Presente e futuro delle strategie di trattamento dell'infezione da HIV

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Conflitti di interesse

- Partecipation to advisory boards or consultancies for Gilead Sciences and ViiV Healthcare

Il Presente: moderne strategie per l'ottimizzazione della cura

• Triplici terapie

- Advanced stages of HIV disease,
- High viral loads,
- Deteriorated immunity,
- Pregnancy,
- Poor adherence,
- Archived resistance-associated mutations,
- Preservation of the efficacy of key components of antiretroviral regimens
- Futility
- Not available in long acting formulation
- lower tolerability/higher toxicity (?)

• Regimi a due farmaci

- Non inferior to triple therapies in people with eligibility criteria
- Lower drug burden without reducing efficacy
- Flexibility of combinations
- Available in long acting formulation (only one regimen)
- Pregnancy,
- Difficult to treat populations,
- Some associations have only observational data on support

Bictegravir/emtricitabine/tenofovir alafenamide as initial treatment for HIV-1: five-year follow-up from two randomized trials

Paul E. Sax,[a,] José R. Arribas,[b] Chloe Orkin,[c] Adriano Lazzarin,[d] Anton Pozniak,[e] Edwin DeJesus,[f] Franco Maggiolo,[g] Hans-Jürgen Stellbrink,[h] Yazdan Yazdanpanah,[i] Rima Acosta,[j] Hailin Huang,[j] Jason T. Hindman,[j] Hal Martin,[j] Jared M. Baeten,[j] and David Wohl,[k] on behalf of the GS-US-380-1489 and GS-US-380-1490 study investigators*

The safety and efficacy of **B/F/TAF** as **initial therapy** was established in two Phase 3 studies: **1489** (vs dolutegravir [DTG]/abacavir/lamivudine) and **1490** (vs DTG + F/TAF). After 144 weeks of randomized follow-up, an open-label extension evaluated B/F/TAF to 240 weeks.

- Screening began in November 2015, with final participant visits for the 240-week analysis occurring in July 2021.
- 634 participants were randomized to and started treatment with B/F/TAF;
- 119/634 (18.8%) had HIV-1 RNA >100,000 copies/mL
- 80/634 (12.6%) had a CD4+ T cell count <200 cells/µL.

Sax P. et al; 2023 Eclinical Medicine May 11:59:101991.

RESULTS: EFFICACY

- Of those with available virologic data, **98.6% (95% CI [97.0%–99.5%], 426/432) maintained HIV-1 RNA <50 copies/mL at Week 240** (missing = excluded)

- Change in CD4+ count from baseline was +338 (236.2) cells/µL.

- Nine participants met criteria for resistance testing, none of whom developed resistance to any component of B/F/TAF in the final resistance analysis population. Of the 9, 7 participants discontinued (investigator discretion/participant decision) and 2 were lost to follow-up.
- **No treatment-emergent resistance to B/F/TAF was detected.**

Research in context

Evidence before this study

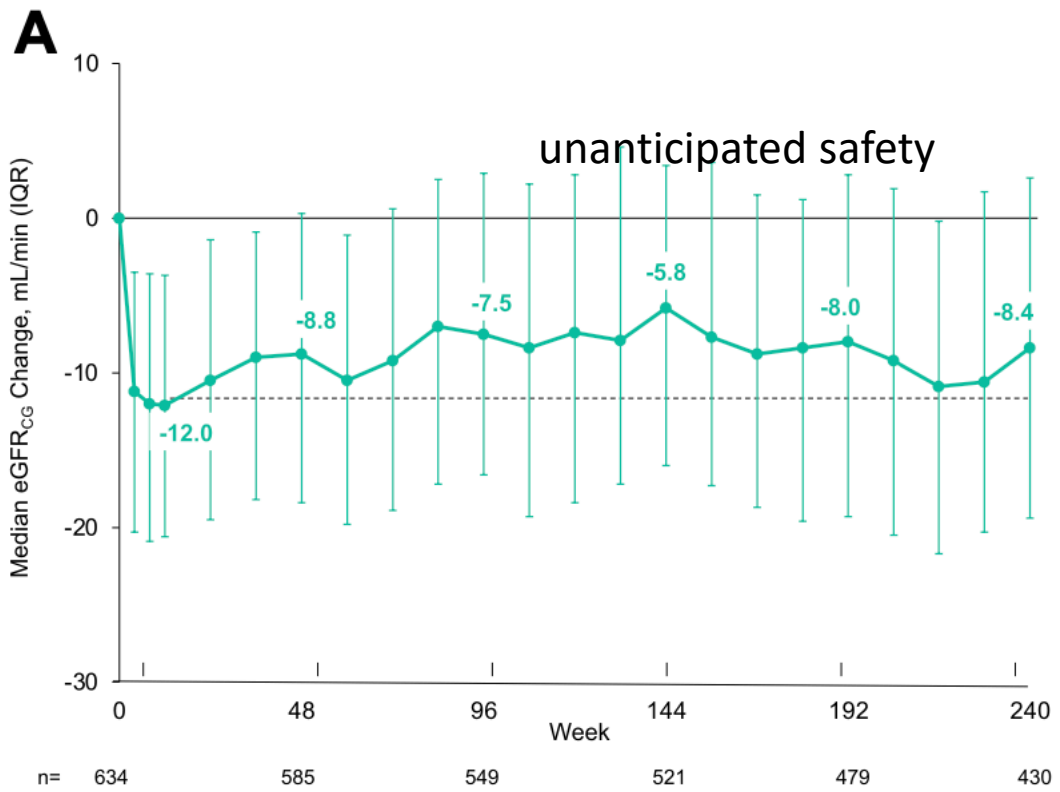
The combination of bictegravir, emtricitabine, and tenofovir alafenamide for initial treatment of HIV-1 has showed non-inferiority to standard-of-care regimens and a similar renal, bone, and lipid safety profile to comparators after 144 weeks. Longer-term data remain necessary to inform clinical care.

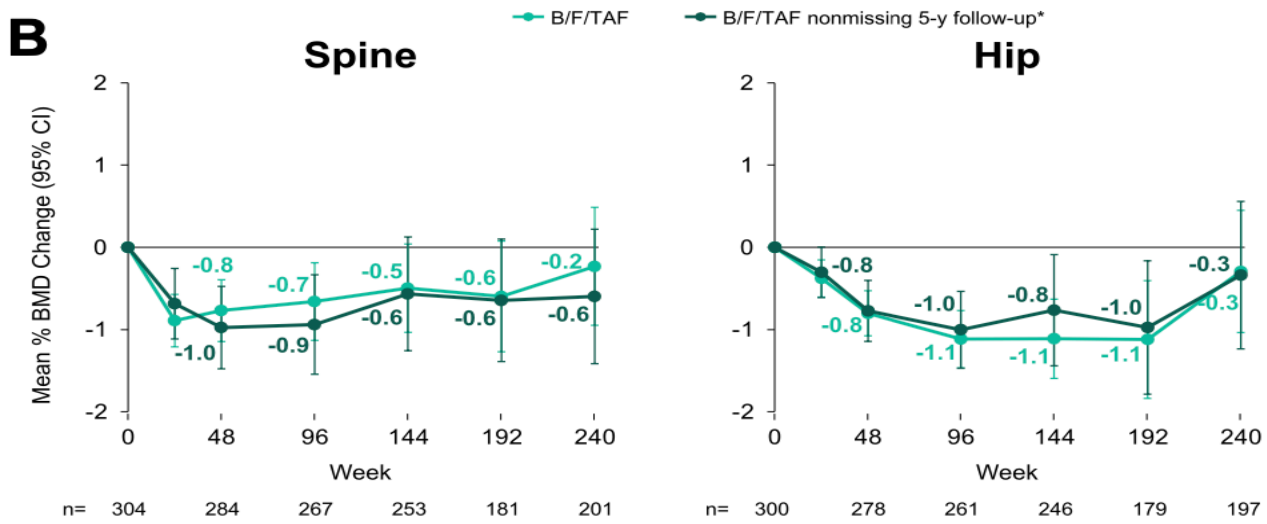
Sax P. et al; 2023 Eclinical Medicine May 11:59:101991.

RESULTS: SAFETY

- Adverse events led to drug discontinuation in 1.6% (n = 10/634) of participants (n = 5 with events considered drug-related). No discontinuations were due to renal adverse events.
- No unanticipated safety signals emerged with long-term treatment with B/F/ TAF.

Study-drug related adverse events	178 (28.1)
Study-drug related adverse events (present in ≥2%)	
Headache	31 (4.7)
Diarrhea	30 (4.7)
Nausea	28 (4.4)
Fatigue	17 (2.7)
Dizziness	15 (2.4)
Insomnia	13 (2.1)
Study-drug related serious adverse events[b]	5 (0.8)
Any adverse event leading to study drug discontinuation[c]	10 (1.6)

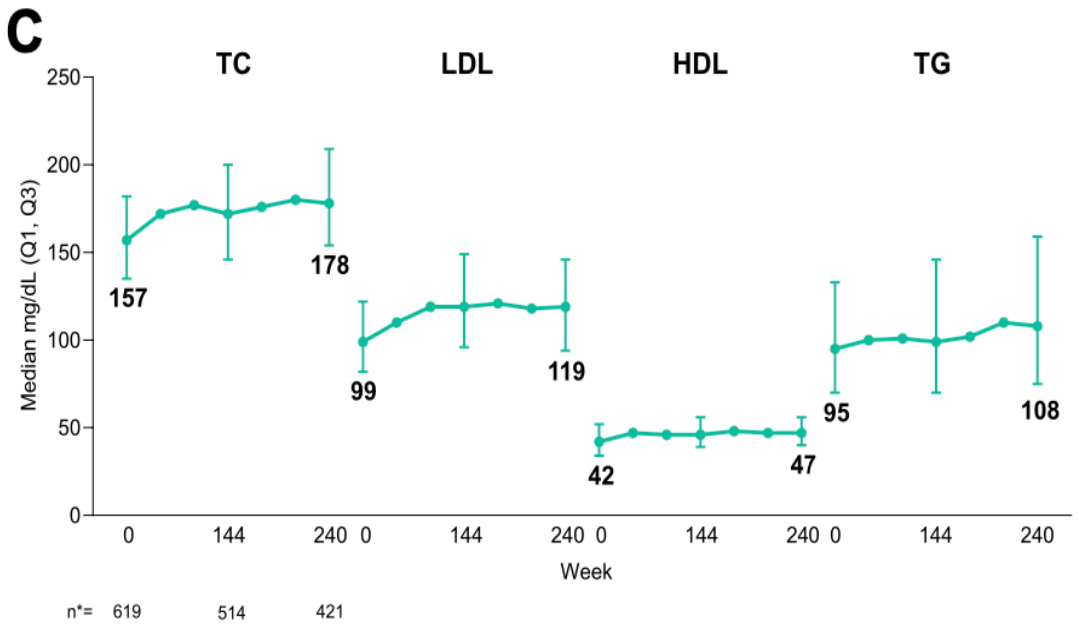


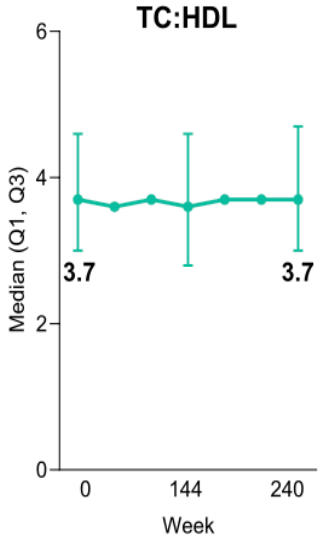


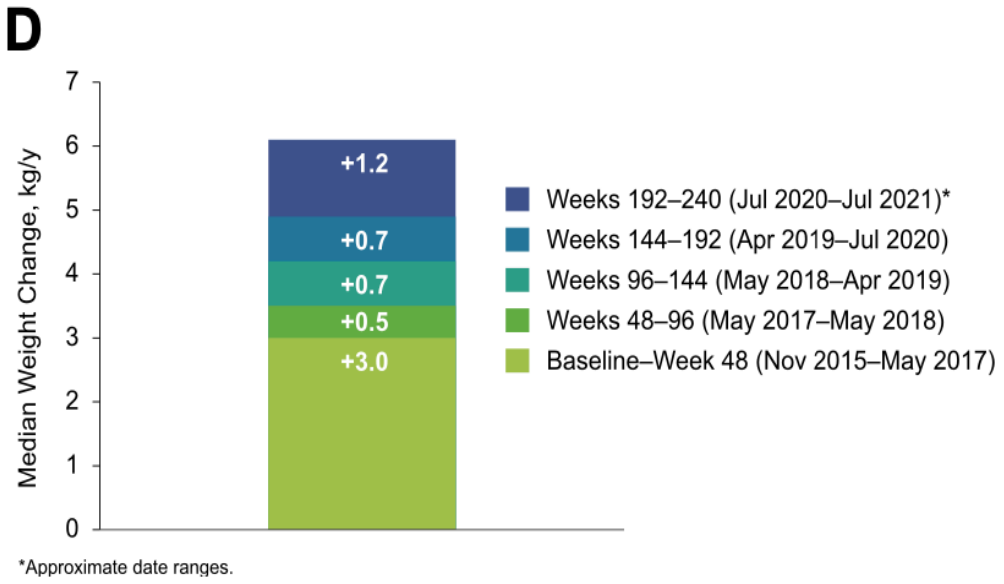
Sax P. et al; 2023 Eclinical Medicine May 11:59:101991.

RESULTS: SAFETY

- Median (IQR) total cholesterol increased 21 (1,42) mg/dL from baseline;
- the change in total cholesterol:HDL was 0.1 (−0.5,0.6).
- Median (IQR) weight change from baseline was +6.1 kg (2.0, 11.7) at Week 240.







Sax P. et al; 2023 Eclinical Medicine May 11:59:101991.

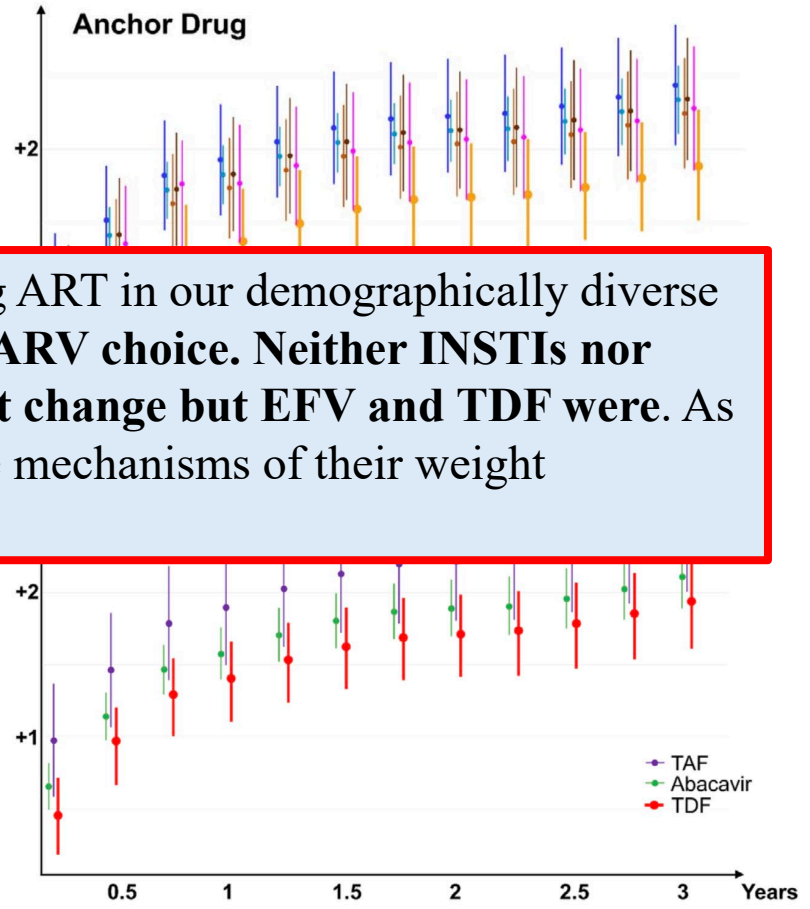
AIDS, Publish Ahead of Print

DOI: 10.1097/QAD.0000000000003950

Choice of Antiretroviral Therapy Has Low Impact on Weight Gain

(Running Head: "ARVs and Weight Gai

Henning DRECHSLER MD[1,2]; Colby A
MD[1,2]; John HANNA MD[1,3]; Christophe
Amneris LUQUE MD[1,4]; Roger BEDIM



In conclusion, **the substantial weight gain** during ART in our demographically diverse cohort was largely **driven by factors other than ARV choice. Neither INSTIs nor TAF were independently associated with weight change but EFV and TDF were**. As both of these older ARVs are still widely used, the mechanisms of their weight suppressive effects deserve further investigation.

Based on the marginal coefficients of determination, overall BMI change was mostly predicted by factors other than ARV choice:

HIV characteristics during ART (CD4 change, VL suppression): 45%

HIV characteristics at baseline (CD4, VL): 36%

ARV choice: 9%

Demographics: 6%

Baseline BMI: 4%

The contribution of individual ARVs to BMI change was assessed using GEE models
Only the first model – which adjusted just for baseline covariates (Table 1) - predicted significantly greater BMI gain for DTG compared to the other "anchor" drugs (except BIC). But after adjustment for concomitant NRTI use in the second model, these differences disappeared - except with EFV.
Within the NRTI category, all three models predicted significantly lower BMI gain for TDF compared to TAF but the difference between ABC and TAF was never significant

Weight Change in VS PWH on ART Versus PWoH Over a 3-Year Period

N=68,656

- VS PWH (n=11,888)
- PWoH (n=56,768)

Outcomes

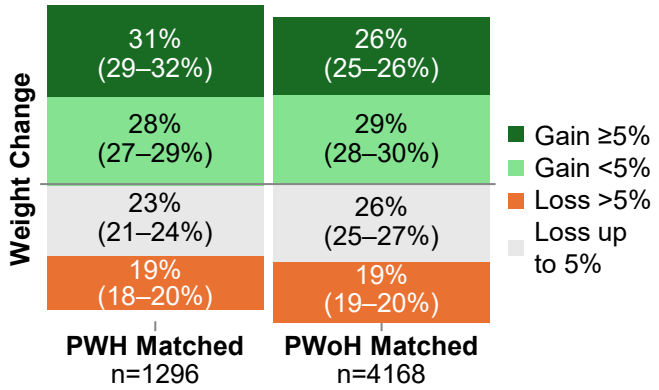
- Weight change and odds of shifting up BMI class from baseline to Year 3
- Unmatched (n=68,656) and matched (n=5464) analyses[a]

January 2015–August 2023

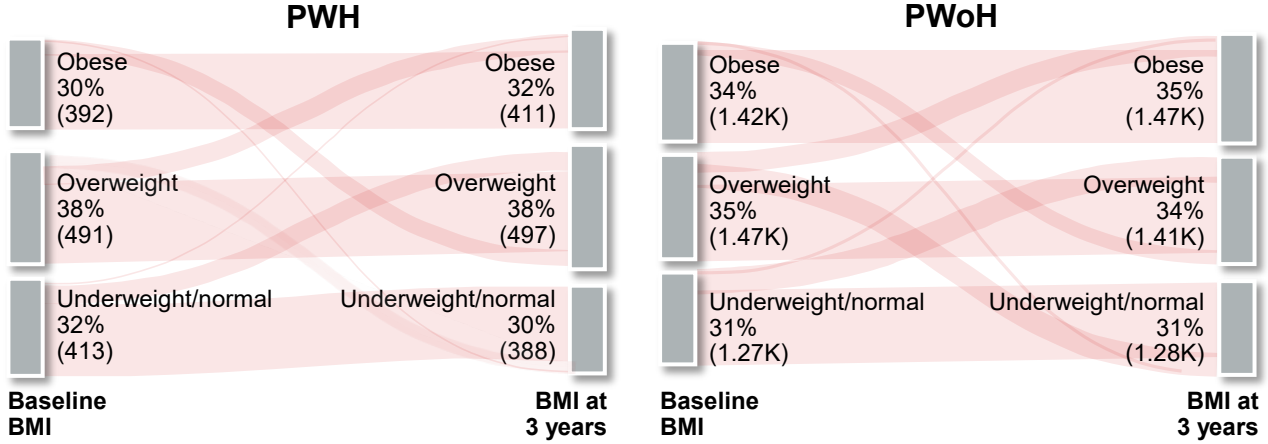
After matching, baseline characteristics were well balanced between PWH and PWoH, except for:

- Higher frequency of neuropsychiatric disorders, smoking, STIs and some concomitant medications[b] in PWH
- Higher BMI, frequency of obesity and diabetes in PWoH

Distribution of Weight Change After 3 Years: Matched Unadjusted



Shift in BMI After 3 Years (Matched Analysis)



PWH and PWoH did not differ in 3-year mean weight change (0.4 kg; 95% CI: -0.1, 0.9)[c]

- In matched analysis, a **greater proportion of PWH (13%) versus PWoH (11%) shifted up a BMI class (*P*=0.02;** odds ratio: 1.2; 95% CI: 1.0, 1.5)
- Results may be influenced by a higher prevalence of obesity at baseline among PWoH

In this analysis of VS PWH, which accounted for return to health and other population differences, mean weight change was similar among PWH and PWoH at 3 years of follow-up

ART choice and switch were not analyzed. [a]PWH and PWoH were matched on baseline characteristics (clinic, baseline year, gender, age, race and propensity score), with additional adjustment for imbalanced covariates after matching; [b]Lipid lowering, heart failure or psychiatric; [c]Matched and adjusted analysis for residual covariate imbalance
PWoH, people without HIV; VS, virologically suppressed
Elion RA, et al. CROI 2024, Poster 815

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Background: The promise of LA ART

In recent years, **monthly and two-monthly LA injectable formulations** of CAB and RPV have been developed[1]

- The **LATTE-2 Phase IIb** study demonstrated that CAB + RPV LA was as effective as a daily oral 3DR (CAB + ABC/3TC) at maintaining viral suppression, and was well accepted and tolerated[1]
- Four Phase III studies (ATLAS, ATLAS-2M, FLAIR and SOLAR) have been completed to evaluate the efficacy, safety and acceptability of these treatments[2–5]
- The development of these therapies has the **potential to redefine HIV care of PLHIV** by addressing the psychosocial burdens (e.g. **fear of disclosure, adherence anxiety and daily reminder of HIV status**) of daily oral treatments[5,6]

Patient perspective on the **potential benefits of LA injectable ART** was compared with daily oral ART[2–5]

- The first Phase III studies of CAB + RPV LA (**ATLAS**, **ATLAS-2M** and **FLAIR**) used PROs to explore aspects of the patient experience, including **tolerability** and **acceptability** of IM injections, treatment **acceptance**, treatment **satisfaction** and **preference**, and **health status** and **QoL**[2–4]
- PROs were also used to assess **psychosocial challenges related to** daily oral ART at BL in the **SOLAR** study[2–5]

ABC, abacavir; **IM,** intramuscular

1. Margolis D, et al. Lancet 2017;390:1499–510; **2.** Swindells S, et al. N Engl J Med 2020;382:1112–23
3. Overton E, et al. Lancet 2021;396:1994–2005; **4.** Orkin C, et al. N Engl J Med 2020;382:1124–35
5. Ramgopal MN, et al. Lancet HIV 2023;10:e566–77 (and suppl. appendix); **6.** Thornhill J & Orkin C. Curr Opin Infect Dis 2021;34:8–15

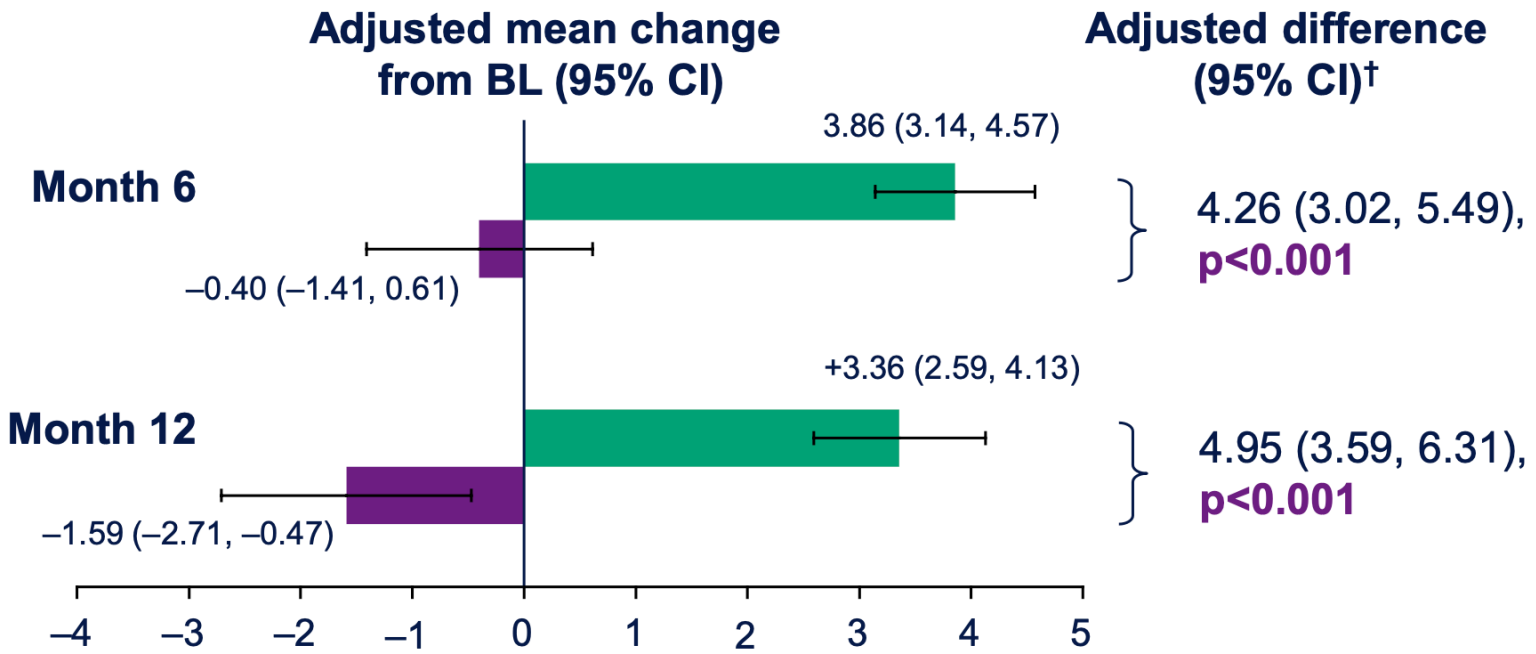
SOLAR: Treatment satisfaction
HIVTSQs:* Change from baseline in total score[1]

/ Mean BL HIVTSQs scores: **CAB + RPV LA**: 57.88; **BIC/FTC/TAF**: 58.38

HIVTSQs total score | **58 (BL)** → Improvement → **66 (maximum)**

CAB + RPV LA Q8W
(BL, n=466;
Month 6, n=436;
Month 12, n=410)

BIC/FTC/TAF QD
(BL, n=222;
Month 6, n=220;
Month 12, n=213)



Significantly greater increase in treatment satisfaction from BL after switching to CAB + RPV LA Q8W compared with continuing current daily oral ART at Months 6 and 12

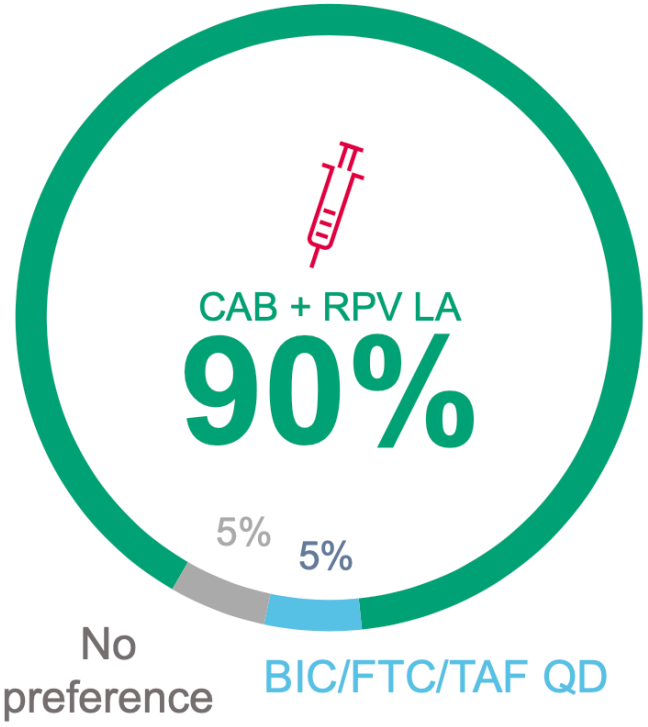
Purple text indicates significance; *HIVTSQs: HIV Treatment Satisfaction Questionnaire, status version; 12 items; range of total score 0–66 (0–6 per item for items 1–11); higher scores indicate greater satisfaction/positive changes indicate improvement[2]; †Based on a mixed model for repeated measures with visit as the repeated factor, including the following variables: treatment, visit, treatment x visit, maintenance BL score, sex at birth (male, female), BL body mass index (<30, ≥30 kg/m2), age (<50, ≥50 years) and race (white, non-white)
QD, once daily

1. Ramgopal MN, et al. Lancet HIV 2023;10:e566–77 (and suppl. appendix)
2. Woodcock A and Bradley C. Value Health 2006;9:320–333

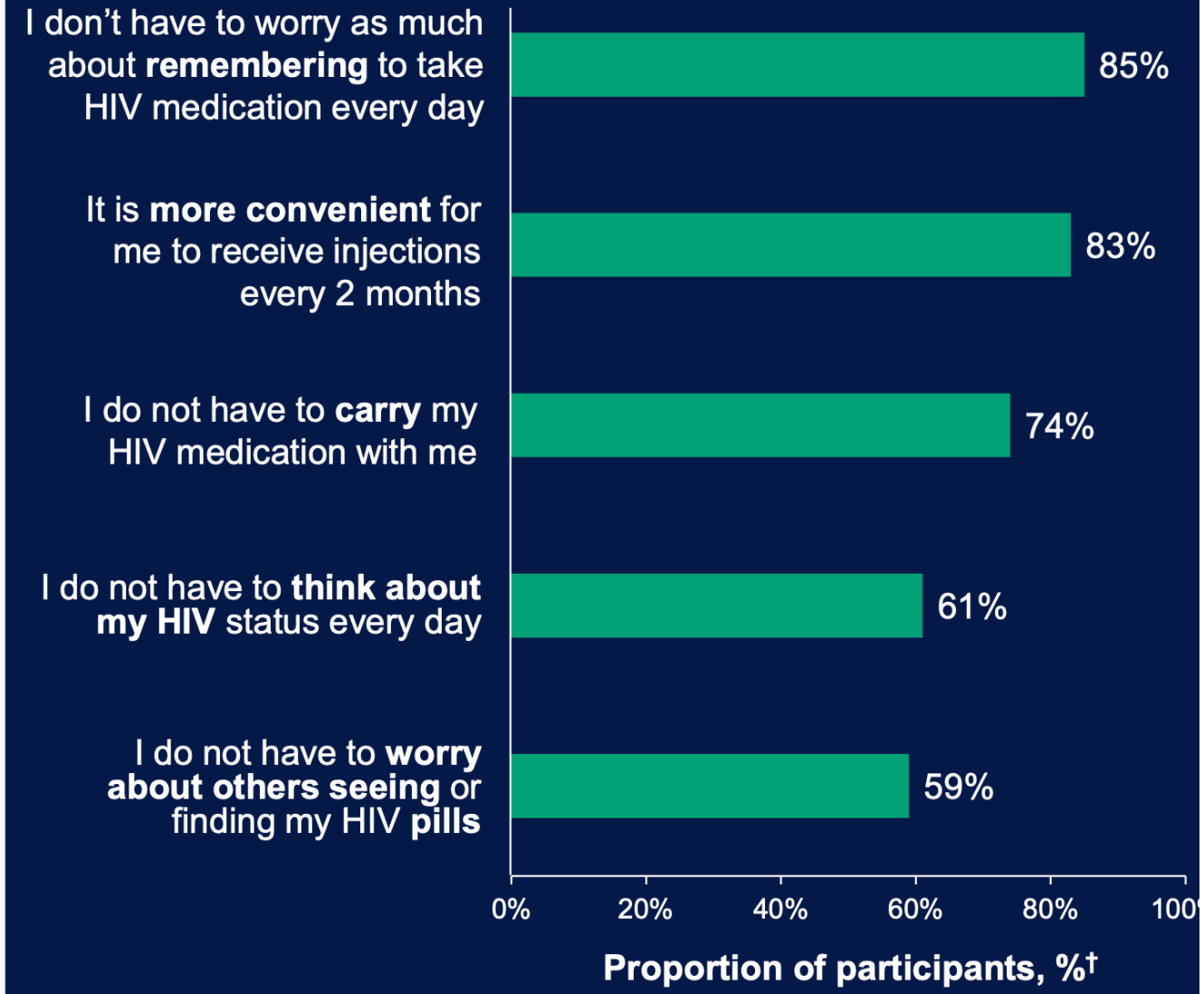
SOLAR

Trial participants preferred CAB + RPV LA to daily oral BIC/FTC/TAF

Which therapy do you prefer? (n=425)*



Why? (n=382)*



*Number of respondents of N=670 included in the study

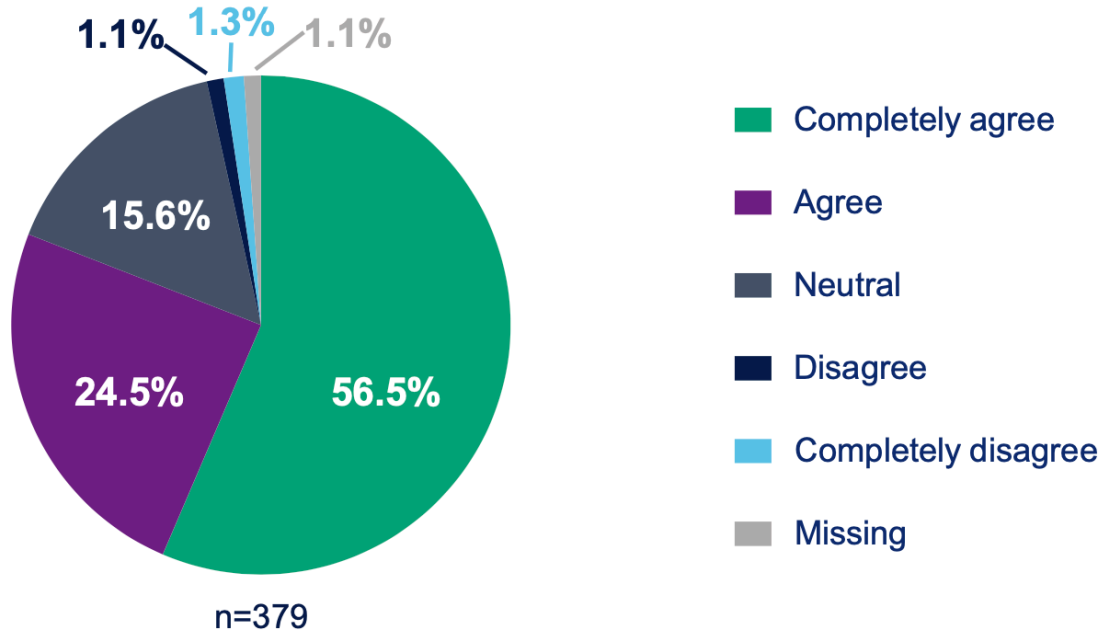
†Proportion of participants who preferred CAB + RPV LA over oral therapy at Month 12 or withdrawal (n=382)

Ramgopal MN, et al. Lancet HIV 2023;10:e566–77 (and suppl. appendix)

CARISEL: Perception of stigma

- Perception of stigma related to LA treatment was assessed for the first time in the CARISEL study

"CAB + RPV LA treatment is less stigmatising than my oral medications"



n=379

81% of patients agreed or completely agreed that CAB + RPV LA was less stigmatising than oral medication

Lutz T, et al. HIV Glasgow 2022. Poster P123

Updated Treatment Recommendation on Use of Cabotegravir and Rilpivirine for People With HIV From the IAS-USA Guidelines Panel

When supported by intensive follow-up and case management services, injectable cabotegravir and rilpivirine (CAB-RPV) may be considered for people with viremia who meet the criteria below when no other treatment options are effective due to a patient's persistent inability to take oral ART (rating AIIa under the conditions described).

- Unable to take oral ART consistently despite extensive efforts and clinical support
- High risk of HIV disease progression (CD4 cell count <200/μL or history of AIDS-defining complications)
- Virus susceptible to both CAB and RPV

If applicable, patients should also be referred for treatment of substance use disorder and/or mental illness.

This change is based on the accumulating evidence cited above. However, no randomized clinical studies exist to support this recommendation, and available data are limited by small numbers with variable follow-up, variation in dosing regimens, and insufficient information regarding the types and intensity of clinical support deployed. To generate more robust data, the panel continues to encourage clinicians to refer eligible patients to prospective clinical trials of this strategy.

Paul E. Sax, MD
Melanie A. Thompson, MD
Michael S. Saag, MD
for the IAS-USA Treatment Guidelines Panel

JAMA March 26, 2024
Volume 331, Number 12

Since publication of the IAS-USA treatment guidelines in December 2022, additional studies of CAB-RPV in people with HIV viremia due to difficulty taking oral ART have been reported. The authors of the original case series have published data on 57 individuals, of whom 94% achieved and maintained viral suppression, **with 2 developing treatment failure with resistance**. The **program used** intensive case- management services, including community-based supports, case managers and harm reduction services, travel support for visits or blood draws, as well as frequent review of the patients by a dedicated clinical team. In other studies of variable size, duration, and baseline demographic and clinical status, the virologic suppression rates with CAB-RPV in people with HIV viremia ranged from **57% to 100%;** however, **follow-up for some patients was only a few months**. A modeling study6 projected that the benefits of CAB-RPV in people with HIV viremia who could not take oral ART are greatest in those with advanced HIV-related immunosup- pression.

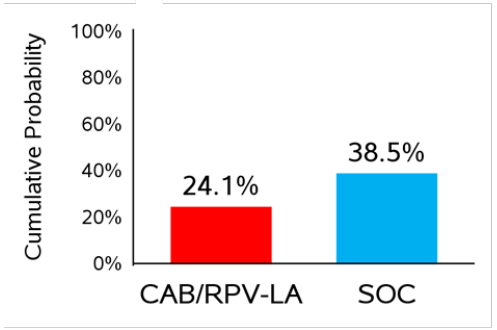
Gandhi M, et al. *Ann Intern Med*. 2023;176(7):969-974. Brock JB, et al. *Clin Infect Dis*. 2023;78(1):122-124. Hsu RK, et al., *Open Forum Infect Dis*. 2023;10(suppl 2):ofad500.059. doi:10.1093/ofid/ofad500.059

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

Primary Outcome

Regimen Failure

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

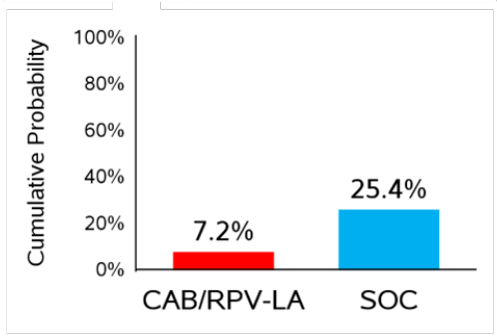


Number of participants		
Regimen Failure	28	47
VF	5	28
TRT-DISC	23	19

Secondary Outcomes

Virologic Failure

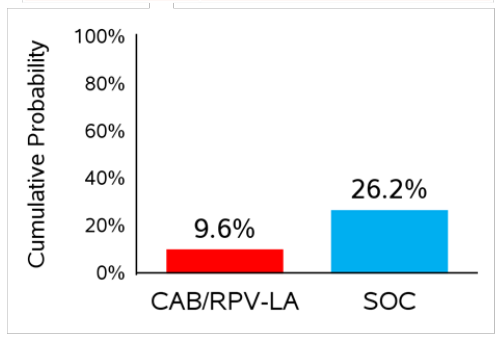
Difference	Nominal 98.75% CI
-18.2%	**(-31.1%, -5.4%)**



Number of participants		
Virologic Failure	6	28

Treatment-related Failure

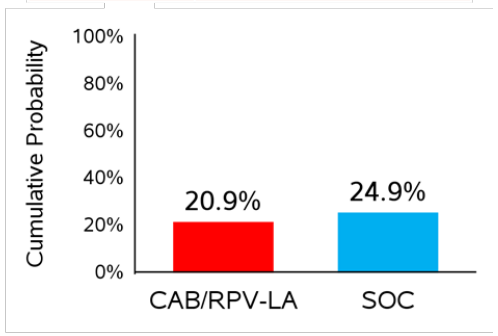
Difference	Nominal 98.75% CI
-16.6%	**(-29.9%, -3.3%)**



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

Permanent Treatment Discontinuation

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



Number of participants		
Permanent TRT-DISC	25	30

Rana et al. CROI 2024; Denver, CO. Oral presentation 212.

Participants With Confirmed VF in Step 2

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

Rana et al. CROI 2024; Denver, CO. Oral presentation 212.

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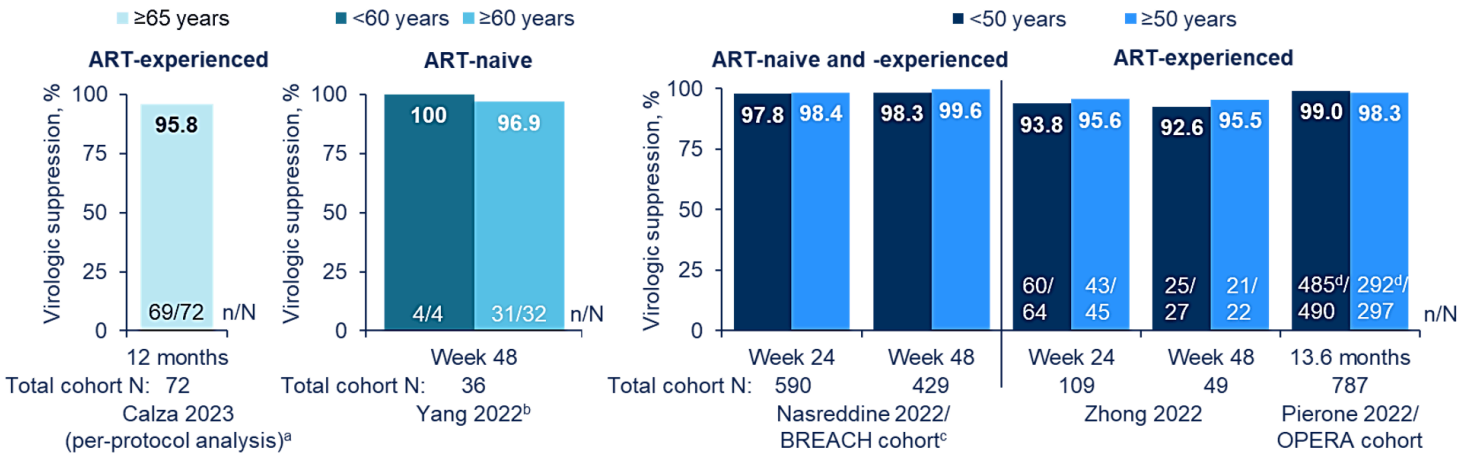
DOLUTEGRAVIR

Systematic Literature Review of Real-world Experience With the 2-Drug Regimen Dolutegravir + Lamivudine (DTG + 3TC) in People With HIV-1 Aged ≥50 Years

Emilio Letang,[1] Simona Di Giambenedetto,[2] Antonella d'Arminio Monforte,[3] José Casado,[4] Alfonso Cabello-Úbeda,[5] Laurent Hocqueloux,[6] Clotilde Allavena,[7] Tristan J. Barber,[8,9] Madhusudan Kabra,[10] Julie Priest,[11] Andrew Clark,[10] Bryn Jones[10]

- High virologic suppression rates were reported in individuals aged ≥50 years across both ART-naive and ART-experienced populations, from 88.9% (defined as HIV-1 RNA <20 c/mL) to 99.6% (defined as HIV-1 RNA <50 c/mL)

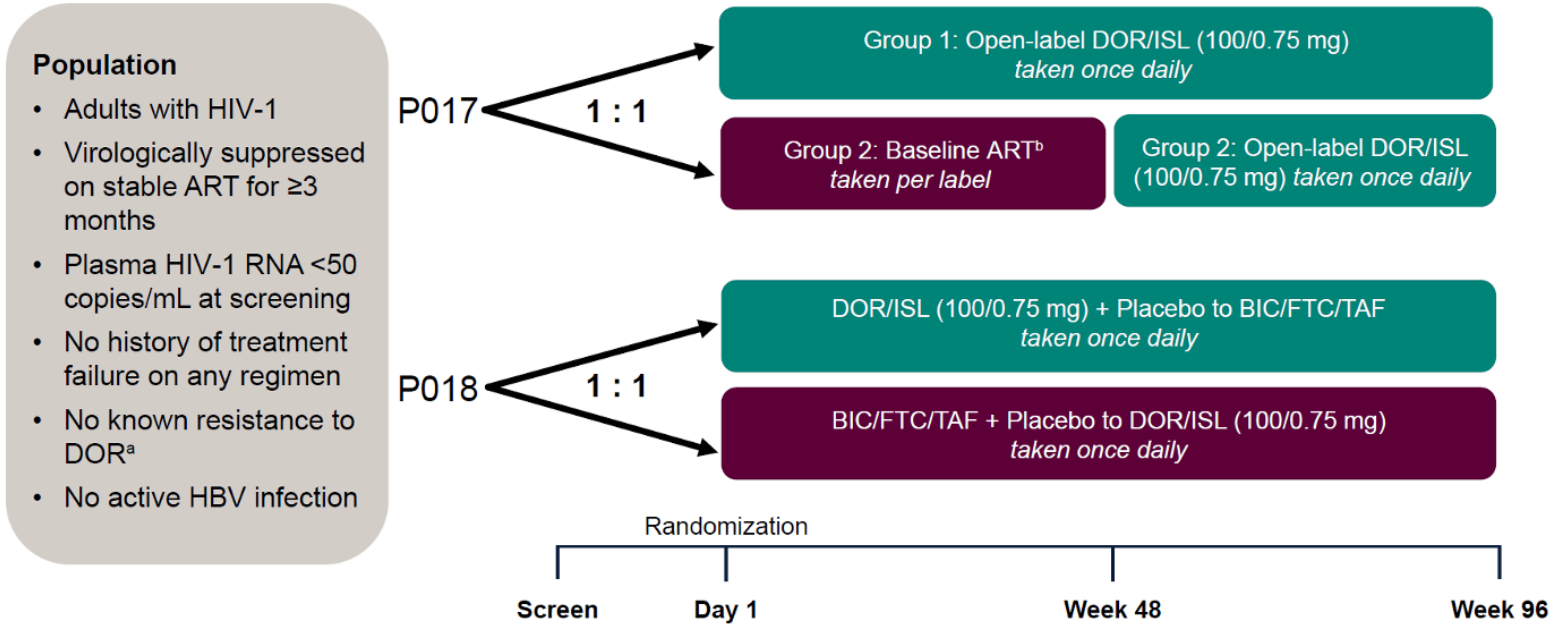


The SLR and post hoc publication addition collectively identified 188 publications representing 147 studies, 67 cohorts, and 36,343 people with HIV-1 using DTG + 3TC

Letang et al. EACS 2023; Warsaw, Poland. Poster eP.A.048.

DORAVIRINE

Switching to Doravirine/Islatravir Maintains Viral Suppression Regardless of Archived Mutations



Ernest Asante-Appiah, PhD; Steffy Joseph, MPH; Jingwen Chai, MS; Megan Green, MS; Karen Eves, BS; Prachi Nair, MS; Feng-Hsiu Su, MPH; Stephanie Klopfer, PhD; Todd A. Correll, PharmD; Jason Kim, MD; Michelle C. Fox, MD

Presented at the 31st Conference on Retroviruses and Opportunistic Infections 2024 (CROI 2024)
March 3 – 6, 2024
Denver, CO, USA

Virologic Outcomes in Participants With Archived RAMs in Proviral DNA

	P017, open-label switch			P018, blinded switch	
	Group 1: DOR/ISL weeks 0-96 N = 336	Group 2: bART weeks 0-48 N = 336	Group 2: DOR/ISL weeks 48-96 N = 326	DOR/ISL weeks 0-96 N = 322	BIC/FTC/TAF weeks 0-96 N = 319
Participants with: baseline resistance data, n (%)	300 (89.3)	307 (91.4)	297 (91.1)	292 (90.7)	280 (87.8)
M184M/I/V at baseline	12/300 (4.0)	20/307 (6.5)	18/297 (6.1)	16/292 (5.5)	12/280 (4.3)
Clinically significant viremia[a]	0	2	0	0	0
Low-level viremia[b]	0	0	0	0	0
Viral blips[c]	1	0	1	0	1
NNRTI RAMs at baseline[d]	94/300 (31.3)	100/307 (32.6)	94/297 (31.6)	99/292 (33.9)	85/280 (30.4)
Clinically significant viremia[a]	0	3	0	2	0
Low-level viremia[b]	1	0	0	2	1
Viral blips[c]	4	1	0	5	4

[a]Clinically significant viremia (CSV) defined as 2 consecutive HIV-1 RNA ≥200 copies/mL measured 2 to 4 weeks apart.
[b]Low-level viremia (LLV) defined as 2 consecutive HIV-1 RNA ≥50 and <200 copies/mL measured 2 to 4 weeks apart.
[c]Viral blip defined as on-treatment HIV-1 RNA ≥50 copies/mL and then re-suppressed (<50 copies/mL) at the next measurement.
[d]V90I, A98G, L100I, K101E/H/P, K103N/R/S, V106A/I/M, V108I, E138A/G/K/Q/R, V179D/F/L/T, Y181C/I/V, Y188C/H/L, G190A/E/S, H221Y, P225H, F227C/I/L/V, M230I/L, L234I, Y318F.

DoDo: Real life experience with an **alternative antiretroviral 2DR of DOR and DTG**

- Descriptive analysis of PWH who received **DOR+DTG** as a 2DR across **8 HIV clinics in Germany and Austria**
- **90 PWH** started on DOR+DTG since Feb 2019 and were followed through Sept 2023
- 70% were male with a **mean age=57.5 years**
- **Median duration of ART 21 years, median number of previous regimens 6**
- **64% had RAMs at baseline**: 52% NRTI RAMs, **33% NNRTI RAMs**, 39% PI RAMs, and **2% had INSTI RAMs**.

✓ Body weight increased 0.31 kg/year on average; **6% had weight loss**

✓ DOR+DTG was **stopped in 14% of subjects** after a median 11.2 months (**persistence of perceived side-effects**), with 12/13 starting a **new NNRTI or INSTI-containing regimen**

Conclusions

➢ DOR+DTG is a **well-tolerated 2DR** that is a **potentially beneficial option for extensively treated PWH**

Table 1: Patient Characteristics at Time of Switch *to DoDo*, N=90		**n**	**(%)**
Gender	male	70	78%
HIV-Associated Conditions/AIDS	CDC category B/C	59	66%
Age [years]: median (range)	57,5	(19 - 81)	
CD4-Nadir [/µl]: median (range)	170	(0 - 922)	
Years of ART: median (range)	21	(0 - 34)	
# Previous Regimens: median (range)	6	(1 - 22)	
ART Experience	NRTI	90	100%
	NNRTI	78	87%
	PI	75	83%
	INSTI	78	87%
	T20	2	2%
	MVC	6	7%
Documented RAM	NRTI	47	52%
	NNRTI	30	33%
	PI	35	39%
	INSTI	2	2%
Tropism-Testing, n=17 (V3-Loop Analysis)	CCR5	10	59%
	dual/mixed/X4	7	41%
Reason for Switch	tolerability	22	24%
	DDI	28	31%
	CVR	18	20%
Switch from	RPV-DTG	24	27%
	DTG-DRVc/r	11	12%
	DTG+ X	58	64%
Gastric Acid Reducing Agents	PPI	46	51%
	H2-blockers	5	6%
VL [cp/ml]	160,000	1	1%
	74-759	4	4%
	<50	85	94%
CD4 [cells/µl]: median (range)	597.5	(110 - 1873)	
Weight [kg]: median (range)	75	(44 - 141)	

Il Presente: moderne strategie per l'ottimizzazione della cura

• Triplici terapie

- Advanced stages of HIV disease,
- High viral loads,
- Deteriorated immunity,
- Pregnancy,
- Poor adherence,
- Archived resistance-associated mutations,
- Preservation of the efficacy of key components of antiretroviral regimens
- Futility
- Not available in long acting formulation
- ~~lower tolerability/higher toxicity (?)~~

• Regimi a due farmaci

- Non inferior to triple therapies in people with eligibility criteria
- Lower drug burden without reducing efficacy
- Flexibility of combinations
- Available in long acting formulation (only one regimen)
- Pregnancy,
- Difficult to treat populations,
- Some associations have only observational data on support

Il futuro

- Nuove combinazioni e nuovi meccanismi d’ azione

- Terapie orali con assunzione settimanale

BIC + LEN in PWH Switching From a Complex ART Regimen: Phase 2 Study Design[1]

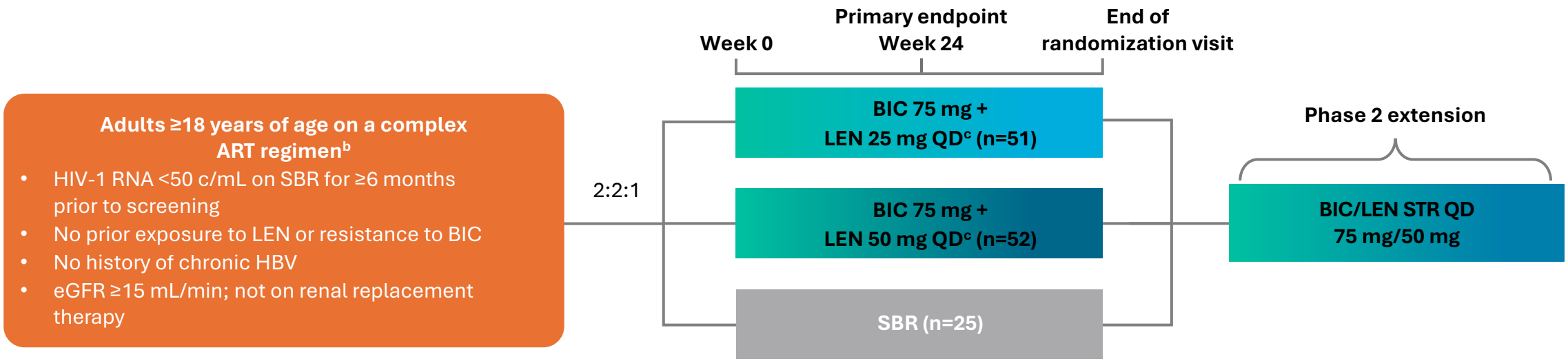
N=128

VSTE PWH on complex ART regimen[a]

Outcome

- **Primary endpoint:** HIV-1 RNA ≥50 c/mL (FDA Snapshot algorithm) at Week 24
- **Secondary endpoints:** HIV-1 RNA <50 c/mL, CD4 cell count and treatment-emergent AEs at Week 24, and pharmacokinetics

August 2022–ongoing[2]



ARTISTRY-1 is an ongoing, randomized, open-label, multicenter Phase 2/3 study

[a]Containing bPI or NNRTI plus ≥1 other third agent from a class other than NRTIs; or consisting of ≥2 pills/day, or requiring dosing more than once daily; or containing parenteral ART (excluding a complete long-acting injectable regimen) plus oral ART; [b]Due to viral resistance, intolerance or contraindication to existing STRs; [c]All participants receiving BIC + LEN received an oral loading dose of LEN 600 mg on Days 1 and 2. SBR, stable baseline regimen; STR, single tablet regimen; VSTE, virologically suppressed treatment-experienced

1. Mounzer K, et al. CROI 2024, Poster 642; 2. NCT05502341. https://classic.clinicaltrials.gov/ct2/show/NCT05502341 (accessed March 23, 2024)

Efficacy of LEN in HTE PWH With No Fully Active Agents in OBR[1]

N=12

HTE PWH with MDR virus, treated with SC LEN and an OBR that had no fully active ARVs

Outcomes

VS (HIV-1 RNA <50 c/mL; FDA Snapshot algorithm); change from baseline in HIV-1 RNA and CD4 cell count; emergent resistance-associated mutations up to Week 104

2019–ongoing[2]

VS by FDA Snapshot Algorithm

Participants with emergent LEN resistance

HIV-1 RNA ≥50 c/mL

HIV-1 RNA <50 c/mL

No virologic data in the FDA Snapshot window

Participant	Baseline CD4 cell count, cells/µL	HIV-1 RNA, c/mL			
		Baseline	Week 26	Week 52	Week 104
1[a]	**3**	**85,100**	**<50**	**<50**	**<50**
4	**50**	**38,300**	**2420**	**2970**	**1880**
10	**249**	**43,900**	**200**	**<50**	**<50**
2[b]	33	75,200	342	574	–
3	176	14,500	<50	<50	<50
5	189	14,000	<50	<50	<50
6	84	1900	<50	<50	<50
7[c]	518	<50	<50	<50	<50
8	159	39,400	<50	<50	<50
9[d]	192	91	<50	<50	<50
11[e]	137	69,500	<50	<50	–
12	313	78,800	<50	<50	<50

9/12 (75%) participants with no fully active ARVs in OBR **were suppressed at Week 104**

- **Nearly half** of these had an ARV with partial activity

3 participants developed emergent LEN resistance[f]:

- **2 had VS at Week 104** and both had a change in OBR (one at Week 21 and one at Week 25)

Mean (95% CI) increase in CD4 cell count from baseline to Week 104:
105 (-10, 220) cells/µL

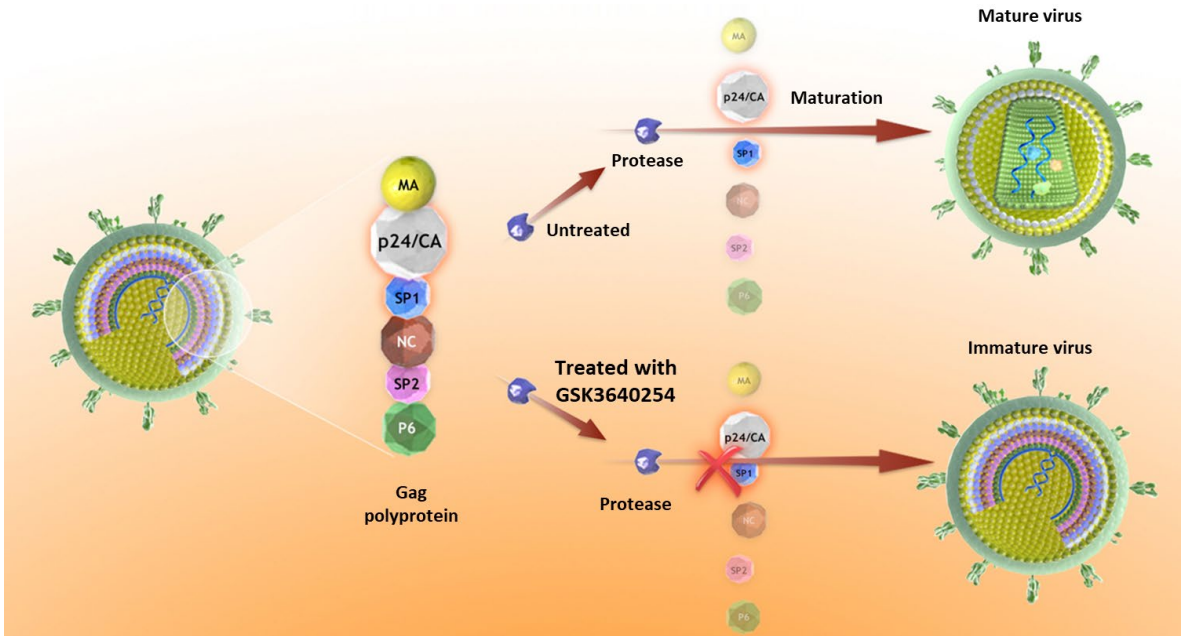
A subset of participants in CAPELLA received LEN with no fully active ARVs in their OBR, and most achieved VS; however, for optimal clinical outcomes, monotherapy with LEN should be avoided

[a]Developed resistance at Week 10 and resuppressed at Week 26; [b]Not suppressed with low-level viremia; [c]HIV-1 RNA at screening was 687 c/mL; [d]HIV-1 RNA at screening was 4800 c/mL; [e]Suppressed at Weeks 26 and 52, but missing virologic data in the Week 104 window and was suppressed at a later visit (Week 114); [f]LEN-resistance emergence was associated with LEN functional monotherapy (no fully active agent in OBR). HTE, heavily treatment-experienced; MDR, multidrug-resistant; OBR, optimized background regimen; VS, virologic suppression

1. Ogbuagu O, et al. CROI 2024, Poster 630; 2. NCT04150068. https://clinicaltrials.gov/study/NCT04150068 (accessed March 23, 2024)

Efficacy and Safety of the HIV-1 Maturation Inhibitor GSK3640254 + 2 NRTIs in Treatment-Naive Adults: 24-Week Results From the Phase IIb, Dose-Range Finding DOMINO Study

- Antiretroviral therapy can be associated with drug resistance[1] and toxicities[2]; thus, there remains a need for antiretrovirals with novel mechanisms of action for people living with HIV-1
- Maturation inhibitors are an investigational class of antiretrovirals that target the last steps of the HIV-1 life cycle[3]
- GSK3640254 (GSK'254) is a maturation inhibitor with a unique mechanism of action that **blocks the final protease cleavage event between the capsid and spacer 1 regions** and has demonstrated broad-spectrum inhibition across various HIV-1 subtypes[4]
- In a proof-of-concept study, GSK'254 demonstrated a 2-log viral load reduction in treatment-naive adults with HIV-1 when provided as monotherapy[5]
- Here, we present efficacy and safety data of GSK'254 + 2 NRTIs in treatment-naive adults with HIV-1 in the phase 2b DOMINO study



Lataillade et al. CROI 2015; Seattle, WA. Slides 114LB.

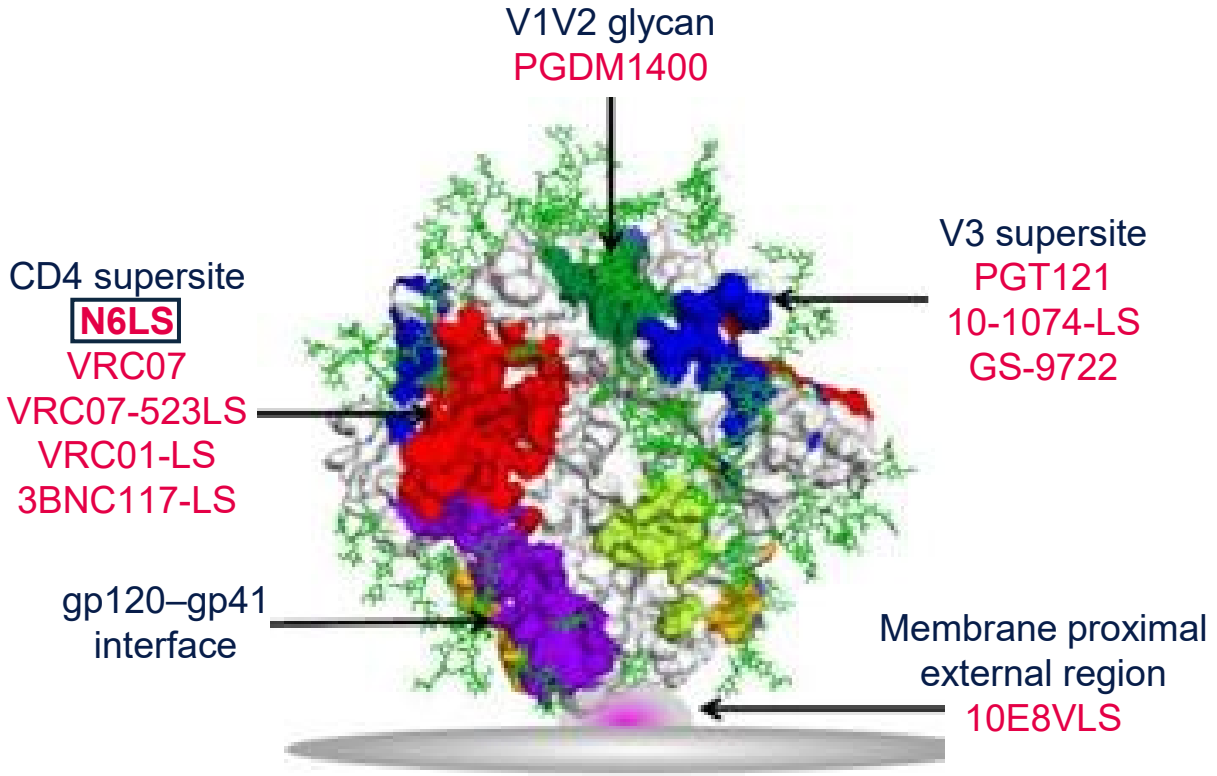
1. Arts and Hazuda. *Cold Spring Harb Perspect Med*. 2012;2:a007161. **2.** Morales-Ramirez et al. *PLoS One*. 2018;13:e0205368. **3.** Wang et al. *Acta Pharm Sin B*. 2015;5:493-499. **4.** Joshi et al. *Pharmacol Res Perspect*. 2020;8:e00671. **5.** Spinner et al. *Clin Infect Dis*. 2022;75:786-794.

Joshi et al. EACS 2023; Warsaw, Poland. Slides RA2.O1.

VH3810109 (N6LS)

- VH3810109 (N6LS) is a novel bNAb with broad and potent neutralization activity in vitro, which targets the CD4 binding site of the HIV-1 envelope protein
- N6LS has demonstrated robust antiviral effect in adults with HIV-1 in part 1 of the proof-of-concept phase 2a BANNER study[1]
- N6LS led to virologic response in 13/14 participants, with a median decline in viremia of 1.72 log10 c/mL and maximum viral nadir from baseline of −2.60 log10 c/mL

bNAbs target 5 conserved regions on the envelope[2-10]



LS-containing bNAbs have been engineered to have long half-lives[11]

ART, antiretroviral therapy; bNAb, broadly neutralizing antibody; IV, intravenous; N6LS, VH3810109; SC, subcutaneous.

1. Leone et al. HIV Drug Therapy Glasgow 2022; Glasgow, Scotland. Slides O34. **2.** Bar et al. *N Engl J Med*. 2016;375:2037-2050. **3.** Kwon et al. *Retrovirology*. 2012;9(suppl 2):O34. **4.** Scheid et al. *Science*. 2011;333:1633-1637. **5.** Mouquet et al. *Proc Natl Acad Sci U S A*. 2012;109:E3268-E3277. **6.** Walker et al. *Nature*. 2011;477:466-470. **7.** Caskey. *Curr Opin HIV AIDS*. 2020;15:49-55. **8.** Doria-Rose et al. *J Virol*. 2015;90:76-91. **9.** Kwon et al. *J Virol*. 2016;90:5899-5914. **10.** Gaudinski et al. *Lancet HIV*. 2019;6:e667-e679. **11.** Huang et al. *Immunity*. 2016;45:1108-1121.

Leone et al. EACS 2023; Warsaw, Poland. Slides PS8.O5.

LEN with bNAbs, Teropavimab and Zinlirvimab in VS PWH[1,2]

N=21

VS PWH, 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

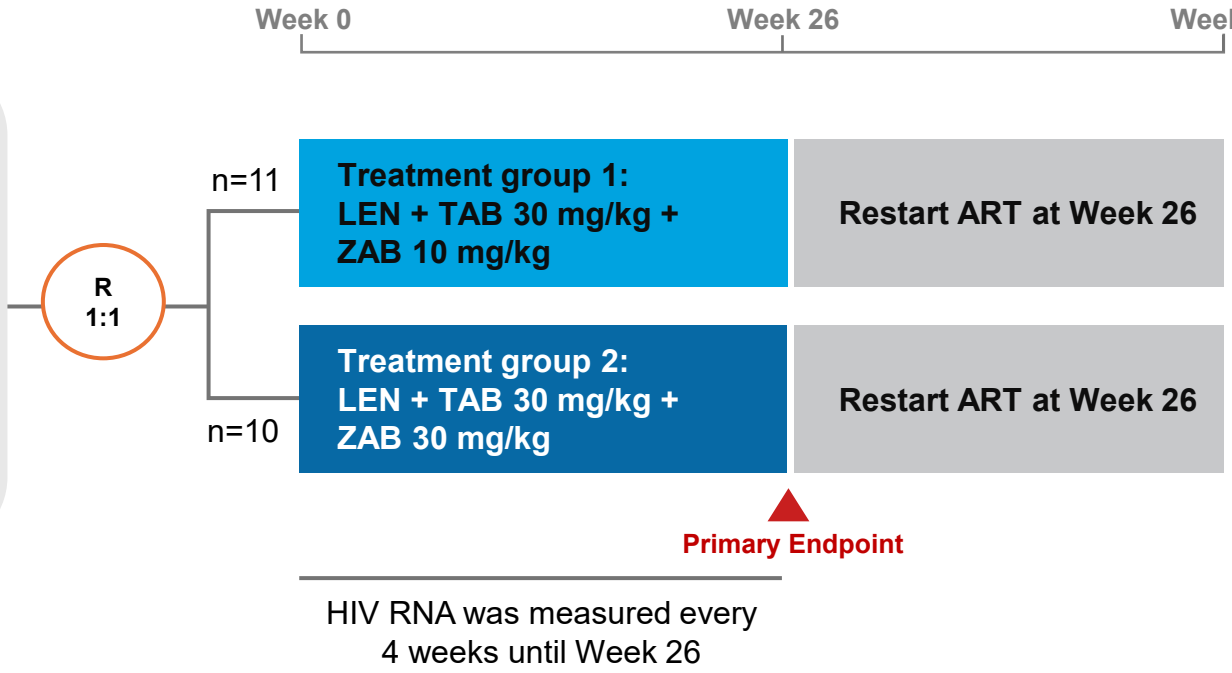
Adults living with HIV-1

VS ≥18 months[a]

Met susceptibility criteria for TAB and ZAB[b,c]

CD4 at entry ≥500 cells/µL

CD4 nadir ≥350 cells/µL



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

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 IC_{90} ≤2 µg/mL to each antibody by PhenoSense mAb Assay (Monogram Biosciences); [c]A pilot cohort is actively assessing safety, efficacy and PK in PWH who have sensitivity to *either* TAB or ZAB

bNAb, broadly neutralizing antibody; PK, pharmacokinetics; TAB, teropavimab; VS, virologically suppressed; ZAB, zinlirvimab

1. Eron J, et al. CROI 2023, Oral 193; 2. Eron J, et al. *Lancet HIV*. 2024;11:e146-55

NCT05052996: Phase 2, randomized, open-label study

Evaluating Efficacy and Safety of Oral **Weekly ISL + LEN** in PWH at 24 Weeks

N=104

PWH ≥18 years; VS on B/F/TAF for ≥24 weeks; CD4 count ≥350 cells/μL; lymphocytes ≥900 cells/μL; without HBV

Day 1 W12 W24 W48 Extension phase

ISL 2 mg + LEN[a] 300 mg QW → ISL 2 mg + LEN 300 mg QW

B/F/TAF QD

Endpoints

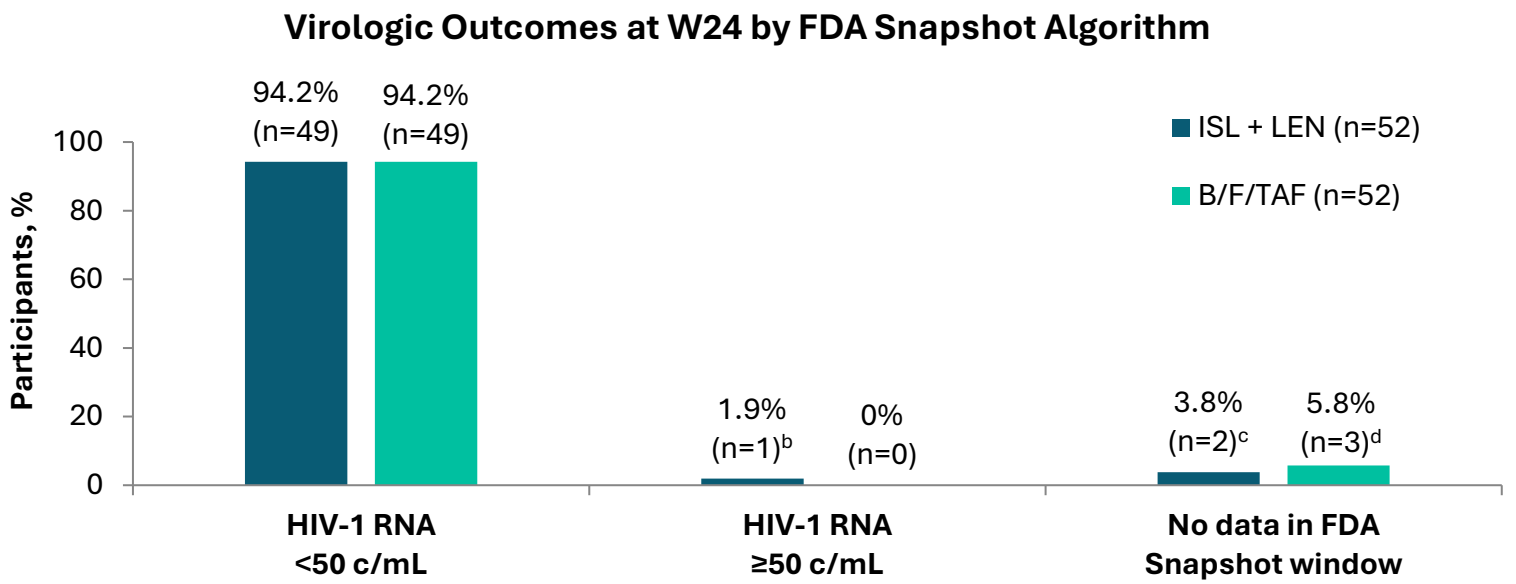
- **Primary:** HIV-1 RNA ≥50 c/mL (FDA Snapshot algorithm) at W24
- **Secondary:** HIV-1 RNA ≥50 c/mL at W12 and W48; HIV-1 RNA <50 c/mL at W12, W24 and W48; change in CD4 cell count; safety; PK

Of the study participants:

18% were **female** at birth

50% were **Black or other race**

29% were **Hispanic or Latine**



At 24 weeks, ISL + LEN oral QW maintained high rates of virologic suppression (94.2%), comparable to B/F/TAF (94.2%)

[a]600 mg of LEN was given on Day 1 and 2 for pharmacologic loading; [b]Participant's HIV-1 RNA was <50 c/mL at screening, 251 c/mL on Day 1, 64 c/mL at W24 and <50 c/mL at W30; adequate levels of plasma ISL and LEN detected; no emergent resistance detected; participant remains on study drug; [c]Discontinued due to non–drug-related AE with HIV-1 RNA <50 c/mL at time of discontinuation, n=2; [d]Discontinued for other reason with HIV-1 RNA <50 c/mL at time of discontinuation, n=3

PK, pharmacokinetics; QW, every week; VS, virologically suppressed; W, Week

Colson AE, et al. CROI 2024, Oral 208

NCT05585307: Phase 1b, first-in-human, open-label study

Evaluating Antiviral Activity and Safety of GS-1720, a Novel Weekly Oral INSTI

N=28

Adults with HIV-1; TN **or** TE but INSTI-naïve and off ART for >12 weeks

- GS-1720 30 mg monotherapy on D1 and D2 (n=7)
- GS-1720 150 mg monotherapy on D1 and D2 (n=7)
- GS-1720 450 mg monotherapy on D1 and D2 (n=7)
- GS-1720 900 mg monotherapy on D1 and D2 (n=7)

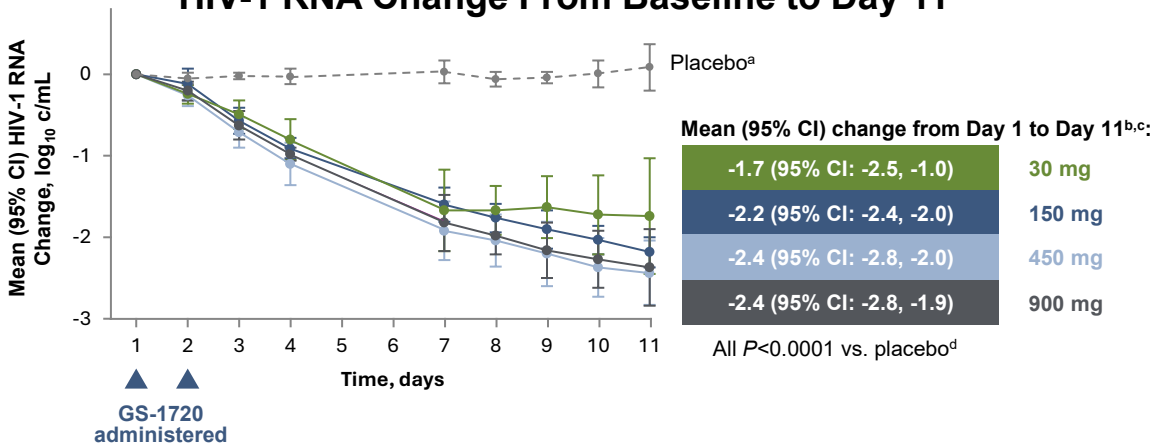
Outcomes

- Primary: Plasma HIV-1 RNA change from baseline to Day 11 vs. historical placebo
- Secondary: Safety and tolerability; resistance to INSTIs at baseline and Day 11

Baseline Characteristics

Characteristic	Total n=28
HIV-1 RNA, log_{10} c/mL, median (IQR)	4.9 (4.5–5.3)
CD4 count, cells/μL, median (IQR)	370 (275–450)
ART-naïve, n (%)	23 (82)
INSTI resistance, n (%)	0 (0)

HIV-1 RNA Change From Baseline to Day 11



No treatment-emergent INSTI resistance was observed at Day 11 for the 150 mg and 450 mg cohorts; resistance testing is ongoing for the other dose cohorts

GS-1720 demonstrated potent antiviral activity (>2 log_{10} c/mL decline in HIV-1 RNA) in the highest dose cohorts over 11 days of monotherapy

[a]Historical placebo (HIV-1 RNA change from Day 1 = +0.01 log_{10} c/mL) includes placebo-treated participants from three previous Gilead-sponsored studies; for historical studies without Day 11 HIV-1 RNA, Day 10 values were used for Day 11; [b]n=7 per cohort; [c]After Day 11, participants initiated a standard-of-care ART regimen, selected by the investigator; [d]Pairwise *P* value vs. placebo
D, day; TE, treatment-experienced; TN, treatment-naïve

Fichtenbaum CJ, et al. CROI 2024, Oral 116

Presente

terapie innovative, minimizzazione
effetti collaterali
minimizzazione stigma

Futuro

nuovi meccanismi d'azione → HTE
nuove modaltà di assunzione → QoL