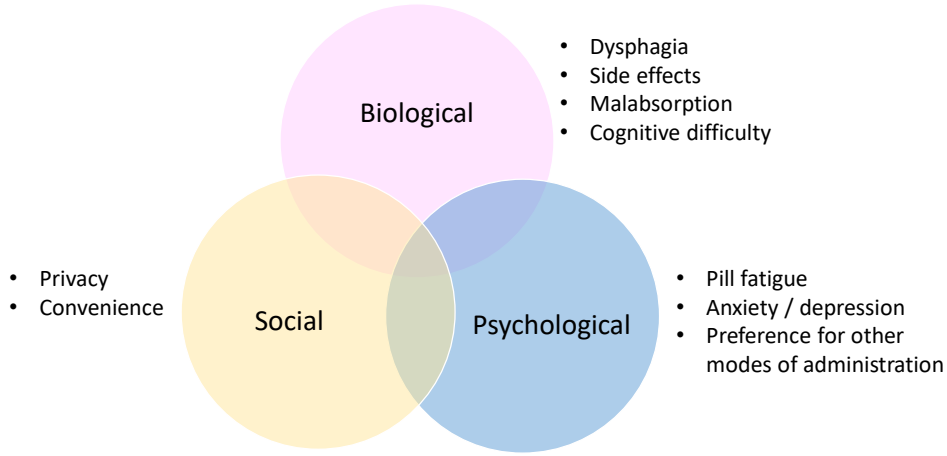
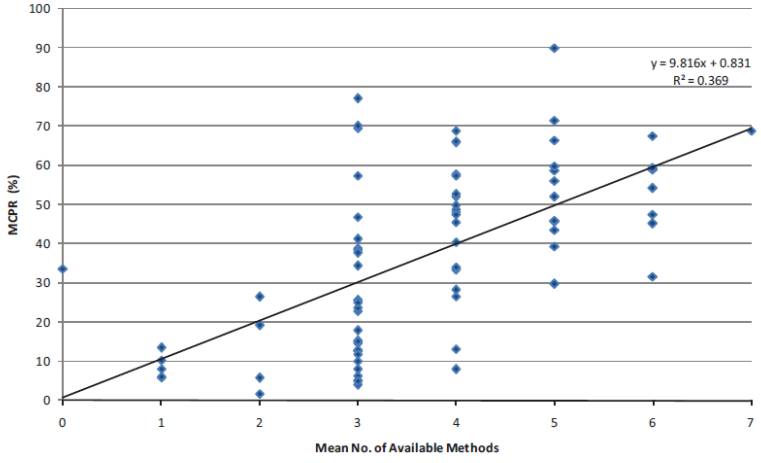
Overview

- 1. Why long-acting drugs for HIV treatment & prevention?
- 2. What should clinicians know about cabotegravir/rilpivirine?
- 3. What should clinicians know about lenacapavir?
- 4. What is still to come?

Why do we need long-acting agents?



The example of contraception: More choice is associated with more uptake

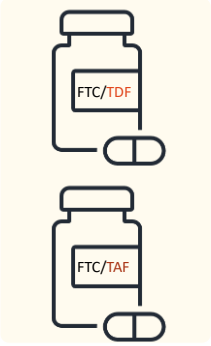


Global Health Sci Pract 2013;1:203

HIV PrEP: Present, Emerging, and Future

Present

Once-daily* oral tablets



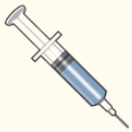
Emerging

Long-acting options

INTRAVAGINAL RING (IVR)

Polymer ring inserted into the vagina releases antiretroviral drug over time.

INJECTABLE



Long-acting antiretroviral drug is injected into the body.

Future

IMPLANT

Device implanted in the body releases antiretroviral drug over time.

ANTIBODY

Antibody is infused or injected into the body.

*Off-label on-demand use of FTC/TDF supported by international guidelines.

www.hiv.gov/hiv-basics/hiv-prevention/potential-future-options/long-acting-prep

Slide credit: clinicaloptions.com

Dapivirine vaginal ring

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Efficacy of a Dapivirine Vaginal Ring for HIV Prevention in Women

Relative risk reduction:

31% (95%CI=1%,51%)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women

27% (95%CI=1%,46%)

NEJM 2016;375:2121; NEJM 2016;375:2133

26 January 2021

WHO recommends the dapivirine vaginal ring as a new choice for HIV prevention for women at substantial risk of HIV infection

Viewpoint

Mosaic effectiveness: measuring the impact of novel PrEP methods

David V Glidden, Megha L Mehrotra, David T Dunn, Elvin H Geng

PrEP options that are less effective than oral PrEP at preventing HIV can still have population-level impact if they attract ‘new’ users

PrEP Preferences among GBM in Toronto: More choices = more (predicted) uptake

www.nature.com/scientificreports

scientific reports

OPEN **Preferences regarding emerging HIV prevention technologies among Toronto men who have sex with men: a discrete choice experiment**

Darrell H. S. Tan[1,2,3,4✉], Jayoti Rana[2], Zavare Tengra[2], Trevor A. Hart[5,6,7], James Wilton[8] & Ahmed M. Bayoumi[2,3,4,9]

# Options	Form of PrEP	Predicted uptake (%)
2	None	**16.5**
	Daily Pill	25.9
	On-demand pill	57.6
3	None	**12.7**
	Daily Pill	14.1
	On-demand pill	36.1
	Monthly injection	37.1
4	None	**12.5**
	Daily Pill	13.9
	On-demand pill	35.8
	Monthly injection	36.8
	Rectal gel	1

Long-acting cabotegravir/rilpivirine q4 wks

- 1st/2nd regimen, no prior VF, VL<50 x6mo
- Compared to SOC oral ART

NEJM 2020;382:1112
AIDS 2022;36:185

- Treatment naïve
- Compared to DTG/3TC/ABC

NEJM 2020;382:1124
Lancet HIV 2021;8:e185

- Both trials:
  - Oral lead-in: CAB 30mg/RPV 25mg x28d
  - Then CAB 600mg/RPV 900mg im, then CAB 400mg/RPV 600mg im q4wks

Week 96 extension results of a Phase 3 study evaluating long-acting cabotegravir with rilpivirine for HIV-1 treatment

Susan Swindells[a], Thomas Lutz[b], Lelanie Van Zyl[c], Norma Porteiro[d], Matthias Stoll[e], Essack Mitha[f], Alyssa Shon[g], Paul Benn[h], Jenny O. Huang[i], Conn M. Harrington[j], Kai Hove[k], Susan L. Ford[l], Christine L. Talarico[j], Vasiliki Chounta[h], Herta Crauwels[m], Rodica Van Solingen-Ristea[m], Simon Vanveggel[m], David A. Margolis[j,n], Kimberly Y. Smith[j], Kati Vandermeulen[m] and William R. Spreen[j]

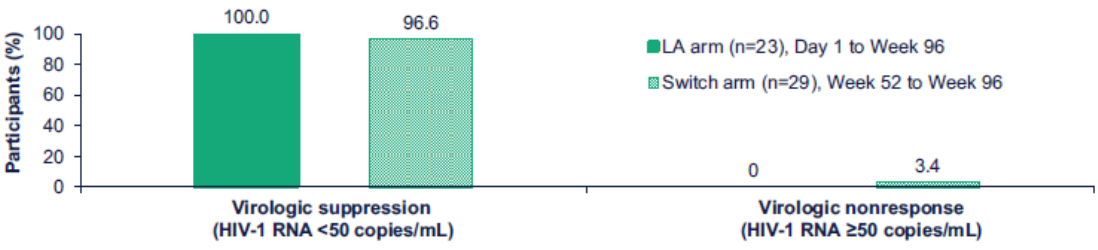


Fig. 2. Efficacy outcomes based on observed viral load values at W 96 analysis. LA, long-acting.

AIDS 2022;36:185

Long-acting cabotegravir plus rilpivirine for treatment in adults with HIV-1 infection: 96-week results of the randomised, open-label, phase 3 FLAIR study

Chloe Orkin, Shinichi Oka, Patrick Philibert, Cynthia Brinson, Ayesha Bassa, Denis Gusev, Olaf Degen, Juan González García, Enrique Bernal Morell, Darrell H S Tan, Ronald D'Amico, David Dorey, Sandy Griffith, Shanker Thiagarajah, Marty St Clair, Rodica Van Solingen-Ristea, Herta Crauwels, Susan L Ford, Parul Patel, Vasiliki Chounta, Simon Vanveggel, Amy Cutrell, Veerle Van Eygen, Kati Vandermeulen, David A Margolis, Kimberly Y Smith, William R Spreen

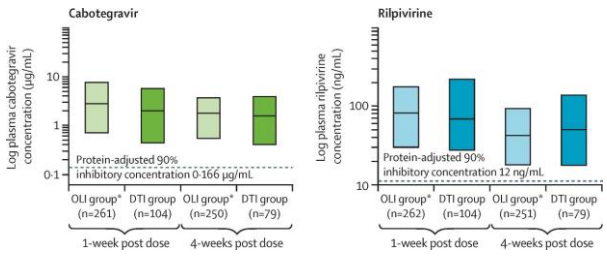
	Long-acting group (n=283)	Standard care group (n=283)	Difference, percentage points (95% CI)*†	Adjusted difference, percentage points (95% CI)*‡
Snapshot outcomes (intention-to-treat population)				
HIV-1 RNA <50 copies per mL§	245 (87%)	253 (89%)	−2·8 (−8·2 to 2·5)	−2·8 (−8·2 to 2·5)
HIV-1 RNA ≥50 copies per mL§	9 (3%)	9 (3%)	0·0 (−2·9 to 2·9)	0·0 (−2·9 to 2·9)
Data in window not below threshold	3 (1%)	2 (<1%)	..	..
Discontinued for absence of efficacy	6 (2%)	5 (2%)	..	..
Discontinued for other reason while not below threshold	0	2 (<1%)¶	..	..
No virological data in week 96 window	29 (10%)	21 (7%)	..	..
Discontinued due to adverse event‖	12 (4%)	4 (1%)	..	..
Discontinued for other reason	16 (6%)**	17 (6%)††	..	..
On study but missing data in window	1 (<1%)	0	..	..

Lancet HIV 2021;8:e185

Initiation of long-acting cabotegravir plus rilpivirine as direct-to-injection or with an oral lead-in in adults with HIV-1 infection: week 124 results of the open-label phase 3 FLAIR study

Chloe Orkin, Enrique Bernal Morell, Darrell H S Tan, Harold Katner, Hans-Jürgen Stellbrink, Elena Belonosova, Rebecca DeMoor, Sandy Griffith, Shanker Thiagarajah, Rodica Van Solingen-Ristea, Susan L Ford, Herta Crauwels, Parul Patel, Amy Cutrell, Kimberly Y Smith, Kati Vandermeulen, Eileen Birmingham, Marty St Clair, William R Spreen, Ronald D'Amico

- Non-randomized comparison of oral lead-in vs direct-to-injection participants in FLAIR extension switch population
- Similar efficacy at 24 weeks
  - DTI: 99% (97-100)
  - OLI: 93% (89-98)
- Similar adverse event profile



Lancet HIV 2021;8:e668

Long-acting cabotegravir/rilpivirine q8 wks

ATLAS 2M

- Virologically suppressed ATLAS pts or newly recruited on oral ART
- Oral lead-in if CAB/RPV naive
- CAB/RPV 400mg/600mg q4wks vs
- CAB/RPV 600mg/900mg q8wks

Lancet 2020;396:1994

SOLAR

- Virologically suppressed pts on BIC/TAF/FTC
- Continue on BIC/TAF/FTC vs
- CAB/RPV 600mg/900mg q8wks (optional oral lead-in, 2 loading doses)

Lancet HIV 2023;10:e566

Clinical Infectious Diseases
MAJOR ARTICLE

ATLAS 2M

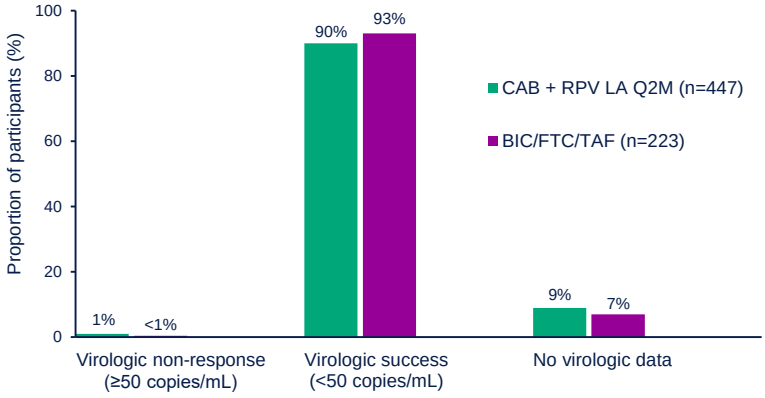
Long-Acting Cabotegravir and Rilpivirine Dosed Every 2 Months in Adults With Human Immunodeficiency Virus 1 Type 1 Infection: 152-Week Results From ATLAS-2M, a Randomized, Open-Label, Phase 3b, Noninferiority Study

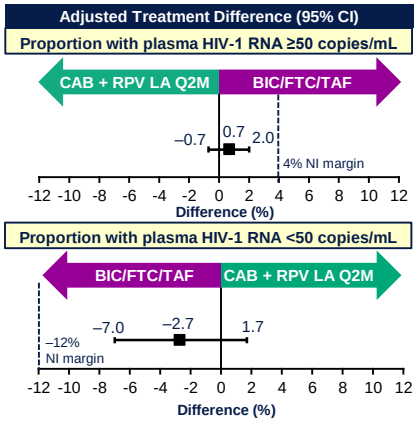
Edgar T. Overton,[1,a] Gary Richmond,[2] Giuliano Rizzardini,[3,4] Anders Thalme,[5] Pierre-Marie Girard,[6] Alexander Wong,[7] Norma Porteiro,[8] Susan Swindells,[9] Jacques Reynes,[10,11] Sebastian Noe,[12] Conn Harrington,[13] Carlos Martin Español,[14] Carolina Acuipil,[15] Asma Aksar,[16] Yuanyuan Wang,[17] Susan L. Ford,[18] Herta Crauwels,[19] Veerle van Eygen,[20] Rodica Van Solingen-Ristea,[21] Christine L. Latham,[22] Shanker Thiagarajah,[23] Ronald D'Amico,[15] Kimberly Y. Smith,[15]

Outcome at Week 152	Q8W (n = 522), n (%)	Q4W (n = 523), n (%)	Adjusted[a] Difference (95% CI)
ITT-E analysis			
HIV-1 RNA ≥50 copies/mL[b]	14 (2.7)	5 (1.0)	1.7 (0.1, 3.3)
Data in window not below threshold	1 (0.2)	0	…
Discontinued for lack of efficacy	12 (2.3)	4 (0.8)	…
Discontinued for other reason while not below threshold	1 (0.2)	1 (0.2)	…
Change in background therapy	0	0	…
HIV-1 RNA <50 copies/mL[c]	456 (87.4)	449 (85.9)	1.5 (−2.6, 5.6)
No virologic data	52 (10.0)	69 (13.2)	…
Discontinued study due to AE or death[d]	23 (4.4)	24 (4.6)	…
Discontinued study for other reason[e]	28 (5.4)	44 (8.4)	…
On study but missing data in window	1 (0.2)[f]	1 (0.2)	…

CID 2023;76:1646

SOLAR
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

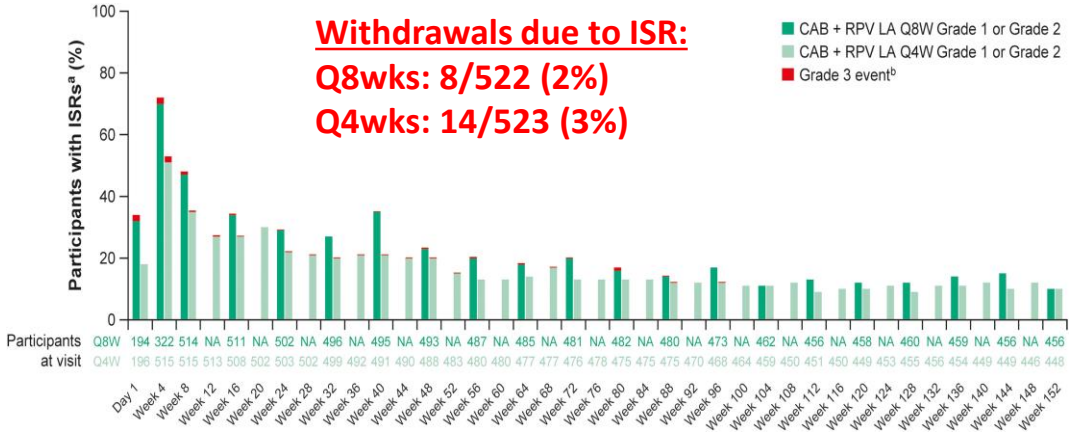
*In the ITT-E population, 89% (n=406/454) and 93% (n=211/227) of participants receiving LA and BIC/FTC/TAF demonstrated virologic success (HIV-1 RNA <50 copies/mL), 1% (n=6/454) and <1% (n=1/227) of participants receiving LA and BIC/FTC/TAF demonstrated virologic non-response (HIV-1 RNA ≥50 copies/mL), and 9% (n=42/454) and 7% (n=15/227) of participants receiving LA and BIC/FTC/TAF had no virologic data, respectively.
BIC/FTC/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CAB, cabotegravir; CI, confidence interval; ITT-E, intention-to-treat exposed; LA, long-acting; mITT-E, modified intention-to-treat exposed; NI, noninferiority; Q2M, every 2 months; RPV, rilpivirine.

Conference on Retroviruses and Opportunistic Infections; February 19-22, 2023; Virtual and Seattle, WA

Ramgopal et al. CROI 2023; Virtual and Seattle, WA. Slides X.

17

Injection site reactions over time in ATLAS-2M



CID 2023;76:1646

Perceptions of Cabotegravir + Rilpivirine Long-Acting (CAB + RPV LA) From People Living With HIV (PLHIV) in the CARLOS Study

EPE0863

Jenny Scherzer[1], Sebastian Noe[2], Celia Jonsson-Oldenbüttel[2], Christoph Wyen[3], Stefan Esser[4], Gordon Weinberg[5], Anja Potthoff[6,7], Ivanka Krznaric[8], Bernd Westermayer[9], Katharina Bernhardt[1], Patricia de los Rios[10]

[1]ViiV Healthcare, Munich, Germany; [2]MVZ München am Goetheplatz, Munich, Germany; [3]Praxis am Ebertplatz, Cologne, Germany; [4]University Hospital Duisburg-Essen, Essen, Germany; [5]Infektiologisches Zentrum Steglitz, Berlin, Germany; [6]WIR-Walk In Ruhr, Center for Sexual Health and Medicine, Bochum, Germany; [7]Ruhr-Universität Bochum, Bochum, Germany; [8]Praxis an der Kulturbrauerei, Berlin, Germany; [9]GSK, Munich, Germany; [10]ViiV Healthcare, Montreal, Quebec, Canada

Figure 6. Most Common Concerns About CAB + RPV LA Therapy at Baseline (n=332) vs. Treatment Difficulties at Month 6 (n=256)

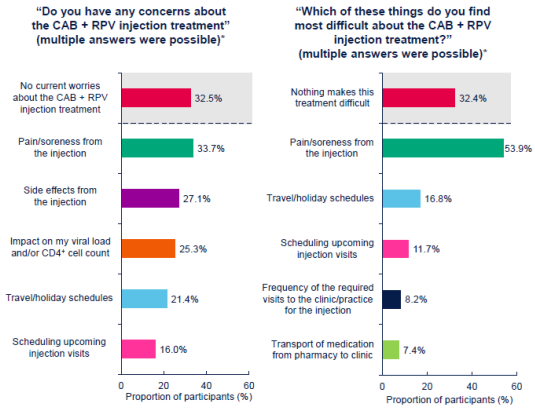
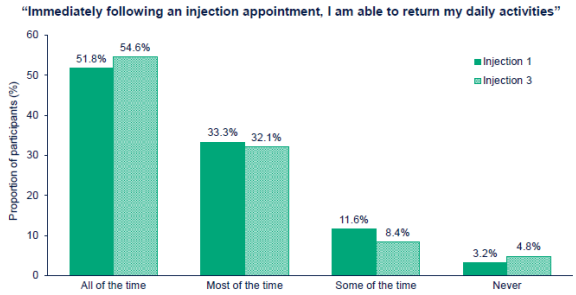


Figure 10. Ability to Return to Daily Activities Following CAB + RPV LA Injections 1 and 3 (n=249)



IAS 2023; EPE0863

SOLAR

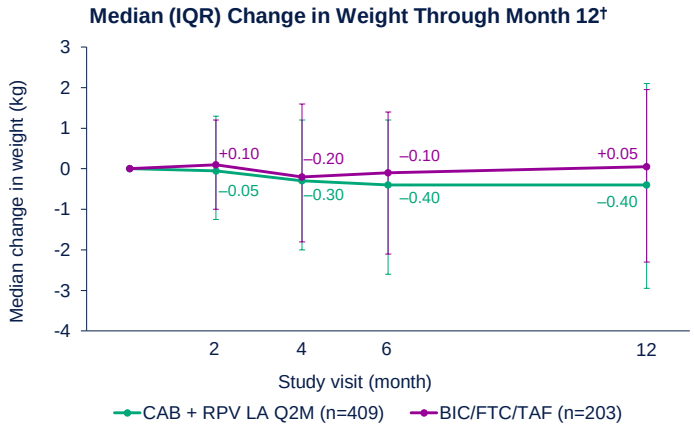
Safety Summary (Excluding Injection Site Reactions [ISRs])

Parameter, n (%)	CAB + RPV LA Q2M (n=454)	BIC/FTC/TAF (n=227)
Any AE	349 (77)	172 (76)
Drug-related AEs	90 (20)	2 (<1)
Any Grade ≥3 AE	42 (9)	26 (11)
Drug-related	7 (2)	0
Leading to withdrawal	16 (4)	2 (<1)
Drug-related	9 (2)*	0
Any serious AE	21 (5)	15 (7)
Drug-related	3 (<1)†	0

- The most commonly reported drug-related AEs in the LA arm were pyrexia (3%), headache (2%), fatigue (2%), and diarrhea (2%). In the BIC/FTC/TAF arm, the two drug-related AEs reported were weight gain (<1%) and abnormal hepatic function (<1%)
- More participants in the CAB + RPV LA arm had AEs leading to withdrawal (4% vs. <1%)

*OLI period: 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; diarrhea/joint stiffness, n=1; Injection period: myocardial infarction, n=1; alanine aminotransferase increase, n=1; fatigue/pyrexia, n=1. †Increased alanine aminotransferase, n=2; acute myocardial infarction, n=1.
AE, adverse event; BIC/FTC/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CAB, cabotegravir; LA, long-acting; OLI, oral lead-in; Q2M, every 2 months; RPV, rilpivirine.

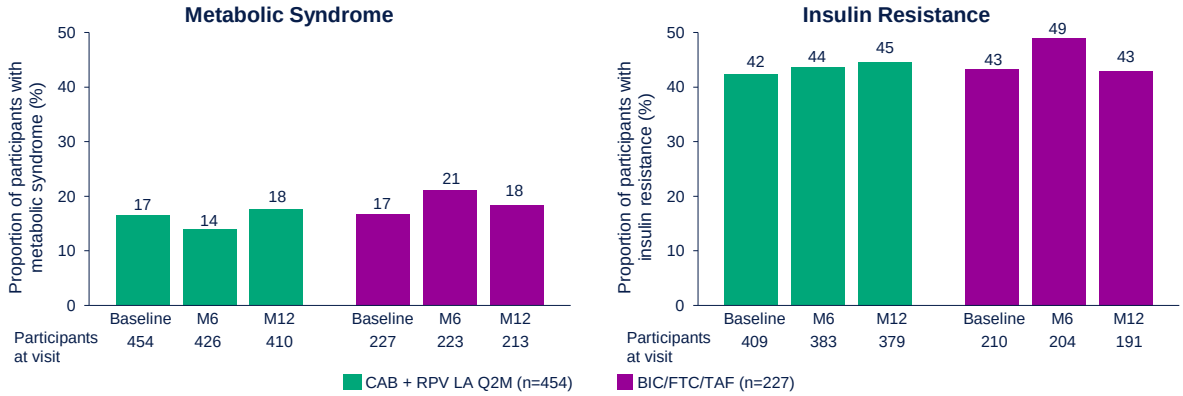
SOLAR
Change in Weight Through Month 12 by Treatment Regimen*



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

*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).

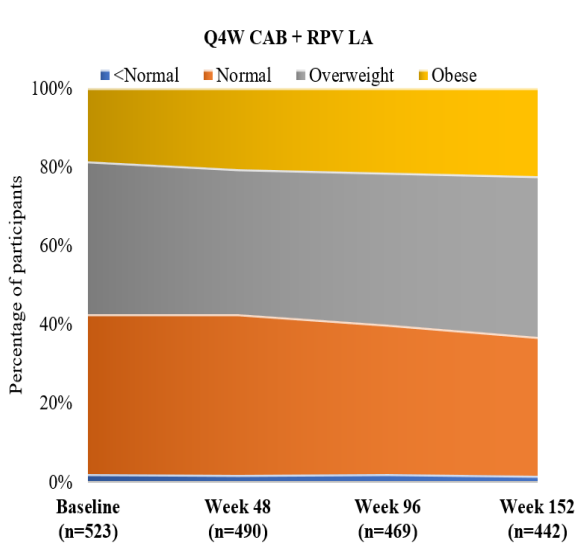
SOLAR
Metabolic Syndrome* and Insulin Resistance† Through Month 12

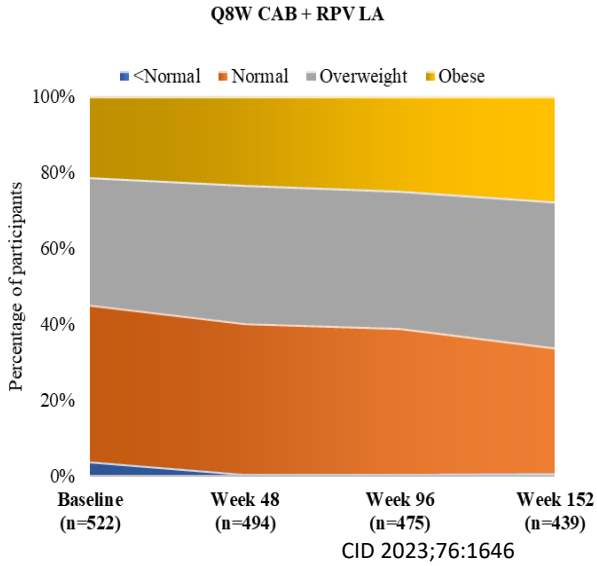


- There were no clinically relevant changes from baseline to Month 12 in the proportion of participants with metabolic syndrome or insulin resistance in either arm

*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.

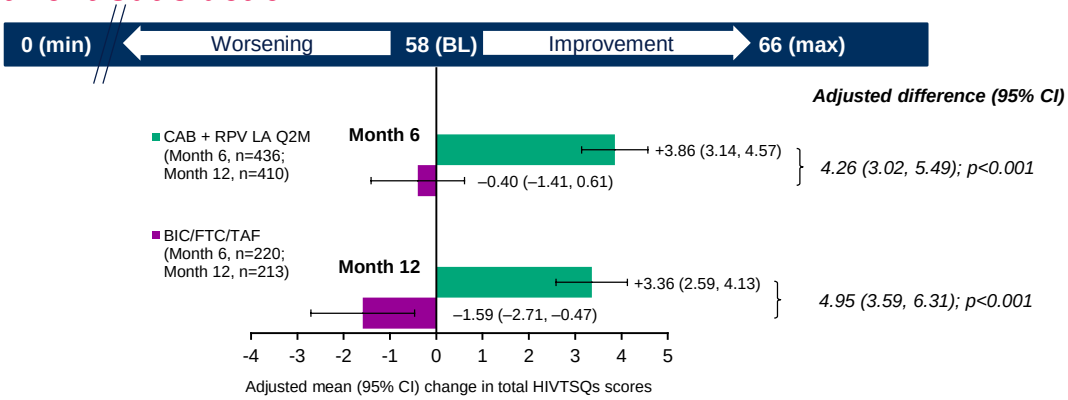
BMI categories over time in ATLAS-2M





CID 2023;76:1646

SOLAR
Treatment Satisfaction

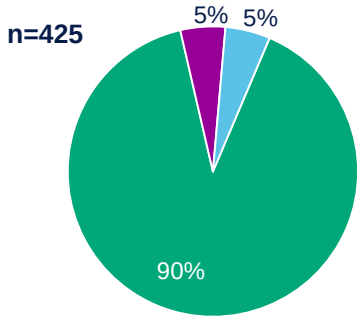


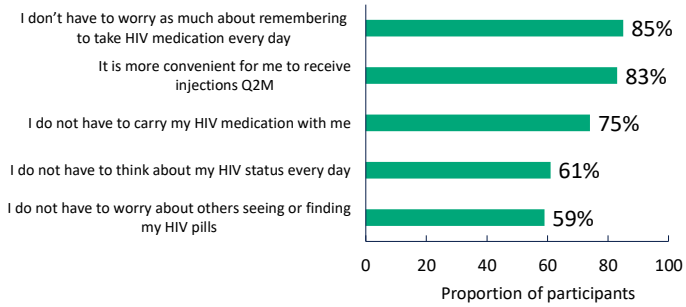
- Mean adjusted HIVTSQs scores improved significantly for CAB + RPV LA vs. BIC/FTC/TAF participants from baseline (LA, 57.88; BIC/FTC/TAF, 58.38) to Month 6 (LA, +3.86; BIC/FTC/TAF, –0.40) and Month 12 (LA, +3.36; BIC/FTC/TAF, –1.59) demonstrating greater improvement from baseline in HIV treatment satisfaction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

BIC/FTC/TAF, bictegravir/emtricitabine/tenofovir alafenamide; BL, baseline; CAB, cabotegravir; CI, confidence interval; HIVTSQs, HIV Treatment Satisfaction Questionnaire status version; LA, long-acting; Q2M, every 2 months; RPV, rilpivirine.

Ramgopal et al. CROI 2023; Virtual and Seattle, WA. Slides X.

SOLAR
Treatment Preference and Reason for Preference*





■ CAB + RPV LA Q2M ■ BIC/FTC/TAF ■ No preference

■ CAB + RPV LA Q2M (n=382)

- 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.
BIC/FTC/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CAB, cabotegravir; LA, long-acting; Q2M, every 2 months; RPV, rilpivirine.

Conference on Retroviruses and Opportunistic Infections; February 19-22, 2023; Virtual and Seattle, WA

Ramgopal et al. CROI 2023; Virtual and Seattle, WA. Slides X.

25

Summary of resistance mutations across FLAIR/ATLAS/ATLAS 2M (1%-5% rate of failure)

Study	INSTI mutations(n)	NNRTI mutation(s) some baseline	Time of virologic failure
FLAIR (4 failures)	N155H, R263K, G140R, Q148R	L74I	Weeks 20, 28, 48, 108
ATLAS (3 failures)	N155H	L74I, E183E/A, V108V/I, E138K	Weeks 8, 12, 30
ATLAS 2M (8wk) 13 failures	Q148R,N155H	K101E, E138E/K, E138A, Y188L, Y181C, M230L	7: before week 24 3: week 24-48 1: week 88 2: weeks 88-152
ATLAS 2M (4wk) 2 failures	N155N/H,E138E/K+ Q148R	K101E, M230L	Before week 24

HIV GLASGOW 2022
Drug Therapy
Hybrid meeting | 23-26 October

1.4% risk of failure 1224 participants across trials

Virologic failures

Parameter	OR (95%CI)
RPV RAM(s) at baseline	40.36 (8.81, >99)
Log_2 week 8 RPV trough concentration	5.00 (1.79, 16.67)
Baseline HIV-1 subtype A6 / A1	5.92 (1.62, 22.89)
BMI (kg/m^2) at baseline	1.13 (1.02, 1.24)

Use 2" needle for injection in obese pts

Exploring predictors of HIV-1 virologic failure to long-acting cabotegravir and rilpivirine: a multivariable analysis

Amy G. Cutrell[a], Jonathan M. Schapiro[b], Carlo F. Perno[c], Daniel R. Kuritzkes[d], Romina Quercia[e], Parul Patel[a], Joseph W. Polli[a], David Dorey[f], Yongwei Wang[g], Sterling Wu[h], Veerle Van Eygen[i], Herta Crauwels[i], Susan L. Ford[j], Mark Baker[k], Christine L. Talarico[a], Marty St Clair[a], Jerry Jeffrey[a], C. Thomas White[a], Simon Vanveggel[i], Kati Vandermeulen[i], David A. Margolis[a,*], Michael Aboud[e], William R. Spreen[a] and Jan van Lunzen[l]

- Pooled analysis of ATLAS, FLAIR, ATLAS-2M
- Of n=1039 adults naïve to CAB/RPV-LA, n=13/1039 (1.25%) had confirmed virologic failure

AIDS 2021;35:1333

Subsequent virologic failures

ATLAS 2M

- Only 6/14 (43%) had 2+ RF

SOLAR

Sex at birth, baseline BMI (kg/m^2), country	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, 21.5, Italy*	B	1327/1409	None	None	M230L	Q148R	3.2/3.1	6
Male, 22.9, Spain†	AE	6348/419	None	G140G/R	K101E	G118R	1.9/8.4	11
Participant With CVF in the ITT-E Population‡								
Male, 30.5, United States	C§	3797/928	Assay failed	Assay failed	E138E/K + Y181Y/C	None	4.2/assay failed	3

Lancet 2020;396:1994

Lancet HIV 2023;10:e566

Annals of Internal Medicine ORIGINAL RESEARCH

Demonstration Project of Long-Acting Antiretroviral Therapy in a Diverse Population of People With HIV

Monica Gandhi, MD, MPH; Matthew Hickey, MD; Elizabeth Imbert, MD; Janet Grochowski, PharmD; Francis Mayorga-Munoz, PhT; John D. Szumowski, MD; Jon Oskarsson, RN; Mary Shiels, RN; John Sauceda, PhD; Jorge Salazar, MD; Samantha Dilworth, MS; Janet Q. Nguyen, MPH; David V. Glidden, PhD; Diane V. Havlir, MD; and Katerina A. Christopoulos, MD, MPH

- Observational cohort of N=133 publicly insured adults at Ward 86 HIV Clinic, San Francisco
- Publicly insured clinic in SF w high prevalence of mental illness, unstable housing, adherence challenges
- Eligibility: No NNRTI/INSTI mutations, willingness to attend q4 wks
- CAB/RPV given q4wks; if suppressed for 3+ mo can switch to q8wks
- 57/133 (43%) initiated LA-ART with viremia

Annals 2023;76:969

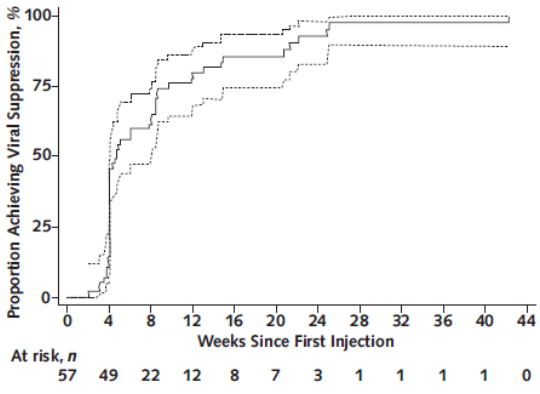
Table. Patient Characteristics, by Virologic Suppression Status at Initiation of LA CAB-RPV*

Characteristic	Patients With Viremia (*n* = 57)	Patients With Virologic Suppression (*n* = 76)	Overall Sample (*n* = 133)
Median age (range), *y*	48.0 (25.0–68.0)	44.5 (29.0–68.0)	46.0 (25.0–68.0)
Gender, *n (%)*			
Cisgender man	51 (89.5)	66 (86.8)	117 (88.0)
Cisgender woman	5 (8.8)	6 (7.9)	11 (8.3)
Transgender woman	1 (1.8)	4 (5.3)	5 (3.8)
Race/ethnicity, *n (%)*			
Black	13 (22.8)	8 (10.5)	21 (15.8)
Latino/Latina	18 (31.6)	25 (32.9)	43 (32.3)
White	23 (40.4)	27 (35.5)	50 (37.6)
Multiracial/other	3 (5.3)	16 (21.1)	19 (14.3)
Housing status, *n (%)*‡			
Experiencing homelessness	6 (10.5)	3 (4.0)	9 (6.8)
Unstable	24 (42.1)	23 (30.3)	47 (35.3)
Stable	27 (47.4)	50 (65.8)	77 (57.9)
Insurance, *n (%)*			
Medicare, Medicaid, or both	55 (96.5)	73 (96.1)	128 (96.2)
ADAP	2 (3.5)	3 (4.0)	5 (3.9)
Current stimulant use, *n (%)*‡	28 (49.1)	17 (22.4)	45 (33.8)
Mean $\log_{10}$ viral load (SD)	4.21 (1.30)	NA	NA
Median CD4 cell count (IQR), × *10³ cells/L*‡	0.215 (0.075–0.402)	0.615 (0.395–0.818)	0.422 (0.219–0.749)

Annals 2023;76:969

- Of 57 viremic participants:
- 54 suppressed at median (IQR) 33 (28,56) days
- 2 virologic failures
  - one had Y181I in RT and recent rifabutin
  - one had T97A in IN
- 1 early virologic rebound (BMI=32, did not use 2" needle); resuppressed on TAF/FTC/DRV/c
- 1 late rebound (VL=182) after 5th injection

Figure. Kaplan–Meier curve of probability of achieving virologic suppression (viral load <30 copies/mL) with long-acting antiretroviral therapy (n = 57).



The dashed lines indicate the 95% CI.

Annals 2023;76:969

Clinical Infectious Diseases

BRIEF REPORT

Long-acting Injectable Cabotegravir/ Rilpivirine Effective in a Small Patient Cohort With Virologic Failure on Oral Antiretroviral Therapy

James B. Brock, Peyton Herrington, Melissa Hickman, and Aubri Hickman

Department of Medicine, Division of Infectious Diseases, University of Mississippi Medical Center. Jackson, Mississippi, USA

Pill burden (mean)	
All medications	6.1 (range 2–14)
Antiretrovirals	1.5 (range 1–3)
Viral load (copies/mL, mean)	152 657 (range 2410–566 000)
Absolute CD4 (cells/μL, mean)	233 (range 131–475)
Baseline resistance-associated mutations (n)	
NNRTI	
K103N	2
V106I	1
P225H	1
INSTI	
D232N	1
N155H	1
E157Q	3

- First 6 pts initiated on Q1M
  - 5/6 achieved VL<200 by 2months
- Next 6 pts initiated on Q2M
- 5/82 (6%) visits late; gave repeat loading dose (no oral bridging)
- All achieved VL<50 within 3mo
- No rebound after 1-17mo f/u

patients on iCAB/RPV requires regular telephone follow-up, appointment reminders, transportation assistance, and proactive rescheduling of missed injection visits. Adult Special Care Clinic's (ASCC's) injectable ART program has grown to a full-time RN for case management and injection administration, which may not be reproducible outside resource-rich clinical settings. Barriers to care were common, including lack of transportation and inconsistent phone service. Reasons for

CID 2023; https://doi.org/10.1093/cid/ciad511

CAB/RPV-LA: Prescribing Considerations

Should I prescribe it?

- Absolute/relative contraindications
  - Concomitant medications
  - Blood thinners
  - Buttock implants
  - HBV co-infection
- Risks of virologic failure
  - Resistance
  - Elevated BMI
  - Clade A1/A6
- Pregnancy intentions
- Patient understanding of efficacy

How should I prescribe it?

- 4-weekly or 8-weekly?
  - Convenience
  - Administrative burden
  - Opportunity for clinical assessment
  - Off-label use in viremic patients
- Oral lead-in?
  - Convenience
  - Pill burden
  - RPV: High-fat meals, PPIs
  - Trough concentrations??

CAB/RPV-LA: Implementation Considerations

Scheduling

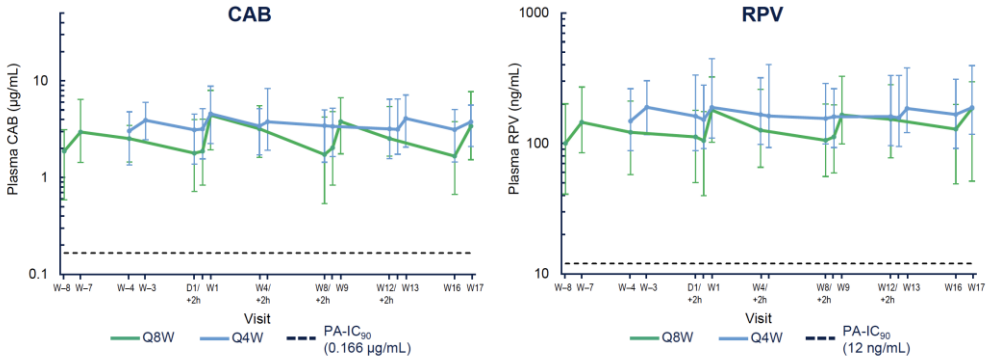
- Personnel
- "Target date"
  - ±7d window for each injection
- Oral bridging options
  - CAB + RPV vs. other
  - RPV requires high-fat meal, no PPI

'Mechanics'

- "**R**ilpivirine on the **R**ight"
- Injections
  - Length of needle
  - Fat distribution
- Monitoring?

Pharmacokinetics (PK) and tolerability of cabotegravir (CAB) and rilpivirine (RPV) long-acting (LA) intramuscular (IM) injections to the vastus lateralis (lateral thigh) muscles of healthy adult participants

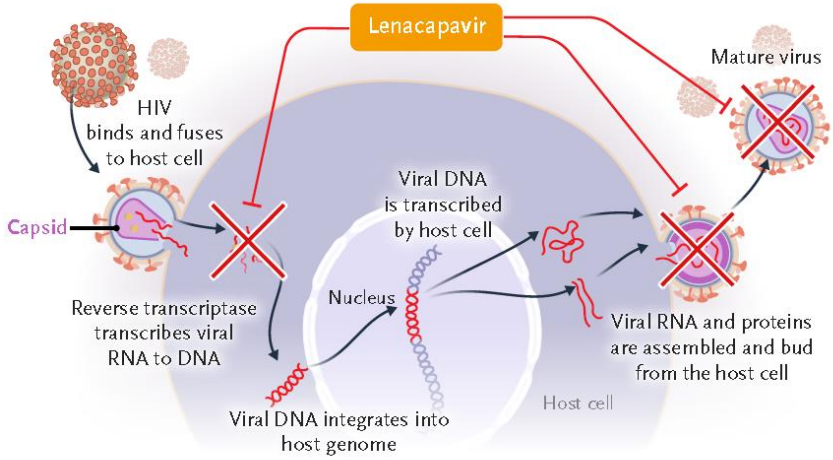
Figure 2. Median (5th, 95th Percentiles) Plasma CAB and RPV Concentration–Time Plots



CAB, cabotegravir; Cτ, concentration at dosing interval; D, day; Q4W, every 4 weeks; Q8W, every 8 weeks; $PA\text{-}IC_{90}$, protein-adjusted 90% inhibitory concentration; PO, oral therapy; RPV, rilpivirine; W, week.

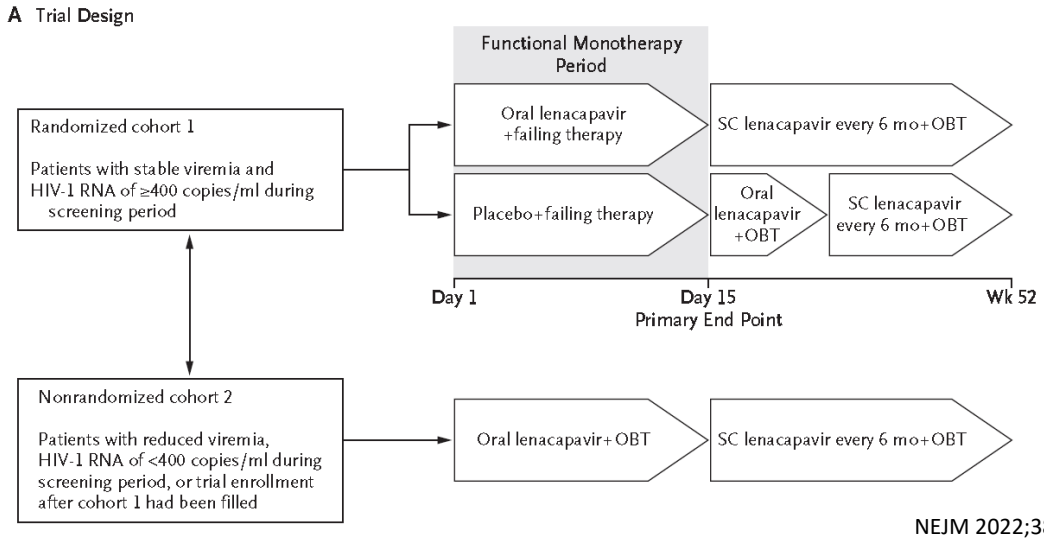
AIDS 2022
29 July – 2 August

Lenacapavir SC q6mo



NEJM 2022;386:1793

Lenacapavir in multidrug-resistant HIV: CAPELLA



NEJM 2022;386:1793

Lenacapavir in multidrug-resistant HIV: CAPELLA

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Cohort 1		Cohort 2	All Patients (N=72)
	Lenacapavir (N=24)	Placebo (N=12)	Lenacapavir (N=36)	
Median age (range) — yr	55 (24–71)	54 (27–59)	49 (23–78)	52 (23–78)
Female sex — no. (%)	7 (29)	3 (25)	8 (22)	18 (25)
Race — no. (%)†				
Black	10 (42)	6 (55)	11 (31)	27 (38)
White	12 (50)	4 (36)	13 (36)	29 (41)
Asian	2 (8)	1 (9)	12 (33)	15 (21)
Data could not be collected	0	1 (9)	0	1 (1)
Hispanic or Latinx ethnic group — no. (%)	6 (25)	4 (36)	5 (14)	15 (21)
Viral load‡				
Mean — $\log_{10}$ copies/ml	3.97±0.92	4.87±0.39	4.06±1.16	4.17±1.03
Median (range) — $\log_{10}$ copies/ml	4.2 (2.3–5.4)	4.9 (4.3–5.3)	4.5 (1.3–5.7)	4.5 (1.3–5.7)
Patients with >100,000 copies/ml — no. (%)	1 (4)	6 (50)	7 (19)	14 (19)

NEJM 2022;386:1793

Lenacapavir in multidrug-resistant HIV: CAPELLA

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Cohort 1		Cohort 2	All Patients (N=72)
	Lenacapavir (N=24)	Placebo (N=12)	Lenacapavir (N=36)	
CD4+ count				
Mean — cells/mm³	199±166	85±63	258±273	210±224
Median (range) — cells/mm³	172 (16–827)	85 (6–237)	195 (3–1296)	150 (3–1296)
Distribution — no. (%)				
<50 cells/mm³	3 (12)	4 (33)	9 (25)	16 (22)
50 to <200 cells/mm³	13 (54)	7 (58)	10 (28)	30 (42)
200 to <500 cells/mm³	7 (29)	1 (8)	12 (33)	20 (28)
≥500 cells/mm³	1 (4)	0	5 (14)	6 (8)
Resistance to ≥2 drugs in major class — no. (%)				
NRTI	23 (96)	12 (100)	36 (100)	71 (99)
NNRTI	22 (92)	12 (100)	36 (100)	70 (97)
Protease inhibitor	20 (83)	8 (67)	30 (83)	58 (81)
INSTI	20 (83)	7 (58)	23 (64)	50 (69)
All 4 major classes	14 (58)	3 (25)	16 (44)	33 (46)

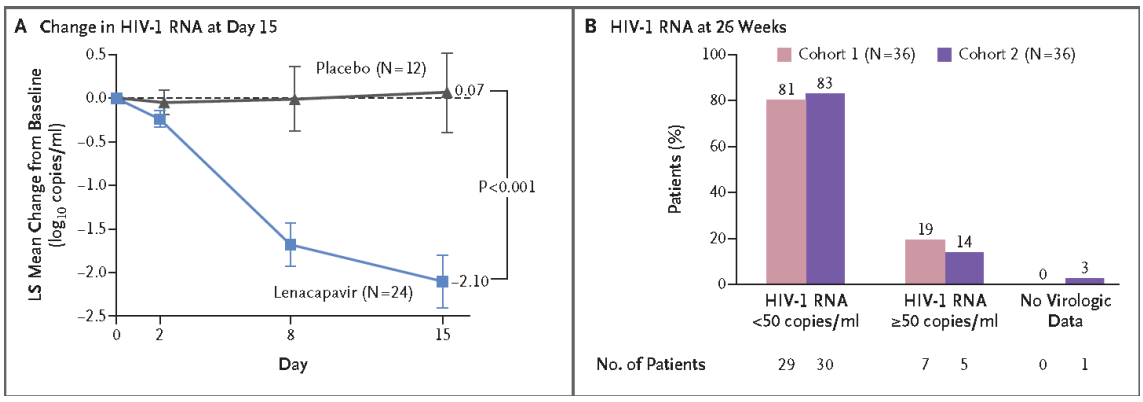
Lenacapavir in multidrug-resistant HIV: CAPELLA

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Cohort 1		Cohort 2	All Patients (N=72)
	Lenacapavir (N=24)	Placebo (N=12)	Lenacapavir (N=36)	
Median overall susceptibility score of optimized background therapy‖	2.0	1.3	2.0	2.0
Number of fully active agents in the optimized background therapy — no. (%)				
0	4 (17)	2 (17)	6 (17)	12 (17)
1	7 (29)	7 (58)	13 (36)	27 (38)
≥2	13 (54)	3 (25)	17 (47)	33 (46)

NEJM 2022;386:1793

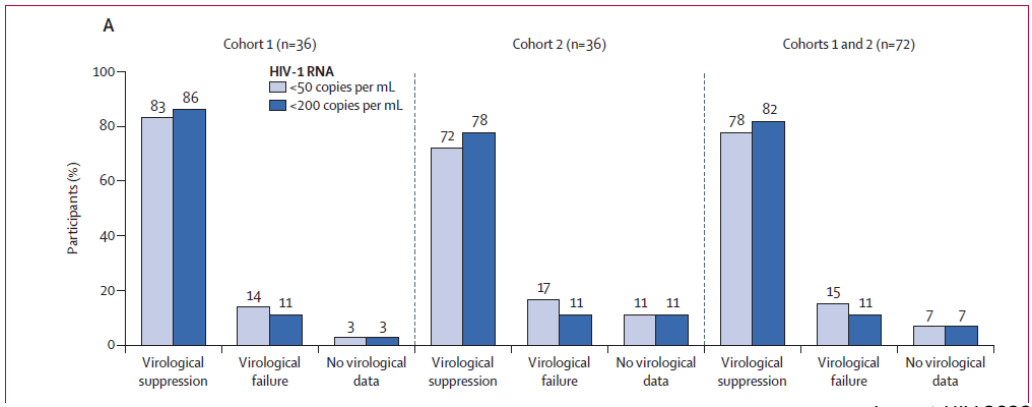
Lenacapavir in multidrug-resistant HIV: CAPELLA



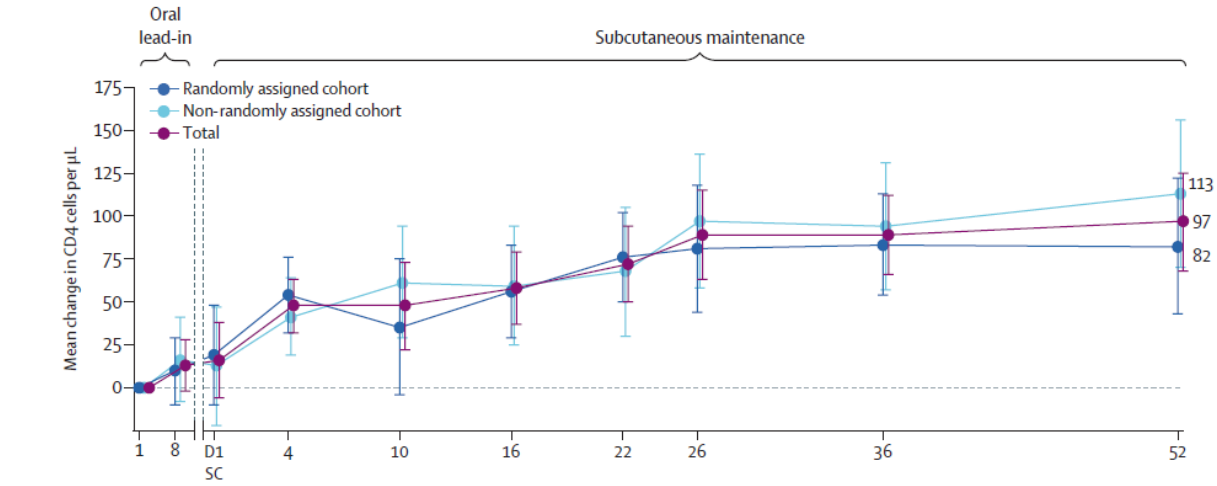
NEJM 2022;386:1793

Efficacy and safety of the novel capsid inhibitor lenacapavir to treat multidrug-resistant HIV: week 52 results of a phase 2/3 trial

Onyema Ogbuagu, Sorana Segal-Maurer, Winai Ratanasuwan, Anchalee Avihingsanon, Cynthia Brinson, Kimberly Workowski, Andrea Antinori, Yazdan Yazdanpanah, Benoit Trottier, Hui Wang, Nicolas Margot, Hadas Dvory-Sobol, Martin S Rhee, Jared M Baeten, Jean-Michel Molina, on behalf of the GS-US-200-4625 Investigators*



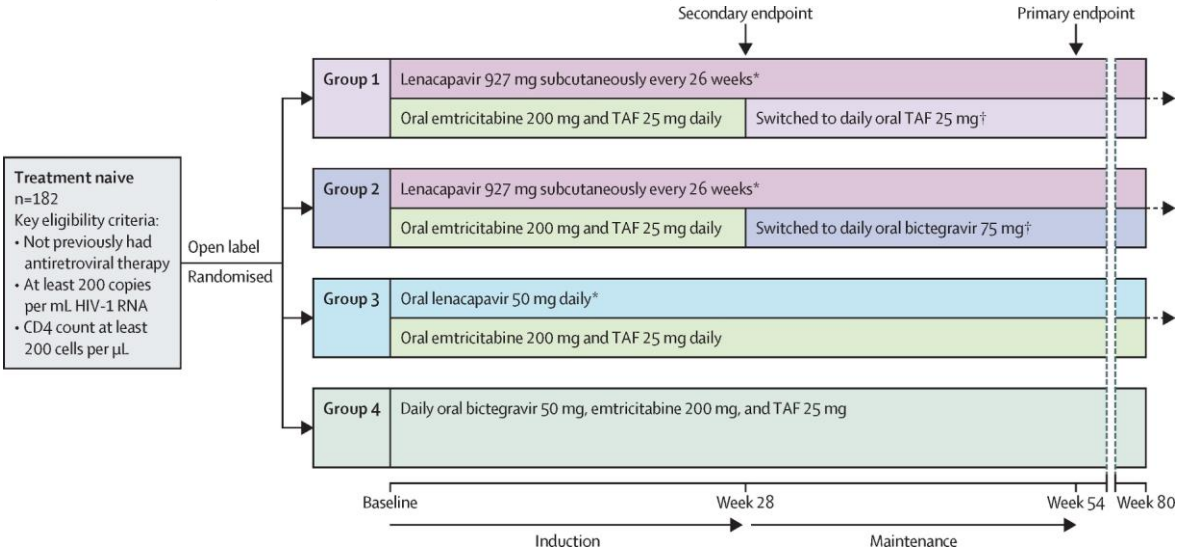
Lancet HIV 2023;10:e497



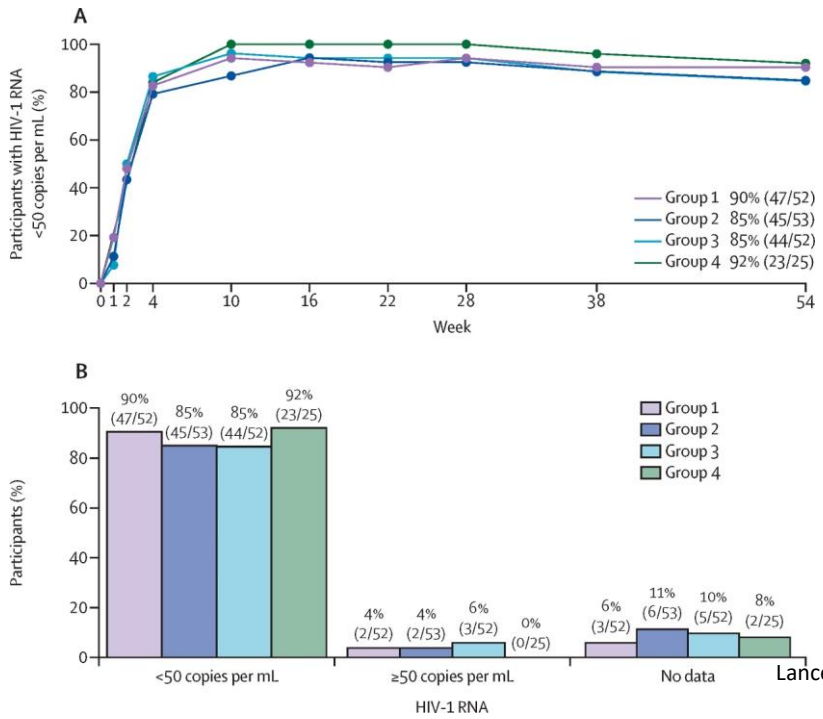
n										
Randomly assigned cohort	36	35	35	36	35	36	34	34	35	35
Non-randomly assigned cohort	36	33	35	35	31	30	33	33	32	31
Total	72	68	70	71	66	66	67	67	67	66

Lancet HIV 2023;10:e497

Lenacapavir in initial therapy: CALIBRATE



Lancet HIV 2023;10:e15

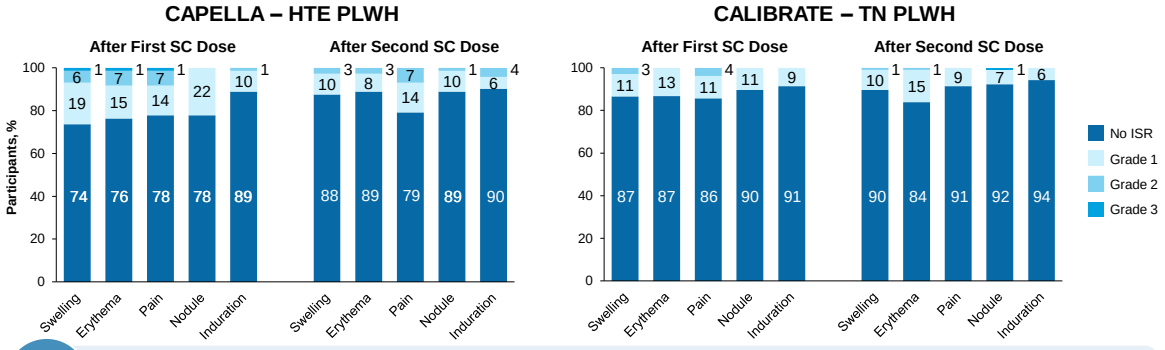


Lancet HIV 2023;10:e15

‡

Incidence of ISRs Related to SC LEN*

Capella Calibrate



- **Most ISRs were Grade 1** (42% [30/72] in CAPELLA and 48% [49/103] in CALIBRATE), and incidence generally declined from 1st to 2nd injection
- No serious or Grade 4 ISRs were reported; 3 participants (2%) had Grade 3 ISRs
- 4/174 (2%) participants discontinued due to ISR, all of which were Grade 1 and participant driven†

LEN was generally well tolerated, with most participants (70–90%) experiencing no ISRs of swelling, erythema, pain, nodule or induration. 2% (4/175) of participants discontinued LEN due to ISRs

*Only includes AEs related to LEN as determined by the investigator and excludes those not related to it; includes ISRs > 10% in both studies; †CAPELLA: Grade 1 nodule discontinuation at Day 379; CALIBRATE: Grade 1 induration discontinuation at Day 211; Grade 1 induration discontinuation at Day 156, and Grade 1 erythema and swelling discontinuation at Day 399
HTE, heavily treatment-experienced; ISR, injection-site reaction; TN, treatment-naïve
Kumar P, et al. AIDS 2022, Poster EPB184

In vitro studies

In Vitro and PK Data

‡

Activity and Resistance Characterization of LEN

Resistance Selected by LEN[1,*]

HIV-1 capsid sequence	LEN fold-resistance†	Replication capacity, % wild-type‡
T107N	3.8	32
Q67H	4.8	58
N74D	16	ND
Q67H + N74S	20	15
Q67H + T107N	87	ND
L56I	204	3.6
Q67H + M66I	1,594	ND
Q67H + N74D	> 2,700	ND
M66I	> 2,700	1.5

- LEN mutations were not found in analysis of 1,500 HIV clinical isolates[2]
  - Lack of pre-existing genotypic resistance to LEN
- In vitro resistance selections identified 7 mutations arising at 6 amino acids in capsid[3]
  - *L56I, M66I, Q67H, K70N, K74S/D, T107N*
  - All mutations map to LEN binding site

- Resistance was associated with low replication capacity for most mutants *in vitro*[3]
- There was no cross resistance between LEN and other ARV classes (NRTIs, NNRTIs, PIs, INSTIs, MIs and EIs)[4,5]

Both single and double LEN-selected mutations conferred reduced LEN susceptibility and decreased viral fitness

*Assessed using PhenoSense Gag-Pro (single cycle). Results were consistent across single- and multi-cycle assay formats and across primary cells and cell lines; †Ratio of Mutant/WT EC_{50}, determined with SC reporter HIV-1 in PhenoSense Gag-Pro assay; ‡Percentage of reference strain, determined with SC reporter HIV-1 in PhenoSense Gag-Pro assay
EC_{50}, 50% effective concentration of half maximal response; ND, not determined
1. VanderVeen L, et al. vCROI 2021, Oral 128; 2. Marcelin AG, J Antimicrob Chemother 2020;75:1588-1590; 3. Link J, et al. Nature 2020;584:614-618; 4. Margot N, et al. Antimicrob Agents Chemother 2021;65(3):e02057-20; 5. Margot N, et al. CROI 2022, Poster 508

Resistance at failure

- CAPELLA 52wks:
  - 22 tested for resistance
  - 9/22 developed LEN RAMs (4 had 0 active drugs in OBR, 5 poor adherence)
  - 4/9 resuppressed on LEN (2 with change in OBR, 2 without)
  - No resistance to OBR

- CALIBRATE:
  - 6 tested for resistance
  - 1 developed LEN RAM + M184I/V at wk 10 on LEN/TAF/FTC
  - 1 developed LEN RAM on rebound at wk 54 on LEN/TAF/FTC

Pharmacokinetics: Phase 1

In Vitro and PK Data ‡

PK of a Simplified LEN Initiation Regimen and the CAPELLA Regimen

Phase 1, single-center, open-label, multicohort study in healthy participants

CAPELLA Initiation Regimen (n = 31)

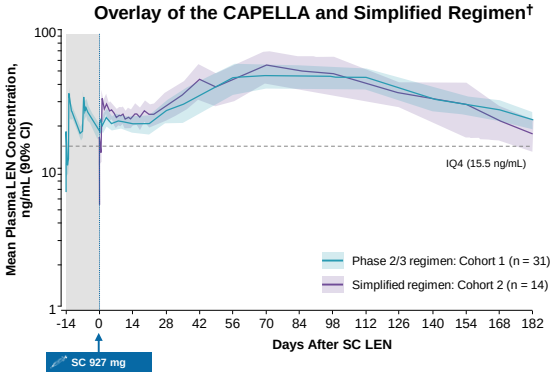
	Sun	Mon	Tues
Week 1	–	Day 1	Day 2
Week 2	–	Day 8	–
Week 3	–	Day 15	–

Simplified LEN Initiation Regimen* (n = 14)

	Sun	Mon	Tues
Week 1	–	Day 1	Day 2

Oral Len (300 mg) SC LEN (927 mg)

Overlay of the CAPELLA and Simplified Regimen†



LEN concentrations following the CAPELLA and simplified initiation regimens were generally comparable and provided similar LEN exposure

*As used in the HIV PrEP PURPOSE trials; †Grey-shaded area represents 14-day oral loading period for the CAPELLA regimen. IQ, inhibitory quotient; PK, pharmacokinetic(s)
Jogiraju V, et al. AIDS 2022, Poster PESUB22

50

Examination of Oral LEN Efficacy and Safety Following Oral Bridging in CAPELLA and CALIBRATE Participants

Dec 20, 2021 — FDA-imposed full clinical hold of SC LEN due to glass vial compatibility concerns[1]

May 16, 2022 — FDA hold lifted, SC LEN resumed[2]

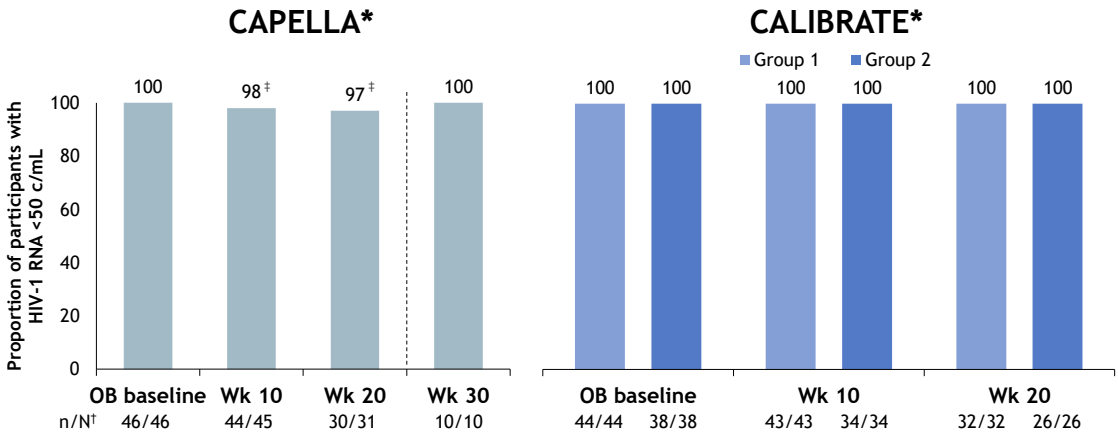
The clinical hold provided the opportunity to examine the efficacy and safety of oral bridging using QW LEN

- Due to the clinical hold, participants in CAPELLA and CALIBRATE were temporarily unable to receive SC LEN
- Oral bridging of LEN was used for participants who had an injection due during the hold period, until SC dosing could be resumed

Objective: Post-hoc analysis to assess efficacy and safety of oral LEN (300 mg PO QW) in MDR and treatment-naïve PWH in CAPELLA and CALIBRATE when SC LEN dosing was interrupted

FDA, Food and Drug Administration; LEN, lenacapavir; MDR, multidrug resistant; PWH, people with HIV; PO, orally; QW, once weekly; SC, subcutaneous.
1. https://www.gilead.com/news-and-press/press-room/press-releases/2021/12/gilead-announces-clinical-hold-on-studies-evaluating-injectable-lenacapavir-for-hiv-treatment-and-prevention-due-to-vial-quality-concerns (Accessed July 2023); 2. https://www.gilead.com/news-and-press/press-room/press-releases/2022/5/fda-lifts-clinical-hold-on-investigational-lenacapavir-for-the-treatment-and-prevention-of-hiv (Accessed July 2023)

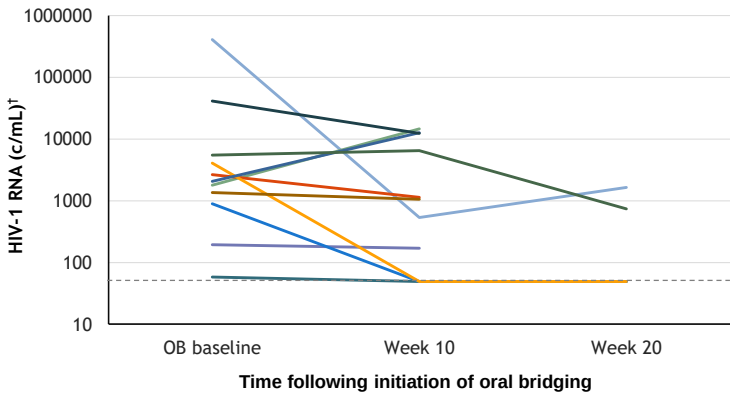
Efficacy (M=E analysis) During Oral Bridging Amongst Participants Suppressed at the Switch to Oral LEN



CD4 counts remained stable throughout oral bridging amongst participants suppressed at oral bridging baseline

*Participants had virologic suppression at oral bridging baseline; missing = excluded; †Denominators reflect participants who reached the specified duration of oral bridging; ‡Of participants with baseline HIV-1 RNA <50 c/mL, one did not maintain HIV-1 RNA <50 c/mL during the oral bridging period at Week 10 and 20 (Week 10 values: 920 c/mL; Week 20 values: 57 c/mL). The participant developed a LEN resistance-associated mutation (N74D), and had missed two, non-consecutive doses of oral LEN prior to the elevated HIV-1 RNA results. The participant resuppressed after the oral bridging period with no optimized background regimen change.
c/mL, copies per milliliter; LEN, lenacapavir; M=E, missing = excluded; OB, oral bridging; wk, week.

Viral Load During Oral Bridging Amongst CAPELLA Participants* Not Suppressed at the Switch to Oral LEN



Amongst the 11 viremic participants at oral bridging baseline, suppression (HIV RNA <50 c/mL) occurred in:

- 3/11 (27%) at Week 10
- 2/4 (50%) at Week 20

None of the 11 viremic participants at oral bridging baseline experienced more than 1 log increase in viral load during oral bridging

*Data are shown for 11 participants in CAPELLA without virologic suppression (i.e. HIV-1 RNA ≥50 c/mL) at oral bridging baseline; no participants in CALIBRATE had HIV-1 RNA ≥50 c/mL at oral bridging baseline. Resistance testing and pharmacokinetic analyses for these participants are ongoing. †For illustrative purposes, samples with <50 c/mL are shown on figure as 49 c/mL
c/mL copies per milliliter; LEN, lenacapavir

Safety Profile of LEN During Oral Bridging

Groups receiving oral LEN (oral bridging analysis set)

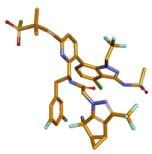
TEAE	CAPELLA (n=57)	CALIBRATE	
		Group 1 (n=44)	Group 2 (n=38)
Any-grade, n (%)	28 (49.1)	28 (63.6)	25 (65.8)
GI disorders	7 (12.3)	4 (9.1)	7 (18.4)
Treatment-related, n (%)	2 (3.5)	1 (2.3)	2 (5.3)
Grade ≥3, n (%)	1 (1.8)	2 (4.5)	1 (2.6)
Serious, n (%)	1 (1.8)	1 (2.3)	1 (2.6)
Selected AEs*, %	Cough: 5.3 Diarrhea: 5.3 URTI: 5.3	**Group 1 and 2 total:** Nasopharyngitis: 4.9 Syphilis: 4.9 Oropharyngeal pain: 4.9	

- Treatment with LEN oral bridging was generally well tolerated in CAPELLA and CALIBRATE, with a safety profile consistent with SC LEN in the primary analysis (excluding ISRs)
- No Grade ≥3 or serious TEAEs were considered related to study drug in either study
- One death occurred during oral bridging (CAPELLA; cause unknown, not deemed related to study treatment by the investigator)
  - Prior to oral bridging, this participant had experienced a TEAE of alcoholic hepatitis
- No TEAE led to early discontinuation in either study

Adverse events were coded according to MedDRA Version 25.0. Severity grades were defined by division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Version 2.1; July 2017). Data collected during oral bridging period were included. *CAPELLA: COVID-19, 7.0%; CALIBRATE: influenza, 8.5%; COVID-19, 4.9%.
AE, adverse event; ISR, injection-site reaction; GI, gastrointestinal; LEN, lenacapavir; MedDRA, medical dictionary for regulatory activities; SC, subcutaneous; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

‡

Investigational Long-Acting and Daily Oral HIV Portfolio



Lenacapavir

Pre-IND	Phase 1	Phase 2	Phase 3
Lenacapavir + GS-1614 (NRTI) Q3M INJECTION Treatment	Lenacapavir + GS-6212 (INSTI) Q3M INJECTION Treatment	Bictegravir + Lenacapavir† DAILY ORAL Treatment	Lenacapavir‡ Q6M INJECTION Prevention
Lenacapavir + GS-1219 (INSTI) Q6M INJECTION Treatment	Lenacapavir + GS-1720 (INSTI) WEEKLY ORAL Treatment	Lenacapavir + Islatravir (NRTI)# WEEKLY ORAL Treatment	
Lenacapavir + GS-3242 (INSTI) Q6M INJECTION Treatment	Lenacapavir + GS-5894 (NNRTI) WEEKLY ORAL Treatment	Lenacapavir + TAB/ZAB (bNAbs)* Q6M INJECTION Treatment	
	GS-4182 (LEN pro-drug) WEEKLY ORAL Treatment		

†For virologically suppressed treatment experienced; ‡Phase 3 PURPOSE-1/-2 studies ongoing with Phase 2 PURPOSE-3/-4 expected to FPI in 2H23; #Subject to Gilead and Merck co-development and co-commercialization agreement; *Teropavimab (TAB) and zinlirvimab (ZAB) are broadly neutralizing antibodies (bNABs).
IND, investigational new drug application; LEN, lenacapavir; Q3M – every 3 months, Q6M – every 6 months.
Gilead Earnings Presentation 3 AUG 2023.

Phase 1b: Investigational LEN + TAB + ZAB in VS PLWH (GS-US-536-5816)

‡

LEN with bNAbs, Teropavimab and Zinlirvimab in Virologically Suppressed PLWH

N = 21

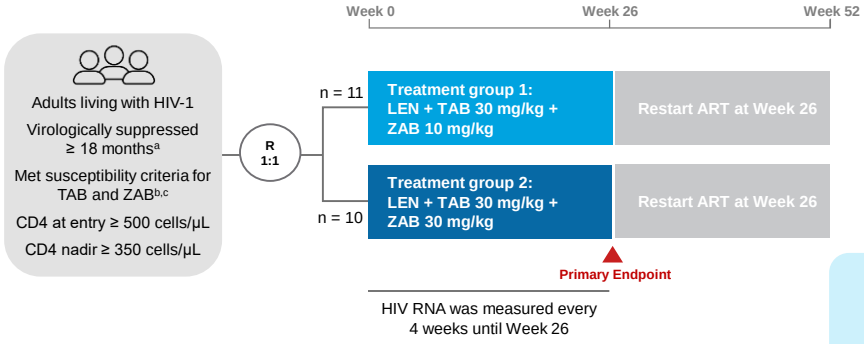
Virologically suppressed PLWH, aged ≥ 18 years

Outcomes

Primary: Safety and tolerability

Secondary: HIV-1 RNA < 50 and ≥ 50 c/mL at Week 26 (FDA snapshot); PK

2021-Ongoing



Dosing	Day 1	Day 2
LEN oral 600 mg	2	2
LEN SC 927 mg	1	-
TAB IV 30 mg/kg	1	-
ZAB IV 10 mg/kg or 30 mg/kg	1	-

The study design was amended to have participants restart ART at Week 26 after the FDA clinical hold on investigational LEN due to stability issues in borosilicate vials

[a]Previous virologic failure was allowed as long as participants had been suppressed for at least 18 months prior to screening.
[b]Susceptibility defined as IC90 ≤ 2 µg/mL to each antibody by PhenoSense mAb Assay (Monogram Biosciences).
[c]A pilot cohort is actively assessing safety, efficacy, and PK in PLWH who have sensitivity to *either* TAB or ZAB
IC, inhibitory concentration; PK, pharmacokinetics; TAB, teropavimab; VS, virologically suppressed; ZAB, zinlirvimab

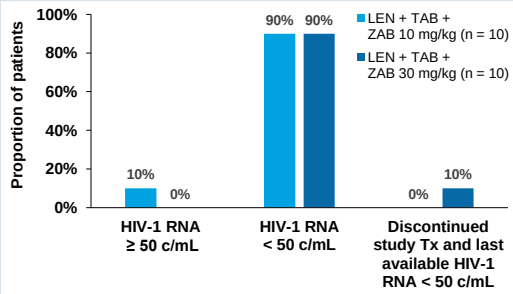
Eron J, et al. CROI, 2023, Oral 193

Phase 1b: Investigational LEN + TAB + ZAB in VS PLWH (GS-US-536-5816)

‡

Week 26: Efficacy and Safety

Virologic Outcomes at Week 26



- One participant withdrew at Week 12 with HIV-1 RNA < 50 c/mL
- One participant had a confirmed virologic rebound at Week 16
- CD4 cell counts remained stable over the course of the study period

Safety and Tolerability

There were no serious AEs, no Grade 4 AEs and no AEs that led to study treatment discontinuation

There were two Grade 3 AEs:

- One injection-site cellulitis on Day 1, which resolved with antibiotics
- One injection-site erythema on Day 3, which resolved without intervention by Day 10

AEs occurring in ≥ 3 participants:

- Injection site pain
- Erythema
- Nodule
- Induration
- Mass
- COVID-19
- Upper respiratory tract infection

LEN with the bNAbs, TAB & ZAB, can sustain viral suppression for 6 months in selected PLWH.

bNAb, broadly neutralizing antibody; TAB, teropavimab; Tx, treatment; VS, virologically suppressed; ZAB, zinlirvimab

Eron J, et al. CROI, 2023, Oral 193