- Cabotegravir + Rilpivirina long acting vs Bictegravir/TAF/FTC: lo studio SOLAR
- Weight gain e Long Acting? Risultati dallo studio SOLAR
- L-A come PrEP
- Impatto sull'infiammazione

CARLA

Efficacia e tollerabilità: dati dai trial clinici

Efficacy of CAB + RPV LA has been demonstrated in Phase III clinical trials

MONTHLY DOSING vs **DAILY ORAL ART**

FLAIR[1] (N=566)

Treatment-naïve adults with HIV-1 virologically suppressed* for 20 weeks on daily oral ARV therapy

ATLAS[2] (N=616)

Adults with HIV-1 virologically suppressed* for ≥6 months on daily oral ARV therapy

EVERY 2-MONTH DOSING vs **MONTHLY DOSING**

ATLAS-2M[3] (N=1,045)

Adults with HIV-1 virologically suppressed* for ≥6 months on daily oral ARV therapy or monthly dosing

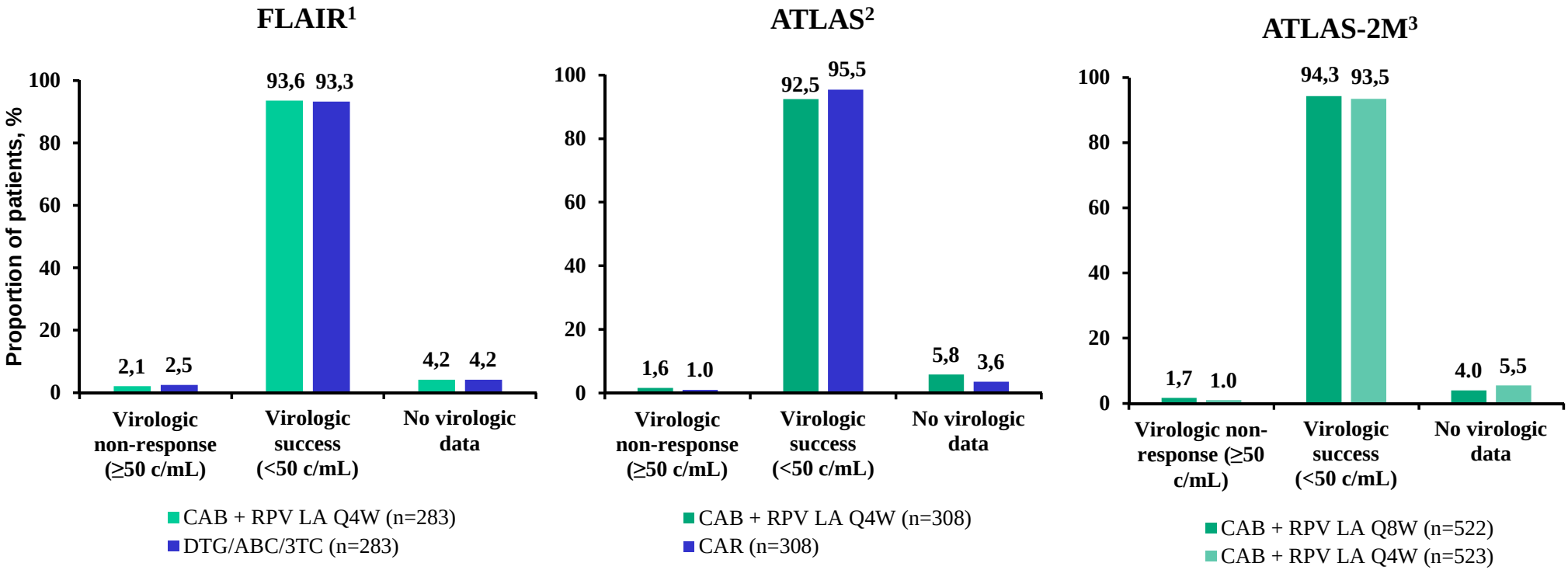
Established non-inferiority of LA therapy compared with daily HIV regimens; every 2-month dosing non-inferior to monthly dosing[1–3]

*HIV-1 RNA <50 c/mL

1. Orkin C, et al. N Engl J Med 2020;382:1124–35
2. Swindells S, et al. N Engl J Med 2020;382:1112–23
3. Overton ET, et al. Lancet 2021;396:1994–2005

CAB + RPV LA (Q4W or Q8W dosing) is efficacious at maintaining virologic suppression

Virologic Snapshot outcomes at Week 48 (ITT-E)*

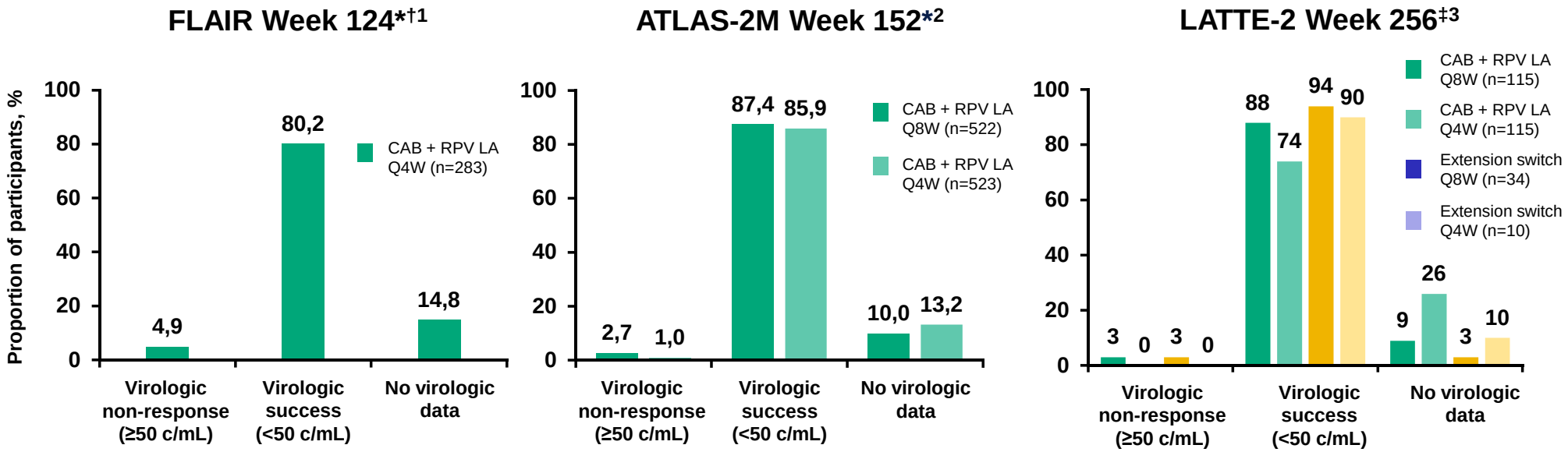


***Primary endpoint: non-inferiority (HIV-1 RNA ≥50 c/mL) to comparator arm; key secondary endpoint: non-inferiority (HIV-1 RNA <50 c/mL) to comparator arm
3TC, lamivudine; **ABC,** abacavir; **CAR,** current antiretroviral regimen; **ITT-E,** intention-to-treat exposed

1. Orkin C, et al. N Engl J Med 2020;382:1124–35
2. Swindells S, et al. N Engl J Med 2020;382:1112–23
3. Overton ET, et al. Lancet 2021;396:1994–2005

CAB + RPV LA maintained high rates of virologic suppression over long-term follow-up

Virologic Snapshot outcomes in Phase IIb and III clinical trials (ITT-E)



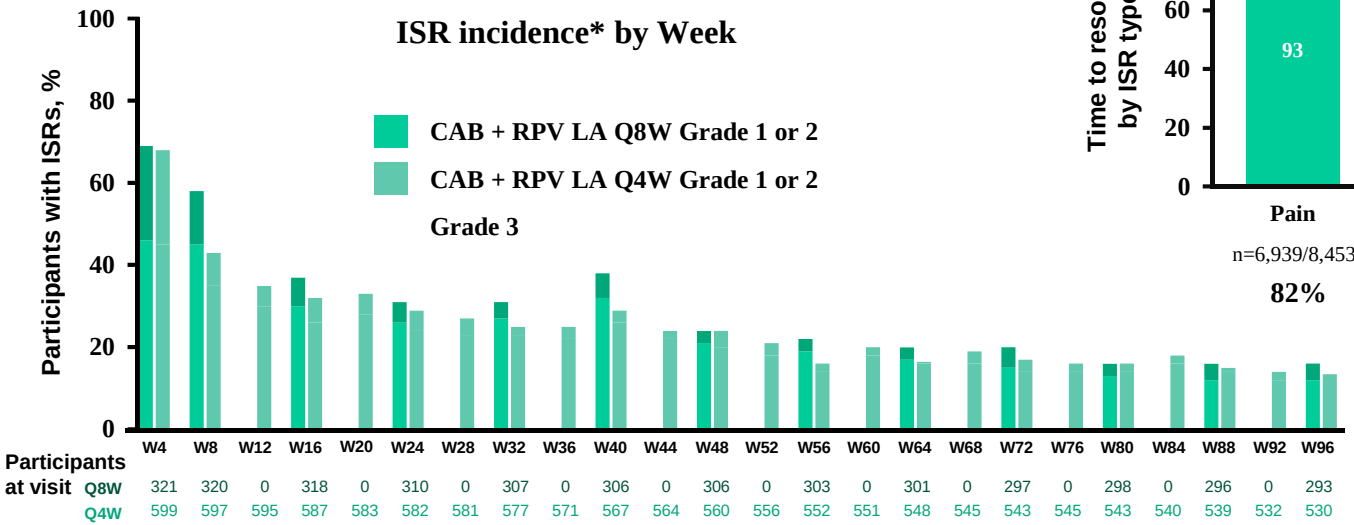
CAB + RPV LA maintained high levels of virologic suppression beyond Week 48[1–3]

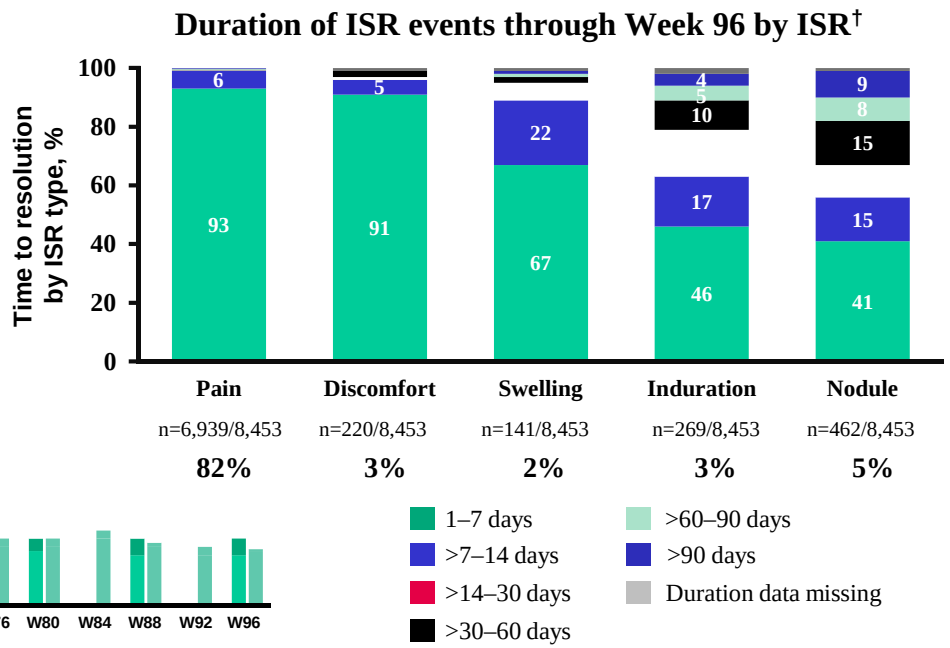
*Primary endpoint: proportion of participants with HIV-1 RNA ≥50 c/mL at Week 48 by FDA Snapshot
†No CAR arm at Week 124. Of those with no virologic data at Week 124 (n=42), most were due to discontinuations due to AEs or other non-virologic reasons
‡Primary endpoints: proportion of participants with viral suppression (HIV <50 c/mL) at Week 32 by FDA snapshot, PVDF and safety events through to Week 96

1. Orkin C, et al. Lancet HIV 2021;8:e668–78
2. Overton ET, et al. CROI 2022. Poster H03
3. Smith GHL, et al. Open Forum Infect Dis 2021;8:ofab439

Pooled FLAIR and ATLAS-2M: ISR incidence decreased through Week 96 and ISR events resolved rapidly

- 99% of ISRs were Grade 1 and 2, with no Grades 4 and 5 reported
- The median (IQR) duration was 3 days (2–4), with no difference between dosing regimens
- The majority (99%) of ISRs were self-limited





ISR incidence decreased over time and >90% of injection site pain and discomfort, as well as 41–67% of swelling, induration, and nodules resolved within 7 days

*Incidence is derived relative to the number of participants who received injections at each respective study visit. AE grade is the maximum grade reported by the participant at each visit
†Each ISR event was counted separately. A participant may have had multiple ISR events following a single injection. Top five most common ISRs reported

Chamay N, et al. AIDS 2022. Poster EPB182

ATLAS, FLAIR, and ATLAS-2M: List of adverse reactions with CAB or RPV[1,2]

Frequently reported adverse reactions

Frequency	AEs	Asymptomatic blood test changes
Very common (≥1/10)	/ ISR / Headache / Pyrexia	**Very common** ↑ Total and LDL cholesterol ↑ Pancreatic amylase
Common (≥1/100 and <1/10)	Depression/depressed mood Anxiety Abnormal dream Insomnia/sleep disorder Dizziness Nausea Vomiting Dry mouth Decreased appetite Flatulence Myalgia Abdominal pain/discomfort Diarrhea Rash Fatigue Asthenia Malaise Weight increase	**Common** ↑ Triglycerides ↑ Lipase ↓ White blood cell, hemoglobin and platelet count **Uncommon** ↑ Bilirubin

LDL, low-density lipoprotein

Rare but serious adverse reactions

Hepatotoxicity

- Hepatotoxicity has been reported in a limited number of patients receiving CAB LA with or without known pre-existing hepatic disease
- Monitoring of liver chemistries is recommended, and treatment with CAB + RPV LA should be discontinued if hepatotoxicity is suspected

Pancreatitis

- One case of fatal pancreatitis with Grade 4 lipase and confounding factors (including history of pancreatitis) was reported in ATLAS-2M, for which causality to the injection regimen could not be ruled out

ISR cellulitis and abscess

- Cellulitis and abscess were uncommon complications of IM injection

1. Vocabria EU SmPC. Sep 2022
2. Rekambys EU SmPC. Sep 2022

ATLAS and FLAIR: No new safety signals were identified after Week 48

	ATLAS Week 96[1]	FLAIR Week 96[2]		FLAIR Week 124[3,4]
Excluding ISRs, n (%) [delta*]	**CAB + RPV LA Q4W n=23†**	**CAB + RPV LA Q4W n=283**	**DTG/ABC/3TC n=283**	**CAB + RPV LA Q4W n=283**
Any AE	[+3]	264 (93) [+18]	242 (86) [+18]	271 (96) [+7]
Grade 3/4 AEs	[+2]	29 (10) [+8]	16 (6) [+5]	38 (13) [+9]
Drug-related AEs	[0]	95 (34) [+16]§	33 (12) [+6]‖	102 (36) [+7]¶
Drug-related Grade 3/4 AEs	[0]	16 (6) [+2]	0 [0]	5 (2) [+1]
SAEs	[+2]	24 (8) [+6]	22 (8) [+10]	33 (12) [+2]
Drug-related SAEs	[0]	1 (<1) [0]	0 [0]	1 (<1) [0]
AEs leading to withdrawal	[+2]‡	14 (5) [+5]	4 (1) [0]	15 (5) [+1]

*Delta value represents new participants with AEs since the Week 48 or Week 96 analysis; †148 participants entered the extension phase; however, this number deteriorated throughout the study leaving 23 participants at the Week 96 analysis; ‡Includes acute hepatitis B and fear; §Pyrexia (2), fatigue (2), headache/nausea (1), presyncope (1), depressed mood (1), pyrexia/chills (1), chronic sinusitis/chronic tonsillitis (1), back pain/nasopharyngitis (1), musculoskeletal pain (1), dizziness (2), anxiety (1), influenza-like illness (1), asthenia/depressed mood (1); ‖Diarrhea/abdominal pain/nasopharyngitis/eye pain (1), insomnia (1), abnormal dreams (1), poor quality sleep (1), nausea (1), hypercholesterolemia/vitamin D decreased (1); ¶Seven participants reported 22 events since the Week 96 analysis, pyrexia (1), fatigue (3), chills (2), influenza-like illness (1), paresthesia (1), autonomic nervous system imbalance (1), hypoesthesia (1), lethargy (1), restless leg syndrome (1), nausea (1), blood creatine phosphokinase increased (1), myalgia (1), back pain (1), erythema (1), syphilis (1), dyspnea (1), cough (1), flushing (1), overdose (1)

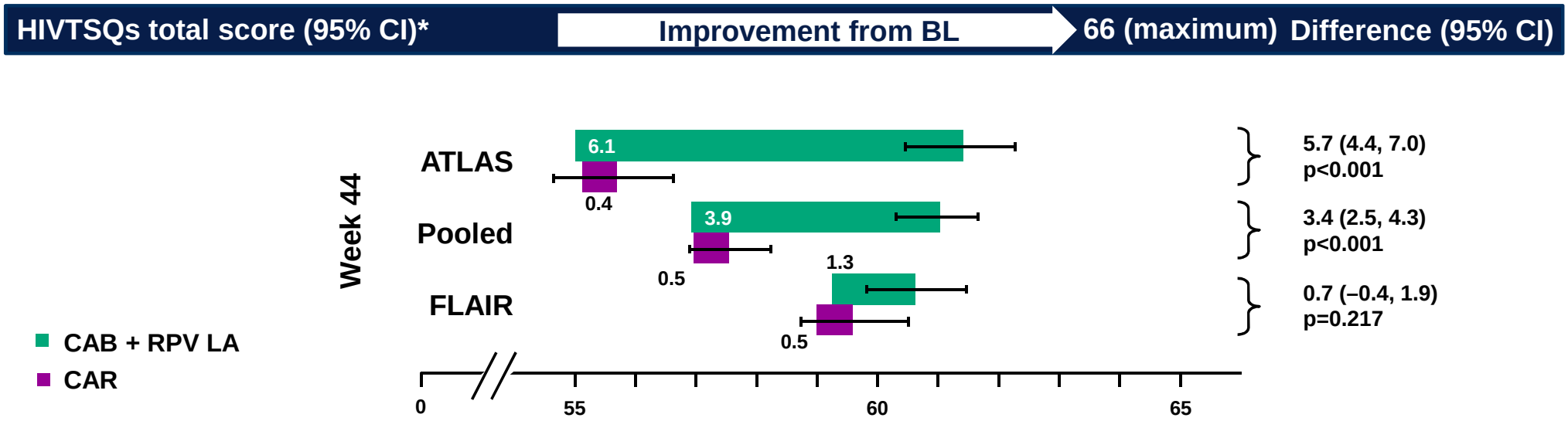
1. Swindells S, et al. AIDS 2021;36:185–94
2. Orkin C, et al. Lancet HIV 2021;8:e185–96
3. Orkin C, et al. IAS 2021. Oral OAB0302
4. Orkin C, et al. Lancet HIV 2021;8:e668–78

L-A injectable agents

Quali sono le preferenze del paziente?

Analisi dei **PROs** dai trial clinici

CAB + RPV LA participants showed greater improvement from Baseline in treatment satisfaction versus CAR (HIVTSQs)



Pooled data from ATLAS and FLAIR showed a significantly greater improvement in treatment satisfaction from baseline with CAB + RPV LA versus CAR at Week 44 (p<0.001)

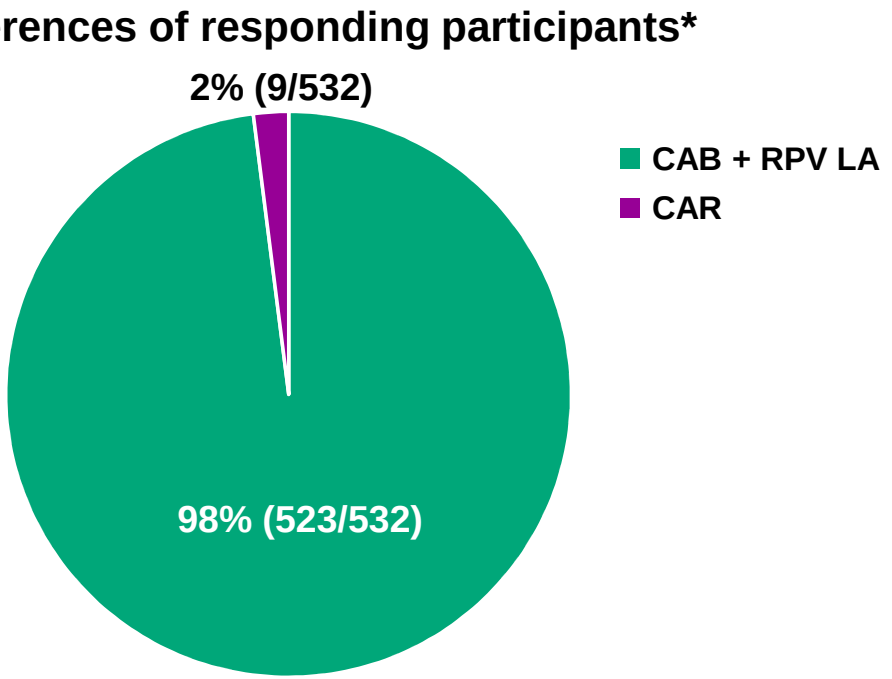
*Adjusted mean change from BL through Week 44 is estimated from an ANCOVA model. On top of sex at birth, age (<50 vs ≥50 years), and race that were covariates for all three analyses; ATLAS also included BL score and third-agent class; FLAIR included maintenance BL score (Day 1) and induction BL (Week –20) HIV-1 RNA (<105 vs ≥105 c/mL); pooled analysis included maintenance BL score. Observed mean BL (SD) for CAB + RPV LA and CAR were respectively 55.3 (9.1) and 55.4 (8.7) for ATLAS, 57.1 (8.6) and 57.1 (8.4) for the pooled analysis, and 59.3 (7.4) and 59.1 (7.6) for FLAIR

ANCOVA, analysis of covariance; **HIVTSQs,** HIV Treatment Satisfaction Questionnaire status version; **SD,** standard deviation

Murray M, et al. AIDS Behav 2020;24:3533–44

Pooled ATLAS and FLAIR: Participants preferred CAB + RPV LA over daily oral ART

"For the past 44 weeks you have received long-acting injectable HIV medication every month. Today we would like you to compare your experience on the long-acting injections with the oral medication you received prior to entering the study. ***Which therapy do you prefer?****"*



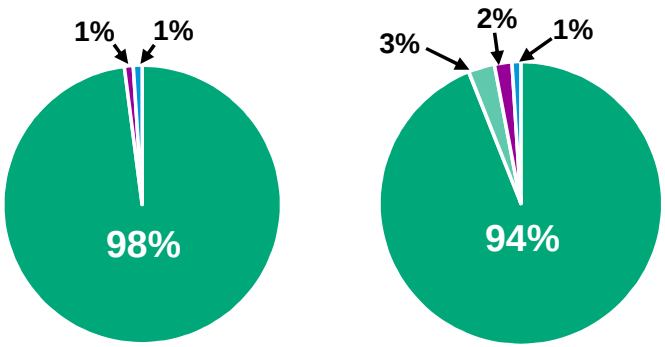
98% of responding participants from ATLAS + FLAIR preferred CAB + RPV LA over CAR at Week 48

*****Responding participants: 98% (523/532) preferred the LA regimen over previous oral therapy

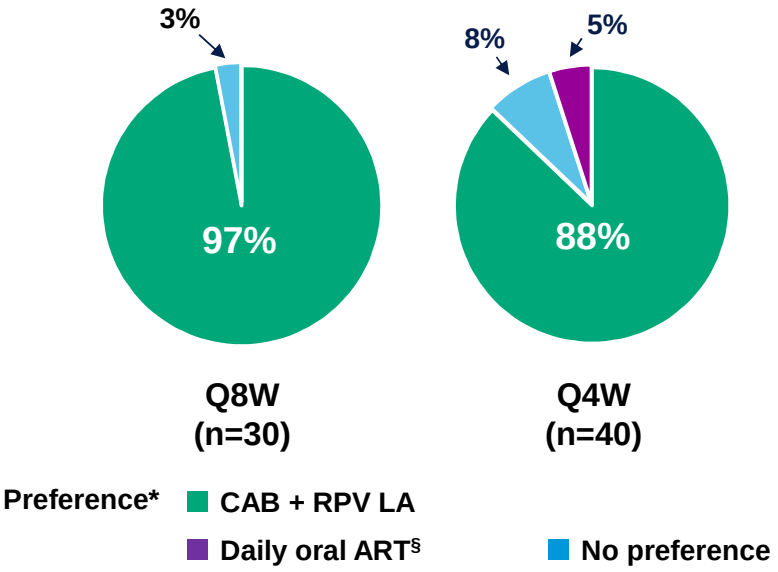
Murray M, et al. AIDS Behav 2020;24:3533–44

ATLAS-2M: Participants preferred CAB + RPV LA (Q8W or Q4W) to daily oral ART at Week 48 and 152

Week 48
Participants on Q8W[1,2]



Week 152
Participants who received oral therapy to cover missed injections¶[3]



*Percentages are based on the number of participants with a recorded response to the preference question; †Transitioned from oral ART ‡Transitioned from Q4W in ATLAS; §Daily oral ART refers to CAB + RPV received during the OLI period during either ATLAS-2M or ATLAS ¶Participants utilized oral therapy when they were unable to comply with the injection visit schedule, including oral therapy to cover missed doses due to COVID-19 pandemic-related interruptions (oral CAB + RPV or other standard-of-care oral therapies were allowed during this time)
COVID-19, coronavirus disease 2019

1. Overton ET, et al. Lancet 2021;396:1994–2005 (and suppl. appendix)
2. Chounta V, et al. Patient 2021;14:849–62
3. Chounta V, et al. HIV Glasgow 2022. Poster P070

L-A agents as Tx switch

Cabotegravir + Rilpivirina long-acting vs Bictegravir/TAF/FTC: lo studio **SOLAR**

SOLAR (Switch Onto Long-Acting Regimen) 12-Month Results – Randomized Switch Trial of CAB + RPV LA vs. Oral BIC/FTC/TAF

Moti N. Ramgopal[1], Antonella Castagna[2], Charles Cazanave[3], Vicens Diaz-Brito[4], Robin Dretler[5], Shinichi Oka[6], Olayemi Osiyemi[7], Kenneth Sutton[8], Denise Sutherland-Phillips[8], Alessandro Berni[9], Christine Latham[8], Feifan Zhang[10], Ronald D'Amico[8], Kimberly Smith[8], Jean van Wyk[11]

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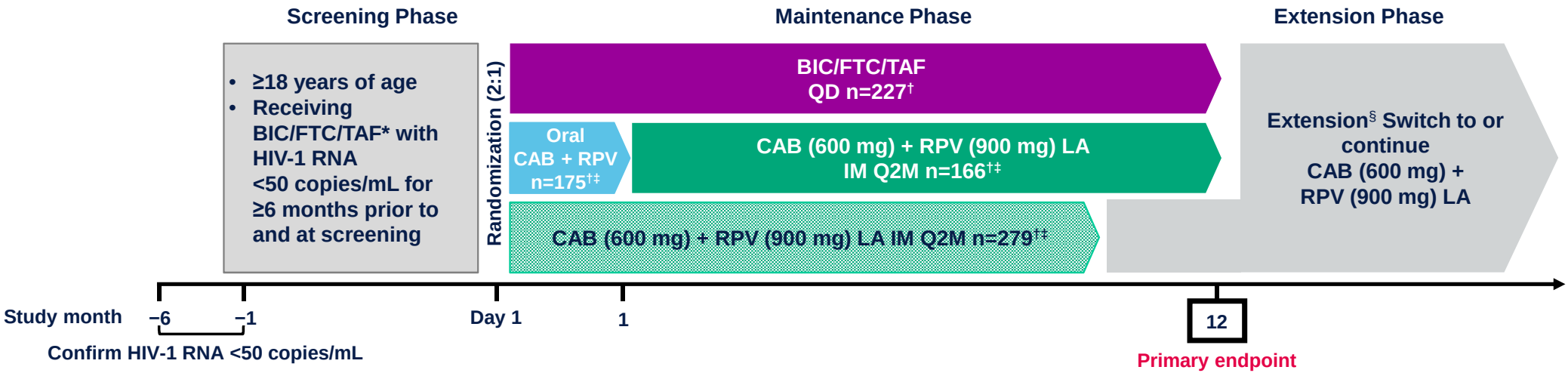
[3]Department of Infectious Diseases, Pellegrin Hospital, University Hospital of Bordeaux, Bordeaux, France;
[4]Department of Infectious Diseases, Parc Sanitari Sant Joan de Deu, Sant Boi de Llobregat, Spain;
[5]Infectious Disease Specialists of Atlanta, Decatur, GA, United States; [6]AIDS Clinical Center, National Center for Global Health and Medicine, Tokyo, Japan;
[7]Triple O Research Institute PA, West Palm Beach, FL, United States; [8]ViiV Healthcare, Durham, NC, United States;
[9]GSK, Brentford, United Kingdom; [10]GSK, Collegeville, PA, United States; [11]ViiV Healthcare, Brentford, United Kingdom

Moti Ramgopal, MD, FACP, FIDSA, has received speaking and/or consulting fees from AbbVie, Gilead Sciences, Janssen, Merck, and ViiV Healthcare

Ramgopal et al. CROI 2023; Virtual and Seattle, WA. Oral presentation 191.

SOLAR Study Design

Phase 3b, Randomized (2:1), Open-Label, Active-Controlled, Multicenter, Parallel-Group, Noninferiority Study



*A single prior INI regimen is allowed if BIC/FTC/TAF is a second-line regimen 6 months prior to screening. Any prior change in regimen, defined as a change of a single drug or multiple drugs simultaneously, must have occurred due to tolerability/safety, access to medications, or convenience/simplification, and must not have been done for treatment failure (HIV-1 RNA ≥400 copies/mL).
†n values are based on the safety population.
‡Participants randomized to the LA arm were offered an optional OLI; the decision was determined by the participants following informed consent discussions with the investigator.
§The extension phase will continue study treatment until CAB LA and RPV LA are either locally approved and commercially available, the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation, or until development of either CAB LA or RPV LA is terminated. Visits will continue to occur Q2M.
IM, intramuscular; LA, long-acting; OD, once daily; OLI, oral lead-in; Q2M, every 2 months.

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Baseline Characteristics

mITT-E population	CAB + RPV LA Q2M (n=447)	BIC/FTC/TAF (n=223)
Median age (range), years	37 (18–74)	37 (18–66)
≥50 years, n (%)	86 (19)	42 (19)
Female (sex at birth), n (%)	77 (17)	41 (18)
Race, n (%)		
Black	95 (21)	49 (22)
White	307 (69)	156 (70)
Asian	23 (5)	11 (5)
Other races*	22 (5)	7 (3)
BMI (kg/m^2), median (IQR)	26.0 (23.2–29.4)	25.4 (23.4–29.6)
Prior duration of ART, median, years	2.58	2.47

- Among study participants, 12 transgender females, 1 transgender male, and 1 gender non-conforming individual were included

*Other race participants: American Indian or Alaska Native, n=14 (CAB + RPV LA Q2M) and n=2 (BIC/FTC/TAF); Native Hawaiian or other Pacific Islander, n=1 (BIC/FTC/TAF); multiple, n=8 (CAB + RPV LA Q2M) and n=4 (BIC/FTC/TAF).
BMI, body mass index; IQR, interquartile range; LA, long-acting; mITT-E, modified intention-to-treat exposed; OLI, oral lead-in; Q2M, every 2 months; SWI, starting with injections.

Psychosocial Challenges With Daily Oral BIC/FTC/TAF at Baseline

- At baseline, 47% (n=315/670) of participants who were virologically suppressed on BIC/FTC/TAF "always/often" reported at least one of the following psychosocial challenges with daily oral therapy:
  - "*Worried about people unintentionally discovering their HIV status*"
  - "*Worried about forgetting to take their HIV medication*"
  - "*Felt that taking their HIV medication was an uncomfortable reminder of their HIV status*"

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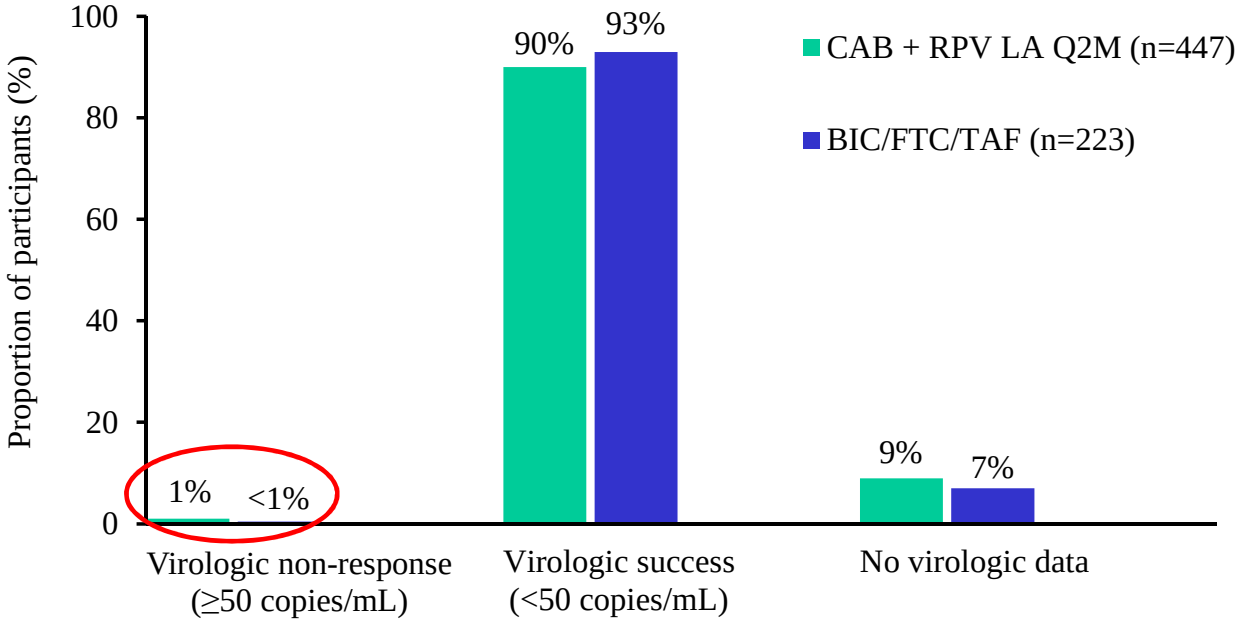
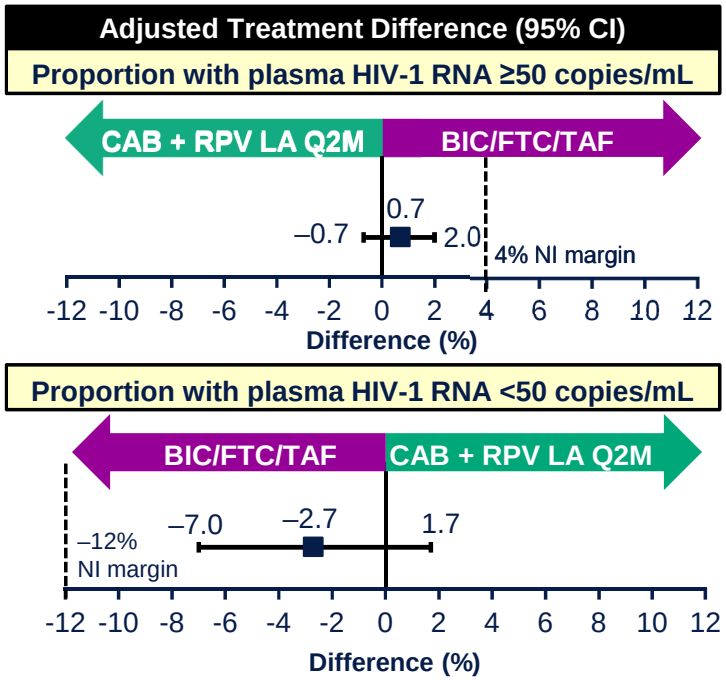
Virologic Outcomes at Month 12 (mITT-E Population)





- At Month 12, CAB + RPV LA demonstrated noninferior efficacy compared with BIC/FTC/TAF for the proportion of participants with HIV-1 RNA ≥50 copies/mL and <50 copies/mL in the mITT-E, ITT-E, and per-protocol populations*

*In the ITT-E population, 89% (n=406/454) and 93% (n=211/227) of participants receiving LA and BIC/FTC/TAF demonstrated virologic success (HIV-1 RNA <50 copies/mL; adjusted treatment difference [95% CI], –3.5% [–7.9, 0.9]), 1% (n=6/454) and <1% (n=1/227) of participants receiving LA and BIC/FTC/TAF demonstrated virologic non-response (HIV-1 RNA ≥50 copies/mL; adjusted treatment difference [95% CI], 0.9% [–0.5, 2.2]), and 9% (n=42/454) and 7% (n=15/227) of participants receiving LA and BIC/FTC/TAF had no virologic data, respectively. In the per protocol population, 91% (n=394/433) and 93% (n=203/218) of participants receiving LA and BIC/FTC/TAF demonstrated virologic success (HIV-1 RNA <50 copies/mL; adjusted treatment difference [95% CI], –2.1% [–6.4, 2.2]), <1% (n=4/433) and <1% (n=1/218) of participants receiving LA and BIC/FTC/TAF demonstrated virologic non-response (HIV ≥50 copies/mL; adjusted treatment difference [95% CI], 0.5
[–0.8, 1.7]). ITT-E, intention-to-treat exposed; mITT-E, modified intention-to-treat exposed; NI, noninferiority.

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Month 12 Snapshot Outcomes (mITT-E Population)

Parameter	CAB + RPV LA Q2M (n=447)	BIC/FTC/TAF (n=223)
HIV-1 RNA ≥50 copies/mL	5 (1)	1 (<1)
Data in window not below 50 copies/mL	3 (<1)	1 (<1)
Discontinued for lack of efficacy	1 (<1)	0
Discontinued for other reason while not below 50 copies/mL	1 (<1)	0
HIV-1 RNA <50 copies/mL	403 (90)	207 (93)
No virologic data	39 (9)	15 (7)
Discontinued due to AE	13 (3)*	0
Discontinued due to death	0	1 (<1)†
Discontinued for other reason	24 (5)‡	13 (6)§
On study but missing data in window	2 (<1)	1 (<1)

- Among participants with no virologic data, the incidence of AEs leading to withdrawal was low, and discontinuations for other reasons were similar between the LA and BIC/FTC/TAF arms

*Injection site pain, n=2; acute myocardial infarction, n=1; dysesthesia/limb discomfort/paresthesia/peripheral swelling, n=1; dizziness, n=1; fatigue, n=1; deafness/ear congestion/fatigue, n=1; blood pressure fluctuation (participant reported)/depression, n=1; alanine aminotransferase increase, n=1; diarrhea/joint stiffness, n=1; acute hepatitis B, n=1; fatigue/pyrexia, n=1; injection site discharge, n=1. †Participant had a fatal SAE of brain injury and encephalopathy.
‡Withdrawal by participant, n=12; lost to follow-up, n=6; protocol deviation, n=5; investigator decision, n=1. §Physician decision (pregnancy), n=1; withdrawal by participant, n=9; protocol deviation, n=1; lost to follow-up, n=2.
AE, adverse event; mITT-E, modified intention-to-treat exposed; Q2M, every 2 months; SAE, serious adverse event.

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Participants With Confirmed Virologic Failure (CVF)

Sex at birth, country	Baseline BMI (kg/m^2)	HIV-1 subtype at baseline	Viral load at SVF/CVF (copies/mL)	RPV RAMs observed at baseline (proviral DNA)	INI RAMs observed at baseline (proviral DNA)	RPV RAMs observed at failure (viral RNA)	INI RAMs observed at failure (viral RNA)	Phenotypic resistance (fold-change) to RPV/CAB	SVF timepoint (month)
Participants With CVF in the mITT-E Population									
Male, Italy*	21.5	B	1327/1409	None	None	M230L	Q148R	3.2/3.1	6
Male, Spain†	22.9	AE	6348/419	None	G140G/R	K101E	G118R	1.9/8.4	11
Participant With CVF in the ITT-E Population‡									
Male, United States	30.5	C§	3797/928	Assay failed	Assay failed	E138E/K + Y181Y/C	None	4.2/assay failed	3

- Two (0.4%) participants receiving CAB + RPV LA in the mITT-E population, and one additional participant receiving CAB + RPV LA in the ITT-E population, met the CVF criterion through Month 12
  - Two of the participants had on-treatment RPV and/or INI RAMs (genotyping for third participant failed at baseline)
- No participants in the BIC/FTC/TAF arm met the CVF criterion through Month 12

*Prior to enrolling in the study, the participant received BIC/FTC/TAF, and after discontinuation re-suppressed on DRV/c/FTC/TAF during long-term follow-up. †Prior to enrolling in the study, the participant had received dolutegravir/lamivudine/abacavir and BIC/FTC/TAF; they re-suppressed on BIC/FTC/TAF and darunavir/cobicistat/emtricitabine/tenofovir alafenamide during long-term follow-up. The participant did not continue in the long-term follow-up phase. ‡Prior to enrolling in the study, the participant had received prohibited prior ART with at least three prior INI regimens; they re-suppressed on BIC/FTC/TAF during long-term follow-up. This participant was excluded from the mITT-E population due to significant and persistent non-compliance to protocol entry requirements at the study site. §Participant had HIV-1 subtype C at Month 3. Baseline analysis failed.
DRV, darunavir; ITT-E, intention-to-treat exposed; LA, long-acting; mITT-E, modified intention-to-treat exposed; NA, not available; RAM, resistance-associated mutation; SVF, suspected virologic failure.

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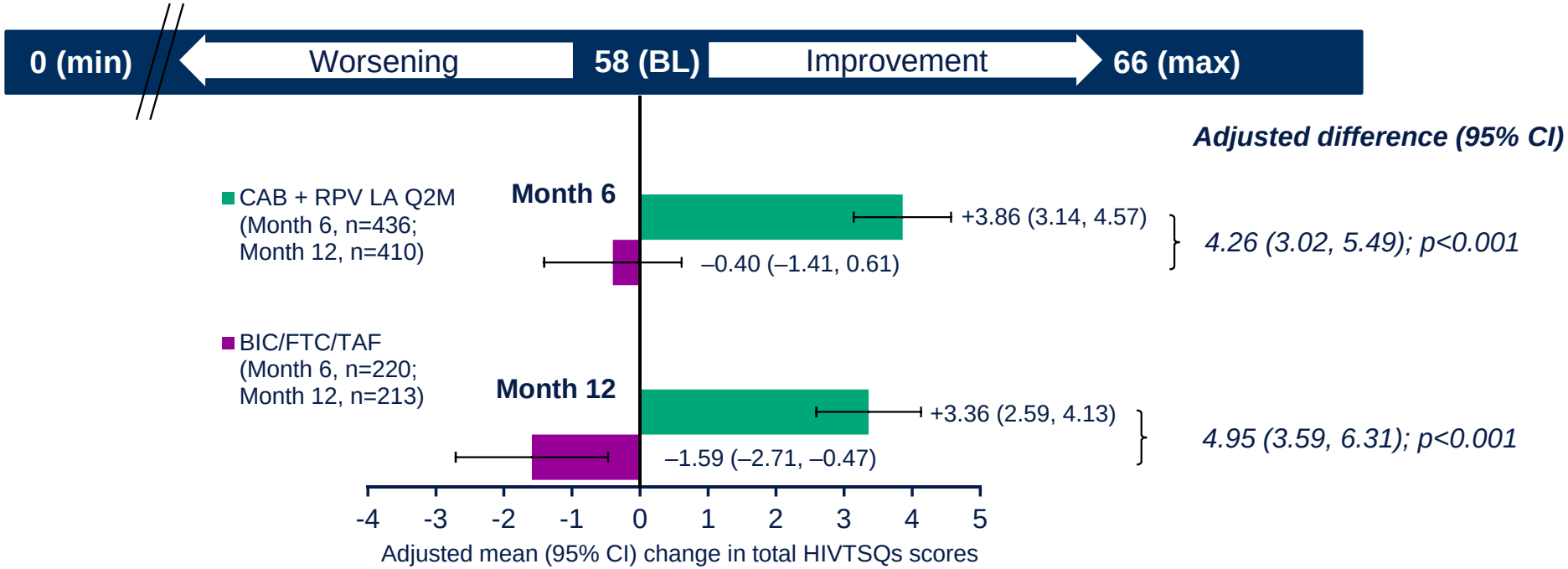
Treatment Satisfaction

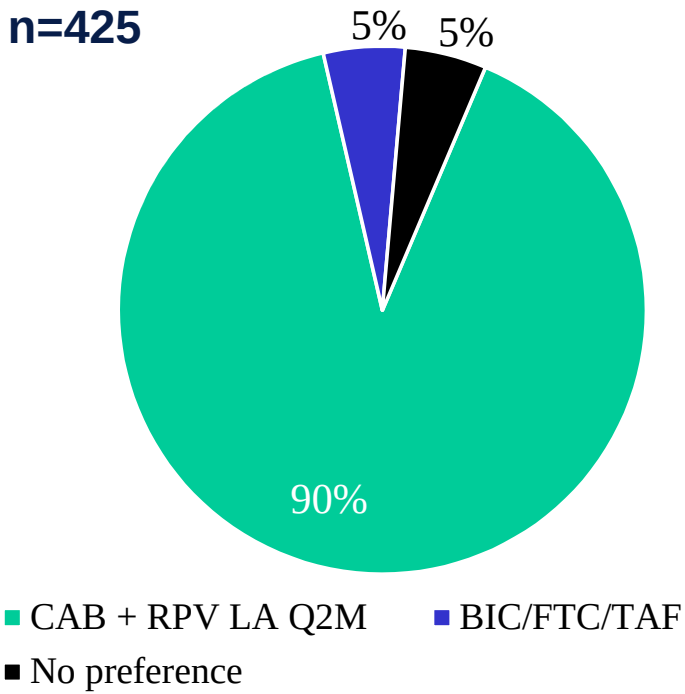


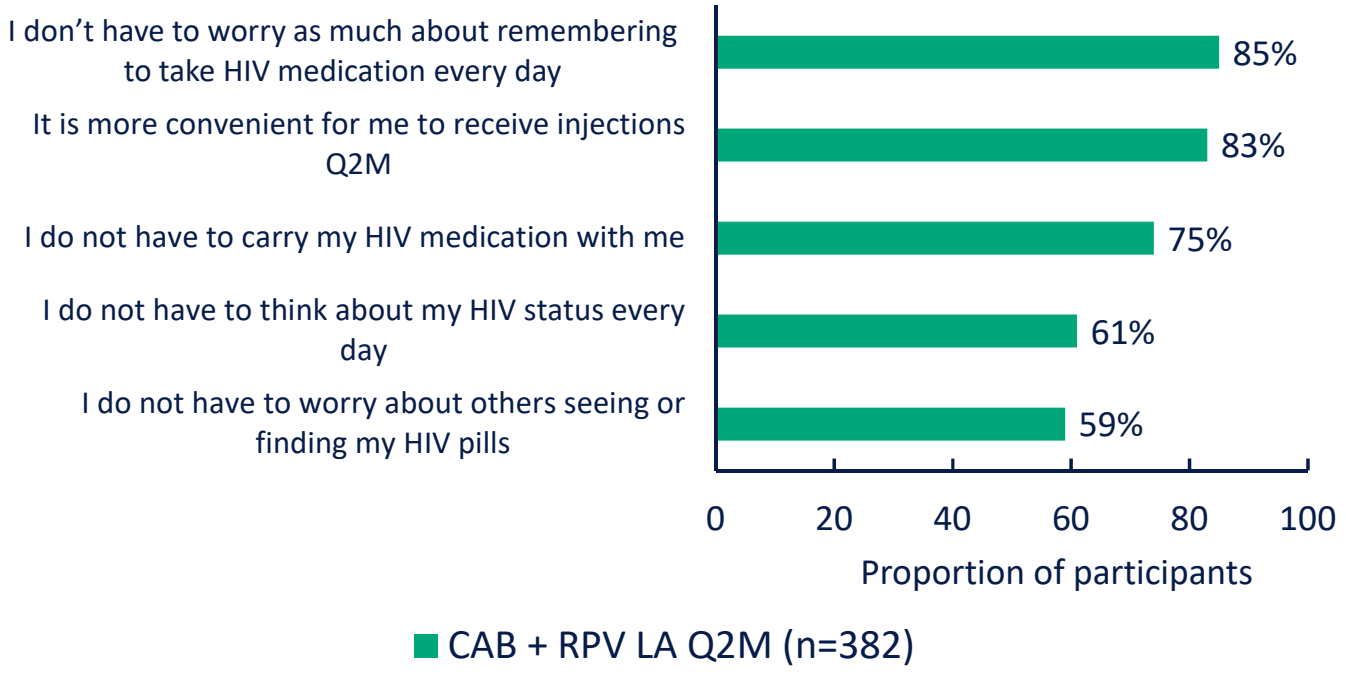
- Mean adjusted HIVTSQs scores improved significantly for CAB + RPV LA vs. BIC/FTC/TAF participants from baseline (LA, 57.88; BIC/FTC/TAF, 58.38) to Month 6 (LA, +3.86; BIC/FTC/TAF, –0.40) and Month 12 (LA, +3.36; BIC/FTC/TAF, –1.59) demonstrating greater improvement from baseline in HIV treatment satisfaction for participants receiving CAB + RPV LA compared with BIC/FTC/TAF

HIVTSQs, HIV Treatment Satisfaction Questionnaire status version.

Ramgopal et al. CROI 2023; Virtual and Seattle, WA. Oral presentation 191.

Treatment Preference and Reason for Preference*





- Overall, at the time of study withdrawal or at Month 12, 90% (n=382/425) of participants preferred CAB + RPV LA compared with 5% (n=21/425) who preferred daily oral BIC/FTC/TAF therapy

*Top five most frequently reported reasons for preference.

Ramgopal et al. CROI 2023; Virtual and Seattle, WA. Oral presentation 191.

Weight gain, or not to Weight gain…

Weight gain e Long Acting?

Risultati dallo studio **SOLAR**

Weight and Metabolic Changes With Cabotegravir + Rilpivirine Long-Acting or Bictegravir/Emtricitabine/Tenofovir Alafenamide

Darrell H. S. Tan[1], Andrea Antinori[2], Beng Eu[3], María José Galindo Puerto[4], Clifford Kinder[5], Donna Sweet[6], Cornelius N. Van Dam[7], Kenneth Sutton[8], Denise Sutherland-Phillips[8], Alessandro Berni[9], Feifan Zhang[10], William R. Spreen[8], Harmony P. Garges[8], Parul Patel[8], Ronald D'Amico[8]

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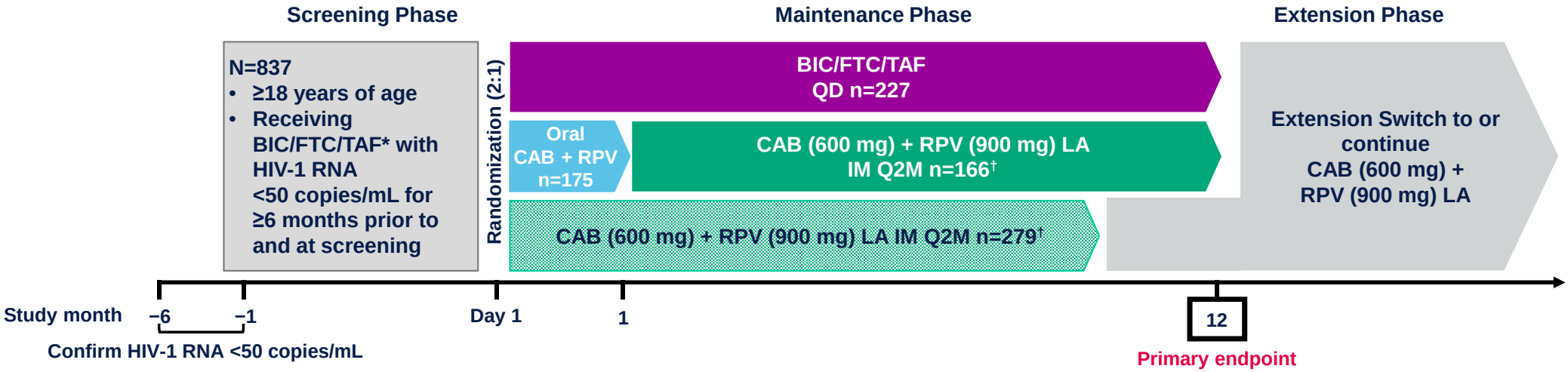
[2]HIV/AIDS Department, National Institute for Infectious Diseases, "Lazzaro Spallanzani" IRCCS, Rome, Italy; [3]Prahran Market Clinic, Prahran, Victoria, Australia;
[4]Universitat de València, Valencia, Spain; [5]AIDS Healthcare Foundation–The Kinder Medical Group, Miami, FL, United States;
[6]University of Kansas School of Medicine-Wichita, KS, United States; [7]Regional Center for Infectious Diseases, Cone Health, Greensboro, NC, United States;
[8]ViiV Healthcare, Durham, NC, United States; [9]GSK, Brentford, United Kingdom; [10]GSK, Collegeville, PA, United States

Darrell Tan, MD, PhD, reports salary support from the Canada Research Chairs Program, investigator-initiated research grants to his institution from Abbott and Gilead Sciences, Inc., and support to his institution for clinical trials sponsored by GSK

SOLAR
Design and Metabolic Objectives

Phase 3b, Randomized (2:1), Open-Label, Active-Controlled, Multicenter, Parallel-Group, Noninferiority Study



- **<u>Metabolic Objectives:</u> Changes in body weight, body mass index (BMI) category, waist and hip circumferences, waist-to-height ratio, waist-to-hip ratio,‡ and the proportion of participants with insulin resistance or metabolic syndrome§ were assessed from baseline (Day 1) to Month 11 (SWI)/12 (OLI) (hereafter referred to as Month 12)**

*A single prior integrase inhibitor regimen is allowed if BIC/FTC/TAF is a second-line regimen 6 months prior to screening. Any prior change in regimen, defined as a change of a single drug or multiple drugs simultaneously, must have occurred due to tolerability/safety, access to medications, or convenience/simplification, and must not have been done for treatment failure (HIV-1 RNA ≥400 copies/mL). †Participants randomized to the LA arm were offered an optional OLI; the decision to dose SWI or with OLI was determined by the participants following informed consent discussions with the investigator. ‡Standardized weight and anthropometric measurements were performed using circumference tapes and Tanita scales. §As defined by standard clinical criteria.

Tan et al. CROI 2023; Virtual and Seattle, WA. Slides 146.

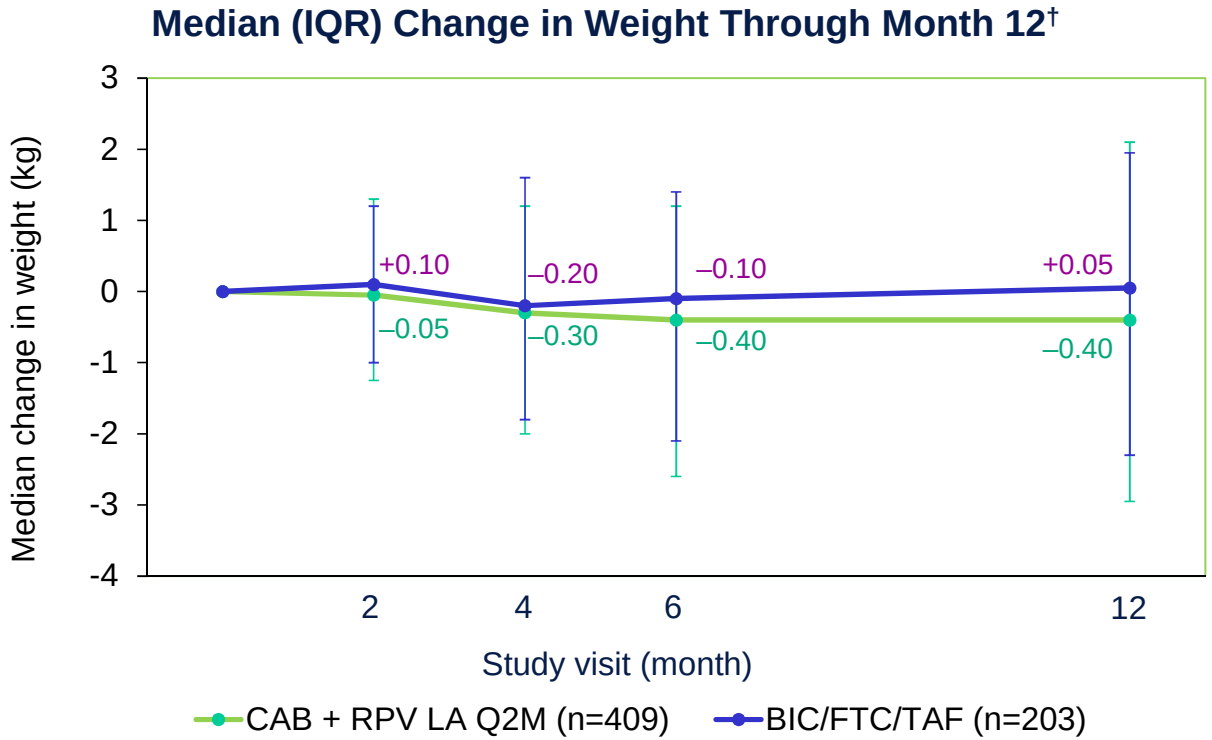
Pertinent Baseline Metabolic Parameters, Medical History, and Co-medications History

Parameter	CAB + RPV LA Q2M arm (n=454)	BIC/FTC/TAF (n=227)
BMI category, n (%)		
Underweight (<18.5 kg/m^2)	8 (2)	3 (1)
Normal (18.5–<25 kg/m^2)	175 (39)	94 (41)
Overweight (25–<30 kg/m^2)	174 (38)	78 (34)
Obesity (≥30 kg/m^2)	97 (21)	52 (23)
Baseline lipids, median (range)		
TG (mmol/L)	1.07 (0.32–20.42)	1.06 (0.38–4.01)
TC (mmol/L)	4.58 (2.25–9.66)	4.77 (2.72–8.94)
LDL (mmol/L)	2.74 (0.55–5.41)	2.77 (1.01–6.97)
HDL (mmol/L)	1.22 (0.47–2.38)	1.26 (0.60–3.06)
TC/HDL ratio	3.71 (1.45–20.55)	3.56 (1.82–8.25)
Relevant medical history, n (%)		
Hypertension	48 (11)	26 (12)
Diabetes	19 (4)	7 (3)
Relevant co-medications, n (%)		
Lipid-lowering therapy*	40 (9)	21 (9)

- In total, 59% (n=401/681) of participants were in the overweight or obesity category at baseline

*Started lipid-lowering medication during maintenance phase: CAB + RPV LA Q2M, n=17 (4%); BIC/FTC/TAF, n=8 (4%).
HDL, high-density lipoproteins; LDL, low-density lipoproteins; TC, total cholesterol; TG, triglycerides.

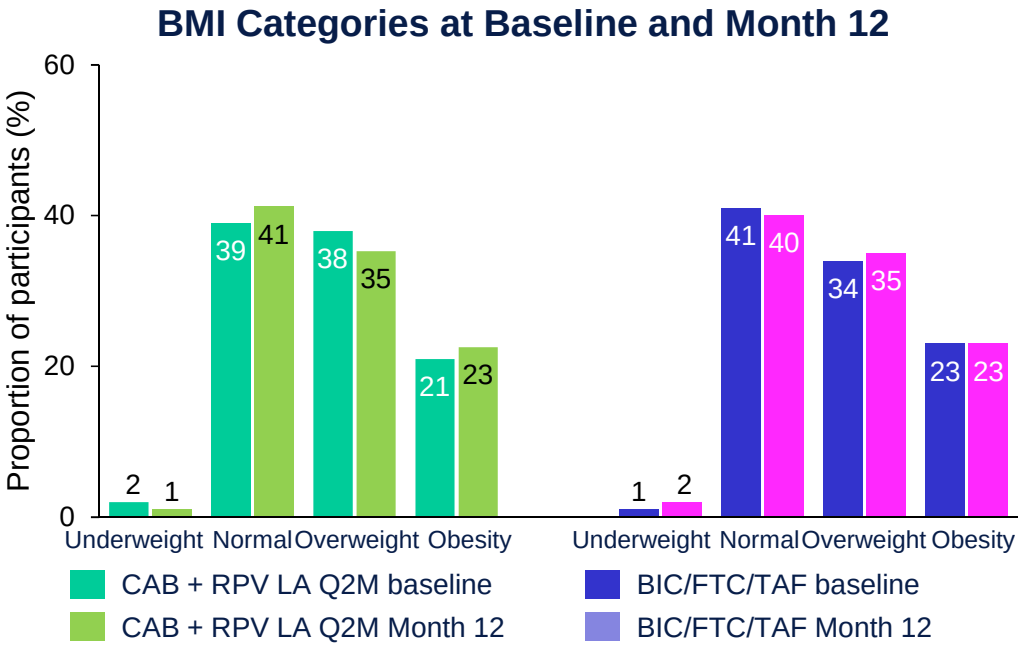
Change in Weight Through Month 12 by Treatment Regimen*

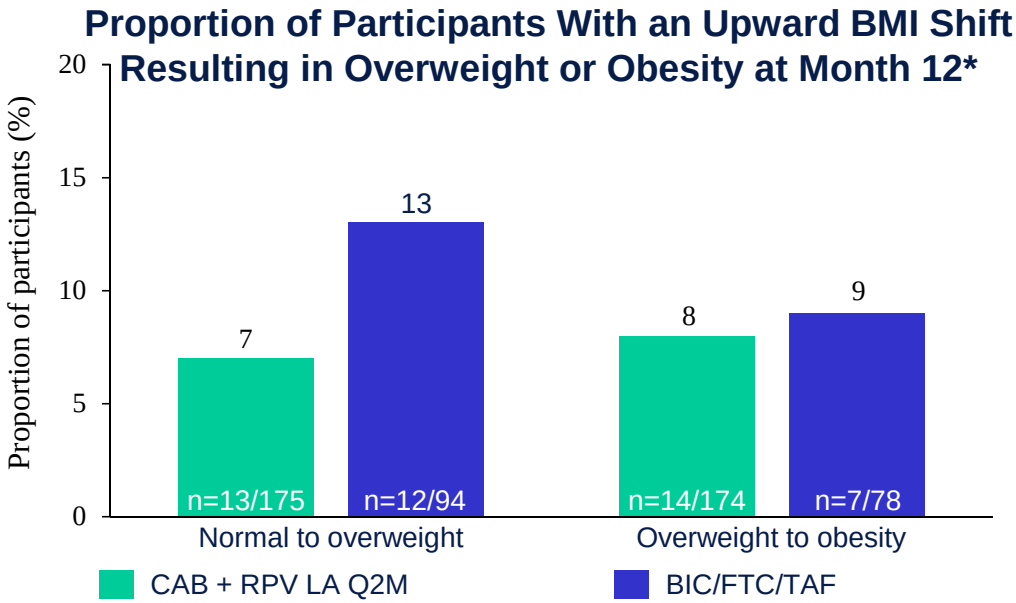


- At Month 12, median (IQR) change in weight in the CAB + RPV LA group was -0.40 (-2.95, +2.10) kg and +0.05 (-2.30, +1.95) kg in the BIC/FTC/TAF group

*Any participant that started lipid-modifying agents during the study was non-evaluable in anthropometric assessments. †Median (IQR) weight (kg) at baseline: CAB + RPV LA, 81.3 (70.70, 91.80); BIC/FTC/TAF, 79.0 (69.40, 91.70).

Change in BMI Through Month 12 by Treatment Regimen



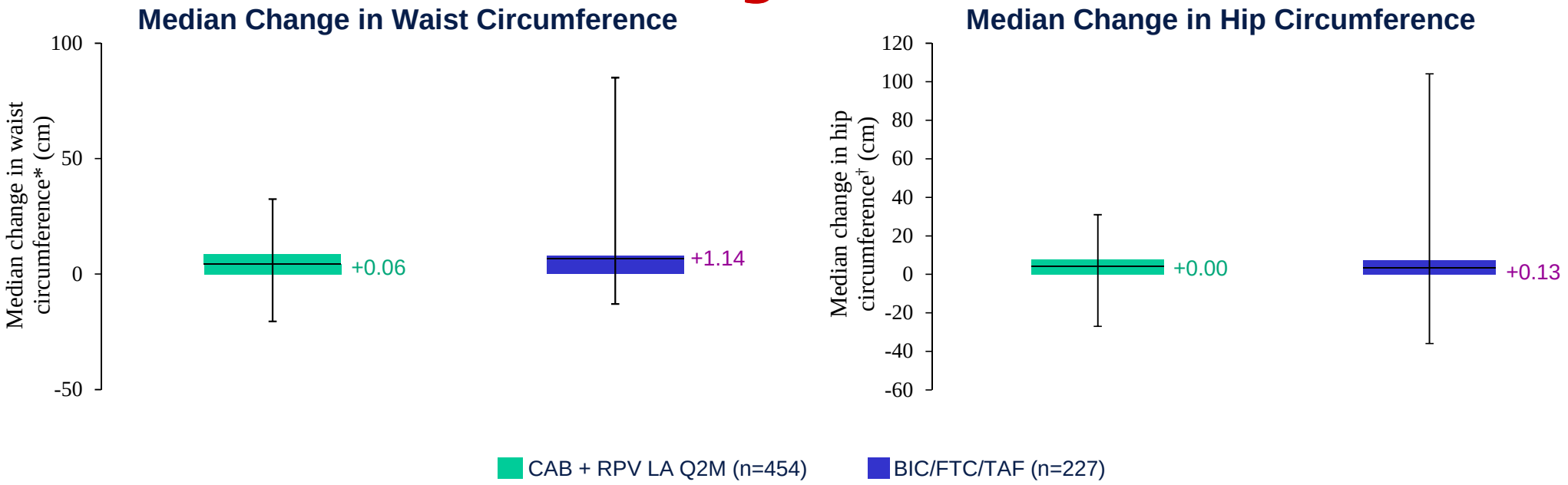


- Overall, the proportion of individuals in BMI categories remained similar at Month 12

*No participant shifted from normal to obesity or underweight to overweight.

Tan et al. CROI 2023; Virtual and Seattle, WA. Slides 146.

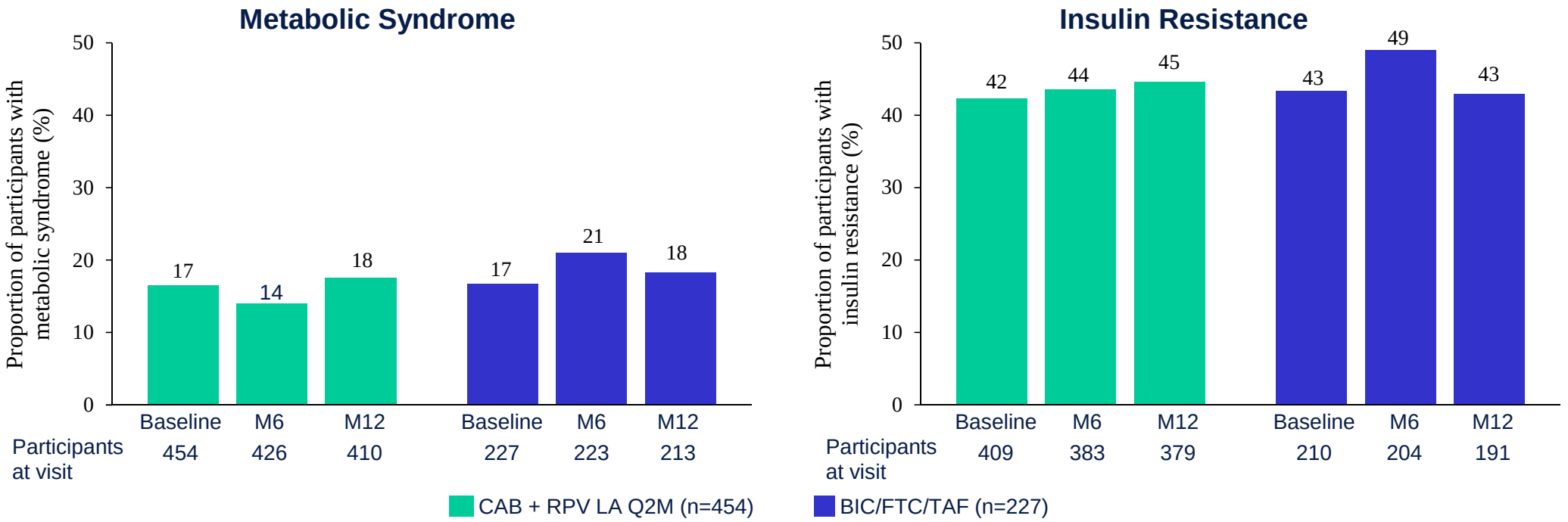
Change in Waist Circumference and Hip Circumference Through Month 12 by Treatment Regimen



- There were no clinically relevant changes from baseline to Month 12 in the median WHtR‡ (CAB + RPV LA Q2M, +0.000; BIC/FTC/TAF, +0.010) and median WHR§ (CAB + RPV LA Q2M, +0.000; BIC/FTC/TAF, +0.010)

*Median (IQR) waist circumference (cm) at baseline: CAB + RPV LA Q2M, 90.35 (82.20, 100.98); BIC/FTC/TAF, 90.00 (81.30, 101.00). †Median (IQR) hip circumference (cm) at baseline: CAB + RPV LA Q2M, 99.00 (92.00, 106.00); BIC/FTC/TAF, 97.0 (90.00, 106.68). ‡Median change (IQR): CAB + RPV LA Q2M, 0.000 (–0.020, 0.020); BIC/FTC/TAF, 0.010 (–0.020, 0.030). §Median change (IQR): CAB + RPV LA Q2M, 0.000 (–0.040, 0.040); BIC/FTC/TAF, 0.010 (–0.030, 0.040).
WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

Metabolic Syndrome* and Insulin Resistance† Through Month 12 by Treatment Regimen



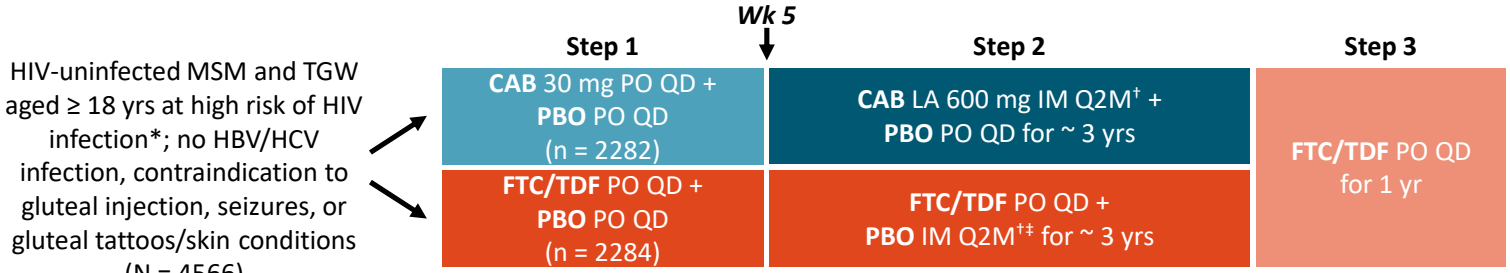
- There were no clinically relevant changes from baseline to Month 12 in the proportion of participants with metabolic syndrome or insulin resistance in either arm

*Three abnormal findings out of the following five qualifies a person for metabolic syndrome: elevated waist circumference (females: ≥88 cm [≥35 in]; males: ≥102 cm [≥40 in]), elevated triglycerides (≥150 mg/dL [1.7 mmol/L]), reduced HDL-C (females: <50 mg/dL [1.3 mmol/L]; males: <40 mg/dL [1.0 mmol/L]), elevated blood pressure (meeting either or both criteria; systolic ≥130 and/or diastolic ≥85 mmHg), and elevated fasting glucose (≥100 mg/dL). †HOMA-IR ≥2.
HDL-C, high-density lipoprotein cholesterol; HOMA-IR, Homeostasis Model of Assessment-Insulin Resistance.

Cabotegravir as PREP: HPTN 083

HPTN 083: Study Design

- International, randomized, double-blind phase IIb/III study
  - At interim analysis on May 14, 2020, with 25% of endpoints accrued, DSMB recommended termination of blinded study due to crossing of prespecified O'Brien-Fleming stopping bound

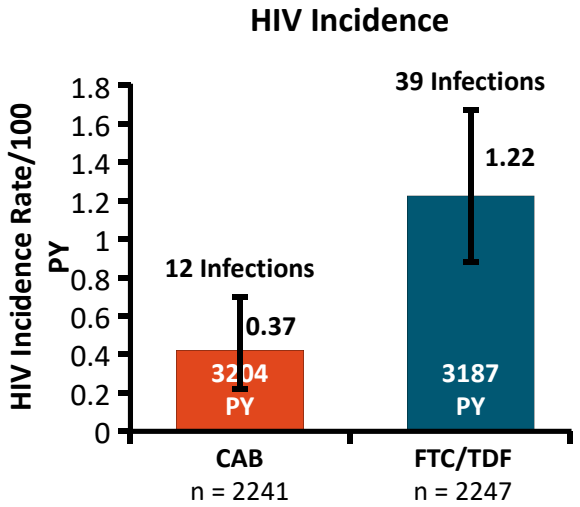


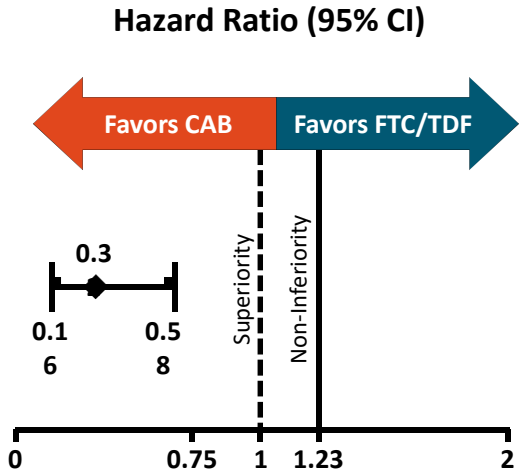
*Any noncondom receptive anal intercourse, > 5 partners, stimulant drug use, incident rectal or urethral STI or incident syphilis in past 6 mos; or SexPro Score ≤ 16 (US only). †First 2 doses given in Wks 5 and 9, then every 2 mos thereafter. ‡PBO for CAB injection was a 20% intralipid solution.

- Primary endpoints: incident HIV infections, grade ≥ 2 clinical and laboratory events
- Analysis of HIV infections in CAB arm: group A) HIV positive test at study enrollment; group B) no recent CAB exposure; group C) Infected during CAB oral lead-in period; group D) Infected in setting of on-time CAB injections

Marzinke. CROI 2021. Landovitz. AIDS 2020. Abstr OAXLB0101. Abstr 153. NCT02720094.

HPTN 083: HIV Incidence





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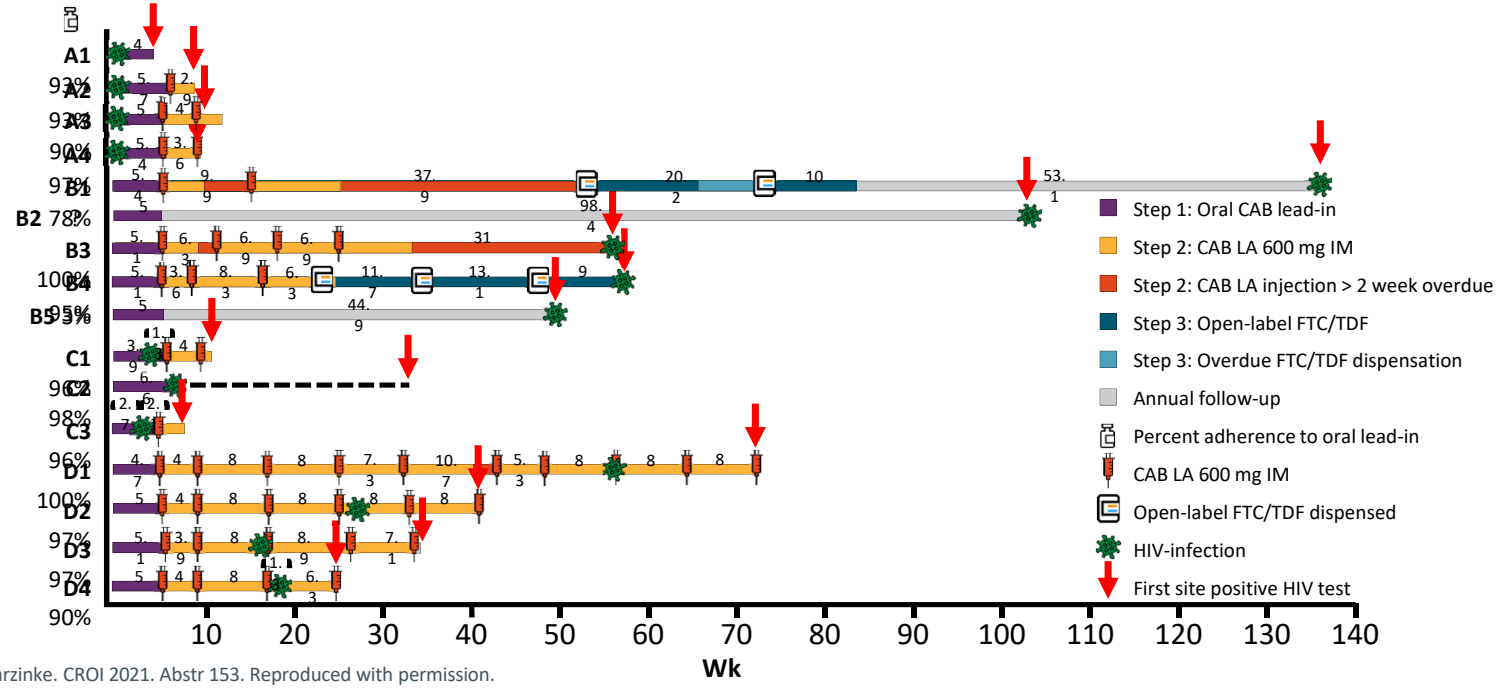
HPTN 083: HIV Infections in Cabotegravir Arm

- 4 baseline and 12 incident HIV infections observed in CAB arm



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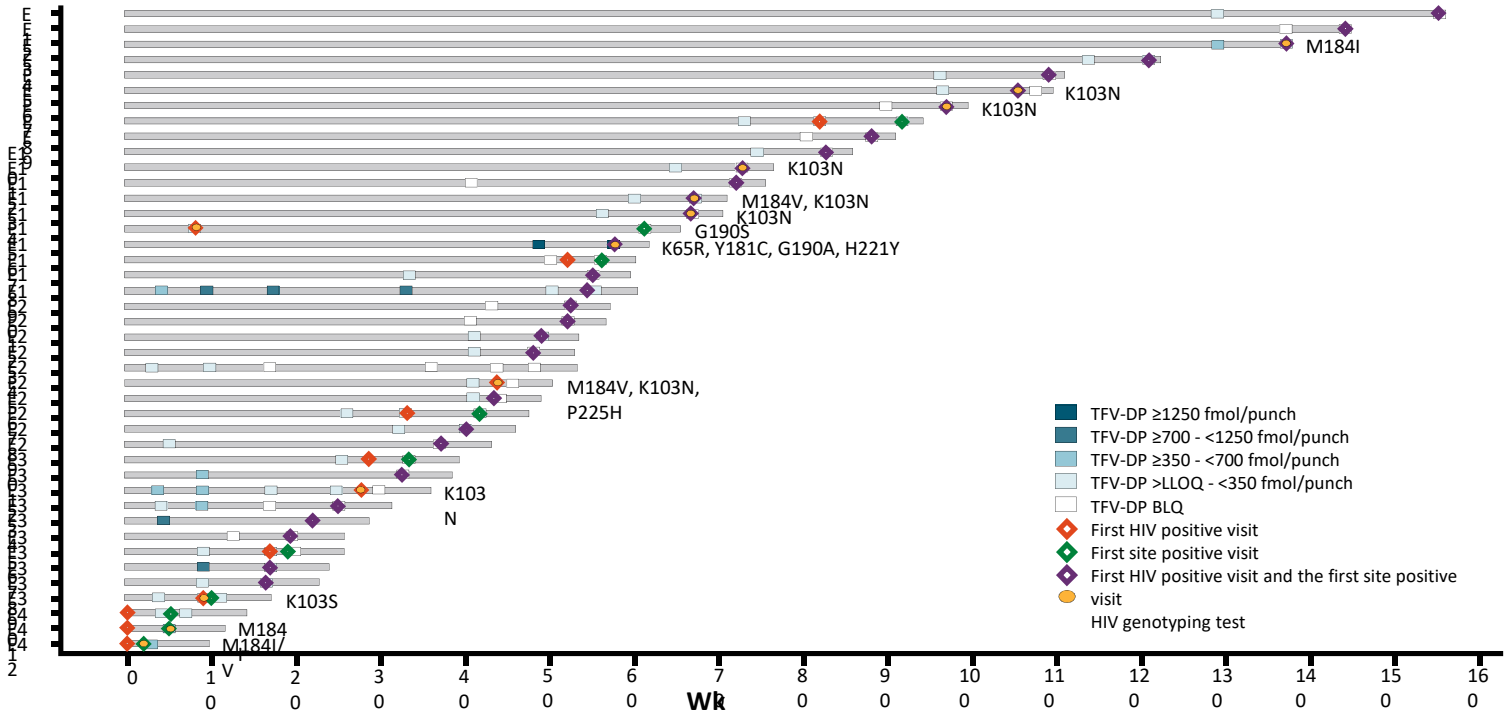
HPTN 083: HIV Infections in FTC/TDF Arm



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HPTN 083: HIV Infections and Resistance Mutations

- **CAB: 16 infections, 12 incident**
  - 7/16 had RAMs
    - 5 had integrase RAMs (Q148R or Q148 with accessory mutations; or R263K); 1 also had a NNRTI RAM
    - 1 had NNRTI RAMs only
    - 1 had NNRTI and NRTI RAMs
  - Retrospective HIV-1 RNA testing identified infection earlier than Ag/Ab testing on study
- **FTC/TDF: 42 infections, 39 incident**
  - 37/39 incident infections in non-adherent participants or those with suboptimal drug concentrations
  - 13/42 had RAMs:
    - 7 to NNRTI RAMs only
    - 3 had NNRTI and NRTI RAMs
    - 3 had NRTI RAMs only

Marzinke. CROI 2021. Abstr 153.

LEVI

The LEVI Syndrome: Characteristics of early HIV infection with cabotegravir for PrEP

Susan Eshleman, MD/PhD
Johns Hopkins University School of Medicine
February 21, 2023

HPTN
HIV Prevention Trials Network

@ CROI 2023

HPTN 083 – CAB arm HIV infections

6 infections occurred despite on-time injections
among 2,282 participants randomized to CAB-LA

Type of case	# Cases
Infected despite on-time injections	**6**
28 other infections	
No recent CAB exposure (within 6 months)	16
HIV+ at enrollment	4
Infected while receiving oral CAB	3
Infected after ≥ 1 delayed injection	3
Infected near the time of CAB re-initiation	2

Delayed detection of HIV infection

- HIV rapid tests and Ag/Ab tests often fail to detect HIV infection in the setting of CAB-LA PrEP
- Viral suppression and delayed/diminished Ab expression can persist for months after infection, even after injections are discontinued

Delayed detection of HIV infection
→ Unnecessary CAB-LA injections
→ Delayed ART initiation
→ Potential to impact personal health or on-going HIV transmission
→ Emergence of INSTI resistance

- In HPTN 083, detection of infection was delayed in ~½ of the CAB arm infections
- This was rarely observed when infection occurred > 6 months after CAB administration

Comparison of acute HIV infection (AHI) to infections that occur in the setting of long-acting early viral inhibition (LEVI)

	AHI	LEVI
Cause	Phase of natural HIV infection	Long-acting anti-viral PrEP agent (prototype: CAB-LA)
Onset	New infection	Infection during PrEP Initiation of PrEP agent during acute/early infection
Viral replication	Explosive	Smoldering
Symptoms	Fever, chills, rash, night sweats, muscle aches, sore throat, fatigue, swollen glands	Minimal, variable, often no symptoms reported
Detection	Ag/Ab assay, RNA assays (including less sensitive POC and pooled tests), DNA assays, total nucleic acid assays	Ultrasensitive RNA assay (often low or undetectable RNA, low/undetectable DNA, diminished/delayed Ab production)
Assay reversion	Rare	Common for many test types
Duration	1-2 weeks (until Ab detection)	Months (until viral breakthrough, drug clearance, or ART start); can persist months after the anti-viral agent is discontinued
Transmission	Very likely	Unlikely (except possibly through blood transfusion)
Drug resistance	No (unless transmitted)	Yes (can emerge early when viral load is low)

INSTI resistance

In HPTN 083, INSTI resistance emerged in 10/18 cases with CAB administration within 6 months of the 1st HIV positive visit

INSTI resistance was not observed when the 1st HIV positive visit was >6 months after CAB administration

Retrospective testing with a sensitive RNA assay detected most infections before INSTI resistance emerged

HIV RNA screening

RNA testing can be used to screen for HIV infection with CAB-LA PrEP

- Included in the US FDA package insert
- Recommended by the US CDC
- Not included in the WHO guidelines

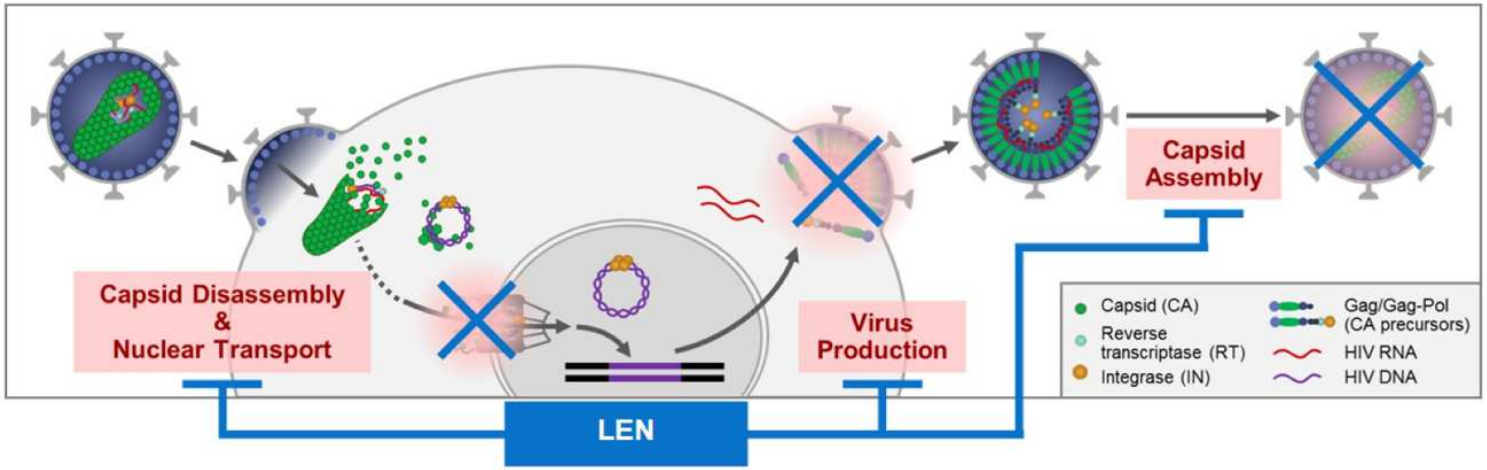
We are evaluating the use of RNA screening in the on-going 083 and 084 open-label studies

Further research is needed to evaluate the pros and cons of HIV RNA screening with CAB-LA PrEP

Lenacapavir

New options

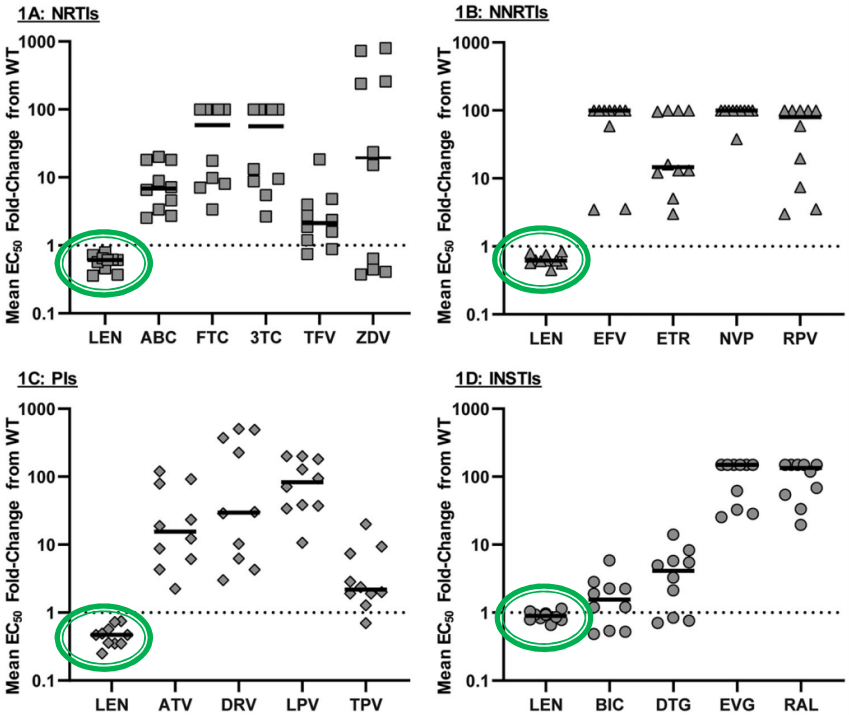
Lenacapavir → targets HIV capsid



- First-in-class capsid (CA) inhibitor
- Picomolar potency (EC50 = 50pM)
- LEN inhibits CA-mediated nuclear entry of HIV DNA, HIV assembly and proper capsid formation

Margot, Glasgow 2020

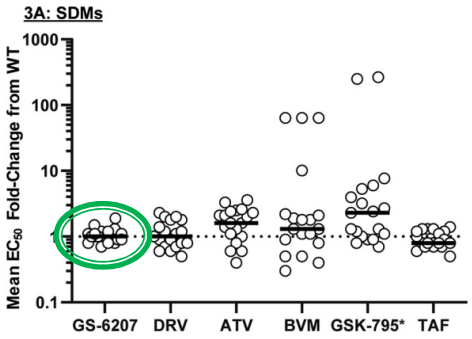
New options
Lenacapavir



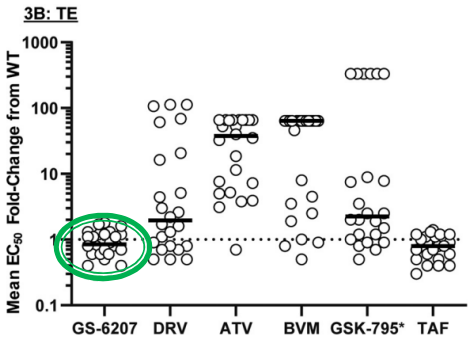
- Activity of LEN in **mutants resistant to other drug classes**
- HIV mutations were inserted into the pXXLAI clone, and the resulting mutants (*n* = 40) were evaluated using a 5-day antiviral assay

Margot, Antimicrobial Agents Chemother 2021

New options
Lenacapavir



Site-directed mutants



Clinical isolates from treatment experienced subjects

*The maturation inhibitor GSK3532795 was discontinued

- Activity of LEN in mutants with **Gag cleavage site mutations**
- HIV mutations were inserted into the pXXLAI clone, and the resulting mutants (*n* = 43) were evaluated using a 5-day antiviral assay

Margot, Antimicrobial Agents Chemother 2021

New options
Lenacapavir

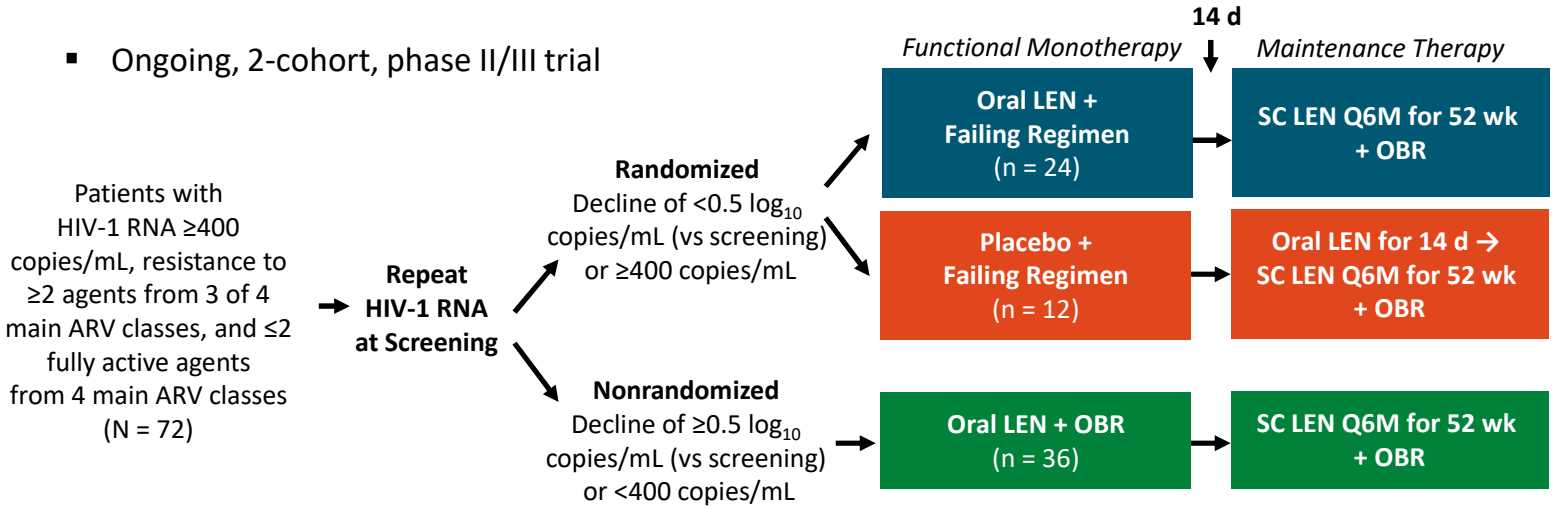
HIV-1 subtype distribution	ART naive (*N* = 500), % (*n*)	ART experienced without PI use (*N* = 500), % (*n*)	ART experienced with history of PI failure (*N* = 500), % (*n*)
B	37 (185)	42 (210)	56 (280)
CRF02_AG	46 (230)	48 (240)	37 (185)
F1	4.6 (23)	2.4 (12)	—
CRF06	4.4 (22)	3.8 (19)	3.4 (17)
A1	2.8 (14)	—	—
D	2.2 (11)	2.2 (11)	1.6 (8)
Other non-B	3.0 (15)	1.6 (8)	1.0 (5)

- CA mutations conferring resistance to LEN in vitro (**L56I, M66I, Q67H, K70N, N74D, N74S, T107N**) evaluated in 1500 patients
  - 500 ART naïve
  - 500 PI naïve ART experienced
  - 500 with history of PI failure
- **None detected**

Marcelin, J Antimicrob Chemother 2020

CAPELLA study design

- Ongoing, 2-cohort, phase II/III trial



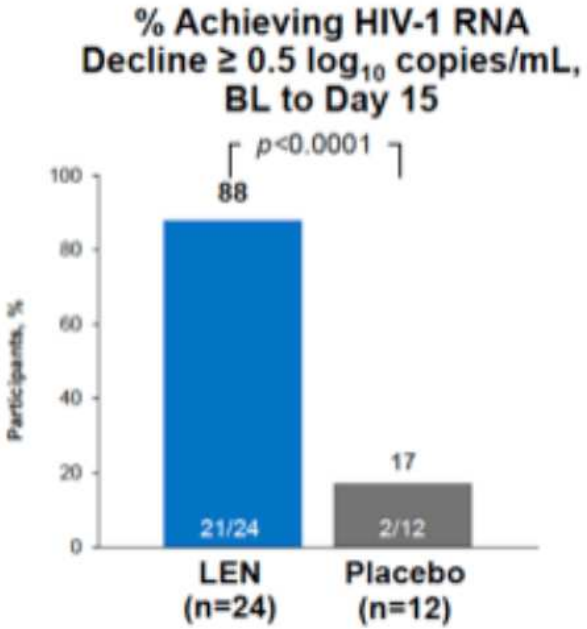
Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8; SC LEN administered as 927 mg (2 x 1.5 mL) in the abdomen on Day 15 and Q6M thereafter.

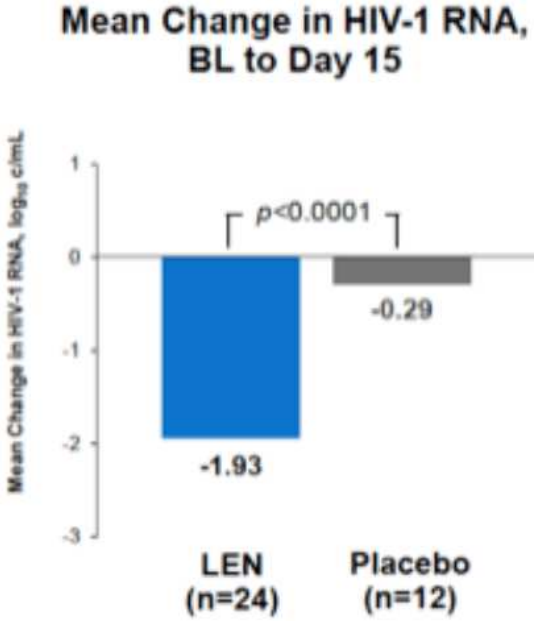
- Primary endpoint achieved in prior analysis: ≥0.5 $\log_{10}$ copies/mL decline in HIV-1 RNA at Day 14 in randomized cohort
- Secondary endpoints: HIV-1 RNA <50 copies/mL, <200 copies/mL at Week 26 in randomized cohort

Molina. IAS 2021. Abstr OALX01LB02.

Slide credit: clinicaloptions.com

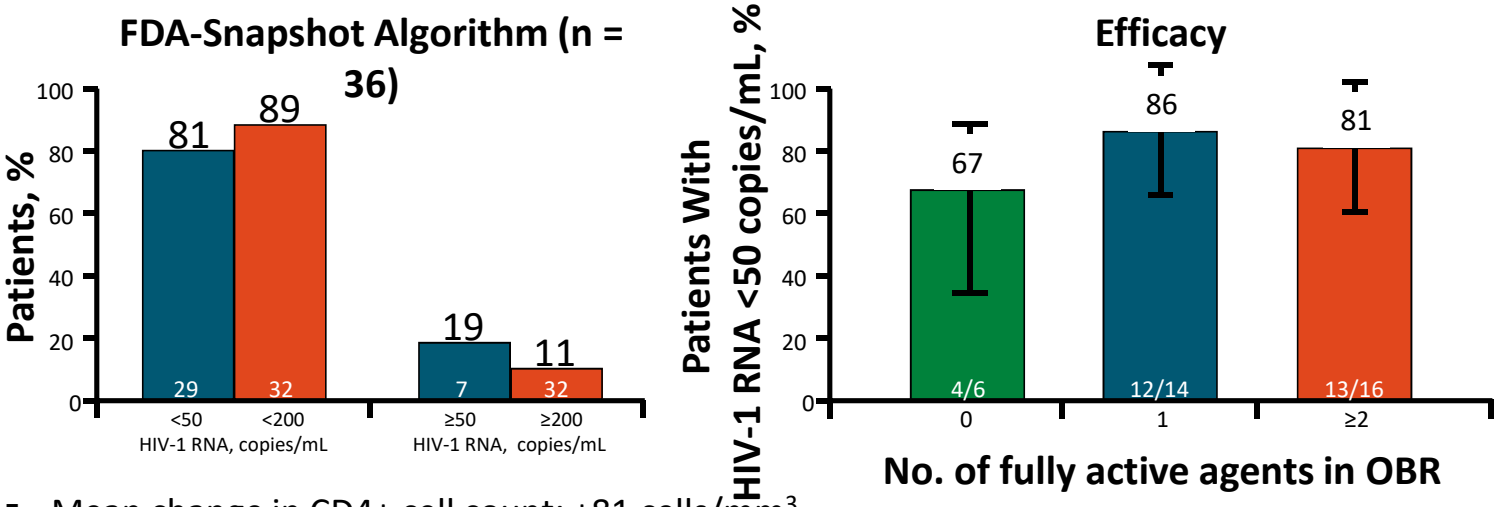
CAPELLA study primary endpoint: HIV-1 RNA decline ≥0.5 log by day 15





Rhee, HIV DART 2020

CAPELLA study secondary endpoint: Efficacy at Week 26 in Randomized Cohort



- Mean change in CD4+ cell count: +81 cells/mm^3
- Incidence of very low CD4+ cell count (<50 cells/mm^3) decreased from 22% (8/36) at baseline to 0% (0/34) at Week 26

Molina. IAS 2021. Abstr OALX01LB02. Reproduced with permission.

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CAPELLA: emergent LEN resistance

Outcome, n (%)	Randomized Cohort (n = 36)
Patients meeting criteria for resistance testing*	11 (31)
No emergent LEN resistance	7 (19)
Emergent LEN resistance	4 (11)
▪ M66I	4
▪ Q67H	1
▪ K70N/R/S	1
▪ N74D	1

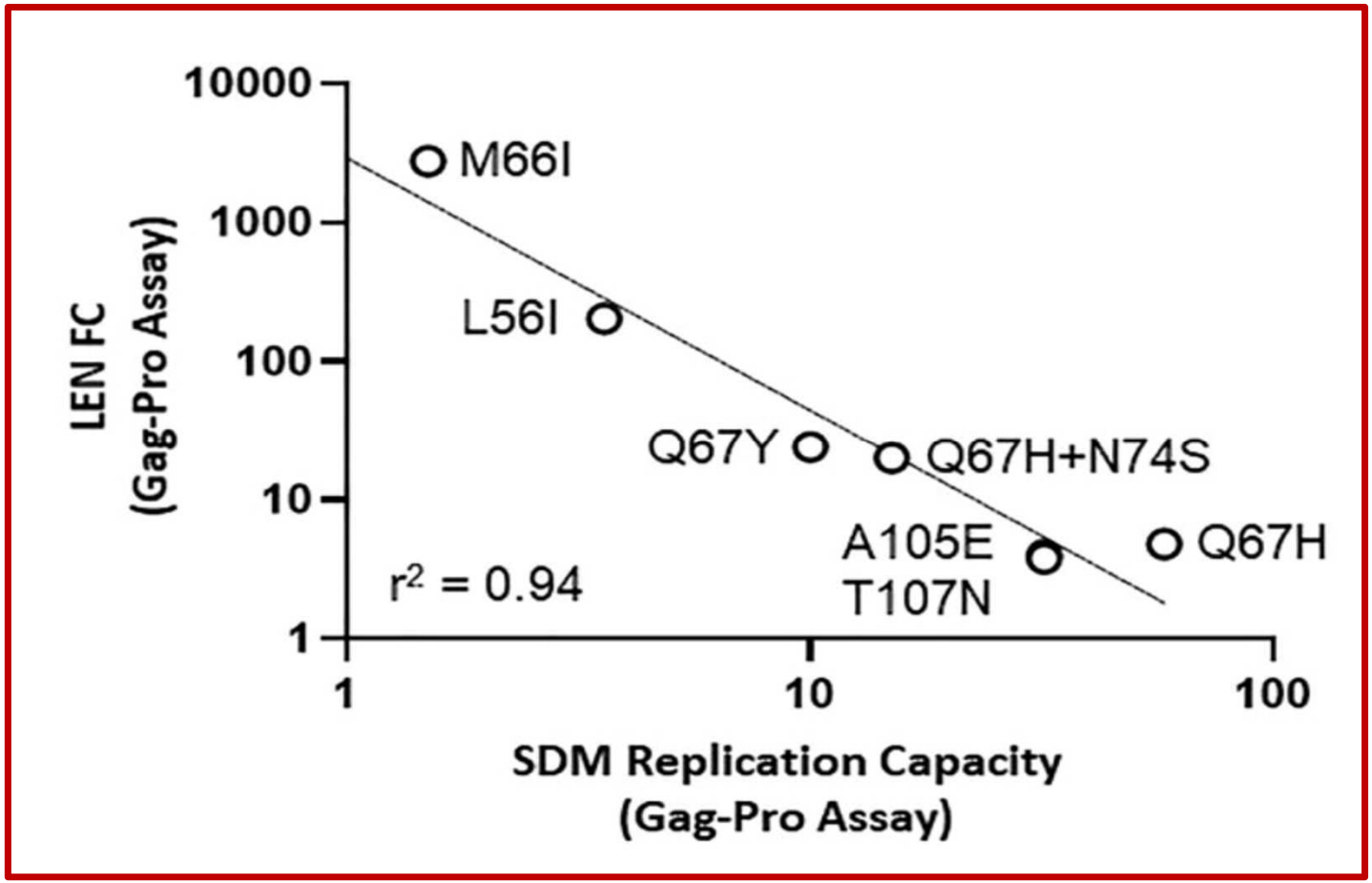
* Capsid genotypic and phenotypic resistance testing performed in any patients with HIV-1 RNA ≥50 copies/mL and <1 $\log_{10}$ HIV-1 RNA decrease from Day 1
at Week 4 appt, at any appt after attaining HIV-1 RNA <50 copies/mL and rebound to ≥50 copies/mL, and at any appt with >1 $\log_{10}$ increase from nadir. If suboptimal virologic response or rebound were confirmed: HIV-1, reverse transcriptase, protease, and integrase genotypic and phenotypic testing were done.

Molina. IAS 2021. Abstr OALX01LB02.

- All 4 patients with emergent LEN resistance remained on LEN
  - 3 patients achieved HIV-1 RNA resuppression at a later visit, 2 without and 1 with OBR change
  - 1 patient with no fully active agents never achieved suppression (max decline in HIV-1 RNA: 1.7 $\log_{10}$ copies/mL)
- No patients developed additional resistance to OBR agents

Slide credit: clinicaloptions.com

Correlation between replication capacity and fold change in lenacapavir susceptibility in the Gag-Pro assay.



N. Margot, JAC 2021

Lenacapavir with bNAbs Teropavimab (GS-5423) and Zinlirvimab (GS-2872) Dosed Every 6 Months in People with HIV

[1]Joseph Eron, [2]Susan J. Little, [3]Gordon Crofoot, [4]Paul Cook, [5]Peter J. Ruane, [6]Dushyantha Jayaweera, [7]Edwin DeJesus, [8]Sarah E. Waldman, [9]Megha L. Mehrotra, [9]Laurie VanderVeen, [9]Hailin Huang, [9]Sean Collins, [9]Jared Baeten, [10]Marina Caskey

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Presenting Author Disclosure: Joseph Eron is a consultant with Gilead Sciences, Inc., ViiV Healthcare, and Merck. He is also an investigator for Gilead Sciences, Inc., and ViiV Healthcare.

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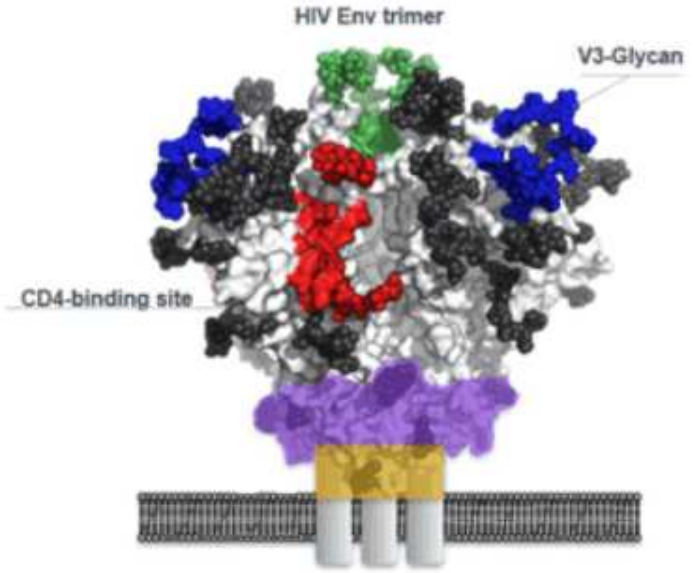
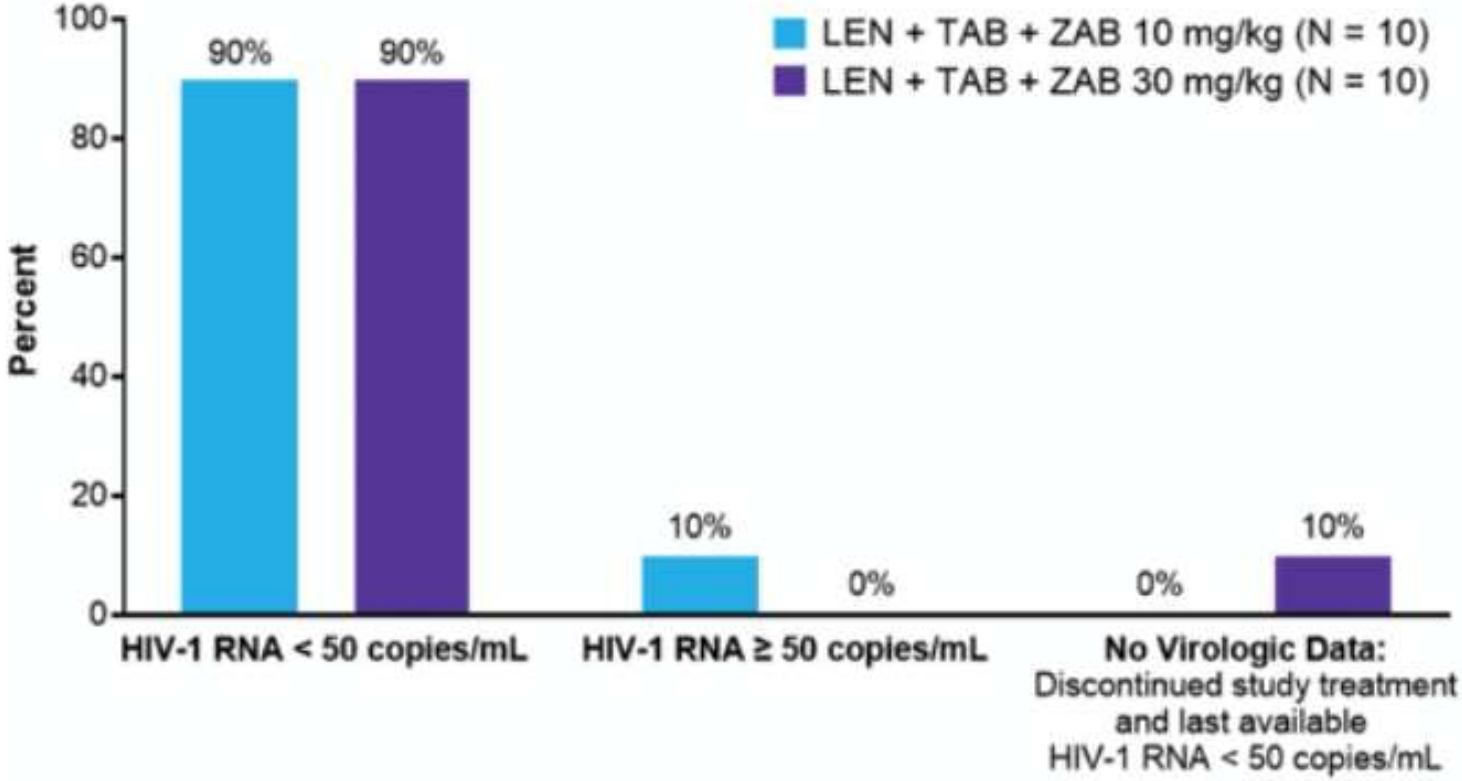


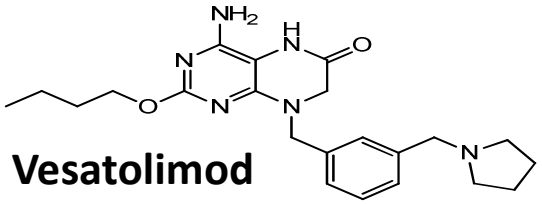
Virologic Efficacy Outcomes at Week 26 by FDA Snapshot Algorithm



- 18 out of 20 participants maintained viral suppression on study regimen through Week 26.
- One participant withdrew[1] at Week 12 with HIV-1 RNA < 50 copies/mL.
- One participant had a confirmed virologic rebound at Week 16 and was resuppressed on baseline oral ART.

[1] Participant withdrew due to personal decision.

TLR7 Agonist Vesatolimod (VES, GS-9620)



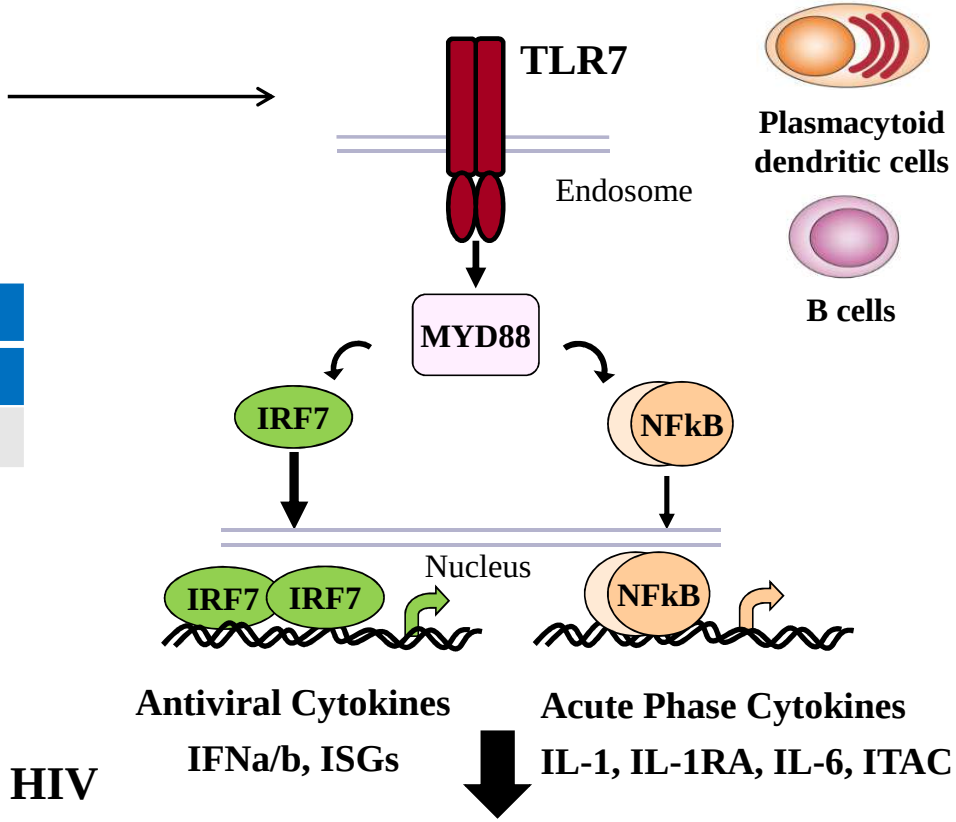
Vesatolimod (GS-9620)

	EC_{50} (nM)		TLR7 Fold
	TLR7	TLR8	Selectivity
GS-9620 (clinical)	130	4100	32

- **Selective, orally bioavailable**
- **Completed clinical trials: Phase 1/1b**
  - Healthy volunteers
  - HIV/ART suppressed

VES is selective for TLR7 and stimulates immunity to HIV through plasmacytoid dendritic cell production of type I IFNs; clinical trials are ongoing

A Tsai, et al. J Virol 2017;91(8):e02166-16
R Ram, et al. CROI 2019. Seattle, WA. Poster 370

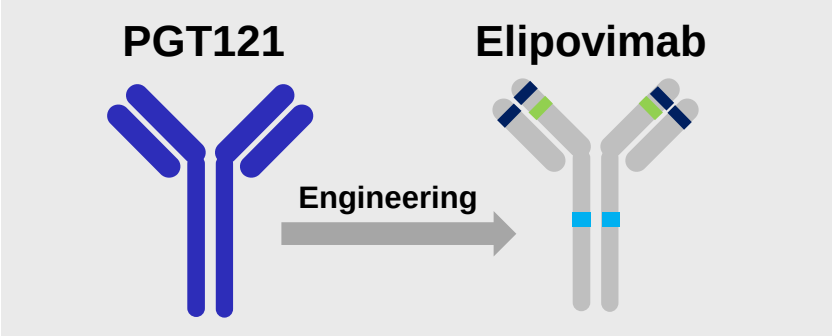


Activate CD4 T cells
Activate CD8 T cells, NKs, monocytes, APCs

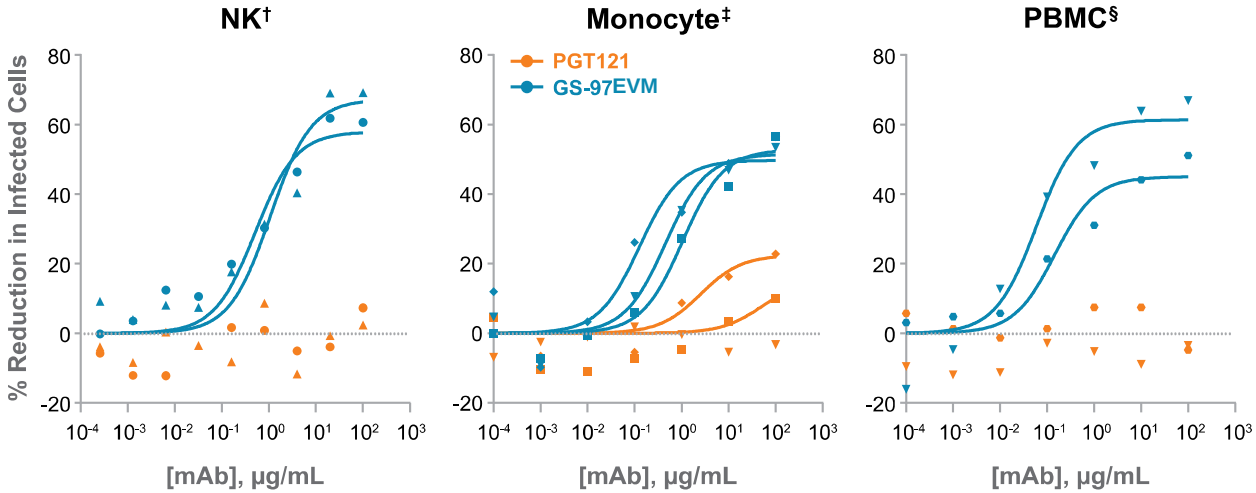
Elipovimab, an effector-enhanced bNAb for HIV cure

- bNAb combinations are being developed to directly target and kill latently HIV-infected cells
- Elipovimab, formerly known as GS-9722, is an engineered variant of human Ab PGT121 with
  - Similar neutralization breadth and potency
  - Improved manufacturability
  - Reduced immunogenicity
  - Enhanced killing
  - Improved pharmacokinetics

Elipovimab demonstrates *in vitro* enhanced effector-cell-mediated killing of HIV-infected cells



Cell-Mediated Killing of HIV-Infected Cells



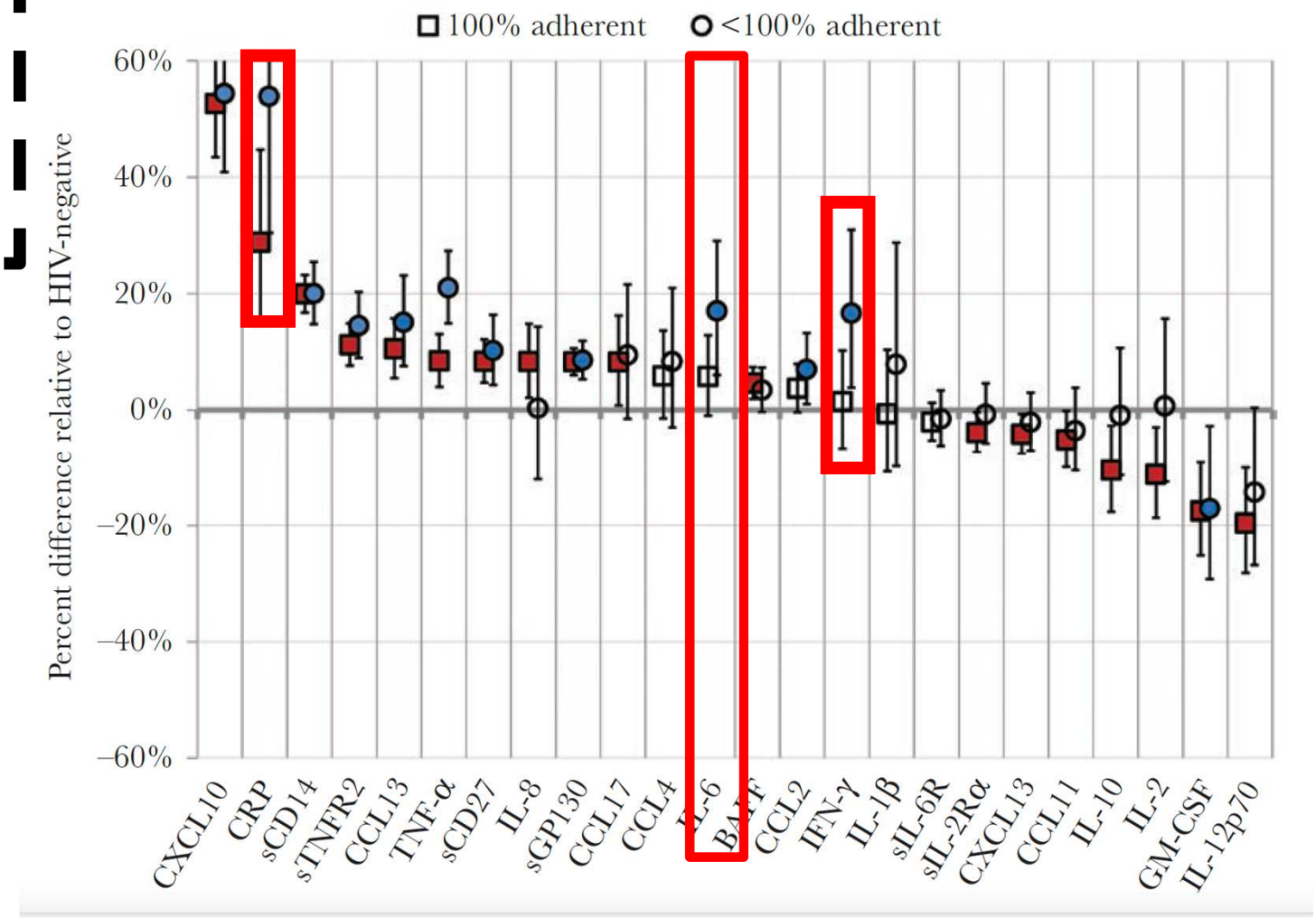
*Effector and target cells were isolated from healthy donors (*symbols* represent different donors); †Target: CD4 T-cell line (CEM.NKr.CCR5+Luc+) infected with HIV isolate 92US657; ‡Target: primary human CD4 T cells infected with HIV isolate 92US657;
§Target: primary human CD4 T cells infected with HIV isolate 92HT593.

P Ruane, et al. CROI 2020. Boston, MA. Oral 39

Low adherence and residual inflammation?

Person-visits (2565 from MWH reporting 100% ART adherence and 1588 from HIV-uninfected men) from a total of 1469 men

100% self-reported adherence: no missed ART in the past 4 weeks



Castillo-Mancilla OFID 2020

Inflammatory Markers After Switching to Cabotegravir + Rilpivirine Long-Acting vs. Continuing Bictegravir/Emtricitabine/ Tenofovir Alafenamide: Data From the Phase 3b SOLAR Study

Emilie Elliot,[1] David Baker,[2] Eisuke Adachi,[3] Jorge Rodriguez,[4] Marta Montero Alonso,[5] Giuliano Rizzardini,[6] Parul Patel,[7] Christine L. Latham,[7] Denise Sutherland-Phillips,[7] Rimgaile Urbaityte,[8] Kenneth Sutton,[7] Harmony P. Garges,[7] Kimberly Smith,[7] Bryan Baugh,[9] Ronald D'Amico,[7] Jean van Wyk[1]

[1]ViiV Healthcare, Brentford, UK; [2]East Sydney Doctors, Darlinghurst, Sydney, Australia; [3]The Institute of Medical Science, The University of Tokyo Hospital, Tokyo, Japan; [4]Global Research Institute, Los Angeles, CA, USA; [5]La Fe University and Polytechnic Hospital, Valencia, Spain; [6]Department of Infectious Diseases, Fatebenefratelli Sacco Hospital, Milan, Italy & School of Clinical Medicine, Faculty of Health Science, University of the Witwatersrand, Johannesburg, South Africa; [7]ViiV Healthcare, Durham, NC, USA; [8]GSK, London, UK; [9]Janssen Research & Development, Titusville, NJ, USA

12th IAS Conference on HIV Science; July 23-26, 2023; Brisbane, Australia

Methods

- Data were stratified by sex at birth (male or female), BMI (≥30, <30 kg/m^2), and age (<35, 35–<50, and ≥50 years)
- Key inflammatory markers (serum interleukin-6 [**IL-6**], C-reactive protein [**CRP**], platelet-poor plasma **D-dimer**, **CD4/CD8 ratio**, and soluble [s] **sCD14 and sCD163**) were measured at baseline and Month 12 and were compared between treatment arms and subgroups
  - IL-6 and CRP are potential biomarkers of HIV-related inflammation[1]
  - D-dimer is a marker of atherogenesis and hypercoagulation[1]
  - CD4/CD8 ratio is an established marker of immune reconstitution[1]
  - sCD14 and sCD163 are biomarkers of monocyte and macrophage activation, used for research purposes.[1] They are potential surrogate indicators of ongoing HIV replication below typical limits of viral load quantification
- Comparisons between CAB + RPV LA Q2M and BIC/FTC/TAF for the overall population were analyzed based on a mixed model for repeated measures with visit as the repeated factor and adjustment for demographic parameters*

*Adjusted for age (continuous), race, baseline BMI, sex at birth, smoking status, and hepatitis C co-infection.

1. Llibre et al. *Open Forum Infect Dis*. 2022;9:ofac068.

Baseline Characteristics

- Of 681 participants, 454 (67%) switched to LA and 227 (33%) continued BIC/FTC/TAF
  - Overall, 18% of the total population were female (sex at birth), 20% were aged ≥50 years, and 22% had a BMI ≥30 kg/m^2

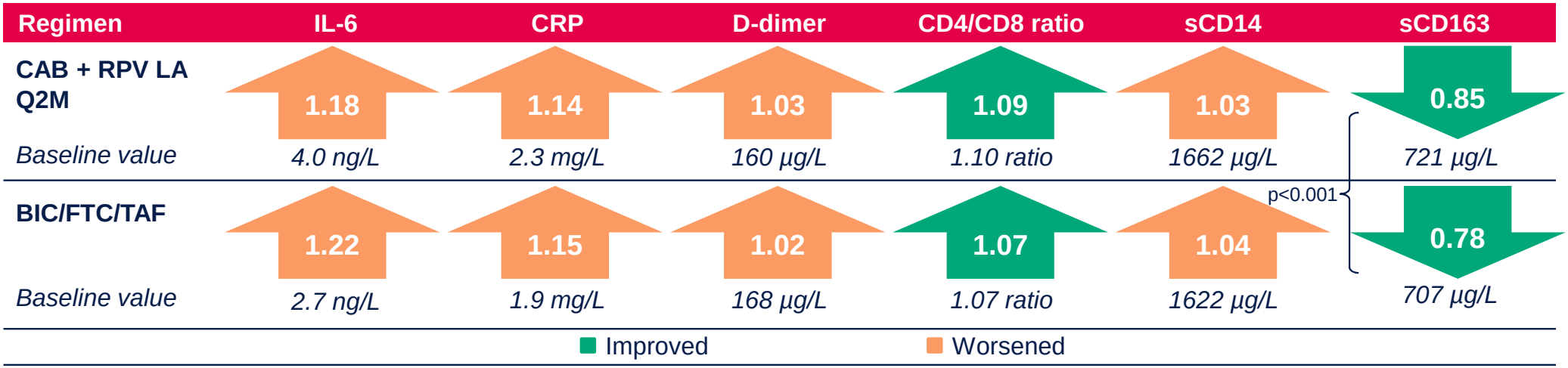
ITT-E population	CAB + RPV LA Q2M (n=454)	BIC/FTC/TAF (n=227)
Median age (range), years	37 (18–74)	37 (18–69)
<35 years, n (%)	192 (42)	99 (44)
35–<50 years, n (%)	173 (38)	83 (37)
≥50 years, n (%)	89 (20)	45 (20)
Female (sex at birth), n (%)	79 (17)	41 (18)
Race, n (%)		
Black	96 (21)	49 (22)
White	313 (69)	160 (70)
Asian	23 (5)	11 (5)
Other races*	22 (5)	7 (3)
BMI (kg/m^2), median (IQR)	26.0 (23.2–29.3)	25.4 (23.6–29.6)
≥30 kg/m^2, n (%)	97 (21)	52 (23)
CD4$^+$ cell count (cells/mm^3), median (IQR)	650 (479–850)	630 (458–842)
Duration of prior ART (years), median (IQR)†	2.6 (1.6–4.9)	2.5 (1.5–4.7)
Duration of prior BIC/FTC/TAF (years), median (IQR)†	1.7 (1.2–2.2)	1.6 (1.2–2.1)

*Other race participants: American Indian or Alaska Native, n=14 (CAB + RPV LA Q2M) and n=2 (BIC/FTC/TAF); Native Hawaiian or other Pacific Islander, n=1 (BIC/FTC/TAF); multiple, n=8 (CAB + RPV LA Q2M) and n=4 (BIC/FTC/TAF).
†BIC/FTC/TAF must have been the participant's first or second regimen. If BIC/FTC/TAF was the second regimen, the first regimen must have been an INSTI-based regimen.
Numbers represent the modified ITT-E population (CAB + RPV LA, n=447; BIC/FTC/TAF, n=223).
ART, antiretroviral therapy; BIC/FTC/TAF, bictegravir/emtricitabine/tenofovir alafenamide; BMI, body mass index; CAB, cabotegravir; IQR, interquartile range; INSTI, integrase strand transfer inhibitor; ITT-E, intention-to-treat exposed; LA, long-acting; Q2M, every 2 months; RPV, rilpivirine.

Elliot et al. IAS 2023; Brisbane, Australia. Poster TUPEB04.

Model-Adjusted Geometric Mean Treatment Ratios for Inflammatory Marker Changes From Baseline to Month 12*

- There were no significant differences between treatment arms in change from baseline for serum IL-6, CRP, D-dimer, CD4/CD8 ratio, or sCD14
- sCD163 was within the normal reference range in both treatment arms at baseline and improved (decreased) in both arms over 12 months, with a statistically slightly greater change in the BIC/FTC/TAF group (~50 units)

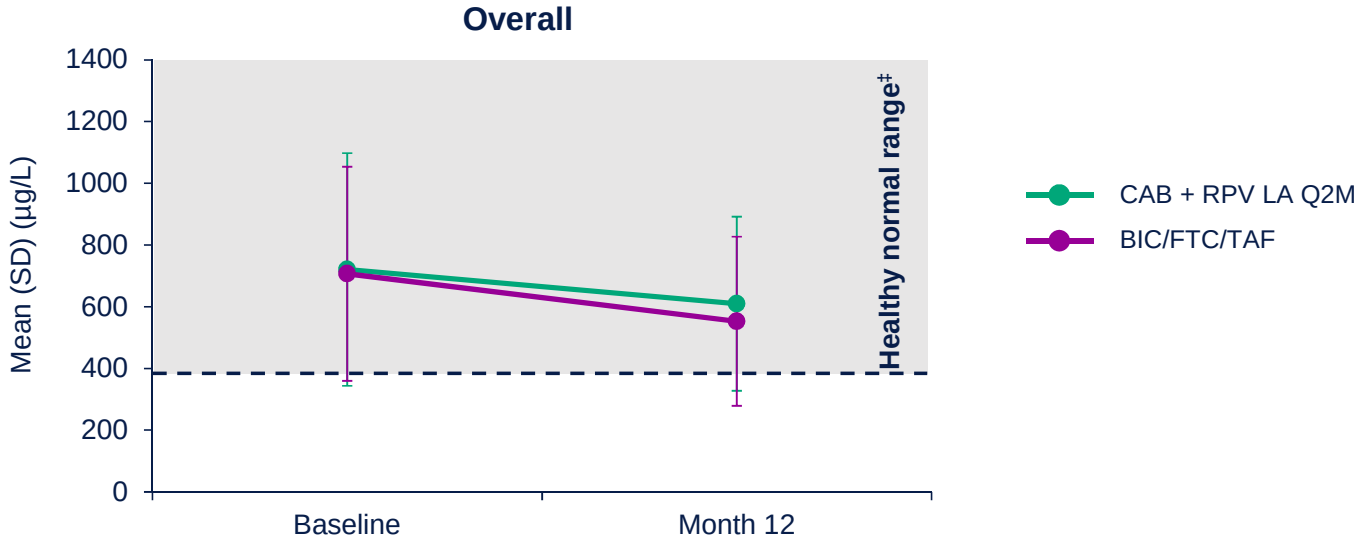


*Reference ranges for individuals living without HIV: IL-6, 0–43.5 ng/L;[1] CRP, ≤50 mg/L;[2] D-dimer, <244 µg/L; CD4/CD8 ratio, ≥1;[3] median sCD14 (95% CI), 1788 (1615–1917) µg/L;[4] sCD163, 387–1785 µg/L.[5] CAB + RPV LA/BIC/FTC/TAF: IL-6, n=397/202; CRP, n=400/205; D-dimer, n=390/201; CD4/CD8 ratio, n=377/193; sCD14, n=399/205; sCD163, n=400/205. Based on a mixed model for repeated measures with visit as the repeated factor: log(value) – log(baseline) = treatment + visit + treatment × visit + log(baseline) + gender at birth (male, female) + baseline BMI (<30, ≥30 kg/m^2) + age (continuous) + race (White, Black/African American, Other) + smoking status (never, former, current) + HCV co-infection (yes, no). Note: p values are not adjusted for presence of cardiometabolic conditions (e.g. cardiovascular disease, diabetes mellitus, or multiple sclerosis), previous ART, CD4, or nadir viral load. ART, antiretroviral therapy; BIC/FTC/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CAB, cabotegravir; CI, confidence interval; HCV, hepatitis C virus; LA, long-acting; Q2M, every 2 months; RPV, rilpivirine.

1. Said et al. *J Med Virol*. 2021;93:3915-3924. **2.** Children's Minnesota. https://www.childrensmn.org/references/Lab/chemistry/c-reactive-protein-(crp).pdf. Accessed June 2023. **3.** Francis-Morris et al. *HIV Med*. 2020;21:109-118. **4.** Gómez-Rial et al. *Front Immunol*. 2020;11:560381. **5.** Children's Minnesota. https://www.childrensmn.org/references/Lab/flowcyt/soluble-cd163-(scd163).pdf. Accessed June 2023.

sCD163 at Baseline* and Month 12† by Key Subgroups and Treatment Arms

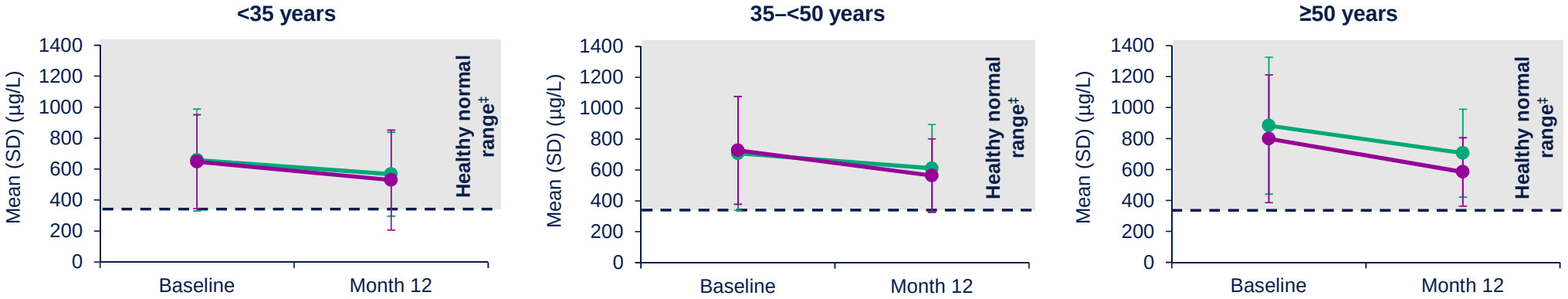
- Subgroup analyses of IL-6, CRP, D-dimer, CD4/CD8 ratio, sCD14, and sCD163 showed no meaningful differences in changes over 12 months between treatment arms



*CAB + RPV LA/BIC/FTC/TAF: overall, n=449/226.
†CAB + RPV LA/BIC/FTC/TAF: overall, n=408/210.
‡Reference range for individuals living without HIV (387–1785 µg/L).[1]
BIC/FTC/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CAB, cabotegravir; LA, long-acting; Q2M, every 2 months; RPV, rilpivirine; SD, standard deviation.

1. Children's Minnesota. https://www.childrensmn.org/references/Lab/flowcyt/soluble-cd163-(scd163).pdf. Accessed June 2023.

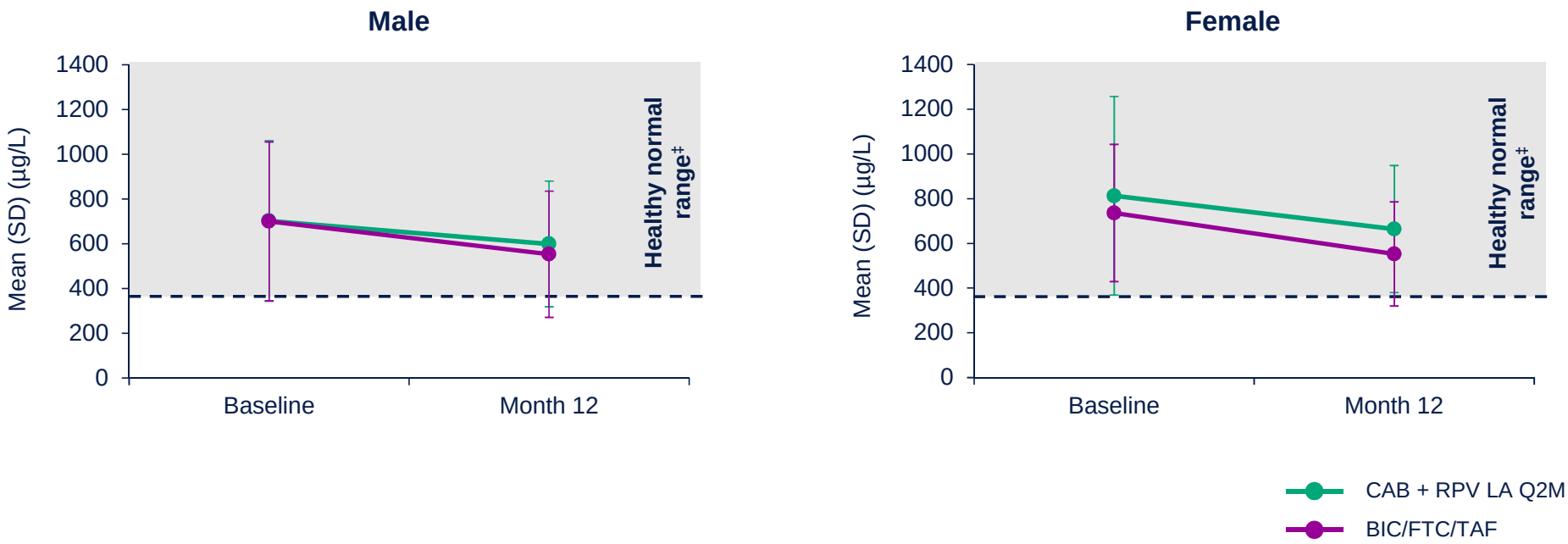
sCD163 at Baseline* and Month 12† by Key Subgroups and Treatment Arms (cont)



*CAB + RPV LA/BIC/FTC/TAF: <35 years, n=189/99; 35–<50 years, n=172/83; ≥50 years, n=88/44.
†CAB + RPV LA/BIC/FTC/TAF: <35 years, n=174/90; 35–<50 years, n=156/78; ≥50 years, n=78/42.
‡Reference range for individuals living without HIV (387–1785 µg/L).[1]
BIC/FTC/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CAB, cabotegravir; LA, long-acting; Q2M, every 2 months; RPV, rilpivirine; SD, standard deviation.

1. Children's Minnesota. https://www.childrensmn.org/references/Lab/flowcyt/soluble-cd163-(scd163).pdf. Accessed June 2023.

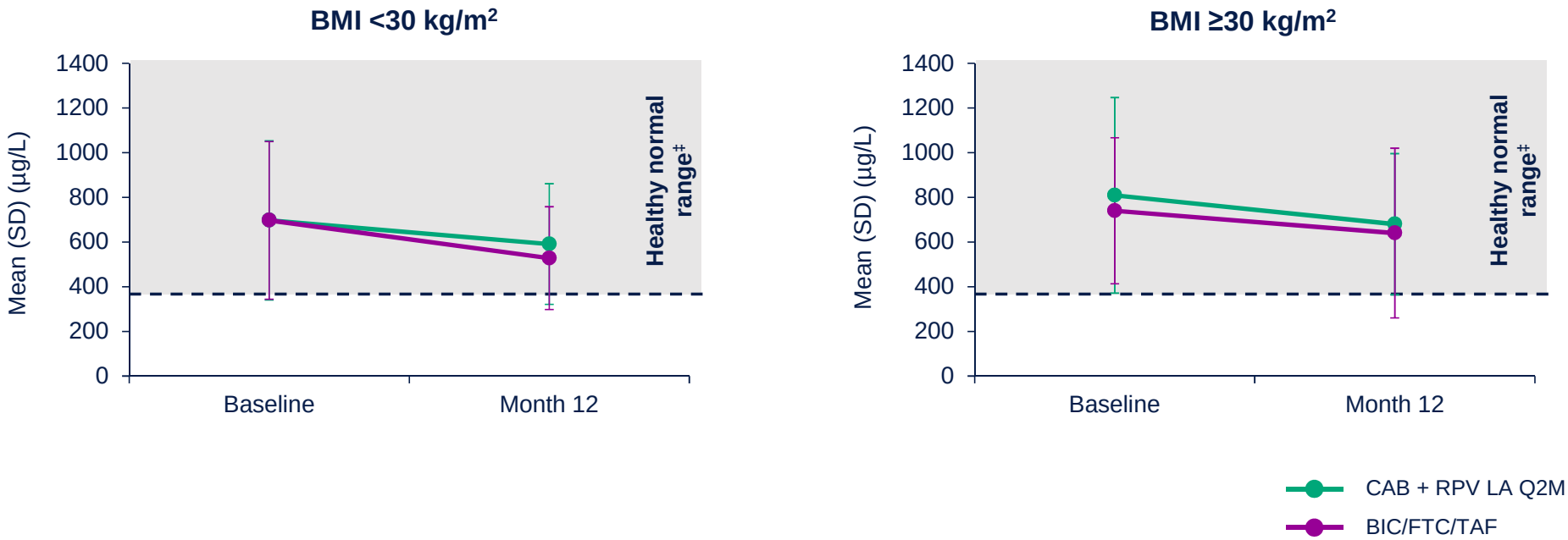
sCD163 at Baseline* and Month 12† by Key Subgroups and Treatment Arms (cont)



*CAB + RPV LA/BIC/FTC/TAF: female, n=79/41; male, n=370/185.
†CAB + RPV LA/BIC/FTC/TAF: female, n=71/34; male, n=337/176.
‡Reference range for individuals living without HIV (387–1785 µg/L).[1]
BIC/FTC/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CAB, cabotegravir; LA, long-acting; Q2M, every 2 months; RPV, rilpivirine; SD, standard deviation.

1. Children's Minnesota. https://www.childrensmn.org/references/Lab/flowcyt/soluble-cd163-(scd163).pdf. Accessed June 2023.

sCD163 at Baseline* and Month 12† by Key Subgroups and Treatment Arms (cont)



*CAB + RPV LA/BIC/FTC/TAF: BMI <30 kg/m^2, n=353/174; BMI ≥30 kg/m^2, n=96/52.
†CAB + RPV LA/BIC/FTC/TAF: BMI <30 kg/m^2, n=321/162; BMI ≥30 kg/m^2, n=87/48.
‡Reference range for individuals living without HIV (387–1785 µg/L).[1]
BIC/FTC/TAF, bictegravir/emtricitabine/tenofovir alafenamide; BMI, body mass index; CAB, cabotegravir; LA, long-acting; Q2M, every 2 months; RPV, rilpivirine; SD, standard deviation.

1. Children's Minnesota. https://www.childrensmn.org/references/Lab/flowcyt/soluble-cd163-(scd163).pdf. Accessed June 2023.

Conclusioni

- Cabotegravir e rilpivirina L-A hanno dimostrato nei trial clinici un’efficacia duratura e un’ottima tollerabilità, la sfida è nel mondo reale.
- Altre molecole, come lenacapavir, si stanno approcciando sulla scena clinica.
- La PrEP.
- Approcci pseudo-vaccinali.
- Attività extra-virale.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