THE FUTURE OF HIV TREATMENT :

AN UPDATE FROM HIV GLASGOW

Pr Jean Cyr Yombi

Internal Medicine and Infectious diseases

CUSL-UCLouvain

BREACH 28/11/2024

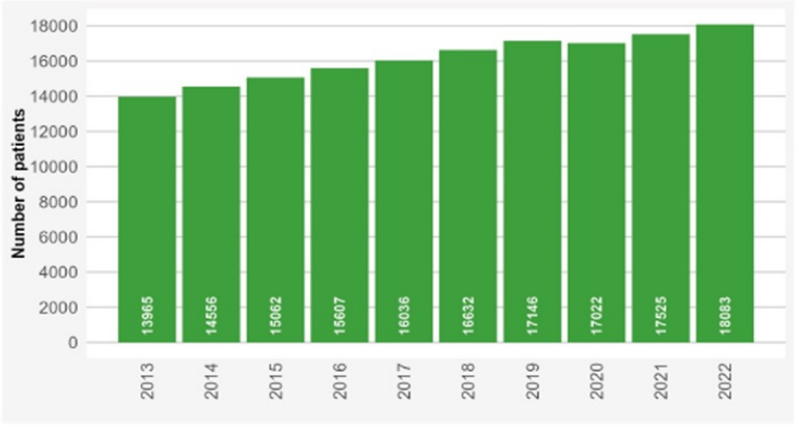
Cliniques universitaires SAINT-LUC UCLouvain BRUXELLES

MY DISCLOSURE

- Grant from GILEAD, VIIV , MSD

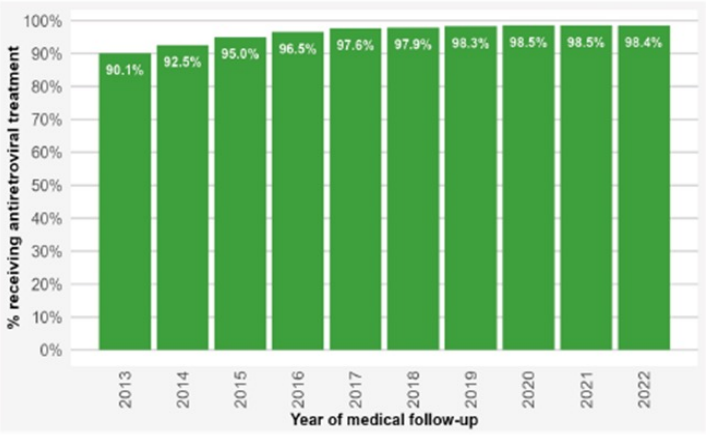
- FOR THE TOPIC
  NO CONFLICT OF INTEREST

Number of patients in HIV care by year & ART coverage



Number of PWHIV in care

ART coverage



MOST OF THE PATIENTS ARE
UNDER STR INSTI BASE REGIMEN

Viral Suppression with TLD in Treatment-Experienced Patients: Results of ACTG 5381

Table 2. Proportion of participants with HIV-1 RNA ≤1000 and ≤200 c/mL at months 6, 12, and 24.

		Cohort 1: switched from 1st-line NNRTI-based ART (N=44)		Cohort 2: switched from 2nd-line PI-based ART (N=173)	
		% (n / N on TLD with RNA results)	Exact 95% CI	% (n / N on TLD with RNA results)	Exact 95% CI
HIV-1 RNA ≤1000 c/mL	6 months	88% (37/42)	74%, 96%	72% (118/165)	64%, 78%
	12 months	88% (30/34)	73%, 97%	74% (104/140)	66%, 81%
	24 months	76% (16/21)	53%, 92%	70% (45/64)	58%, 81%
HIV-1 RNA ≤200 c/mL	6 months	83% (35/42)	69%, 93%	67% (110/165)	59%, 74%
	12 months	88% (30/34)	73%, 97%	65% (91/140)	57%, 73%
	24 months	76% (16/21)	53%, 92%	61% (39/64)	48%, 73%

- Wallis CL et al., *CROI 2024* Abstract LB 675

Table: Pooled B/F/TAF Efficacy and Safety Data at 240 weeks*

	All B/F/TAF (N=634 originally randomized to B/F/TAF)				
	BL HIV-1 RNA <100,000 c/mL (N=515)	BL HIV-1 RNA 100,000-400,000 c/mL (N=99)	BL HIV-1 RNA >400,000 c/mL (N=20)	BL CD4 count <200 cells/μL (N=80)	BL HIV-1 RNA >100,000 c/mL AND CD4 count <200 cells/μL (N=39)
Efficacy at Week 240, n/N (%)					
HIV-1 RNA <50 c/mL (M=E)	350/353 (99%)	63/65 (97%)	13/14 (93%)	49/50 (98%)	20/21(95%)
HIV-1 RNA <50 c/mL (M=F)[‡]	350/515 (68%)	76/99 (64%)	13/20 (65%)	49/80 (61%)	20/39 (51%)
Safety at Week 240, n (%)					
Any DRAE	144 (28%)	30 (30%)	4 (20%)	20 (25%)	8 (21%)
DRAE ≥ 2%					
Nausea	24 (5%)	4 (4%)	0	3 (4%)	1 (3%)
Headache	22 (4%)	7 (7%)	2 (10%)	6 (8%)	4 (10%)
Diarrhea	21 (4%)	7 (7%)	2 (10%)	5 (6%)	3 (8%)
Fatigue	13 (3%)	4 (4%)	0	2 (3%)	1 (3%)
Insomnia	12 (2%)	1 (1%)	0	2 (3%)	1 (3%)
Dizziness	11 (2%)	3 (3%)	1 (5%)	0	0
Serious DRAE	5 (1%)	0	0	0	0
AE Leading to Premature Study Drug Discontinuation	9 (2%)	1 (1%)	0	2 (3%)	0
Drug-Related	5 (0.8%)	0	0	1 (1%)	0

AE: adverse event; BL: baseline; DRAE: Drug-Related Adverse Event; LTFU: lostto follow-up; M=E: missing = excluded; M=F: missing = failure; OLE: open-label extension
*Includes only participants originally randomized and treated with B/F/TAF
‡of 634, 115 prematurely discontinued study drug during randomized phase: 13 did not enter OLE, 62 prematurely discontinued study drug during OLE (LTFU 28, participant decision 22, AE 4, investigator's discretion 3, non-compliance with study drug 2, death 1, lack of efficacy 1, protocol violation 1)

Monica Gandhi MD, MPH
Medical Director, Ward 86 HIV Clinic and Director, Center for AIDS Research
Division of HIV, Infectious Diseases, and Global Medicine, UCSF
November 11, 2024

Adherence Challenges with ART

Overall rates of VS in US 65%

Challenges, including structural barriers such as housing instability, poverty, or transportation access, may prevent people from getting and staying in HIV care.

For every 100 people with diagnosed HIV in 2022:

Ending the HIV Epidemic | Overall Goal: Increase the percentage of people with diagnosed HIV who are virally suppressed to at least 95% by 2025 and remain at 95% by 2030.

Rates of virologic suppression worldwide:
- **In adults on ART, 79% suppression at 1 year, 65% by 3 years**
- In children/adolescents on ART, 36% suppression at 1 year, 24% at 3 years (Han. Lancet HIV 2021)

Barriers to ART adherence:
- Systematic review of 125 studies identified main barriers to ART adherence
  - Forgetting
  - Being away from home
  - Change to daily routine
  - Depression
  - Alcohol/substance misuse
  - Secrecy/stigma
  - Feeling sick
  - Far distance to clinic
  - Stock outs

McConsey, G. A., et al. Real-World Adherence to Antiretroviral Therapy Among HIV-1 Patients Across the United States. *Advances in therapy, 2021*
Min Han W et al. Global estimates of viral suppression in children and adolescents and adults on antiretroviral therapy adjusted for missing viral load measurements: a multiregional, retrospective cohort study in 31 countries. Lancet HIV 2021.
Shubber, Z., et al. Patient-Reported Barriers to Adherence to Antiretroviral Therapy: A Systematic Review and Meta-Analysis. *PLoS medicine, 2016.* 13(11), e1002183.
Altice, F., et al. . Adherence to HIV treatment regimens: systematic literature review and meta-analysis. *Patient preference and adherence*, 2019

Reduction over time OF VS Due THO ADHERENCE CHALLENGES WITH ART

‘Drugs don’t work in patients who don’t take them’ (C. Everett Koop, MD, US Surgeon General, 1985)

PEOPLE DON’T FAIL DRUGS
DRUGS FAIL PEOPLE
(Charles Flexner CROI 2004)

SO →LONG ACTING ART FORMULATION
IS THE FUTURE OF HIV TREATMENT

Long-acting medications help with adherence challenges in multiple fields

Treatment of psychiatric disorders

Adherence Challenges and Long-Acting Injectable Antipsychotic Treatment in Patients with Schizophrenia

Contraception

Long-Acting Reversible Contraception for Adolescents: A Review of Practices to Support Better Communication, Counseling, and Adherence

Substance use disorder treatment

What is long-acting (XR) buprenorphine injection?

Long-acting buprenorphine injection (XR-buprenorphine, currently available brand name: Sublocade) is an injectable formulation of buprenorphine that is given once a month to assist people in obtaining and sustaining long-term recovery from opioid use disorder (OUD). There may be additional XR-

Long-acting injectable naltrexone for the treatment of alcohol dependence

Only combination treatment for LA ART -Cabotegravir (CAB)/ Rilpivirine (RPV) - Trials done in those with virologic suppression

(Real world: IMPAACT 2017 MOCHA – single arm; JABS; CARISEL, CARLOS, DAT;AIDS, BEYOND, ATHENA, UK Share)

	Confirmed Virologic failure rate & resistance
FLAIR: CAB/RPV LA in treatment naïve; First put on DTG/ABC/3TC for 20 weeks then LA ART (n=283)	**1.8% at 124 weeks;** 4 out of 5 with emergent INSTI/NNRTI resistance
ATLAS: CAB/RPV LA in treatment experienced participants every 4 weeks, on suppressive regimen for 6 months prior to switch (n=308)	**0.9% at 96 weeks;** 3 out of 3 with emergent INSTI/NNRTI resistance
ATLAS 2M: CAB/RPV LA in treatment experienced participants every 8 weeks after VS x ≥ 6 months (n=522)	**2.3% at 152 weeks;** 11 out of 12 with emergent INSTI/NNRTI resistance
SOLAR: CAB/RPV LA every 8 weeks in treatment experienced participants (47% expressed internal or external stigma) switched BIC/TAF/FTC when VS (n=447)	**0.7% at 48 weeks;** 3 out of 3 with emergent INSTI/NNRTI resistance
CARES: CAB/RPV LA every 8 weeks in treatment experienced participants who switched from oral ART in Uganda, Kenya, South Africa (n=512)	**0.7% at 48 weeks;** 2 out of 2 with emergent INSTI/NNRTI resistance

Orkin C. Lancet HIV 2021; Swindells S. AIDS 2022; Overton E. CID 2023; Ramgopal M. Lancet HIV 2023; Kityo C Lancet ID 2024

Gandhi M.HIV Drug Therapy Glasgow 2024
10-13 November

Why might we need LA formulations to treat and prevent HIV infection?

- Despite having nearly perfect co-formulated single tablet daily oral regimens for HIV treatment and prevention:
  - Persistence on treatment is surprisingly low.
  - Failure rates are still unacceptably high.
  - Non-adherence is common.
- LA formulations may provide the best solution to failure of daily oral regimens, since oral failure is largely driven by non-adherence.
  - Superiority of q8weekly injectable cabotegravir versus daily oral TDF/FTC for PrEP, and LATITUDE Study for treatment, as recent examples.
- Surveys of PLWH consistently show a preference for LA formulations over daily pills.

CROI 2024

Charles Flexner ; CROI March 3-6 2024, Denver Colorado, USA

Who Wants to Switch? Gauging Patient Interest in Novel Antiretroviral Therapies

Caroline B. Derrick,[1] Jan Ostermann,[2,3] Sharon B. Weissman,[1] Amy Hobbie,[3] Noor Alshareef,[2] Andrew Weinhold,[3] Valerie Yelverton,[2,4] and Nathan M. Thielman[3,5]

Table 1. Distribution and Correlates of Interest in Switching to Novel ART Regimens (n = 263)

		1 Pill Once a Week	2 Shots Every Other Month	2 Implants Every 6 Months
Interest in switching, No. (%)				
Not at all interested		38 (14)	100 (38)	152 (58)
Somewhat interested		52 (20)	60 (23)	61 (23)
Very interested		173 (66)	101 (39)	5 (18)
No.		263	261	261
		β (SE)	β (SE)	β (SE)
Clinic, Duke vs South Carolina, No. (%)	132 (50.2)	0.02 (0.20)	0.22 (0.23)	0.22 (0.22)
Age, mean (SD), years	46.7 (11.8)	–0.01 (0.01)	–0.02* (0.01)	–0.01 (0.01)
Gender, male vs female, No. (%)	148 (56.3)	–0.33 (0.20)	–0.12 (0.24)	0.10 (0.22)
More than high school education, yes vs no, No., (%)	109 (41.4)	0.43* (0.21)	1.04*** (0.24)	0.72** (0.23)
Race, white vs minority, No. (%)	51 (19.4)	–0.04 (0.25)	0.16 (0.30)	–0.24 (0.28)
Time on ART, mean (SD), years	12.1 (8.3)	–0.02 (0.01)	–0.03 (0.02)	–0.01 (0.01)
AIDS diagnosis, ever vs never, No. (%)	41 (15.6)	0.32 (0.25)	0.27 (0.30)	–0.12 (0.28)
Viral load <200, self-reported, yes vs no, No. (%)	215 (81.7)	0.28 (0.24)	–0.23 (0.29)	0.27 (0.27)
Missed dose, past 2 weeks, any vs none, No. (%)	58 (22.1)	–0.09 (0.23)	–0.15 (0.27)	0.00 (0.25)
Current side effects, any vs none, No. (%)	90 (34.2)	0.26 (0.20)	0.22 (0.23)	0.10 (0.22)
Long-term effects, any vs none, No. (%)	103 (39.2)	0.34 (0.20)	0.56* (0.24)	0.21 (0.22)
Single-tablet regimen, yes vs no, No. (%)	155 (58.9)	–0.44* (0.20)	–0.15 (0.23)	–0.44* (0.22)
Food restriction, any vs none, No. (%)	148 (56.3)	0.04 (0.19)	0.27 (0.23)	0.15 (0.21)
No.	263	247	247	247

Results from a multivariate linear regression model. Dependent variables range from 1–5. Positive values for β indicate greater interest in switching. *, **, and *** denote statistical significance at the 0.05, 0.01, and 0.001 levels, respectively. Sixteen observations were excluded from the multivariate model due to missing data on 1 or more outcome variables (n = 3) or covariates (n = 13).

Abbreviation: ART, antiretroviral therapy; No., number of patients; SD, standard deviation; SE, standard error.

OPEN

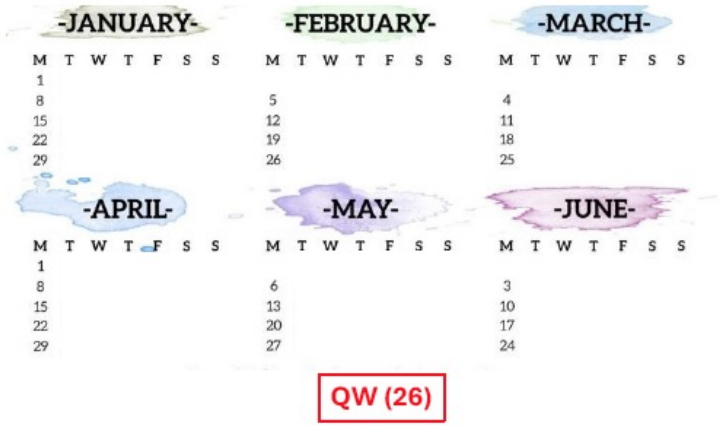
Preference for daily oral pills over long-acting antiretroviral therapy options among people with HIV

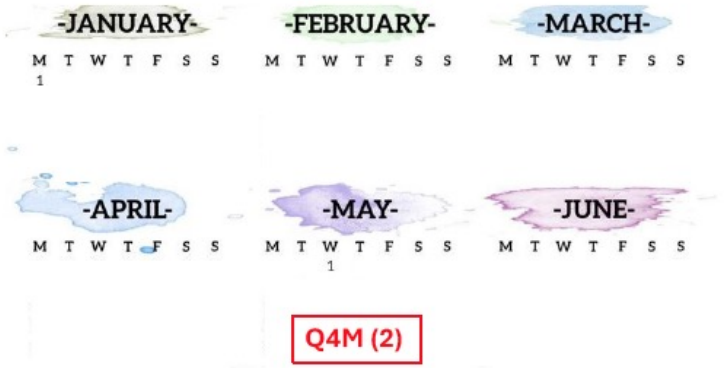
Douglas Barthold[a], Enrique M. Saldarriaga[a], Aaron T. Brah[b], Brett Hauber[a,c], Pallavi Banerjee[d], Shanil M. Fuller[e], Divine McCaslin[e], Ana Maria Moldoveanu[e], Vincent C. Marconi[f,g], Jane M. Simoni[h,i] and Susan M. Graham[j,j,k]

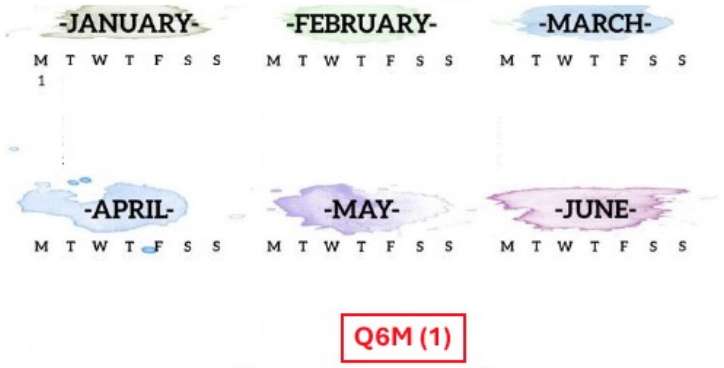
Table 4. Multivariable associations between preference for current ART over long-acting antiretroviral therapy and selected participant characteristics.

	Adjusted odds ratio	95% CI	*P*-value
Washington State	0.43	(0.22–0.83)	0.01
Age <30	0.27	(0.06–1.27)	0.10
Age 30–49	0.56	(0.30–1.06)	0.07
Education – high school or less	2.73	(1.41–5.27)	<0.01
Good adherence[a]	2.51	(1.42–4.46)	<0.01
Substance use[b]			
Tobacco	1.92	(0.99–3.71)	0.05
Alcohol	2.03	(0.96–4.27)	0.06
Aversion to injections[c]	2.63	(1.50–4.59)	<0.01
No consent to link chart data	1.93	(0.71–5.22)	0.20
PNTS – education	4.37	(1.29–14.78)	0.02
PNTS – HIV-related[d]	0.76	(0.12–4.88)	0.77
PNTS – other health-related[e]	2.83	(0.71–11.30)	0.14

Results of a multivariable logistic regression with robust standard errors, and a binary dependent variable equal to 1 if the participant chose to remain on their current daily oral therapy in 100% of choice scenarios in a discrete choice experiment examining preferences for long-acting antiretroviral therapies among 700 people living with HIV aged 18+ in Washington State and Atlanta, Georgia. ART, antiretroviral therapy; PNTS prefer not to say.
[a]Good adherence was defined as reporting to always or almost always take ART as instructed.







In the next 6 months, how many days will I need to worry about taking my medication?

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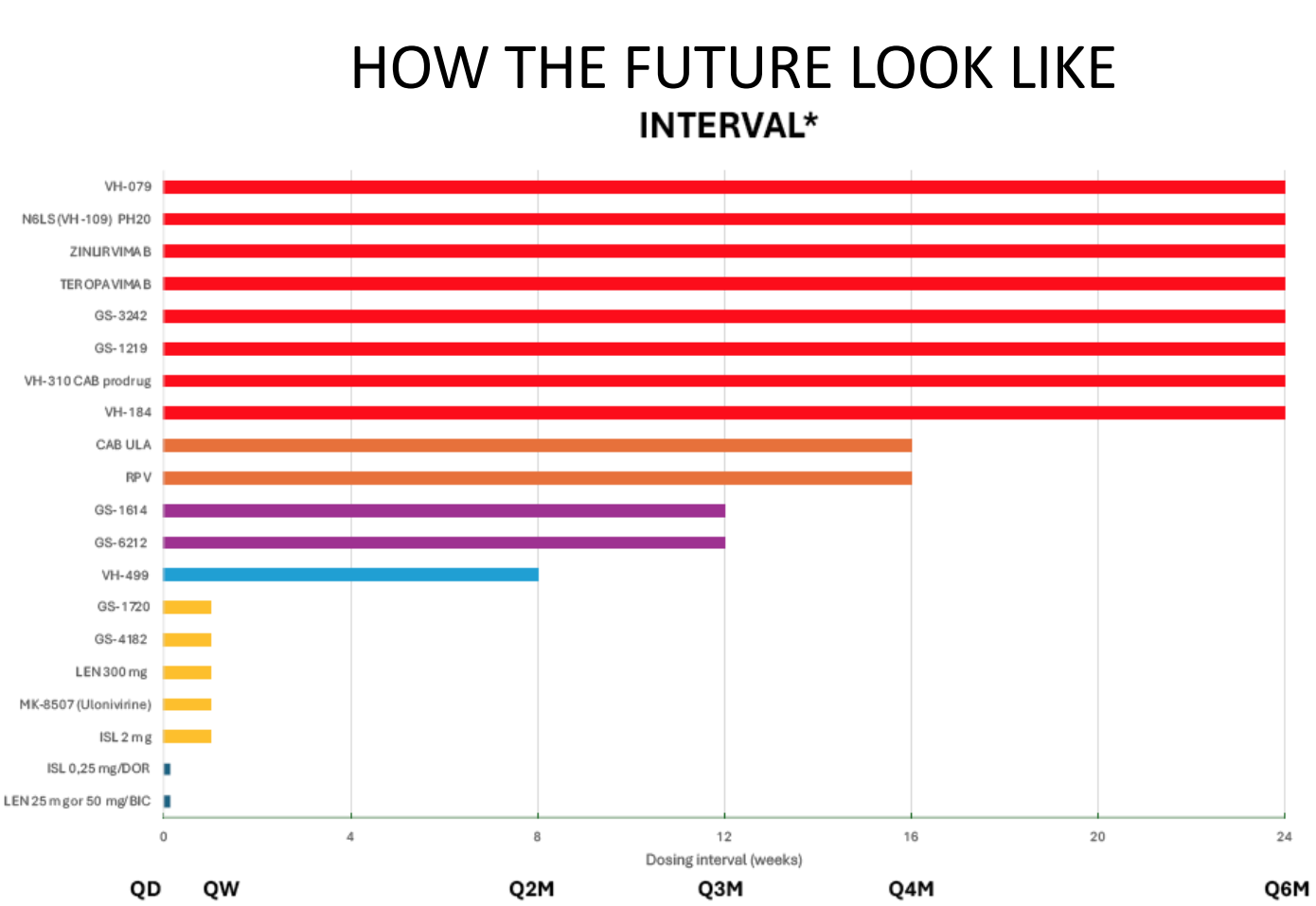
HOW THE FUTURE LOOK LIKE



*For a number of drugs the interval is aspirational, still under investigation

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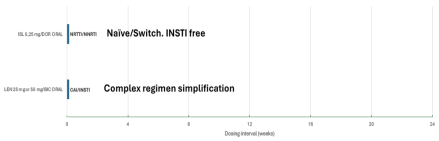
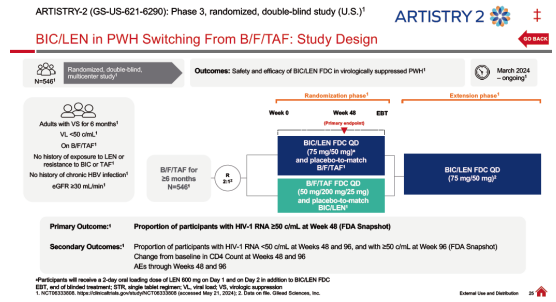
QD

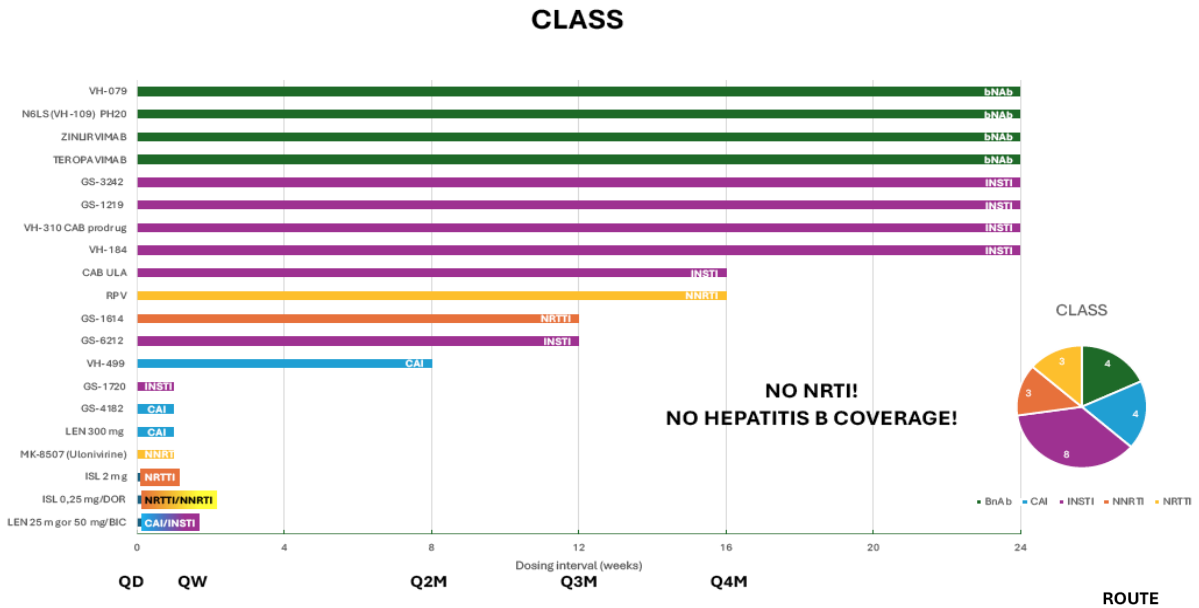


DOR/ISL (100 mg/0.25 mg)
Phase 3 Studies for HIV-1 Treatment

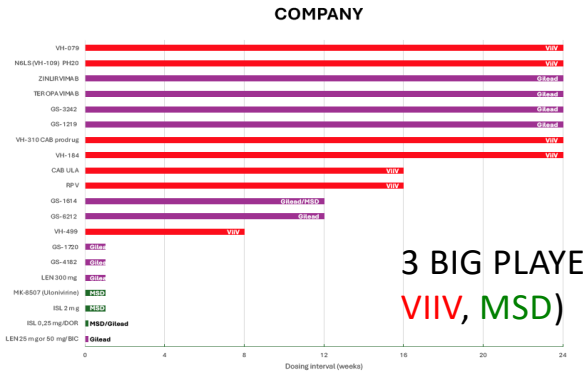
Study*	Study Intervention	Design	Population	Sample Size
051[1]	DOR/ISL (100 mg/0.25 mg) QD compared with *baseline ART*	Open-label; 2:1 randomization	Virologically Suppressed	N=501
052[2]	DOR/ISL (100 mg/0.25 mg) QD compared with *BIC/FTC/TAF*	Blinded; 2:1 randomization	Virologically Suppressed	N=501
053[3]	DOR/ISL (100 mg/0.25 mg) QD compared with *BIC/FTC/TAF*	Blinded; 1:1 randomization	ART-naive	N=500
054[4]	DOR/ISL (100 mg/0.25 mg) QD	Open-label, single arm, de-escalation from DOR/ISL (100 mg/0.75 mg)	Virologically Suppressed	N~650

* Study numbers are hyperlinks to ClinicalTrials.gov
DOR: doravirine; ISL: islatravir; ART: antiretroviral therapy; BIC: bictegravir; FTC: emtricitabine; TAF: tenofovir alafenamide

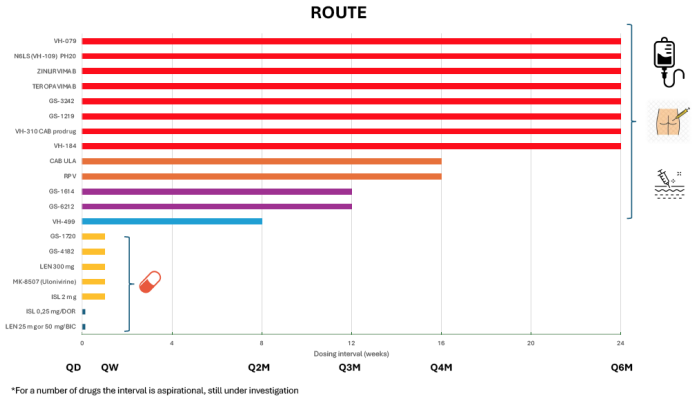




bNabs,
INSTI,
CAI,
NNRTI
NRTTI(ISL)



3 BIG PLAYERS (GILEAD, VIIV, MSD)



IV, IM, SC so we will face logistic challenges

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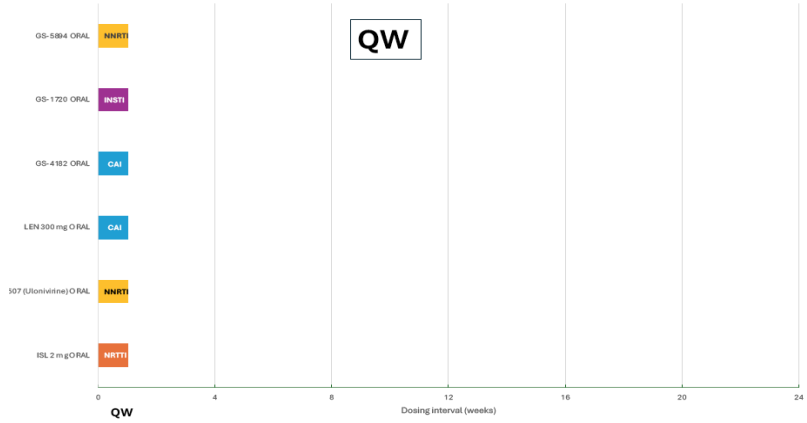
ONCE WEEK (QW)



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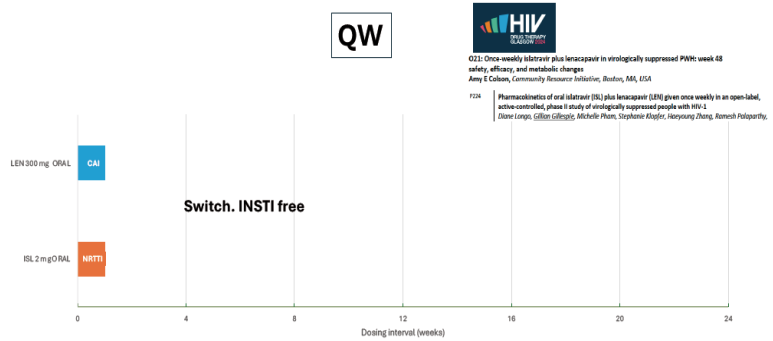

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Once-Weekly Islatravir Plus Lenacapavir in Virologically Suppressed PWH: Week 48 Safety, Efficacy, and Metabolic Changes

Amy E. Colson[1], Gordon E. Crofoot[2], Peter J. Ruane[3], Moti N. Ramgopal[4], Alexandra W. Dretler[5], Ronald G. Nahass[6], Gary I. Sinclair[7], Mezgebe Berhe[8], Fadi Shihadeh[9], Shan-Yu Liu[9], Stephanie Klopfer[10], Sharline Madera[9], Hadas Dvory-Sobol[9], Martin S. Rhee[9], Elizabeth G. Rhee[10], Jared Baeten[9], Joseph Eron[11]

[1]Community Resource Initiative, Boston, Massachusetts, USA; [2]The Crofoot Research Center, Houston, Texas, USA; [3]Ruane Clinical Research, Los Angeles, California, USA; [4]Midway Immunology & Research Center, Fort Pierce, Florida, USA; [5]Metro Infectious Disease Consultants, Decatur, Georgia, USA; [6]IDCare, Hillsborough, New Jersey, USA; [7]Prism Health North Texas, Dallas, Texas, USA; [8]North Texas Infectious Diseases Consultants, Dallas, Texas, USA; [9]Gilead Sciences, Foster City, California, USA; [10]Merck & Co., Inc., Rahway, New Jersey, USA; [11]University of North Carolina, Chapel Hill, North Carolina, USA

HIV Drug Therapy Glasgow 2024, November 10–13, Glasgow, United Kingdom

Background

- Once-weekly (QW) oral antiretrovirals (ARVs) have the potential to address pill fatigue and adherence challenges related to daily oral treatment for HIV-1 infection[1]
- Islatravir (ISL) is a nucleoside reverse transcriptase translocation inhibitor[2]
  - Prior ISL studies have shown dose/exposure-related decreases in CD4+ T-cell and lymphocyte counts[3]
    - Pharmacokinetic modelling indicates such declines are not expected with the 2 mg dose chosen for this study[4]
- Lenacapavir (LEN) is a first-in-class capsid inhibitor[5]
- Both ISL and LEN have multiple mechanisms of action, potent ARV activity at low doses, and long half-lives ($t_{1/2}$) that allow for QW dosing[6–8,a]
- Primary endpoint data (Week 24) from the current, ongoing Phase 2 study (NCT05052996) were previously reported
  - Most participants (94.2%) maintained viral suppression in the QW oral ISL+LEN group[9]

Objective: To investigate the efficacy and safety of QW oral ISL+LEN in virologically suppressed people with HIV-1 (PWH) at Week 48

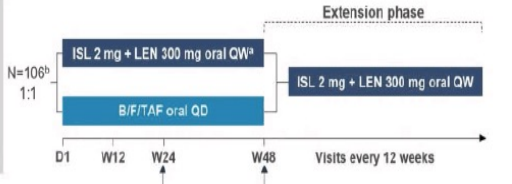
[a]LEN $t_{1/2}$=10–12 days; ISL-triphosphate $t_{1/2}$=7–9 days.

1. Claborn KR, et al. *Psychol Health Med* 2015;20:255–65; 2. Schürmann D, et al. *Lancet HIV* 2020;7:e164–72; 3. Squires K, et al. CROI 2023; Abstract 192; 4. Vargo RC, et al. CROI 2023; Poster 497; 5. Sunlenca® Prescribing Information, available at https://www.gilead.com/-/media/files/pdfs/medicines/hiv/sunlenca/sunlenca_pi.pdf (accessed November 2024); 6. Zhang H, et al. CROI 2022; Abstract 433; 7. Shaik N, et al. AIDS 2022; Poster PESUB23; 8. Matthews R, et al. *Clin Trans Sci* 2021;14:1933–44; 9. Colson A, et al. CROI 2024; Abstract 208.

Methods

A Phase 2, Open-label, Active-Controlled Study in Virologically Suppressed PWH

Eligibility criteria
- Aged ≥18 years
- On B/F/TAF for >6 months
- HIV-1 RNA <50 c/mL for >6 months
- No history of virologic failure
- CD4+ T-cell count ≥350 cells/µl
- Lymphocyte count ≥900 cells/µl
- No HBV infection



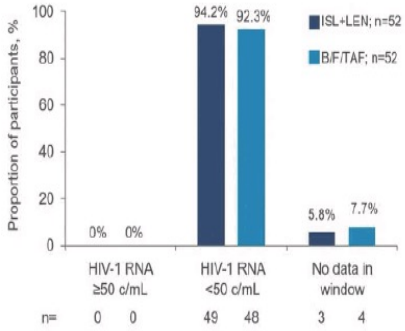
Primary endpoint:[1]
- Proportion with HIV-1 RNA ≥50 c/mL at Week 24 per FDA Snapshot Algorithm

Secondary endpoints included in this presentation:
- Proportion with HIV-1 RNA ≥50 c/mL at Week 48
- Proportion with HIV-1 RNA <50 c/mL at Week 48
- Change from baseline in CD4+ T-cell count
- AEs leading to study drug discontinuation

Other assessments:
- Change in BMI, body weight, and adherence

[a]600 mg of LEN was given on Day 1 and Day 2 for pharmacologic loading. [b]Randomized, N=106; dosed, n=104.
AE, adverse event; **B/F/TAF**, bictegravir/emtricitabine/tenofovir alafenamide; **BMI**, body mass index; **c/mL**, copies/mL; **D**, Day; **FDA**, Food and Drug Administration; **HBV**, hepatitis B virus; **ISL**, islatravir; **LEN**, lenacapavir; **PWH**, people with HIV-1; **QD**, daily; **QW**, weekly; **W**, Week.
1. Celum A, et al. CROI 2024; Abstract 208.

Virologic Outcomes at Week 48 by FDA Snapshot Algorithm



Participants with no data in window:

ISL+LEN (n=3)
- Two participants discontinued due to AEs not related to study drug
- One participant discontinued due to other reasons not related to study drug
- All participants had HIV-1 RNA <50 c/mL at study discontinuation

B/F/TAF (n=4)
- Three participants discontinued due to other reasons not related to study drug and had HIV-1 RNA <50 c/mL at study discontinuation
- One participant had missing data during window, but remained on study drug

Participants in both treatment groups maintained high rates of virologic suppression

AE, adverse event; **B/F/TAF**, bictegravir/emtricitabine/tenofovir alafenamide; **c/mL**, copies/mL; **FDA**, Food and Drug Administration; **ISL**, islatravir; **LEN**, lenacapavir.

Baseline Demographic and Disease Characteristics

	ISL+LEN (n=52)	B/F/TAF (n=52)	Total (N=104)
Median (range) age, years	40 (28–67)	40 (26–76)	40 (26–76)
Assigned female at birth, n (%)	10 (19.2)	9 (17.3)	19 (18.3)
Gender identity, n (%)			
Transgender female	1 (1.9)	0	1 (1.0)
Non-binary/third gender	0	1 (1.9)	1 (1.0)
Race, n (%)			
White	25 (48.1)	27 (51.9)	52 (50.0)
Black	21 (40.4)	16 (30.8)	37 (35.6)
Asian	2 (3.8)	1 (1.9)	3 (2.9)
American Indian or Alaska Native	1 (1.9)	2 (3.8)	3 (2.9)
Native Hawaiian or Pacific Islander	0 (0)	1 (1.9)	1 (1.0)
Other	3 (5.8)	5 (9.6)	8 (7.7)
Hispanic or Latinx ethnicity, n (%)	13 (25.0)	17 (32.7)	30 (28.8)
Mean (SD) CD4+ T-cell count, cells/µL	755 (223.6)	818 (271.3)	786 (249.5)
Mean (SD) lymphocyte count x 10^3 cells/µL	1.94 (0.445)	1.95 (0.652)	1.94 (0.556)
Median (IQR) body weight, kg	79.3 (70.4–87.4)	83.2 (76.1–92.5)	80.5 (74.4–88.7)
Median (IQR) BMI, kg/m²	26.9 (23.8–30.0)	27.2 (25.5–29.3)	27.1 (24.5–29.4)

B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; **BMI**, body mass index; **IQR**, interquartile range; **ISL**, islatravir; **LEN**, lenacapavir.

Adverse Events

Participants, n (%)	ISL+LEN (n=52)	B/F/TAF (n=52)
Any AE	42 (80.8)	40 (76.9)
Treatment-related AE	10 (19.2)	3 (5.8)
Grade 1 or 2	10 (19.2)	3 (5.8)
≥2 participants in ISL+LEN group		
Dry mouth	2 (3.8)	0
Nausea	2 (3.8)	0
Grade 3 or 4	0	0
Serious AE	3 (5.8)[a]	0
Treatment-related	0	0
AE leading to study drug discontinuation	2 (3.8)[b]	0
Treatment-related	0	0

No Grade 3 or higher AEs, serious AEs, or AEs leading to discontinuation were considered related to the study drug by the investigator

[a]Serious AEs included large intestine perforation and renal colic (in the same participant), pneumonia, and neurologic anesthetic complication. [b]Large intestine perforation and renal colic, n=1; acute hepatitis B infection, n=1 (both participants had HIV-1 RNA <50 c/mL at study discontinuation).
AE, adverse event; **B/F/TAF**, bictegravir/emtricitabine/tenofovir alafenamide; **c/mL**, copies/mL; **ISL**, islatravir; **LEN**, lenacapavir.

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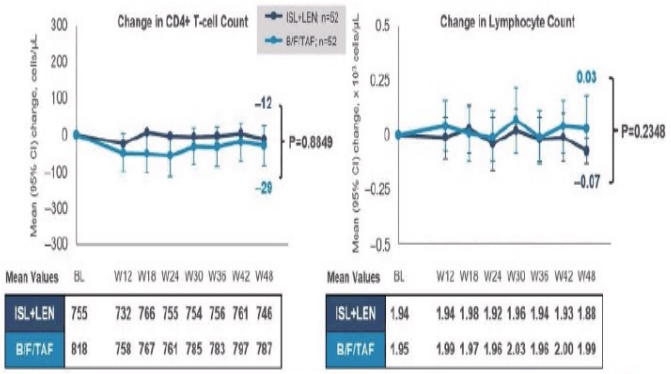
Laboratory Abnormalities

Laboratory abnormalities occurring in ≥1 participant in the ISL+LEN group, n/N (%)	ISL+LEN (n=52)	B/F/TAF (n=52)
Grade 3		
Creatinine (increased)	1/52 (1.9)	0/51
Creatinine clearance (decreased)	2/52 (3.8)	2/51 (3.9)
Non-fasting hyperglycemia	1/43 (2.3)	2/43 (4.7)
Glycosuria[a]	1/52 (1.9)	2/51 (3.9)
Hyperkalemia	1/52 (1.9)	0/51
ALT (increased)[b]	1/52 (1.9)	0/51
Grade 4		
Creatine kinase (increased)[c]	2/52 (3.8)	0/51

No Grade 3 and 4 laboratory abnormalities were clinically significant, except ALT elevation seen in a participant with acute hepatitis B

[a]Glycosuria occurred in participants with type 2 diabetes mellitus. [b]Increased ALT occurred in the participant with acute hepatitis B. [c]Increased creatinine kinase occurred after vigorous exercise in both participants. **ALT**, alanine transaminase; **B/F/TAF**, bictegravir/emtricitabine/tenofovir alafenamide; **ISL**, islatravir; **LEN**, lenacapavir.

CD4+ T-cell and Lymphocyte Count Changes Through Week 48



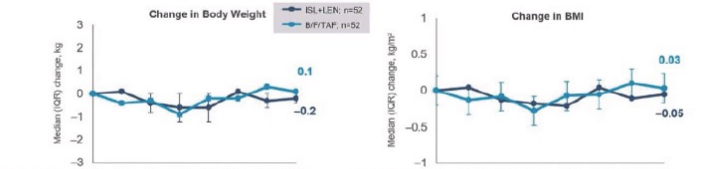
Mean Values	BL	W12	W18	W24	W30	W36	W42	W48
ISL+LEN	755	732	766	755	754	756	761	746
B/F/TAF	818	758	767	761	785	783	797	787

Mean Values	BL	W12	W18	W24	W30	W36	W42	W48
ISL+LEN	1.94	1.94	1.98	1.92	1.96	1.94	1.93	1.88
B/F/TAF	1.95	1.99	1.97	1.96	2.03	1.96	2.00	1.99

- There were no significant differences between groups in mean change from baseline in CD4+ T-cell or lymphocyte counts at Week 48
- No participants discontinued due to a decrease in CD4+ T-cell or lymphocyte counts

B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; **BL**, baseline; **ISL**, islatravir; **LEN**, lenacapavir; **W**, Week.

Body Weight and BMI Changes Through Week 48

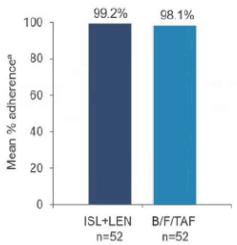


Median Values	BL	W12	W18	W24	W30	W36	W42	W48
ISL+LEN	79.3	79.1	77.2	77.9	77.7	78.8	77.9	77.6
B/F/TAF	83.2	83.4	82.8	82.0	84.7	84.7	84.2	84.0

Median Values	BL	W12	W18	W24	W30	W36	W42	W48
ISL+LEN	26.9	26.8	26.9	26.6	27.2	27.1	26.6	26.7
B/F/TAF	27.2	27.4	27.3	27.3	27.4	27.9	27.6	27.7

No between-group differences in median change in body weight and BMI at Week 48

Adherence (by Pill Count) Through Week 48



Adherence was high for ISL+LEN and B/F/TAF through Week 48

HIV Drug Therapy Glasgow 2024, November 10–13, Glasgow, United Kingdom

Conclusions

- Weekly oral ISL+LEN maintained high rates of virologic suppression (94.2%) at Week 48 in virologically suppressed PWH
  - No participant on ISL+LEN had HIV-1 RNA ≥50 c/mL at Week 48 or at study discontinuation
- Weekly oral ISL+LEN was well tolerated, as evidenced by the absence of any treatment-related Grade ≥3 AEs or serious AEs
- There were no between-group differences in CD4+ T-cell or lymphocyte count changes from baseline through Week 48
- There were no between-group differences in body weight or BMI changes from baseline through Week 48
- Participants demonstrated high rates (99.2%) of adherence to oral weekly ISL+LEN
- The Phase 2 results support advancing the weekly oral ISL+LEN regimen to Phase 3 trials: ISLEND-1 and ISLEND-2 (NCT06630286; NCT06630299)

ISL + LEN has the potential to become the first oral weekly complete regimen for the treatment of HIV-1 infection

AE, adverse event; **BMI**, body mass index; **c/mL**, copies/mL; **ISL**, islatravir; **LEN**, lenacapavir; **PWH**, people with HIV-1.

Pharmacokinetics of oral islatravir plus lenacapavir given once weekly in an open-label active-controlled, phase 2 study of virologically suppressed people living with HIV-1

HIV Drug Therapy Glasgow; Glasgow, United Kingdom; November 10-13, 2024

Diane Longo1; Gillian Gillespie1*; Michelle Pham1; Stephanie Klopfer1; Haeyoung Zhang2; Ramesh Palaparthy2; Angela S. Y. Liu2; Randolph P. Matthews1; Cyril Llamoso1; Elizabeth G. Rhee1; S. Aubrey Stoch1; Dhananjay D. Marathe2; Ryan Vargo1
1Merck & Co., Inc., Rahway, NJ, USA;
2Gilead Sciences, Foster City, CA, USA
*Presenting author

Pharmacokinetics of oral islatravir plus lenacapavir given once weekly in an open-label, active-controlled, phase 2 study of virologically suppressed people living with HIV-1

Conclusions

- Based on the plasma PK observed in this study, ISL 2 mg QW is predicted to produce ISL-TP exposure sufficient to cover wild-type HIV-1 and M184V/I variants with no negative impact on CD4+ T-cell or lymphocyte counts
- LEN 300 mg QW resulted in efficacious LEN exposure, consistent with approved subcutaneous LEN[8]
- These results are consistent with previous model-based predictions[9] and support ISL/LEN QW dosing in phase 3 clinical trials (NCT06630286; NCT06630299)

Table 2. Plasma pharmacokinetic parameters of ISL and LEN (intensive PK substudy)

	PK parameter	Day 1 ISL 2 mg + LEN 600 mg n = 13	Day 2 LEN 600 mg n = 13	Steady state ISL 2 mg + LEN 300 mg N = 14
ISL	C_{max}, ng/mL	18.4 (42.3)	–	17.7 (42.4)
	T_{max}, h	0.583 (0.50, 1.00)	–	0.783 (0.50, 1.00)
	C_{8h}, ng/mL	1.80 (58.7)[a]	–	1.38 (28.8)
	C_{trough}, ng/mL	–	–	0.169 (55.5)
	AUC_{0-8h}, h·ng/mL	52.0 (25.6)[a]	–	42.2 (18.7)
	AUC_{tau}, h·ng/mL	–	–	131 (74.7)
LEN	C_{max}, ng/mL	46.4 (62.4)	183 (103)	99.2 (72.6)
	T_{max}, h	7.97 (4.00, 24.0)	6.18 (6.00, 7.93)	6.00 (4.00, 6.17)
	C_{8h}, ng/mL	39.0 (64.2)	151 (84.2)	82.2 (78.4)
	C_{trough}, ng/mL	–	–	35.9 (60.5)[b]
	AUC_{0-8h}, h·ng/mL	235 (64.5)	1040 (104)	625 (76.6)
	AUC_{tau}, h·ng/mL	–	–	9730 (73.9)[b]

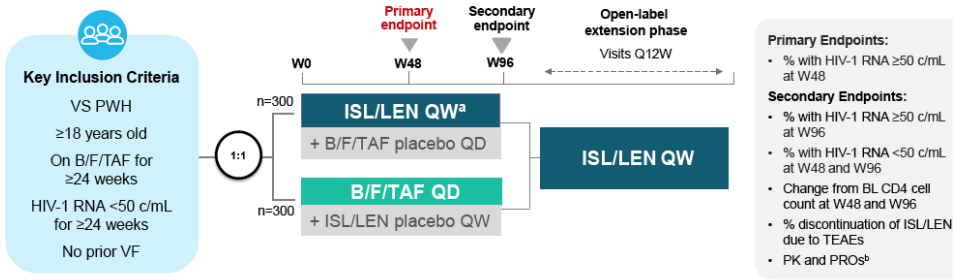
AUC_{0-8h}, area under the concentration-time curve from time 0 to 8 hours; AUC_{tau}, area under the concentration-time curve over the dosing interval; C_{8h}, concentration 8 hours after dosing; C_{max}, maximum drug concentration; C_{trough}, trough concentration; CV, coefficient of variation; ISL, islatravir; LEN, lenacapavir; PK, pharmacokinetics; T_{max}, time to maximum drug concentration.

ISLEND-1: Phase 3 ISL/LEN LAO QW Study Design

HIV Pipeline

ISL/LEN Long-Acting Oral Weekly in VS PWH

Phase 3, Randomized, Double-Blind, Active-Control, Multicenter Study to Evaluate Efficacy, Safety, and PK of ISL/LEN in VS PWH (N=600)[1,2]



Primary Endpoints:
- % with HIV-1 RNA ≥50 c/mL at W48

Secondary Endpoints:
- % with HIV-1 RNA ≥50 c/mL at W96
- % with HIV-1 RNA <50 c/mL at W48 and W96
- Change from BL CD4 cell count at W48 and W96
- % discontinuation of ISL/LEN due to TEAEs
- PK and PROs[b]

[a]Participants will receive ISL/LEN 1 mg/600 mg on Day 1 and Day 2 (provided as 2 tablets of ISL/LEN 0.5mg/300mg) and an oral weekly ISL/LEN 2 mg/300 mg tablet on Day 8 and every week thereafter; [b]PROs are an exploratory endpoint
BL, baseline; PK, pharmacokinetics; PRO, participant-reported outcome; QD, every day; QW, every week; Q12W, every 12 weeks; TEAE, treatment-emergent adverse event; VF, virologic failure; VS, virologically suppressed; W, Week
1. NCT06630286. https://clinicaltrials.gov/study/NCT06630286 (accessed October 08, 2024); 2. Data on file

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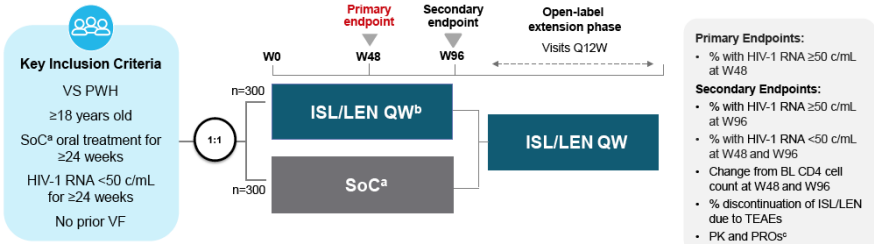
ISLEND-2: Phase 3 ISL/LEN LAO QW Study Design

HIV Pipeline

ISL/LEN Long-Acting Oral Weekly in VS PWH

Phase 3, Randomized, Open-Label, Active-Control, Multicenter Study to Evaluate Efficacy, Safety, and PK of ISL/LEN in VS PWH (N=600)[1,2]

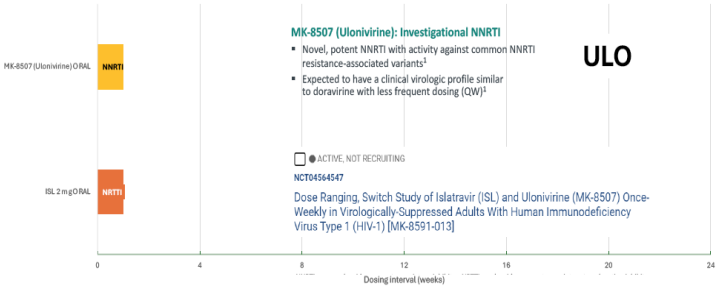


Primary Endpoints:
- % with HIV-1 RNA ≥50 c/mL at W48

Secondary Endpoints:
- % with HIV-1 RNA ≥50 c/mL at W96
- % with HIV-1 RNA <50 c/mL at W48 and W96
- Change from BL CD4 cell count at W48 and W96
- % discontinuation of ISL/LEN due to TEAEs
- PK and PROs[c]

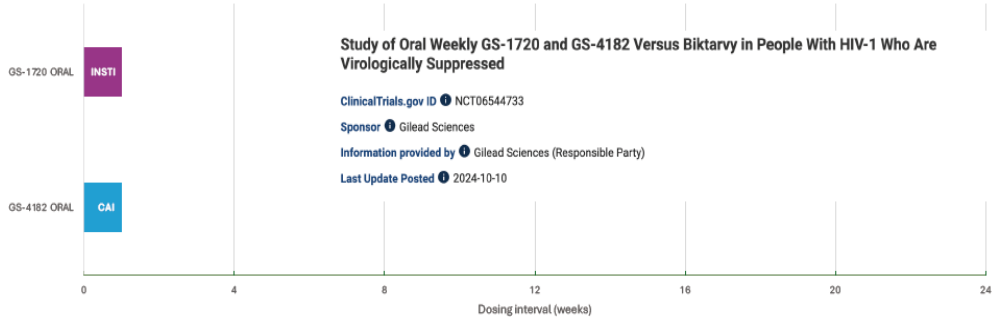
[a]SoC oral regimen: INSTI + 1 or 2 NRTIs, boosted PI + 2 NRTIs, or NNRTI + 2 NRTIs; [b]Participants will receive ISL/LEN 1mg/600mg on day 1 and day 2 (provided as 2 tablets of ISL/LEN 0.5mg/300mg) and an oral weekly ISL/LEN 2mg/300mg tablet on day 8 and every week thereafter; [c]PROs are an exploratory endpoint
BL, baseline; PK, pharmacokinetics; PRO, participant-reported outcome; QW, every week; Q12W, every 12 weeks; SoC, standard of care; TEAE, treatment-emergent adverse event; VF, virologic failure; VS, virologically suppressed; W, Week

QW



ULO

QW



HIV DRUG THERAPY GLASGOW 2024

P036 **Effect of acid reducing agents on the pharmacokinetics of oral GS-4182**
Naveed Shaik, Sean Regan, Deqing Xiao, Furong Wang, Jason Hindman,

Phase 1 pharmacokinetic and nonclinical pharmacology studies

HIV Treatment ‡

Treatment Pipeline Data Presented at AIDS 2024: GS-1720 and GS-4182

	GS-1720 A novel, oral weekly INSTI[1,2]	GS-4182 A novel, oral weekly LEN prodrug[3,4]
Dosing	Once per week	Once per week
Profile	• Potent INSTI (IC_{50} = 6.2 ± 0.4 nM) • Potential high *in vitro* barrier to resistance similar to BIC[5] • Activity against common INSTI-R site-directed HIV-1 mutants[a] • Median $t_{½}$: 9.3 days	• Novel, solubilizing prodrug with greater intestinal LEN absorption and improved systemic exposure in comparison with oral LEN • Smaller tablet size may reduce pill burden • Median LEN $t_{½}$ ~11 days
Safety	Favorable safety profile and well tolerated at doses up to 1350 mg in Phase 1	Well tolerated with a favorable safety profile at doses of 200 or 400 mg QW in Phase 1

GS-1720 and GS-4182 are being developed as a first-in-class QW oral INSTI + capsid inhibitor combination for HIV treatment, moving into Phase 2

Click for study info

[a]Mean EC_{50} fold change relative to wild type was 2.7 for E92Q, 2.5 for Y143R, 1.0 for Q148R, 1.9 for N155H, 2.0 for R263K, 1.8 for E92Q/N155H, 9.5 for E138K/Q148K and 5.5 for G140S/Q148R
EC_{50}, effective concentration of half maximal response; QW, once weekly. 1. Hansen D, et al. AIDS 2024, Abstract and Poster THPEA025; 2. Zhang H, et al. AIDS 2024, Poster WEPEB116; 3. Subramanian R, et al. AIDS 2024, Abstract and Poster WEPEA031; 4. Shaik N, et al. AIDS 2024, Poster WEPEB117; 5. Data on file. Gilead Sciences, Inc.

External Use and Distribution 40

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WONDERS 2 (GS-US-695-7156): Phase 2/3, randomized study

Oral Weekly GS-1720 + GS-4182 in Treatment-Naïve PWH

Phase 2 Study Design

GS-1720, a novel and potent INSTI, and GS-4182, a novel oral QW LEN prodrug, are being developed as a first-in-class QW oral INSTI + capsid inhibitor combination for HIV treatment

N=75 | Treatment-naive PWH

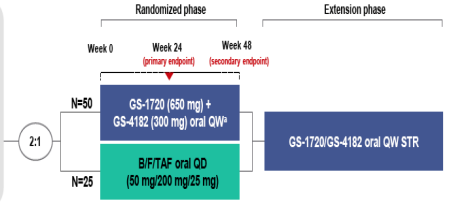
Outcomes

Primary: HIV-1 RNA <50 c/mL at Week 24 (FDA Snapshot)

Secondary: HIV-1 RNA <50 c/mL at Week 12 and Week 48 (FDA Snapshot)

August 2024–Ongoing

- ART-naive adults ≥18 years old
- HIV-1 RNA ≥500 c/mL
- CD4 count ≥200 cells/mm³
- No documented INSTI resistance
- No active or history of chronic HBV infection
- eGFR ≥60 mL/min



Countries participating in Phase 2: Canada, Germany, Poland, Portugal, Puerto Rico, Romania, South Africa, Spain, United States

[a]Participants will receive a 1-day oral loading dose of GS-1720 (1300 mg) and GS-4182 (600 mg) on Day 1

QW, once weekly; STR, single tablet regimen

WONDERS 1 (GS-US-695-6509): Phase 2/3 randomized study ‡

Oral Weekly GS-1720 + GS-4182 in Virologically Suppressed PWH[1]

Phase 2 Study Design *(Data presented on this slide were not part of the AIDS 2024 program)*

GS-1720, a novel and potent INSTI, and GS-4182, a novel oral QW LEN prodrug, are being developed as a first-in-class QW oral INSTI + capsid inhibitor combination for HIV treatment

N=75 | VS PWH on B/F/TAF

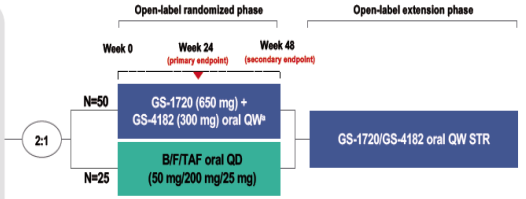
Outcomes

Primary: HIV-1 RNA ≥50 c/mL at Week 24 (FDA Snapshot)

Secondary: HIV-1 RNA ≥50 c/mL at Week 12 and Week 48 (FDA Snapshot)

Estimated Start: September 2024

- Adults ≥18 years old
- HIV-1 RNA <50 c/mL for ≥24 weeks
- B/F/TAF use for ≥24 weeks
- CD4 count ≥200 cells/mm³
- No history of exposure to LEN, GS-1720 or GS-4182
- No documented INSTI resistance or failure
- No active or history of chronic HBV infection
- eGFR ≥60 mL/min



Countries participating in Phase 2: Canada, Puerto Rico, United States[2]

[a]Participants will receive a 1-day oral loading dose of GS-1720 (1300 mg) and GS-4182 (600 mg) on Day 1

QW, once weekly; STR, single tablet regimen; VS, virologically suppressed

1. NCT06544733. https://clinicaltrials.gov/study/NCT06544733 (accessed August 12, 2024); 2. Data on file. Gilead Sciences, Inc.

External Use and Distribution

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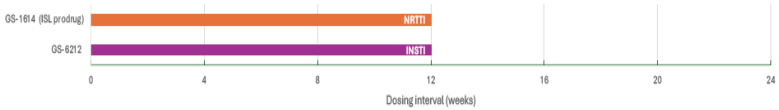
Q3M



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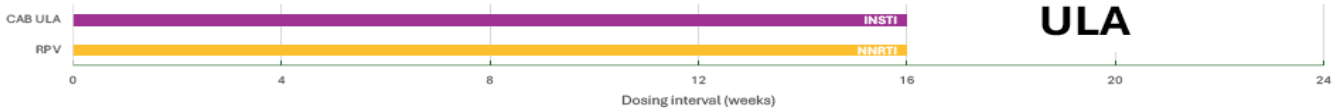
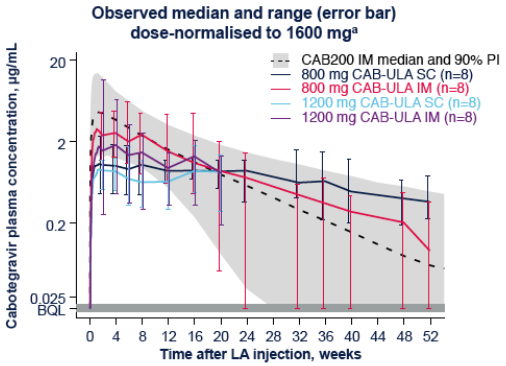


Ultra long-acting CAB exhibits a PK profile that supports 3x/year dosing[1]

A new CAB-ULA formulation was administered SC or IM in an open-label, single-dose, dose-escalation Phase 1 study[1]



- The CAB-ULA doses investigated exhibited slower absorption and longer $t_{1/2}$ than the CAB200 IM (currently approved CAB formulation[2]), with flatter PK profiles[1]
- CAB-ULA $t_{1/2}$ for SC and IM was predicted to be >6x and >2x the $t_{1/2}$ of CAB200 IM[2], respectively[1,b]
- CAB-ULA IM was better tolerated than SC and was comparable to the currently approved CAB200 IM ISR profile[2], despite higher single doses of CAB-ULA[1]
- **The new CAB-ULA formulation exhibited favourable tolerability and safety, with a PK profile that supports dose intervals of ≥4 months[1]**

[a]Error bars before Week 2 are not displayed for visibility [b]Current follow-up time is insufficient to calculate final $t_{1/2}$ value for CAB-ULA
BQL, below quantification limit of 0.025 ug/mL; **ISR**, injection-site reaction; **n**, number of participants with valid PK parameters; **PI**, prediction interval

1. Han K et al. CROI 2024 Presentation 130;
2. Vocabria EU SmPC. March 2024

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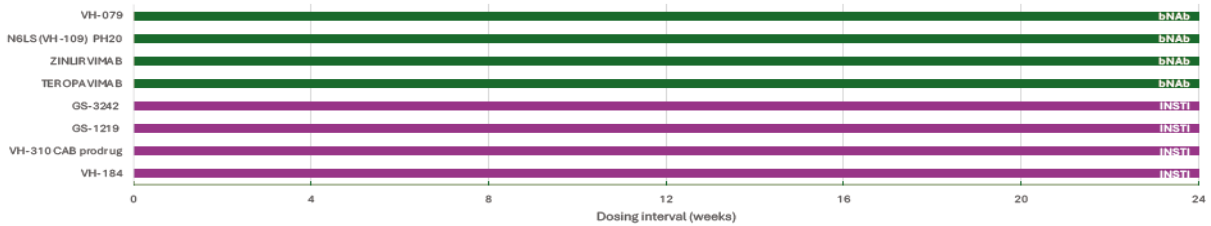
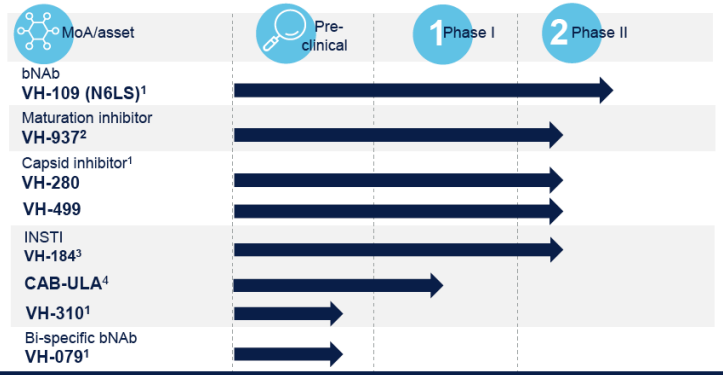
Q6M



O23: Efficacy and safety analysis of lenacapavir with broadly neutralising antibodies, teropavimab and zinlirvimab, in people with HIV-1 highly sensitive to one or both broadly neutralising antibodies
Paul P Cook, *Division of Infectious Diseases and Global Public Health, University of California, San Diego, CA, USA*

P037	**Correlation of baseline phenotypic sensitivity with virological response to VH3810109 (N6LS) in BANNER** *Margaret Gartland, Peter Leone, Judah Abberbock, Kathryn Brown, Paul Wannamaker, Rulan Griesel, Viviana Wilches, Jan Losos (Durham, NC, USA)*
P208	**VH3810109 (N6LS) administration dose-responsively enhances anti-HIV antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) activity in ex vivo models** *Michael Keegan, Margaret Gartland, Saikat Chakraborty, Judah Abberbock, Wilson Chen, Paul Wannamaker, Peter Leone, Jan Losos, Richard Dunham (London, UK)*

The future of our innovative pipeline is long acting[1]



Multiple pathways to self-administration and LA/ULA therapies

1. GSK. ViiV Healthcare meet the management: Getting ahead of HIV together, 2023. Available at: https://www.gsk.com/media/10566/gsk_viiv-mtm_getting-ahead-of-hiv-together_20230928.pdf. Accessed March 2024
2. NCT06051081. Available at: https://www.clinicaltrials.gov/study/NCT06051081. Accessed March 2024; 3. NCT06214052. Available at: https://clinicaltrials.gov/study/NCT06214052. Accessed March 2024 4. Han K, et al. CROI 2024. Oral Presentation 130

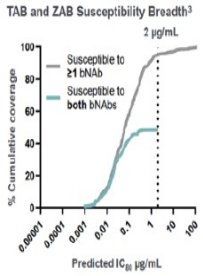
Efficacy and Safety Analysis of Lenacapavir With Broadly Neutralising Antibodies, Teropavimab and Zinlirvimab, in People With HIV-1 Highly Sensitive to One or Both Broadly Neutralising Antibodies

Susan J Little[1], Paul P Cook[2*], Kwad Mponponsuo[3], Edwin DeJesus[4], Gordon E Crofoot[5], Hailin Huang[3], Linda Gorgos[6], Sean E Collins[3], Joseph J Eron[7]

[1]Division of Infectious Diseases, University of California, San Diego, CA, USA; [2]East Carolina University, Greenville, NC, USA; [3]Gilead Sciences, Inc.

Background

- Teropavimab (TAB) and zinlirvimab (ZAB) are broadly neutralising antibodies (bNAbs)[1]
  - TAB targets the CD4-binding site of gp120 and ZAB targets a non-overlapping epitope on the V3 glycan of HIV-1 Env[1]
- ~50% of clade B viruses are highly susceptible to both TAB and ZAB with a 90% inhibitory concentration (IC_{90}) ≤2 µg/mL[2]
  - >90% are highly susceptible to either TAB or ZAB[2]
  - The optimal bNAb sensitivity threshold required to achieve efficacy in the context of HIV-1 treatment has not yet been established
- TAB and ZAB have extended half-lives that allow for dosing every 6 months[1]
- Lenacapavir (LEN), the first-in-class, small molecule capsid inhibitor, can be administered subcutaneously (SC) every 6 months and is indicated for the treatment of multidrug-resistant HIV-1[4]



1. Gautam R, et al. *Nat Med* 2018; 24:610–6. 2. Selzer L, et al. CROI 2023; Poster 580. 3. Estimated coverage given predicted IC90 closely resembles coverage given IC_{90} shown here. Data from CATNAP CombiNAber (Yoon H, et al. *Nucleic Acid Res.* 2015;43:W213-9, Wagh K, et al. *PLoS Pathog.* 2016;12:e1005520) using 479 clade B viruses. 4. Sunlenca® Summary of Product Characteristics, available at www.ema.europa.eu/en/documents/product-information/sunlenca-epar-product-information_en.pdf (accessed October 2024)

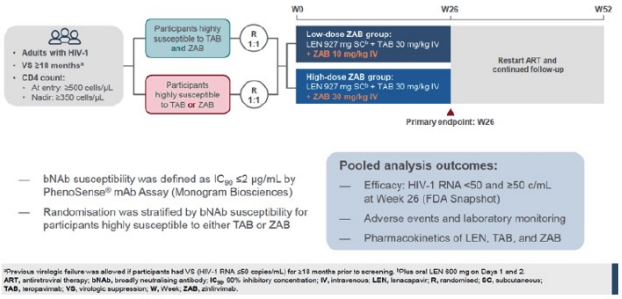
Objective

- We conducted a randomised Phase 1b study (NCT04811040)[1,2] to assess the safety and efficacy of a single dose of LEN + TAB + ZAB in virologically suppressed people with HIV-1 (PWH) who were:
  - Highly susceptible to both bNAbs (primary cohort[1])
  - Highly susceptible to one of TAB or ZAB (pilot cohort[2])

Here, we report pooled outcomes for both cohorts through Week 26 stratified by dose of ZAB

1. Eron J, et al. Lancet HIV 2024;11:E146–55. 2. Eron J, et al. CROI 2024; Abstract 120.
bNAb, broadly neutralising antibody; **LEN**, lenacapavir; **TAB**, teropavimab; **ZAB**, zinlirvimab.

Study Design

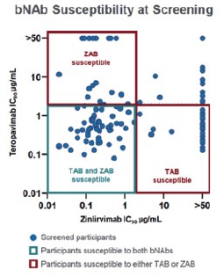


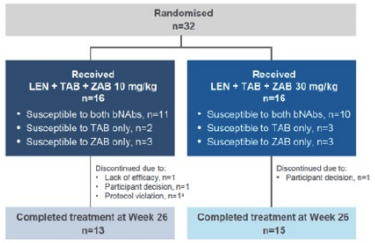
- bNAb susceptibility was defined as IC_{90} ≤2 µg/mL by PhenoSense® mAb Assay (Monogram Biosciences)
- Randomisation was stratified by bNAb susceptibility for participants highly susceptible to either TAB or ZAB

Pooled analysis outcomes:
- Efficacy: HIV-1 RNA <50 and ≥50 c/mL at Week 26 (FDA Snapshot)
- Adverse events and laboratory monitoring
- Pharmacokinetics of LEN, TAB, and ZAB

[a]Previous virologic failure was allowed if participants had VS (HIV-1 RNA ≤50 copies/mL) for ≥18 months prior to screening. [b]The oral LEN 600 mg on Days 1 and 2.
ART, antiretroviral therapy; **bNAb**, broadly neutralising antibody; **IC_{90}**, 90% inhibitory concentration; **IV**, intravenous; **LEN**, lenacapavir; **R**, randomised; **SC**, subcutaneous; **TAB**, teropavimab; **VS**, virologic suppression; **W**, Week; **ZAB**, zinlirvimab.

bNAb Susceptibility and Participant Disposition





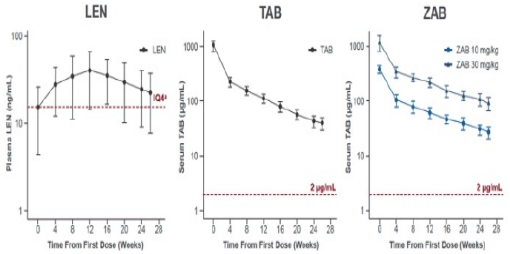
[a]Due to chronic hepatitis B virus infection; participant restarted antiretroviral therapy.
bNAb, broadly neutralising antibody; **IC_{90}**, 90% inhibitory concentration; **LEN**, lenacapavir; **TAB**, teropavimab; **ZAB**, zinlirvimab.

Baseline Characteristics

	LEN + TAB + ZAB 10 mg/kg (n=16)	LEN + TAB + ZAB 30 mg/kg (n=16)
Median (range) age, years	46 (29–63)	48 (25–59)
Female sex at birth, n (%)	2 (12.5)	4 (25.0)
Race, n (%)		
Asian	2 (12.5)	1 (6.3)
Black	3 (18.8)	4 (25.0)
White	10 (62.5)	8 (50.0)
Other	1 (6.3)	3 (18.8)
Hispanic or Latinx ethnicity, n (%)	6 (37.5)	4 (25.0)
Median (range) weight, kg	88 (59–150)	89 (60–143)
Median (range) CD4 cell count, cells/mL	915 (449–1916)	912 (667–1644)
Median (range) duration of baseline ART, years	3 (2–7)	3 (2–7)
Median (range) time since HIV-1 diagnosis, years	6 (2–26)	6 (2–23)

ART, antiretroviral therapy; **LEN**, lenacapavir; **TAB**, tercpavimab; **ZAB**, zinlirvimab.

Mean (SD) Drug Concentrations Over Time



— Therapeutic concentrations of LEN, TAB, and ZAB were maintained through Week 26

ª15.5 ng/mL, 4-fold higher than the *in vitro* protein-adjusted 90% effective concentration in MT-4 cells.
IQ4, inhibitory quotient 4; **LEN**, lenacapavir; **TAB**, tercpavimab; **ZAB**, zinlirvimab.

Efficacy at Week 26

Virologic Outcomes at Week 26 by FDA Snapshot Algorithm

	LEN + TAB + ZAB 10 mg/kg (n=14)	LEN + TAB + ZAB 30 mg/kg (n=16)
HIV-1 RNA ≥50 copies/mL, n	3	0
% (95% CI)	21.4 (4.7; 50.8)	0.0 (0.0; 20.6)
HIV-1 RNA <50 copies/mL, n	11	15
% (95% CI)	78.6 (49.2; 95.3)	93.8 (69.8; 99.8)
No virologic data in Week 26 window, n (%)	0	1[a] (6.3)

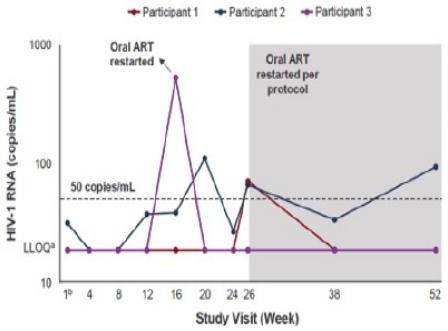
— No participants in the high-dose ZAB group had virologic rebound 6 months after dosing

— CD4 cell counts remained stable; median (95% CI) change from baseline to Week 26:
- LEN + TAB + ZAB 10 mg/kg: +20 (–149; 107) cells/mL
- LEN + TAB + ZAB 30 mg/kg: +36 (–166; 124) cells/mL

[a]Participant withdrew from the study after Week 12 (participant decision), with HIV-1 RNA <50 copies/mL at last available visit.
LEN, lenacapavir; **TAB**, tercpavimab; **ZAB**, zinlirvimab.

Participants with Virologic Rebound

HIV-1 RNA by Study Visit



	Participant 1	Participant 2	Participant 3
bNAb susceptibility at screening:	ZAB only	TAB only	TAB and ZAB
Pre-existing LEN RAMs at screening:	None	None	None
Treatment-emergent drug resistance	None detected	None detected	Assay failure[c]

Participant 2 had acute COVID-19 infection at Week 13, prior to viral rebound

[a]For illustrative purposes, viral loads <20 copies/mL (the LLOQ) are shown as 19 copies/mL. [b]Day 1. [c]Genotypic and phenotypic resistance testing was unsuccessful at time of virological rebound due to low plasma viral load.
ART, antiretroviral therapy; **LEN**, lenacapavir; **LLOQ**, lower limit of quantification; **RAM**, resistance-associated mutation; **TAB**, tercpavimab; **ZAB**, zinlirvimab.

Safety Overview

n (%)	LEN + TAB + ZAB 10 mg/kg (n=16)	LEN + TAB + ZAB 30 mg/kg (n=16)
TEAEs	13 (81.3)	15 (93.8)
Grade ≥3	3 (19.8)	2 (12.5)
TRAEs	10 (62.5)	12 (75.0)
Grade ≥3	0	2 (12.5)
SAEs	0	0
TEAEs leading to study drug discontinuation	0	0

- There were no Grade ≥3 clinically significant laboratory abnormalities
- One participant in the low-dose ZAB group had an infusion-related reaction (Grade 1 pyrexia) after completing administration of both bNAbs, which resolved without treatment
- Treatment-emergent anti-drug antibodies (ADAs) against TAB occurred in six participants, and against ZAB in seven participants
  - ADAs were generally low in titres and did not impact PK or efficacy

bNAb, broadly neutralising antibody; **LEN**, lenacapavir; **PK**, pharmacokinetics; **SAE**, serious adverse event; **TAB**, teropavimab; **TEAE**, treatment-emergent adverse event; **TRAE**, treatment-related adverse event; **ZAB**, zinlirvimab.

Most Common TEAEs

Most common TEAEs (occurring in ≥5% of participants), n (%)	LEN + TAB + ZAB 10 mg/kg (n=16)	LEN + TAB + ZAB 30 mg/kg (n=16)
Injection site pain	5 (31.3)	7 (43.8)
Injection site induration	2 (12.5)	7 (43.8)
Injection site erythema	4 (25.0)	5 (31.3)
Injection site nodule	5 (31.3)	3 (18.8)
COVID-19	5 (31.3)	2 (12.5)
Injection site mass	3 (18.8)	1 (6.3)
Upper respiratory tract infection	3 (18.8)	1(6.3)

- The most common TEAEs were SC LEN-related injection site reactions; most were Grade 1 (mild)
- Across both groups, median (IQR) durations of resolved nodules and indurations were:
  - Nodules: 85 (63–194) days
  - Indurations: 246 (158–305) days

IQR, interquartile range; **LEN**, lenacapavir; **SC**, subcutaneous; **TAB**, teropavimab; **TEAE**, treatment-emergent adverse event; **ZAB**, zinlirvimab.

Conclusions

- The long-acting combination of LEN + TAB + ZAB had a favourable safety profile through Week 26, with no difference in safety or tolerability between ZAB dose groups
- All participants who received LEN, TAB, and high-dose ZAB maintained viral suppression through Week 26[a]
- These results suggest high treatment efficacy for the combination of LEN, TAB, and high-dose ZAB can be achieved when ≥1 antibody is highly active in PWH highly susceptible to one or both bNAbs
  - The higher ZAB dose was selected for an ongoing Phase 2 study (NCT05729568) investigating the efficacy and safety of switching to twice-yearly LEN + TAB + ZAB vs continuing baseline therapy in PWH highly susceptible to both bNAbs

[a]No data in Week 26 window, n=1.
bNAb, broadly neutralising antibody; **LEN**, lenacapavir; **PWH**, people with HIV-1; **TAB**, teropavimab; **ZAB**, zinlirvimab.

Phase 2: Investigational LEN + TAB + ZAB in VS PWH (GS-US-536-5939)[1]

‡

LEN with bNAbs, TAB and ZAB, Dosed Every 6 Months in PWH

N ≈ 83[1]

VS PWH aged 18–65 years[1]

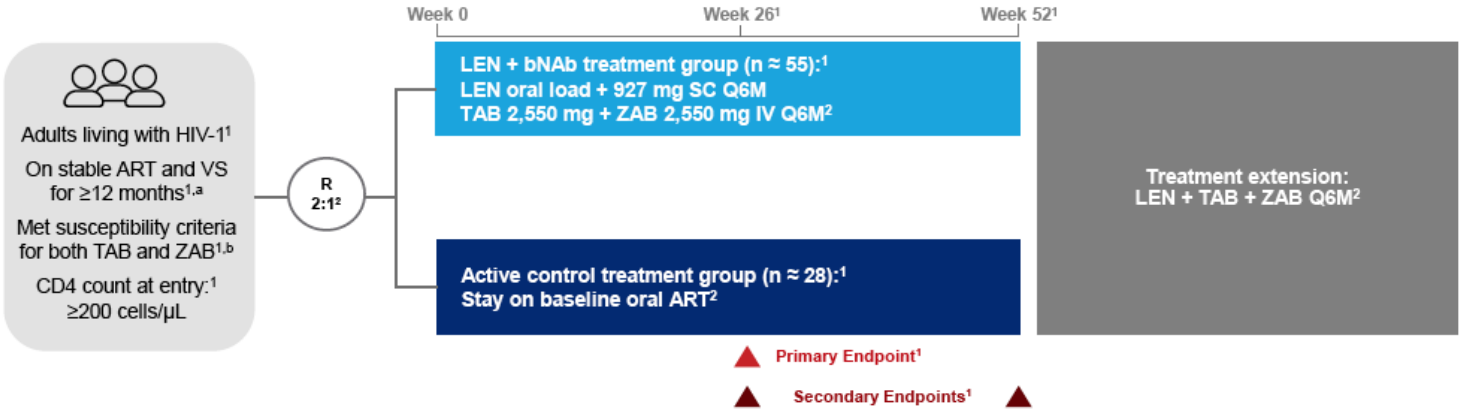
Outcomes[1]

Primary: HIV-1 RNA ≥50 c/mL at Week 26 (FDA snapshot)

Key secondary: Safety and tolerability, PK

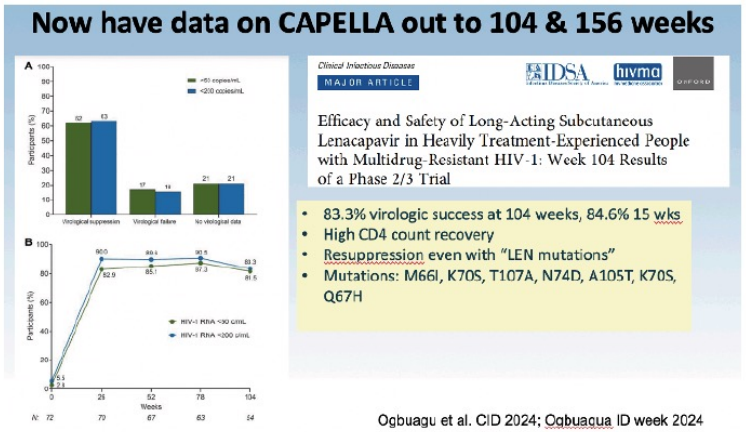
2023–ongoing (fully enrolled)[1]

Study sites: United States, Australia, Canada and Puerto Rico[1]

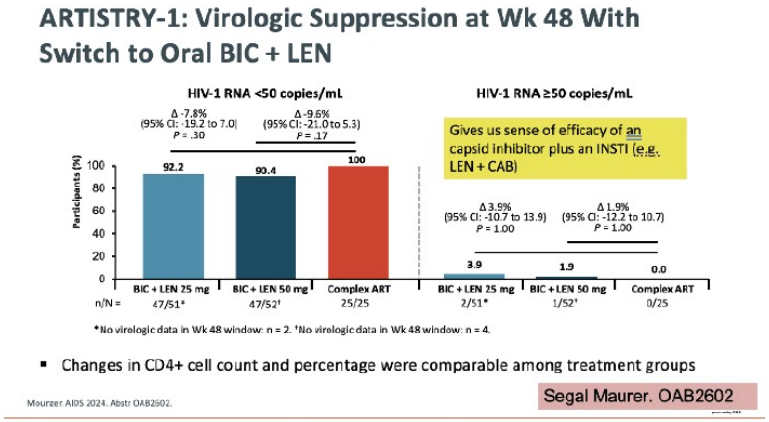


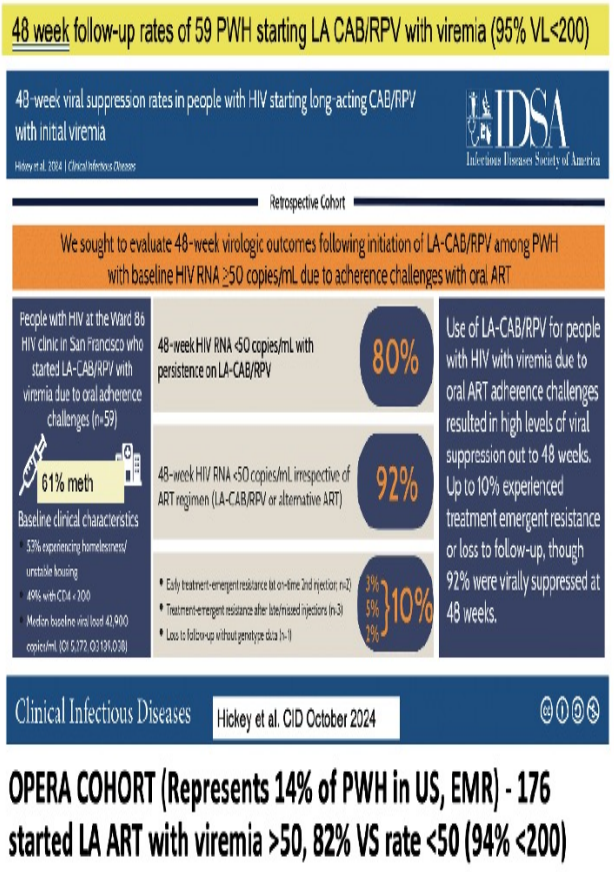
[a]Virologic elevations of ≥50 c/mL (transient detectable viremia or "blips") prior to screening are acceptable;[1]
[b]Susceptibility defined as IC90 ≤2 µg/mL to each antibody by PhenoSense Monoclonal Antibody Assay (Monogram Biosciences)[2]
IC, inhibitory concentration; Q6M, every 6 months; TAB, teropavimab; VF, virologic failure; VS, virologically suppressed; ZAB, zinlirvimab
1. NCT05729568. https://clinicaltrials.gov/ct2/show/NCT05729568 (accessed July 14, 2023); 2. Data on file. Gilead Sciences, Inc.

THE NEAR FUTURE



Ogbuagu et al. CID 2024; Ogbuagua ID week 2024





Gandhi M.HIV Drug Therapy Glasgow 2024
10-13 November

DO NOT forget this

Open Forum Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Gandhi OFID 2024

Case Series of People With HIV on the Long-Acting Combination of Lenacapavir and Cabotegravir: Call for a Trial

Monica Gandhi,[1,6] Lucas Hill,[2] Janet Grochowski,[1] Alexander Nelson,[3] Catherine A. Koss,[1] Francis Moyorga-Munoz,[1] Jon Oskarsson,[1] Mary Shiels,[1] Ann Avery,[4] Laura Bamford,[2] Jillian Bann,[5,6] William R. Short,[5] and Corrilynn O. Hileman[4]

[1]Division of HIV, Infectious Diseases and Global Medicine, University of California, San Francisco (UCSF), San Francisco, California, USA, [2]Division of Infectious Diseases and Global Public Health, University of California San Diego (UCSD), San Diego, California, USA, [3]Department of Specialty Pharmacy, MetroHealth Medical Center, Cleveland, Ohio, USA, [4]Division of Infectious Diseases, MetroHealth Medical Center, and Case Western Reserve University (CWRU), Cleveland, Ohio, USA, and [5]Division of Infectious Diseases, Hospital of the University of Pennsylvania (UPenn), Philadelphia, Pennsylvania, USA

Background. Injectable cabotegravir (CAB)/rilpivirine (RPV) is the only combination long-acting (LA) antiretroviral regimen approved for HIV. RPV may not be effective among individuals with non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance, which has >10% prevalence in many countries. Lenacapavir (LEN) is an LA capsid inhibitor given every 6 months, but has not been studied in combination with other LA agents.

In this case series compiled from four US academic medical centers, 34 patients with adherence challenges were prescribed LA LEN subcutaneously off-label every 26 weeks with LA CAB (+/- LA RPV) every 4-8 weeks.24 After starting LA LEN therapy, 32/34 (94%) achieved virologic suppression at a median of 8 (4-16) weeks, with all 21 patients with documented or suspected NNRTI mutations (10 without VS at baseline) maintaining or achieving VS.

Gandhi M.HIV Drug Therapy Glasgow 2024
10-13 November

ACTG A5341: Trial of LEN/CAB approved

- These pharmaceutical companies have not historically worked together before
- After much advocacy, small trial (n=38) finally approved from the pharmaceutical companies of LEN/CAB in the ACTG
- Inclusion criteria:
  - NNRTI resistance
  - Viremic
  - Experiencing adherence challenges with oral ART
- Hoping ACTG study will open door to larger trial in LMICs
  - In those with virologic suppression switching over from TLD (non-inferior)
  - In those failing TLD due to adherence difficulties without suspicious for resistance (superior)

Cliniques universitaires SAINT-LUC UCLouvain BRUXELLES

THANK YOU