Conference
NOVEL DATA ON
NEW AND OLD EPIDEMICS
Milan, 12 September 2023

Long Acting Art: from simplification switch to salvage therapy

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Long-acting HIV strategies

Treatment

cabotegravir + rilpivirine (CAB + RPV LA)

lenacapavir

ibalizumab

islatravir

bNAbs-based strategies

PrEP

cabotegravir (CAB LA)

lenacapavir

islatravir

CABO + RPV LA

> 2300 patients on CAB+RPV LA

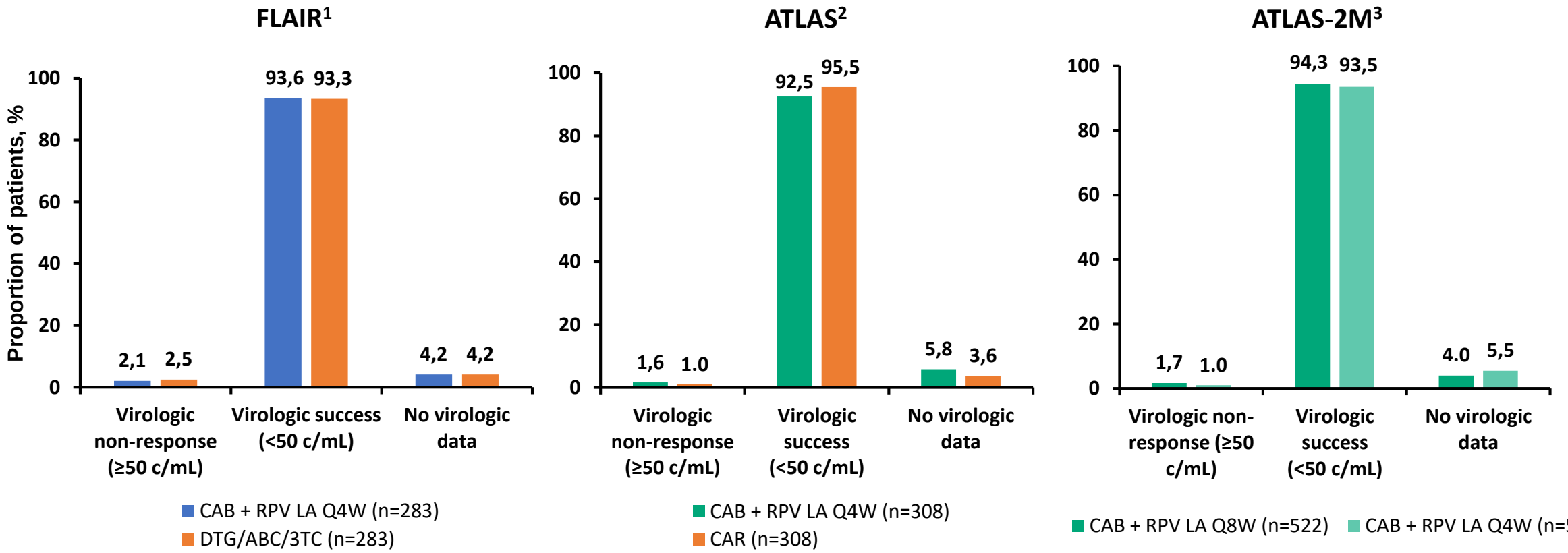
Inclusion criteria

- ✓ Virologically suppressed (at least 6 mos)
- ✓ No previous virological failure
- ✓ No resistance to study drug
- ✓ No HBV coinfection

Study N. of patients	Study arms
LATTE-2 **230 vs 56**	**CAB + RPV LA** (Q1M+Q2M) *versus* CAB/ABC/3TC
ATLAS **308 vs 308**	**CAB + RPV LA** (Q1M) *versus* cARV
FLAIR **283 vs 283**	**CAB + RPV LA** (Q2M) versus ABC/3TC/DTG
ATLAS 2M **522 vs 523**	**CAB + RPV LA** (Q2M) *versus* **CAB + RPV LA** (Q1M)
SOLAR **453 vs 227**	**CAB + RPV LA** (Q2M) *versus* BIC/FTC/TAF

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

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

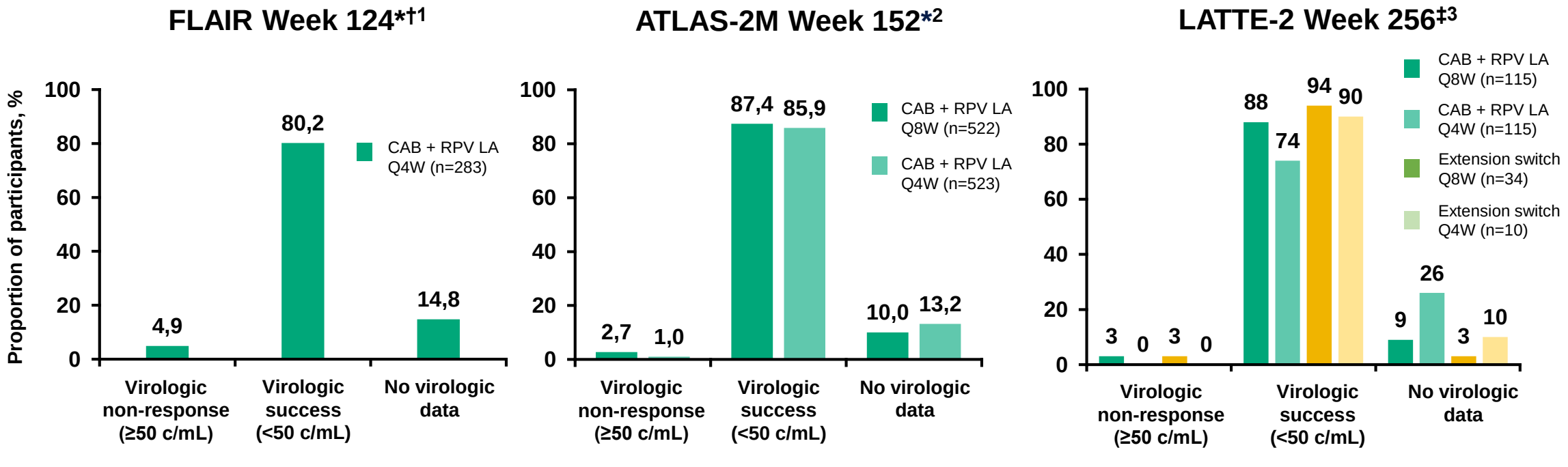


*Primary endpoint: non-inferiority (HIV-1 RNA ≥50 c/mL) to comparator arm; key secondary endpoint: non-inferiority (HIV-1 RNA <50 c/mL) to comparator arm
3TC, lamivudine; **ABC,** abacavir; **CAR,** current antiretroviral regimen; **ITT-E,** intention-to-treat exposed

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

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

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



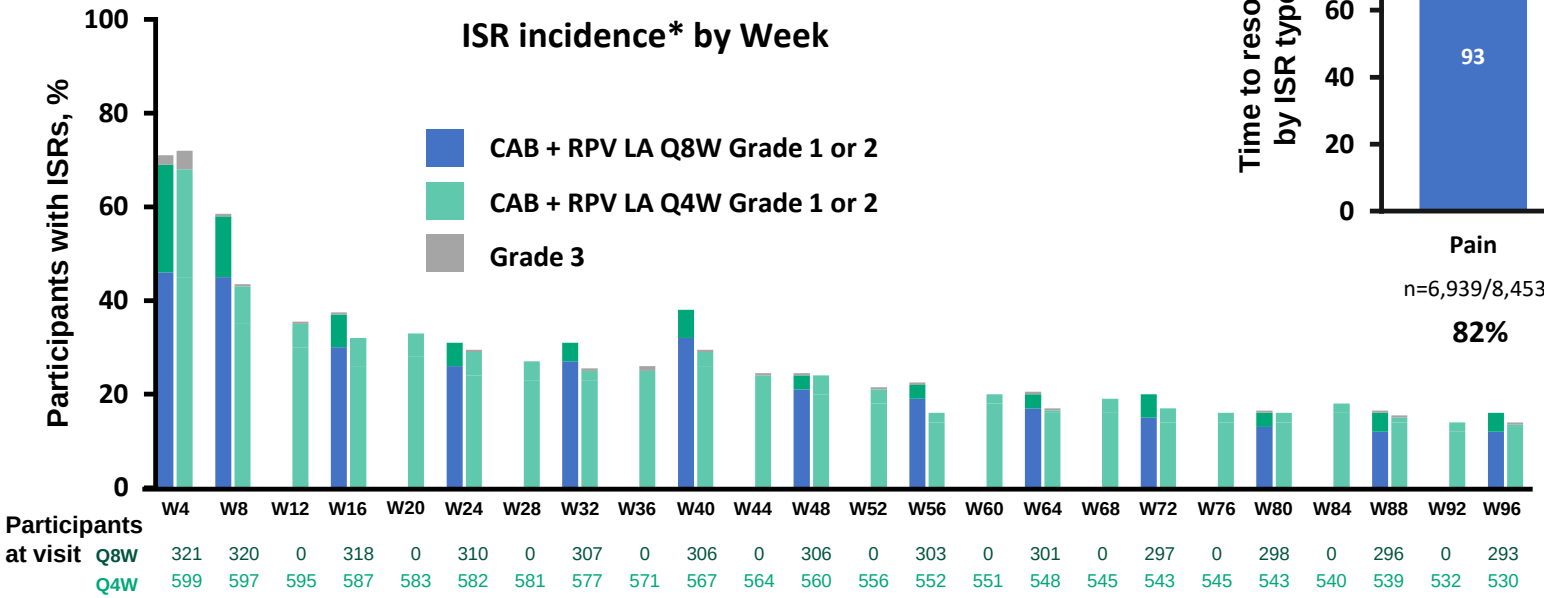
CAB + RPV LA maintained high levels of virologic suppression beyond Week 48[1–3]

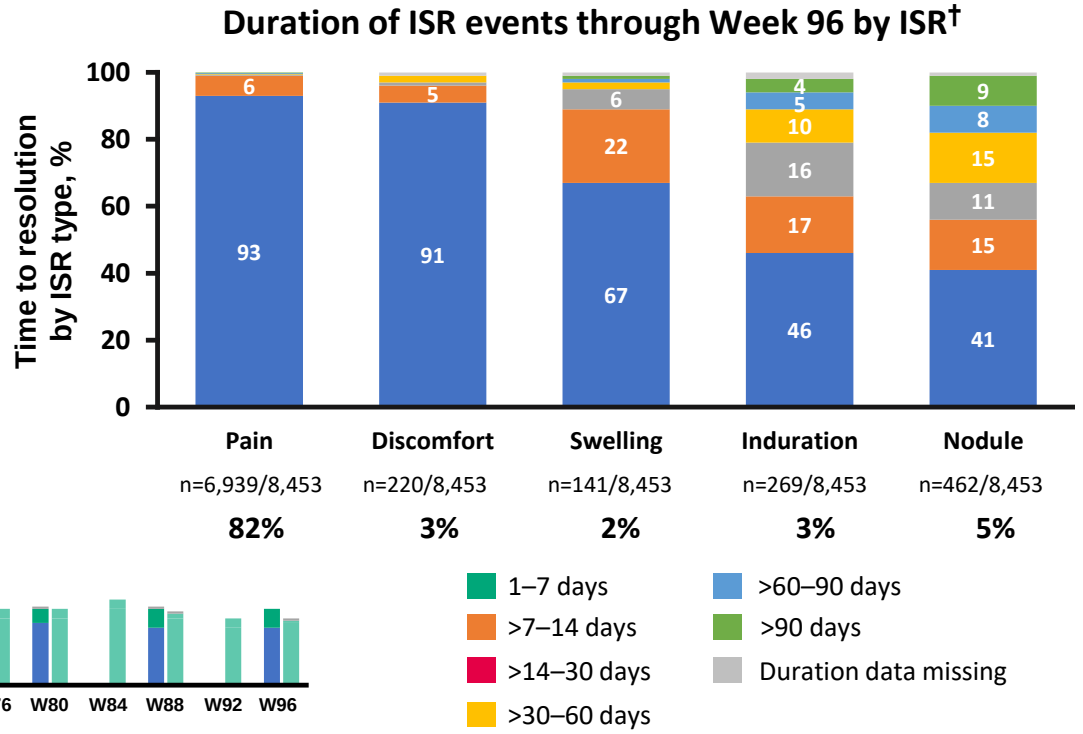
*Primary endpoint: proportion of participants with HIV-1 RNA ≥50 c/mL at Week 48 by FDA Snapshot
†No CAR arm at Week 124. Of those with no virologic data at Week 124 (n=42), most were due to discontinuations due to AEs or other non-virologic reasons
‡Primary endpoints: proportion of participants with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

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

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

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





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

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

Chamay N, et al. AIDS 2022. Poster EPB182

ATLAS and FLAIR: Pooled safety overview through Week 48 in the maintenance phase (excludes ISRs)

n (%)	CAB + RPV LA N=591	CAR N=591
Any AE	**506 (86)**	**444 (75)**
Any Grade ≥3 AE*	**44 (7)**	**35 (6)**
Any drug-related AE	**165 (28)**	**35 (6)**
Any Grade ≥3 drug-related AE*	**8 (1)**	**1 (<1)**
Any AEs leading to withdrawal†	**22 (4)**	**9 (2)**
Any SAE	**24 (4)**	**25 (4)**
SAEs related to study treatment‡	**1 (<1)**	**1 (<1)**
Common AEs (≥5%)		
Nasopharyngitis	108 (18)	88 (15)
Headache	71 (12)	38 (6)
Upper respiratory tract infection	66 (11)	52 (9)
Diarrhea	52 (9)	38 (6)
Back pain	40 (7)	23 (4)
Influenza	41 (7)	34 (6)
Pyrexia	43 (7)	13 (2)
AEs of special interest		
Anxiety	27 (5)	20 (3)
Depression	16 (3)	14 (2)
Suicidal ideation/behavior	4 (<1)	5 (<1)

Most drug-related AEs were Grade 1 or 2, and mild-to-moderate in severity.
There was no pattern of events leading to treatment discontinuation

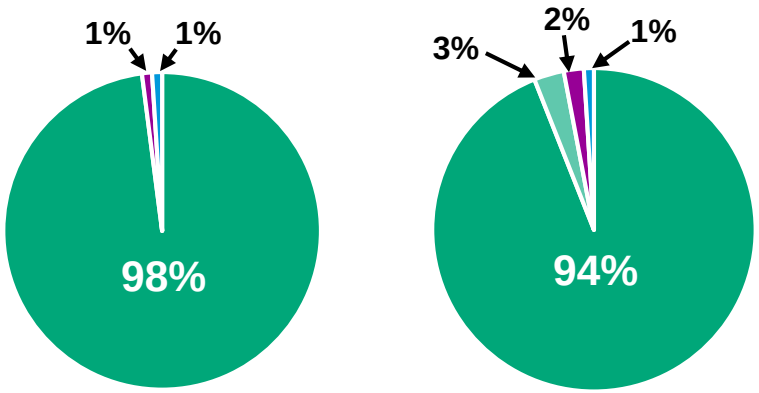
*There was only one (<1%) participant with a Grade 5 AE (death), in the CAR arm during the maintenance phase, which was due to a methamphetamine overdose that was determined to be unrelated to study treatment; †AEs leading to withdrawal in >1 participant were injection site pain (n=6), hepatitis (hepatitis A, n=4; acute hepatitis B and C, n=3 and n=1, respectively); headache (n=2); and diarrhea (n=2). No single AE leading to withdrawal was reported in >1 participant in the CAR arm; ‡SAEs related to study treatment: LA arm, right knee mono-arthritis; CAR arm, suicidal ideation

SAE, serious adverse event

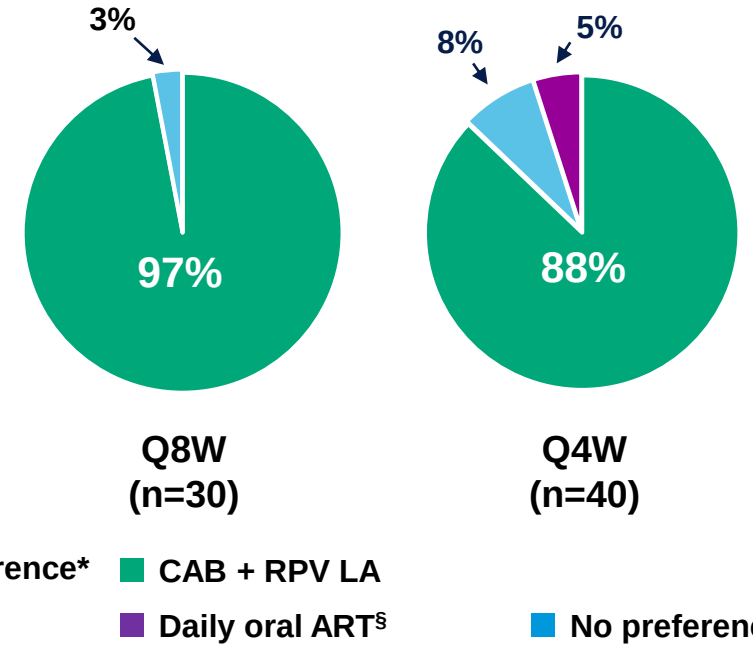
Rizzardini G, et al. J Acquir Immune Defic Syndr 2020;85:498–506

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

Week 48
Participants on Q8W[1,2]



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



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

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

Emergent resistance mutations in CAB+RPV LA arms by study

Study, N. of patients	Study arms	Patients with CVF § at week 48	Patients with CVF § in the extension phase
LATTE-2 **230 vs 56**	**CAB + RPV LA** (Q1M+Q2M) *versus* CAB/ABC/3TC	2	(**week 256**) 0 single arm, 252 pts
ATLAS **308 vs 308**	**CAB + RPV LA** (Q1M) *versus* cARV	3	(**week 96**) 0 single arm, 54 pts
FLAIR **283 vs 283**	**CAB + RPV LA** (Q2M) *versus* ABC/3TC/DTG	4	(**week 124**) 2 single arm, 515 pts
ATLAS 2M **522 vs 523**	**CAB + RPV LA** (Q2M) *versus* **CAB + RPV LA** (Q1M)	8	(**week 152**) 4 889 pts
SOLAR **453 vs 227**	**CAB + RPV LA** (Q2M) *Versus* BIC/FTC/TAF	5	ongoing

§ CVF: confirmed virological failure (i.e. HIV RNA cut-off for confirmed > 200 copies/ml).

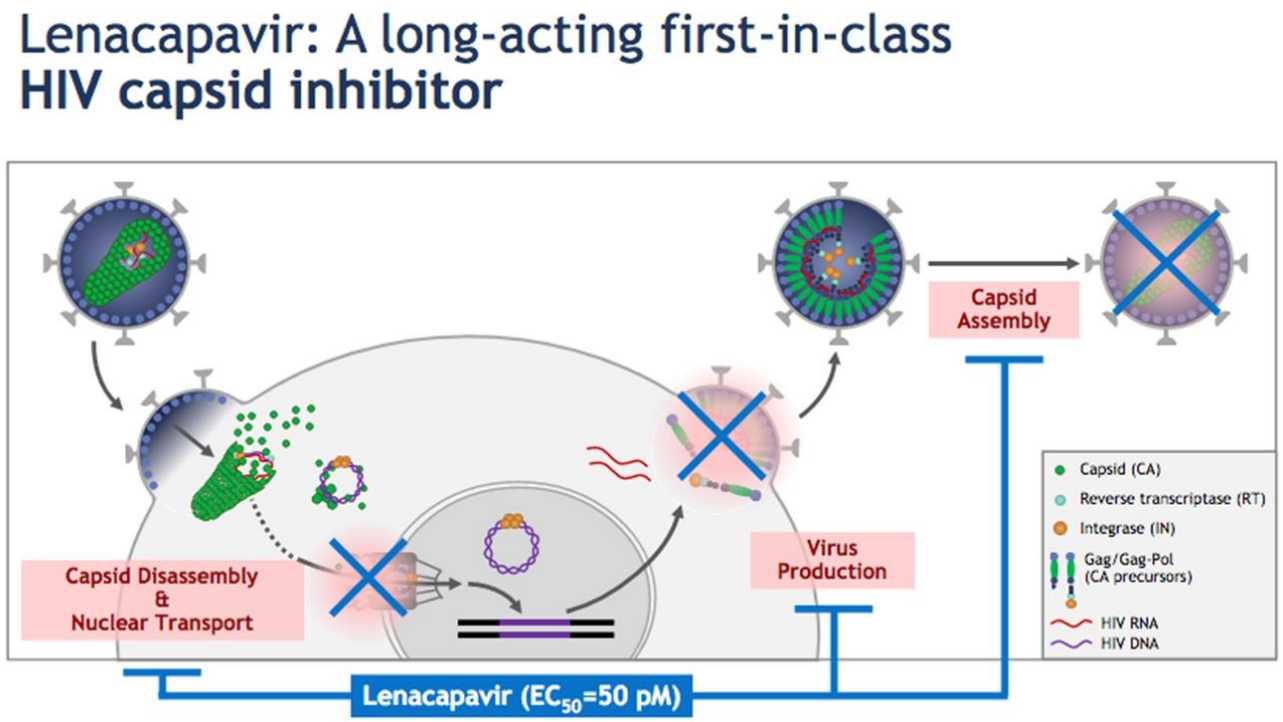
Exploring predictors of HIV-1 virologic failure to long-acting cabotegravir and rilpivirine: a multivariable analysis

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

Table 2. Multivariable logistic regression analysis of confirmed virologic failure through Week 48.

N	Parameter	Full model OR (95% CI), *P*[a]	Backwards elimination model OR (95% CI), *P*[a]
1039	RPV RAM(s) at baseline	30.23 (6.25–>99), <0.001	40.36 (8.81–>99), <0.001
	Log_2 of *post hoc* Week 8 RPV trough concentration	3.85 (1.15–14.29)[b], 0.029	5.00 (1.79–16.67)[b], 0.002
	Baseline HIV-1 subtype A6/A1	2.37 (0.34–22.14), 0.394	5.92 (1.62–22.89), 0.008
	BMI (kg/m^2) at baseline	1.08 (0.96–1.22), 0.192	1.13 (1.02–1.24), 0.020
	Prespecified INSTI polymorphism (excluding L74I [excluding mixtures with L74M]) at baseline	0.16 (0.01–1.05), 0.057	0.14 (0.01–0.91), 0.038
	NNRTI RAM(s) (excluding RPV RAMs) at baseline	2.64 (0.72–9.21), 0.137	2.78 (0.78–9.63), 0.111
	Q8W regimen	2.76 (0.65–11.68), 0.164	2.77 (0.67–11.38), 0.156
	L74I (excluding mixtures with L74M) INSTI polymorphism at baseline	2.51 (0.33–13.85), 0.347	Eliminated from model
	Female (sex at birth)	1.09 (0.26–4.36), 0.899	Eliminated from model
	Log_2 of *post hoc* Week 8 CAB trough concentration	0.66 (0.25–1.74), 0.395	Eliminated from model

Lenacapavir



Capella

Heavily Treatment-Experienced

Calibrate

naive patients

EMA approved in June 2023 for patients with limited treatment options due to safety, intolerance, and resistance

HIV Treatment

LEN HTE

Capella

Lenacapavir in Heavily Treatment-Experienced PLWH

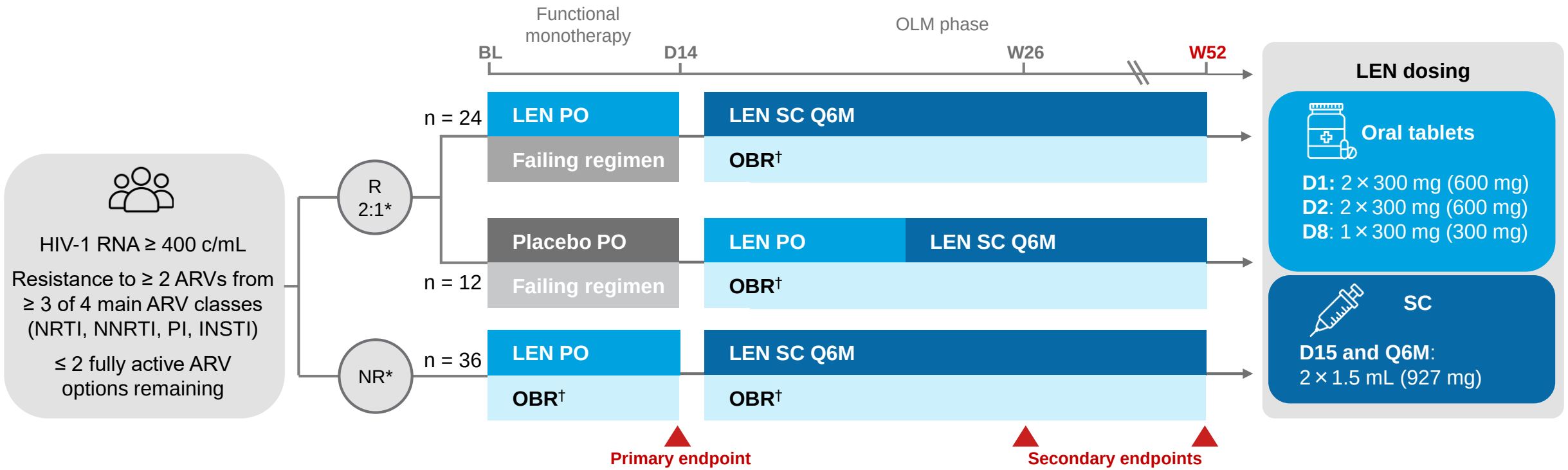
N = 72

HTE PLWH with MDR, aged ≥ 12 years and weighing ≥ 35 kg

Outcomes (randomized cohort)

Primary: ≥ 0.5 log_{10} c/mL reduction in HIV-1 RNA from BL at D15
Secondary: HIV-1 RNA < 50 c/mL and < 200 c/mL at W26 and W52 (FDA Snapshot)

2019–present (ongoing)



*Participants with < 0.5 log_{10} c/mL decline in HIV-1 RNA during screening entered the randomized cohort; participants with ≥ 0.5 log_{10} c/mL decline in HIV-1 RNA during screening entered the nonrandomized cohort; †Investigational agents (e.g., FTR) permitted; ATV, ATV/COBI, ATV/RTV, EFV, ETR, NVP, TPV not permitted
BL, baseline; D, Day; HTE, heavily treatment-experienced; MDR, multidrug resistance; NR, nonrandomized; OBR, optimized background regimen; OLM, open-label maintenance; PO, orally; Q6M, every 6 months; R, randomized; W, Week

Ogbuagu O, et al. CROI 2023, Poster 523

Baseline Characteristics

Characteristic	Randomized		Nonrandomized	Total (N = 72)
	LEN (n = 24)	Placebo (n = 12)	LEN (n = 36)	
Age, years, median (range)	55 (24–71)	54 (27–59)	49 (23–78)	52 (23–78)
Female at birth, %	29	25	22	25
Black race, %	42	55	31	38
Hispanic/Latinx, %	25	36	14	21
HIV-1 RNA, log_{10} c/mL, median (range)	4.2 (2.3–5.4)	4.9 (4.3–5.3)	4.5 (1.3–5.7)	4.5 (1.3–5.7)
HIV-1 RNA > 75,000 c/mL, %	17	50	28	28
CD4 count, cells/μL, median (range)	172 (16–827)	85 (6–237)	195 (3–1,296)	150 (3–1,296)
CD4 count ≤ 200 cells/μL, %	67	92	53	64
Years since HIV diagnosis, median (range)	27 (13–39)	26 (14–35)	23 (9–44)	24 (9–44)
Number of prior ARV agents, median (range)	9 (2–24)	9 (3–22)	13 (3–25)	11 (2–25)
Number of ARV agents in failing regimen, median (range)	3 (1–7)	3 (2–6)	4 (2–7)	3 (1–7)
Known resistance to ≥ 2 drugs in class, %				
NRTI	96	100	100	99
NNRTI	92	100	100	97
PI	83	67	83	81
INSTI	83	58	64	69

HTE, heavily treatment-experienced

Ogbuagu O, et al. CROI 2023, Poster 523; Segal-Maurer S, et al. vCROI 2021, Oral 127; Molina JM, et al. vIAS 2021, Oral OALX01LB02; Segal-Maurer S, et al. N Engl J Med 2022;386:1793-803

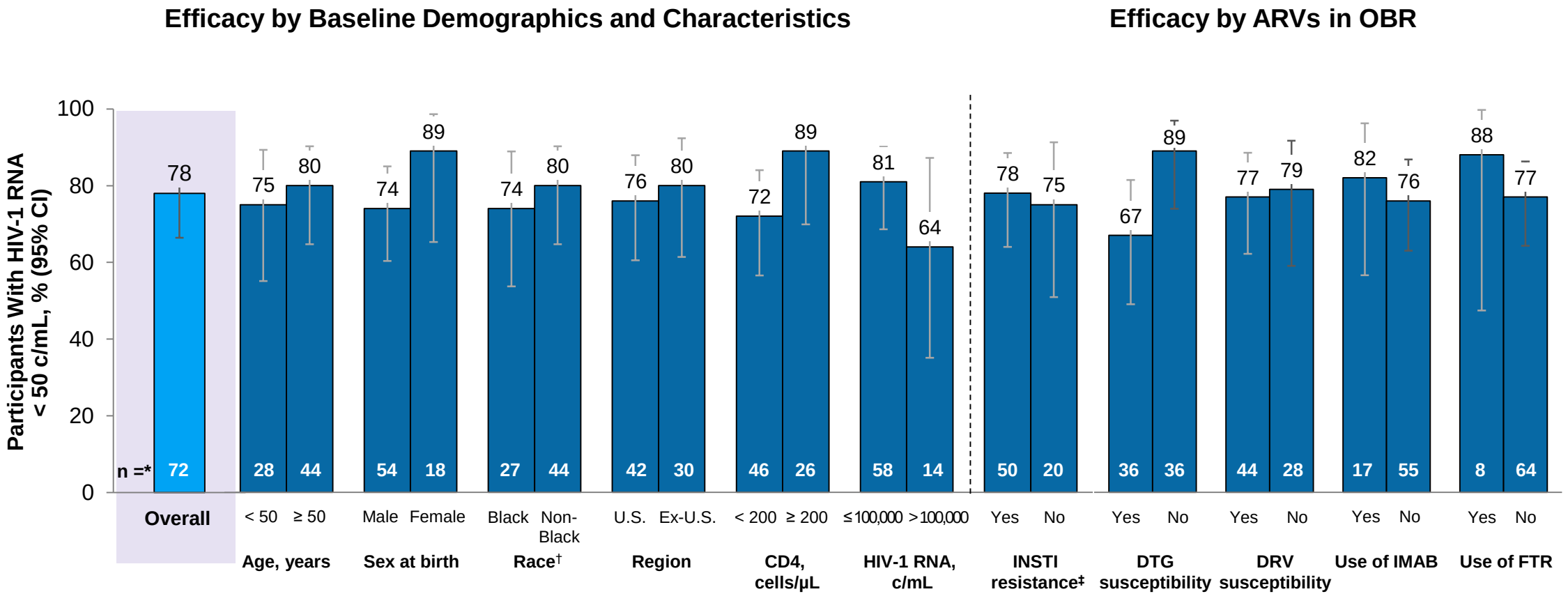
HIV Treatment

LEN HTE

Capella

Post Hoc Subgroup Analysis at Week 52 of HIV-1 RNA < 50 c/mL

Randomized and Nonrandomized Cohorts



The efficacy of LEN in combination with an OBR was consistent across diverse subgroups

*Total n in each subgroup; †Reported as "not permitted" for one participant; ‡Included phenotypic and genotypic resistance to bictegravir, cabotegravir, dolutegravir, elvitegravir and raltegravir; data missing for two participants. FTR, fostemsavir; HTE, heavily treatment-experienced; IMAB, ibalizumab; OBR, optimized background regimen

Ogbuagu O, et al. CROI 2023, Poster 523

Lenacapavir for Treatment-Naïve PLWH

N = 182

Treatment-naïve PLWH with HIV-1 RNA ≥ 200 c/mL and no HBV or HCV

Outcomes

Primary (W54): HIV-1 RNA < 50 c/mL at W54. Secondary (W28, W38 and W80): HIV-1 RNA < 50 c/mL, and change from BL in log_{10} HIV-1 RNA and CD4 count

2019–present (ongoing)

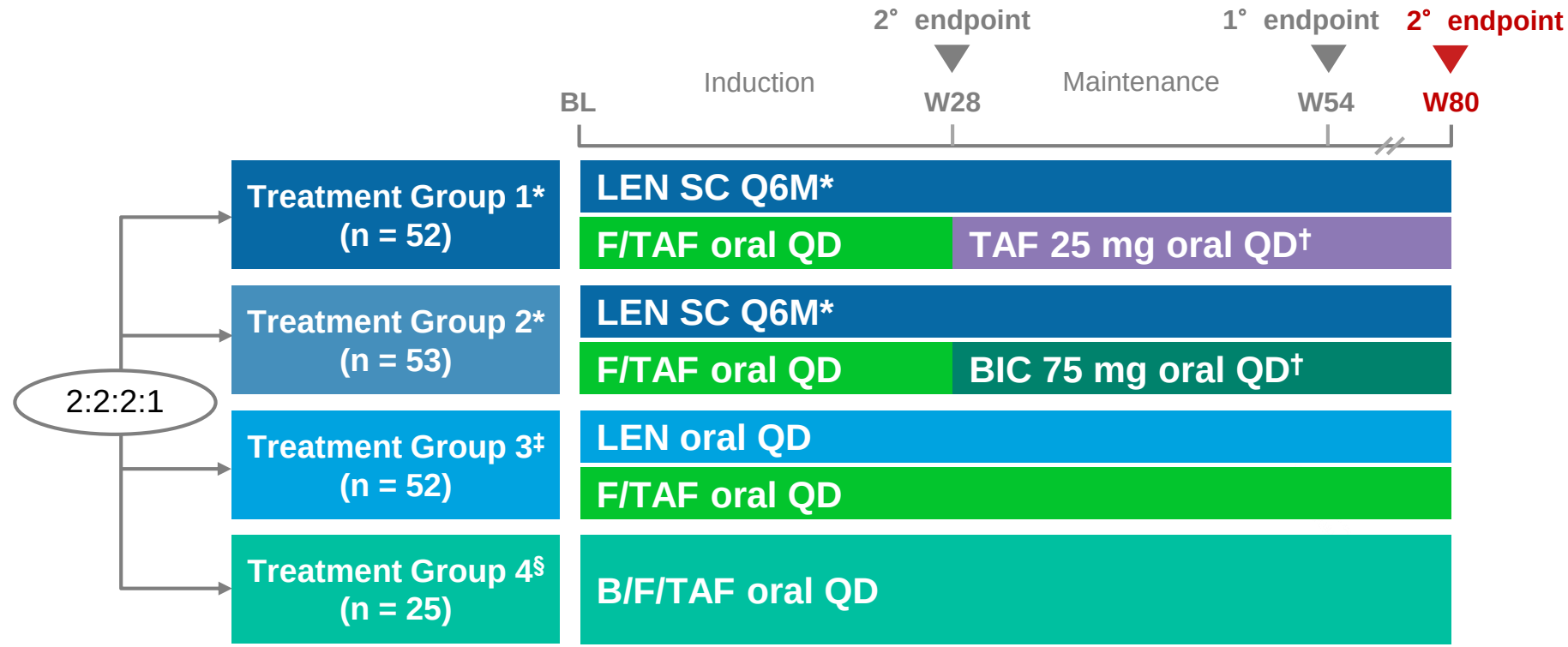
ART-naïve PLWH

HIV-1 RNA ≥ 200 c/mL

CD4 count ≥ 200 cells/μL

No HBV or HCV

2:2:2:1



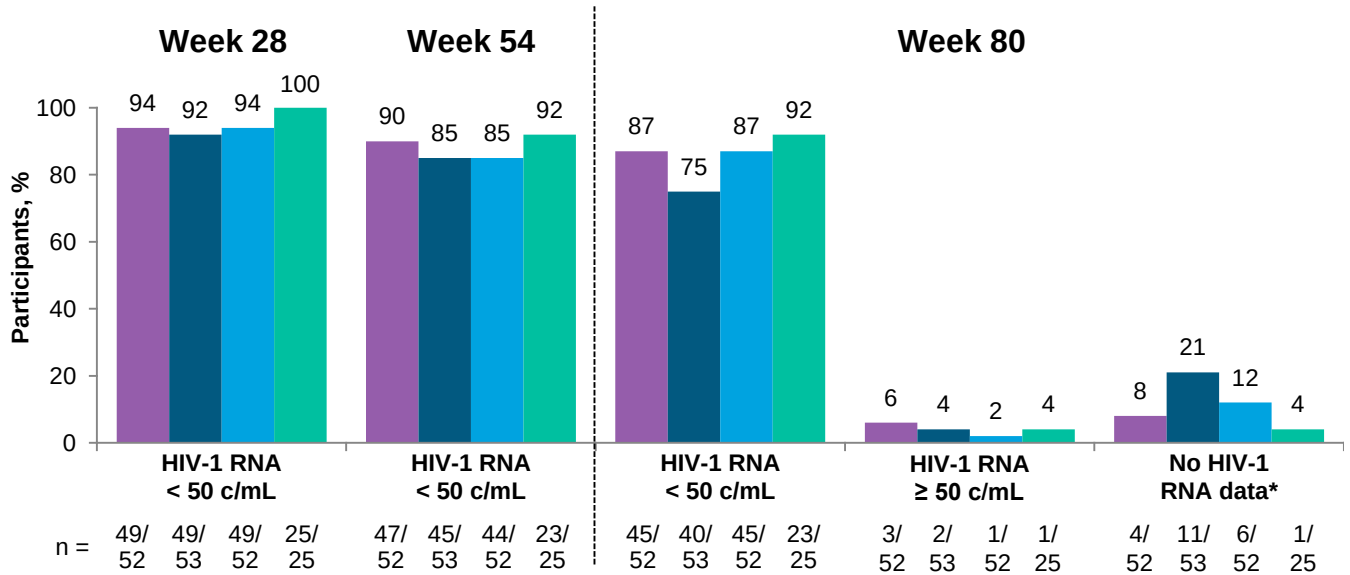
*LEN oral initiation (600 mg on D1 and D2, 300 mg on D8), followed by LEN SC 927 mg on D15; F/TAF, 200/25 mg; †Participants in Treatment Groups 1 and 2 required HIV-1 RNA < 50 c/mL at W16 and W22 to initiate either TAF or BIC at W28; those with HIV-1 RNA ≥ 50 c/mL discontinued study at W28; ‡LEN 600 mg on D1 and D2, followed by LEN 50 mg from D3; F/TAF, 200/25 mg; §B/F/TAF, 50/200/25 mg. BL, baseline; D, Day; Q6M, every 6 months (every 26 weeks); TN, treatment naïve; W, Week

Hagins D, et al. CROI 2023, Poster 522; Gupta SK, et al. CROI 2022, Oral 138

Efficacy at Week 80

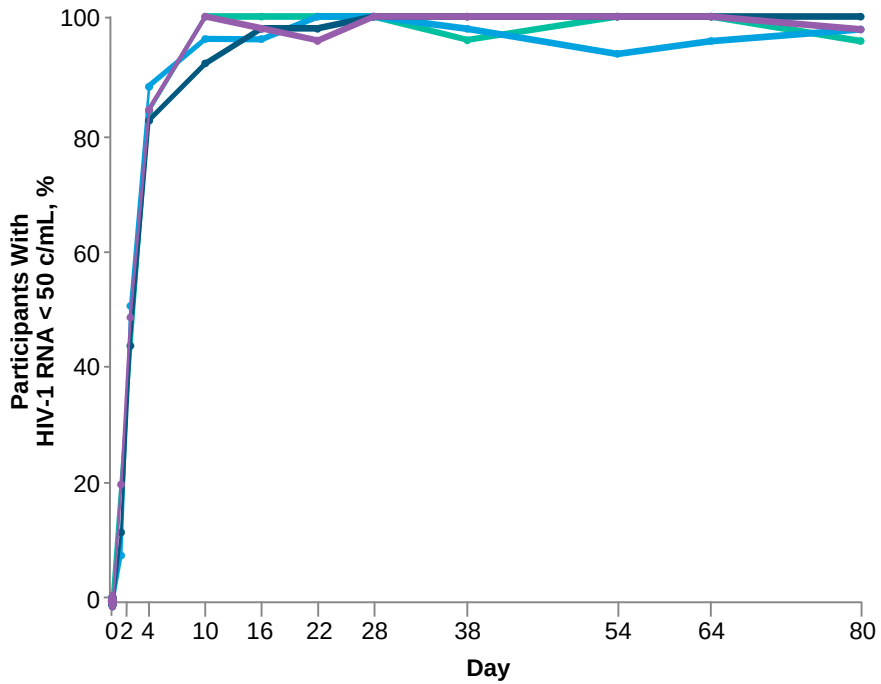
LEN SC + F/TAF to LEN SC + TAF | LEN SC + F/TAF to LEN SC + BIC | LEN QD + F/TAF | B/F/TAF

Virologic Outcomes (FDA Snapshot)



- In the pooled SC LEN group (TG 1 + 2) at Week 80:
  - 81% (85/105) achieved and maintained virologic suppression

Participants With HIV-1 RNA < 50 c/mL by Visit (M = E; On Treatment)



In TN PLWH, SC LEN in combination with oral F/TAF, TAF or BIC, and oral LEN in combination with F/TAF maintained high rates of virologic suppression at Week 80

*4 participants (1 in TG 1; 2 in TG 2) discontinued study drug due to AE or death. M = E, missing = excluded; TG, Treatment Group; TN, treatment-naïve

Hagins D, et al. CROI 2023, Poster 522

Resistance Analysis at Week 80

Participants, n*,[1]	TG 1 (n = 52)	TG 2 (n = 53)	TG 3 (n = 52)	TG 4 (n = 25)
Met resistance testing criteria	2	1	3	1
Emergent LEN resistance • Q67H + K70R	1	1	1	0

TG 1: LEN SC + F/TAF to LEN SC + TAF

TG 2: LEN SC + F/TAF to LEN SC + BIC

TG 3: LEN QD + F/TAF

TG 4: B/F/TAF

- In the LEN groups:
  - One participant (TG 1) developed Q67H + K70R at Week 80†
  - One participant (TG 2) developed M184M/I in RT prior to Q67H + K70R in capsid at Week 10 (incomplete adherence suspected)[2,3]
  - One participant (TG 3) developed Q67H in capsid at Week 54 with subsequent emergence of K70R, and demonstrated nonadherence by pill count and drug levels

Cases of treatment-emergent LEN resistance were infrequent (2%) and occurred primarily in participants with likely or confirmed nonadherence to oral ARVs

*Genotypic and phenotypic resistance testing performed on any participants with confirmed HIV-1 RNA ≥ 50 c/mL and < 1 $\log_{10}$ HIV-1 RNA reduction from Day 1 at Week 10 visit, any visit after achieving HIV-1 RNA < 50 c/mL and rebound to ≥ 50 c/mL, and any visit with > 1 $\log_{10}$ increase from nadir; †No additional data on viral kinetics or adherence at this time

. TG, Treatment Group; TN, treatment naïve

1. Hagins D, et al. CROI 2023, Poster 522; 2. Gupta SK, et al. IAS 2021, Abstract OALB0302; 3. VanderVeen L, et al. IDWeek 2021, Oral 73

ISRs and AEs

Non-ISR AEs

- No SAEs or Grade 4 AEs related to study drug
- No discontinuations due to non-ISR AEs

Gastrointestinal AEs (LEN SC [TG 1 + 2] vs. oral LEN [TG 3])

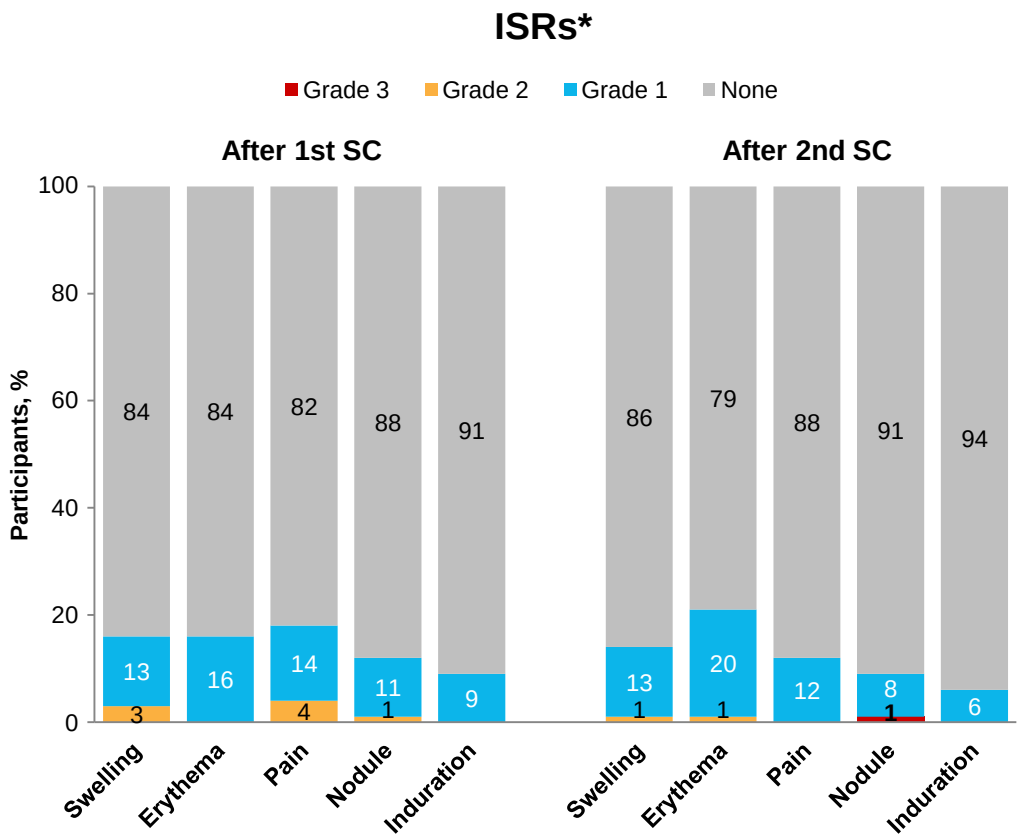
- Nausea: 14% versus 12%
- Diarrhea: 10% versus 12%
- Vomiting: 5% versus 10%

Most LEN-related ISRs were Grade 1 or 2 in severity*

- One Grade 3 ISR (nodule) after the 2nd SC dose

4 participants discontinued due to ISRs*

- 3 due to induration (all Grade 1; 2 after the 1st SC dose and 1 after the 3rd SC dose)
- 1 due to erythema and swelling (Grade 1 after the 2nd SC dose)



LEN was generally well tolerated, with few discontinuations (~2.5%) due to AEs

*ISR types include those > 5% at both Week 1 and 26. ISR, injection-site reaction; TG, Treatment Group; TN, treatment naïve

Hagins D, et al. CROI 2023, Poster 522

islatravir

First in class: NRTTI (multiple mechanisms)

Intracellular triphospate

Plasma $t_{1/2}$: 50-60 hrs

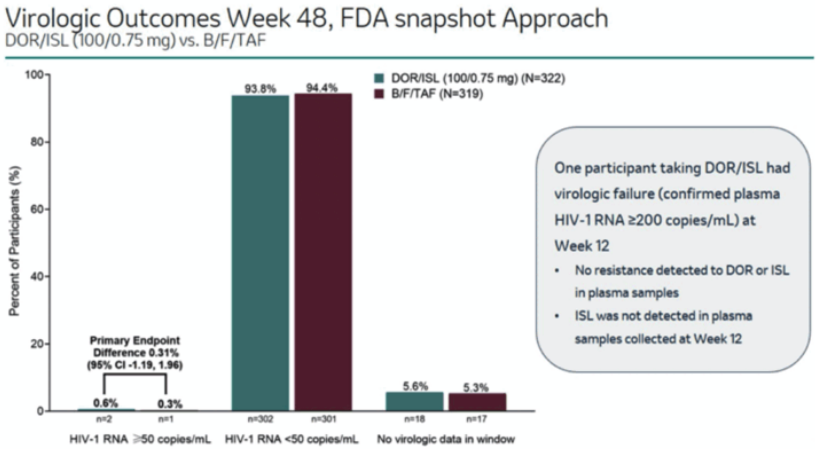
Intracellular $t_{1/2}$: 130-210 hrs

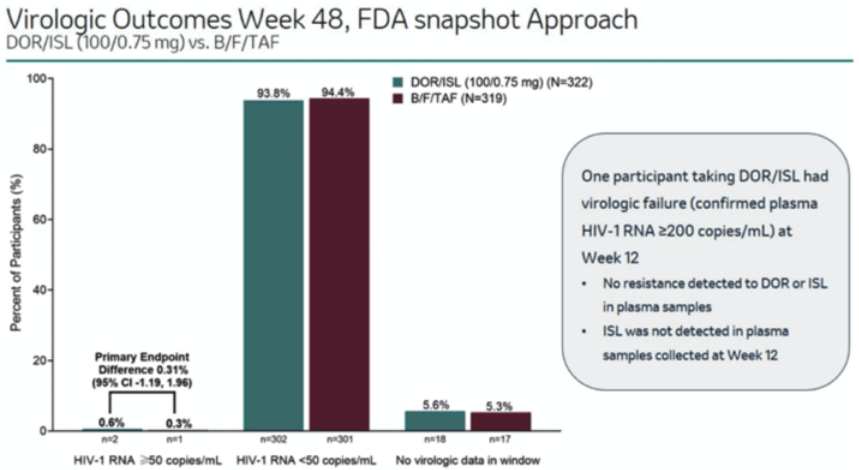
Intracellular concentration: 1000x

Effective against NRTI resistance viruses

High genetic barrier

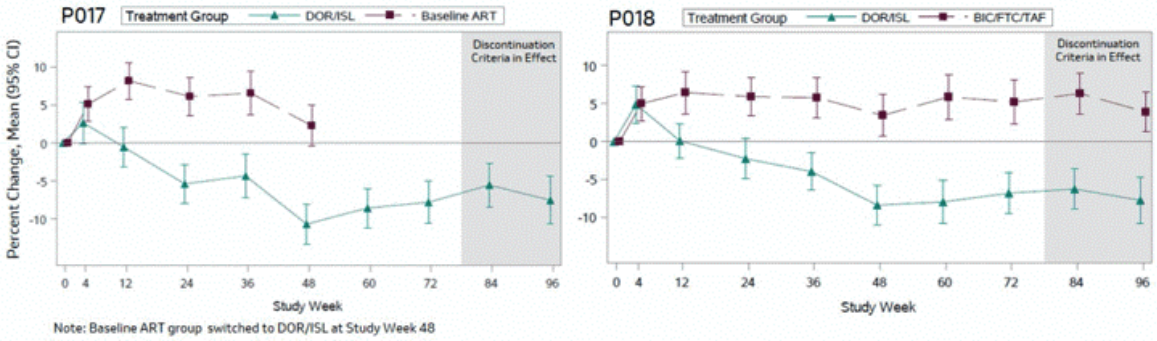
Study #	Design	Population	Dose	N	Comparator	N
HIV Prevention						
MK8591-016 phase 2	Blinded; 2:2:1 randomization	Adults without HIV	ISL 60 or 120 mg once monthly (QM)	194	Placebo	48
MK8591-022 phase 3	Blinded; 1:1 randomization	Cisgender women	ISL 60 mg QM	362	FTC/TDF	365
MK8591-024 phase 3	Blinded; 2:1 randomization	Cisgender men & transgender women	ISL 60 mg QM	328	FTC/TDF or FTC/TAF	166
HIV-1 Treatment						
MK8591-013 phase 2	Blinded; 1:1:1:1 randomization	Virologically suppressed	ISL 20 mg + 8507 100, 200, or 400 mg once weekly (QW)	121	BIC/FTC/TAF	40
MK8591A-017 phase 3	Open-label; 2:1 randomization	Virologically suppressed	ISL 0.75/DOR 100 mg once daily (QD)	662	Baseline ART	336
MK8591A-018 phase 3	Blinded; 2:1 randomization	Virologically suppressed	ISL 0.75/DOR 100 mg QD	322	BIC/FTC/TAF	319
MK8591-011 phase 2	Blinded; 1:1:1:1 randomization	Treatment-naïve	ISL 0.25, 0.75, or 2.25 mg + DOR 100 mg QD	112	DOR/3TC/TDF	31





Squires KE et al. CROI 2023 Feb 20-23

Phase 3 DOR/ISL 100/0.75 mg QD in HIV-1 Switch (MK8591A-017/018)
Total Lymphocyte Count

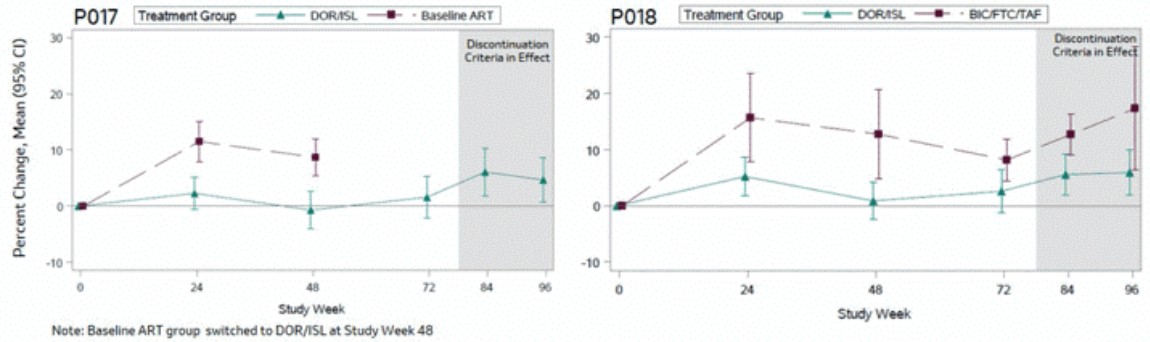


Note: Baseline ART group switched to DOR/ISL at Study Week 48

- Declines in total lymphocyte counts were observed in ISL-treated participants over 48 Weeks and subsequently stabilized on continued ISL 0.75 mg QD dosing
- Prior to implementation of total lymphocyte count discontinuation criteria (approximately at Week 84), the mean percent change from baseline in total lymphocyte count had declined from baseline in the ISL 0.75 mg group and increased in the comparator group

Mean values at baseline (10^9/L): P017, DOR/ISL 1.97; bART 1.95. P018, DOR/ISL 1.91; B/F/TAF 1.96.

Phase 3 DOR/ISL 100/0.75 mg QD in HIV-1 Switch (MK8591A-017/018)
CD4+ T-Cell Count



Note: Baseline ART group switched to DOR/ISL at Study Week 48

Next step

Clinical development of ISL for treatment of HIV-1 has resumed:

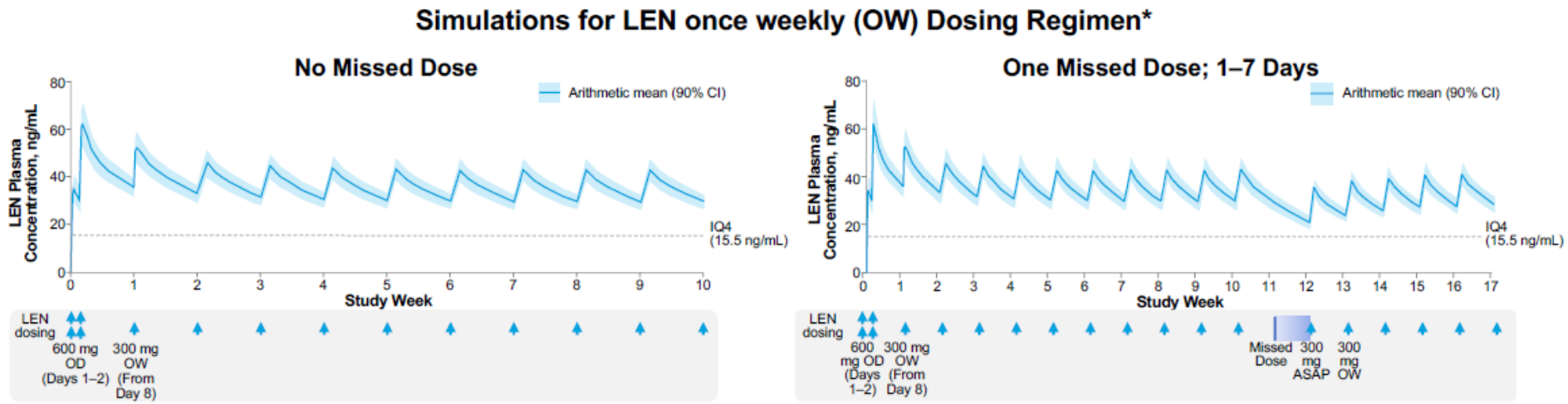
DOR/ISL 100/**0.25** mg orally once daily

ISL 2mg + LEN 300mg orally once weekly

Squires KE et al. CROI 2023 Feb 20-23

Long acting – oral once weekly, including ISL

Simulations for Once-Weekly Dosing of Oral LEN



- Oral loading dose of 600 mg on Days 1 and 2 followed by oral 300 mg OW doses maintained the lower bound of the 90% CI of mean C_{trough} above IQ4 through the dosing interval
- If one oral LEN OW dose is missed, it should be taken ASAP and then normal dosing regimen can be resumed (i.e., taking one dose (300 mg) on scheduled day)

Simulations suggested that LEN 300 mg once weekly allows for a 7-day forgiveness window.

*Oral loading 600 mg QD on Days 1–2, then 300 mg QW from Day 8
ASAP, as soon as possible; C_{trough}, concentration at end of dosing interval; IQ, inhibitory quotient; OD, once daily; OW, once weekly; PK, pharmacokinetic(s)

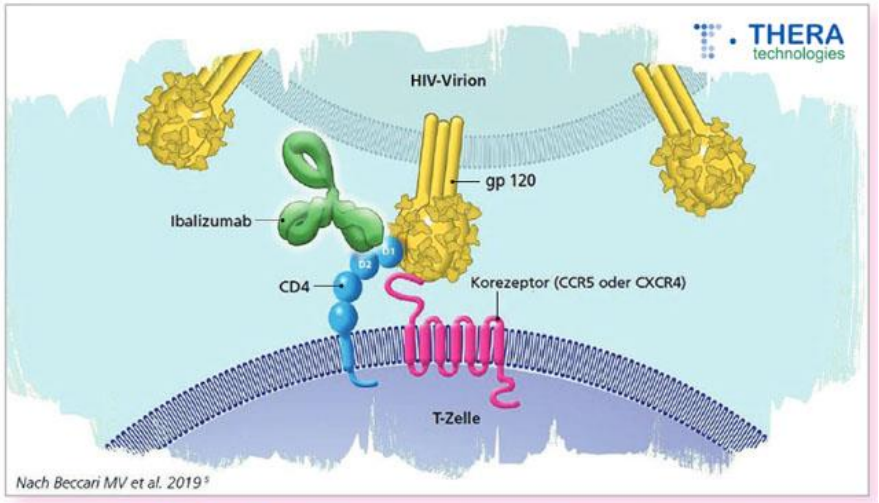
Shaik N, et al. AIDS 2022, Poster PESUB23

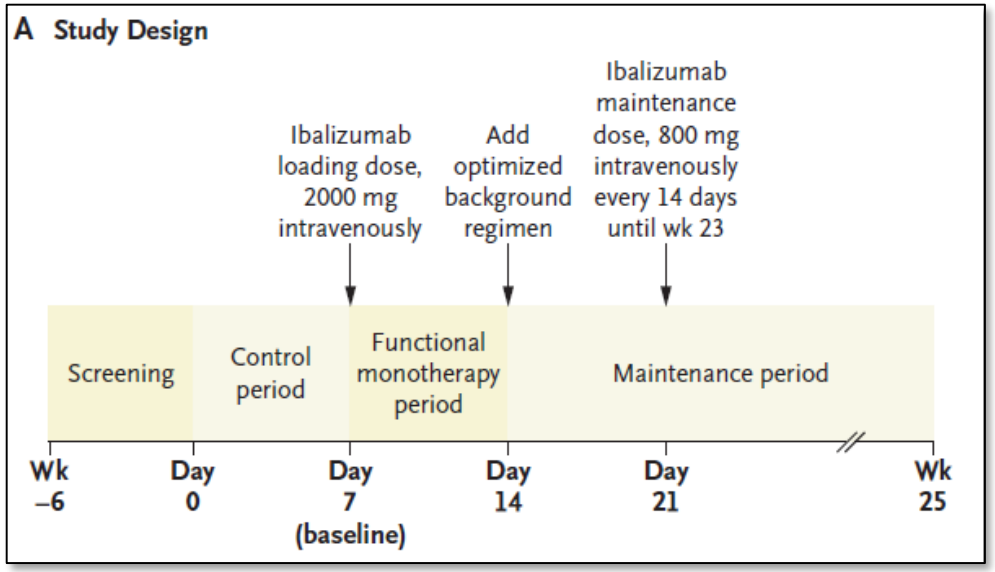
ORIGINAL ARTICLE

Phase 3 Study of Ibalizumab for Multidrug-Resistant HIV-1

Brinda Emu, M.D., Jeffrey Fessel, M.D., Shannon Schrader, M.D., Princy Kumar, M.D., Gary Richmond, M.D., Sandra Win, M.D., Steven Weinheimer, Ph.D., Christian Marsolais, Ph.D., and Stanley Lewis, M.D.

N Engl J Med 2018;379:645-54.

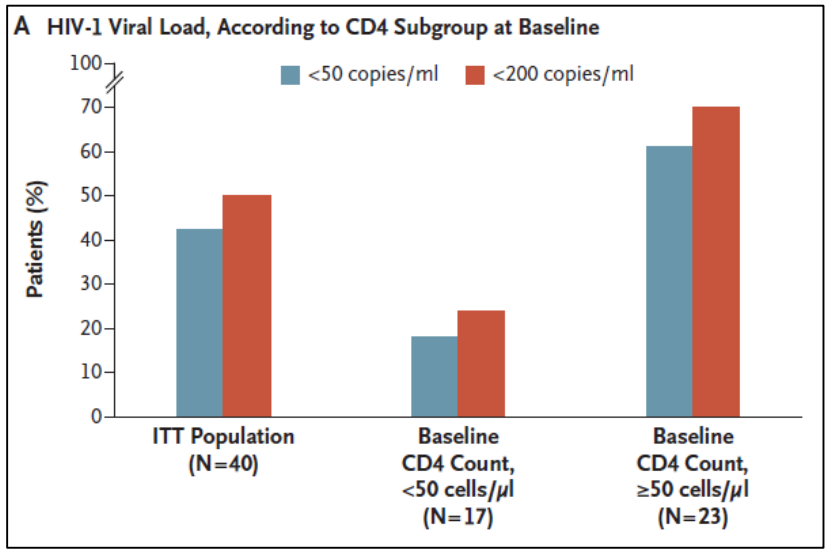


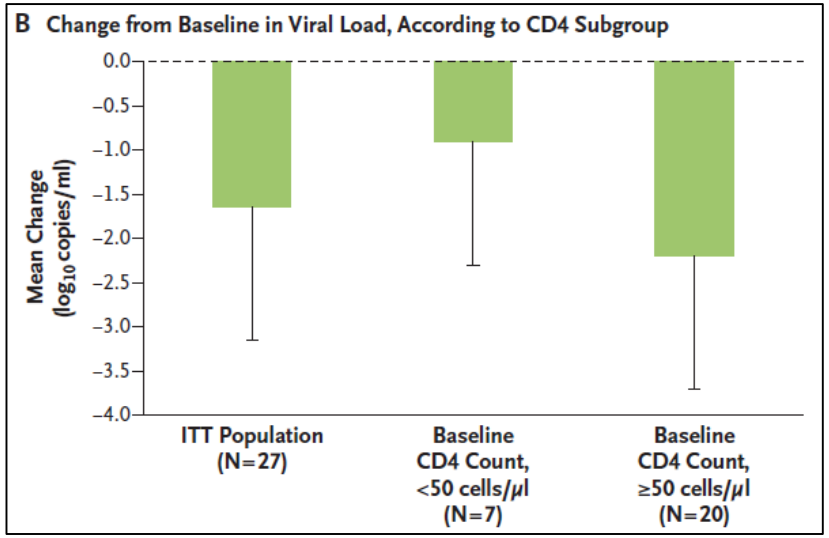


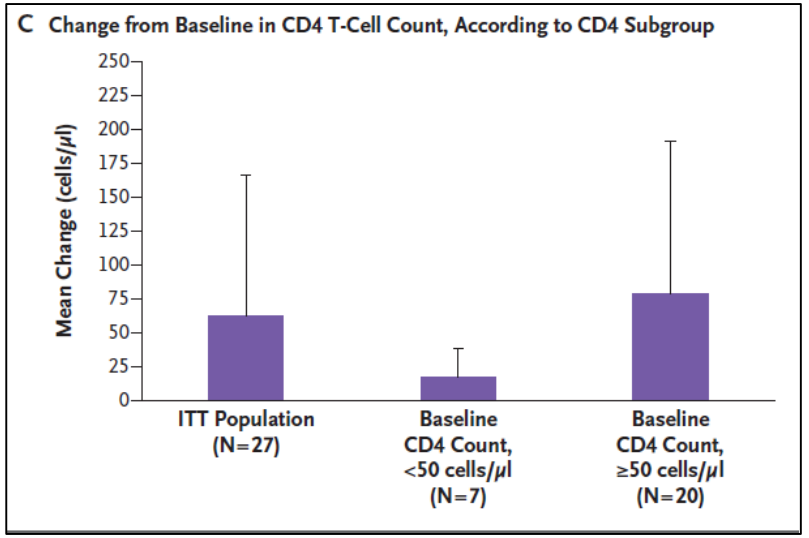
Ibalizumab: anticorpo monoclonale di IgG4.
Meccanismo d'azione: blocca l'infezione da parte dell'HIV-1 dei linfociti T CD4+ legandosi al dominio 2 di CD4 e interferendo con le fasi successive al legame necessarie per l'ingresso delle particelle del virus dell'HIV-1 nelle cellule

19 ottobre 2022 in Gazzetta Ufficiale la Determina AIFA

Patients with viral load of >100,000 copies/ml — no. (%)	7 (18)
CD4 count	
Mean — no. of cells/μl	150±182
Median (range) — no. of cells/μl	73 (0–676)
Distribution — no. of patients (%)	
<10 cells	12 (30)
<50 cells	17 (43)
50–200 cells	10 (25)
>200 cells	13 (33)







N Engl J Med 2018;379:645-54.

bNAbs-based strategies

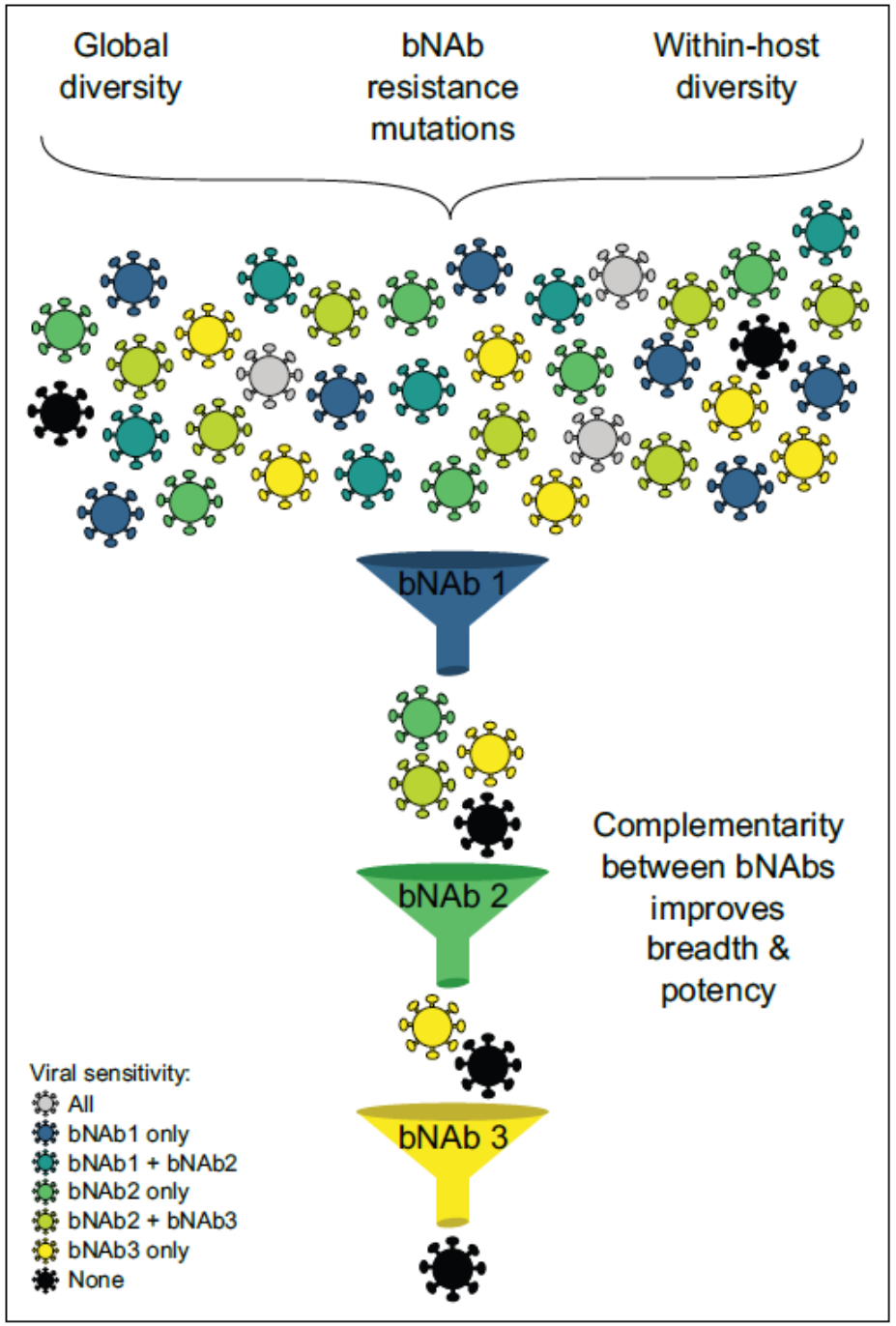
Divide and conquer: broadly neutralizing antibody combinations for improved HIV-1 viral coverage

Kshitij Wagh[a] *and Michael S. Seaman*[b]

Curr Opin HIV AIDS. 2023 Jul 1;18(4):164-170.

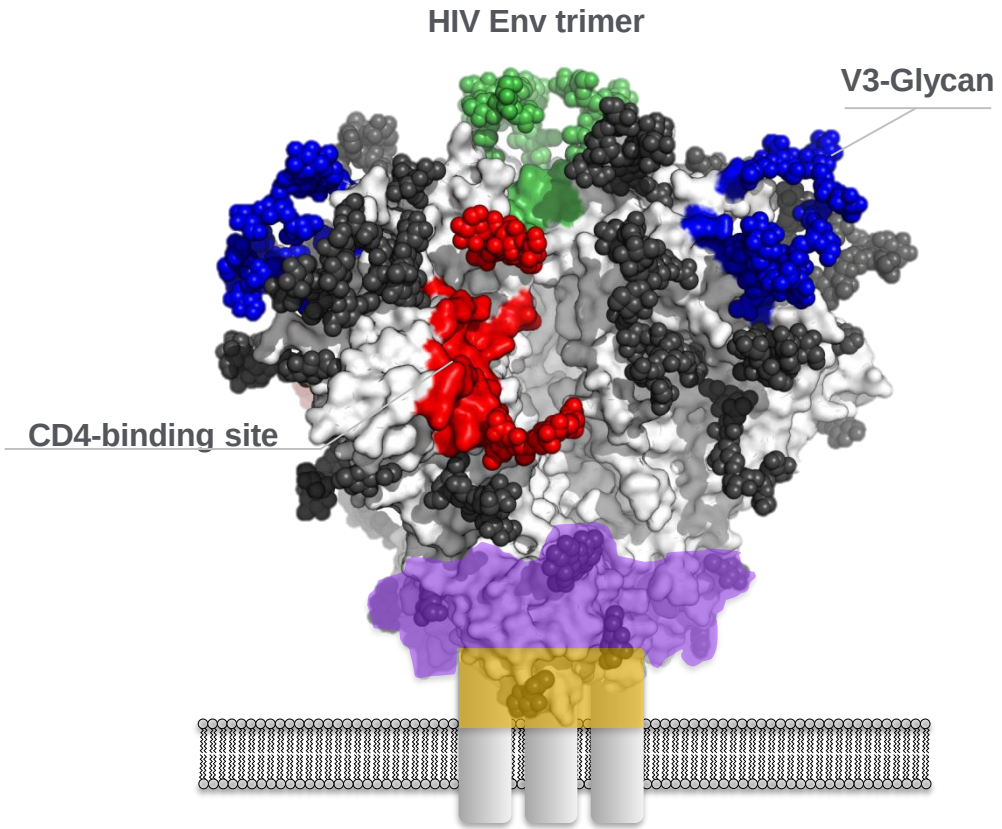
Improved potency and breadth of neutralization by bNAb combinations.

bNAb: broadly neutralizing antibody.



bNAbs Teropavimab and Zinlirvimab

- Teropavimab (TAB; GS-5423; 3BNC117-LS) and zinlirvimab (ZAB; GS-2872; 10-1074-LS) are broadly neutralizing antibodies (bNAbs) against the *CD4-binding site of gp120* and a non-overlapping *epitope on the V3 glycan* of HIV-1 Env, respectively.
- Both antibodies were modified to extend their half-lives for long-acting therapy that may allow for dosing every 6 months.
- An estimated > 50% of clade B viruses are highly susceptible to both bNAbs and > 90% are highly susceptible to either bNAb with a 90% inhibitory concentration (IC_{90}) < 2 µg/mL.



- We hypothesize that combining **TAB** and **ZAB** with a long-acting antiviral agent could provide a complete long-acting therapeutic regimen for HIV treatment.

Yoon H, et al. CATNAP: a tool to compile, analyze and tally neutralizing antibody panels. *Nucleic Acid Res.* 2015 Jul 1;43(W1):W213-9. PMID 26044712.

LEN + bNAbs

LEN With bNAbs Teropavimab and Zinlirvimab in PLWH (GS-US-536-5816)

N = 21

VS PLWH, aged ≥ 18 years

Outcomes

Primary: Safety and tolerability

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

2021–present (ongoing)

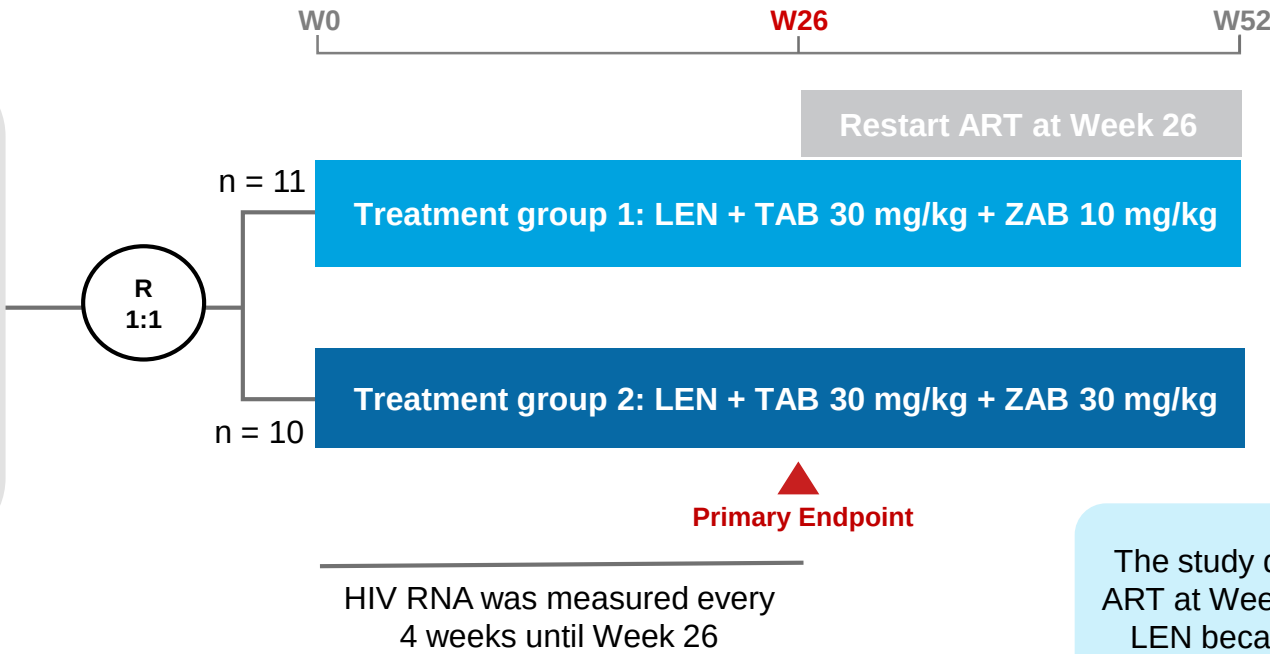
Adults living with HIV-1

VS ≥ 18 months*

Met susceptibility criteria for TAB and ZAB†

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 because of compatibility issue with borosilicate vials

*Previous virologic failure was allowed as long as participants were VS for ≥ 18 months prior to screening

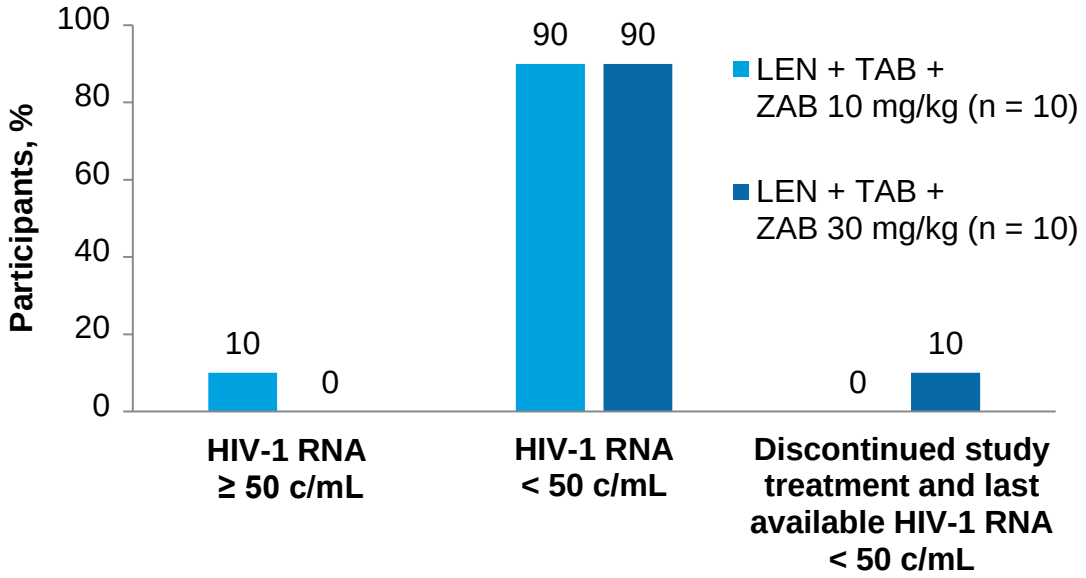
†Susceptibility defined as IC_{90} ≤ 2 μg/mL to each antibody by PhenoSense mAb Assay (Monogram Biosciences)

bNAb, broadly neutralizing antibody; IC_{90}, 90% inhibitory concentration; PK, pharmacokinetics; R, randomized; TAB, teropavimab; VS, virologically suppressed; W, Week; ZAB, zinlirvimab

Eron J, et al. CROI 2023, Oral 193

Week 26: Efficacy and Safety

Virologic Outcomes at Week 26



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

Safety and Tolerability

- There were no SAEs, no Grade 4 AEs and no AEs that led to study treatment discontinuation
- There were two Grade 3 AEs:
  - One injection-site cellulitis on Day 1, which resolved with antibiotics
  - One injection-site erythema on Day 3, which resolved without intervention by Day 10
- AEs occurring in ≥ 3 participants:
  - Injection-site pain
  - Erythema
  - Nodule
  - Induration
  - Mass
  - COVID-19
  - Upper respiratory tract infection

Combination of the bNAbs TAB and ZAB with LEN can sustain VS for 6 months in selected PLWH; Gilead has announced a planned Phase 2 study of LEN + TAB + ZAB in VS PLWH

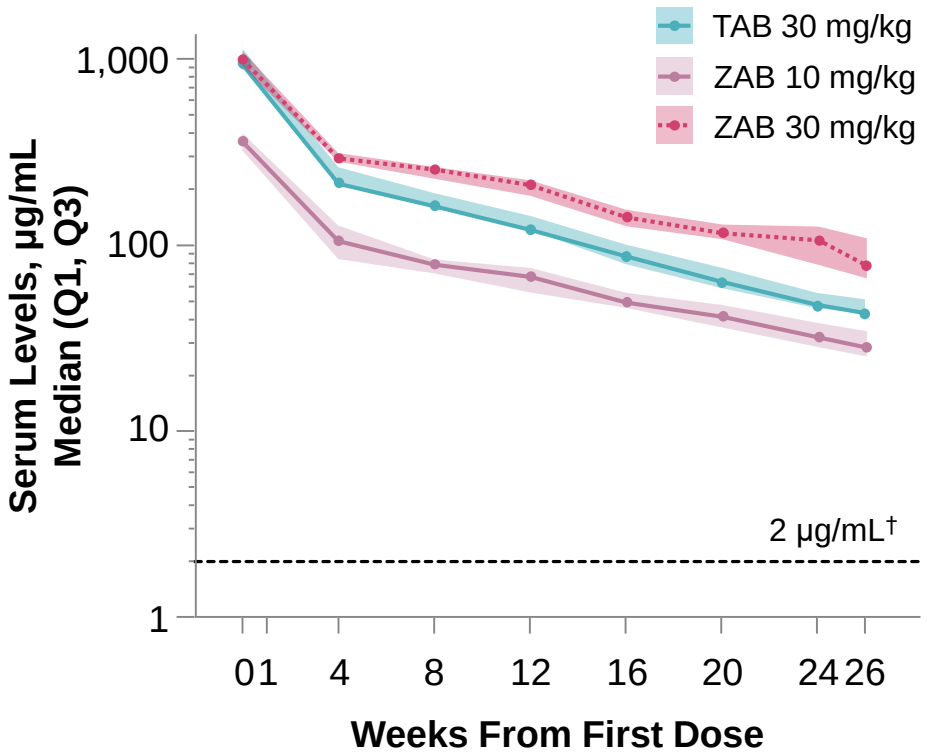
bNAb, broadly neutralizing antibody; TAB, teropavimab; VS, virologically suppressed/virologic suppression; ZAB, zinlirvimab

Eron J, et al. CROI 2023, Oral 193

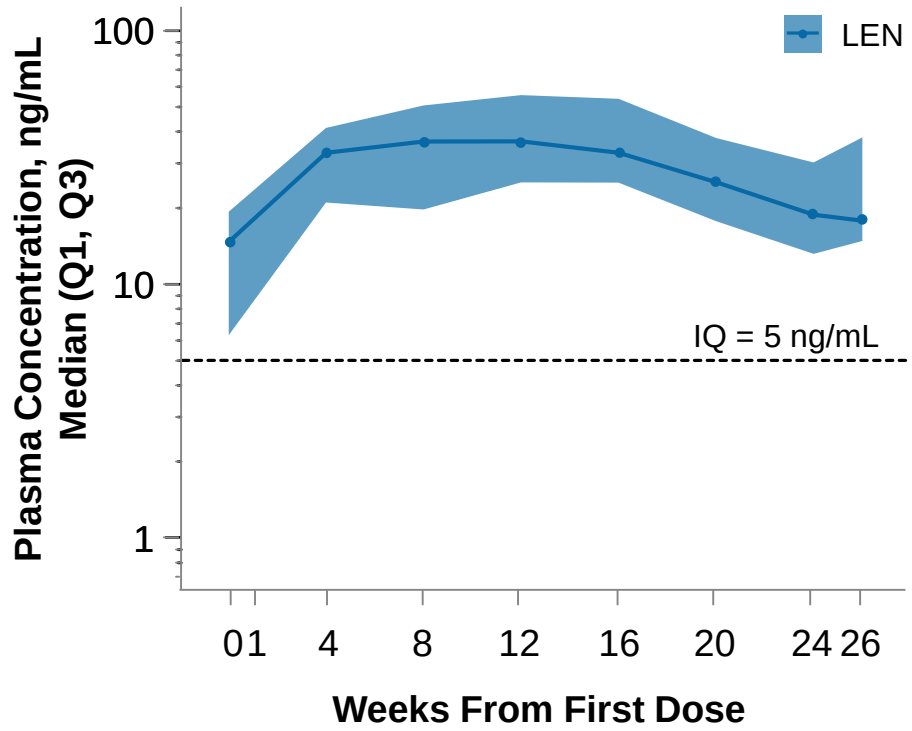
LEN + bNAbs

Pharmacokinetics: TAB, ZAB and LEN

Median Concentration–Time Profiles*



Median Concentration–Time Profile



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

*Values are medians (lines) and IQRs (shaded regions); †2 µg/mL was the level required for sensitivity in the screening assay
bNAb, broadly neutralizing antibody; IQ, inhibitory quotient; TAB, teropavimab; VS, virologically suppressed; ZAB, zinlirvimab

Eron J, et al. CROI 2023, Oral 193

Long-acting injectable PrEP

Risk of incident HIV infections in patients on oral (TDF/FTC) and long-acting injectable prophylaxis (CAB LA)

Table 2. Emergent resistance mutations by study arm in randomized HIV prevention trials.

Study (ref)	Population (N. of patients)	Study arms	Observed HIV infections	HIV incidence 100 per person-years
HPTN 083	MSM and transgender women (4566)	CAB LA (every 8 weeks) versus TDF/FTC (daily)	13 (+3*) versus 39 (+3*)	0.41 versus 1.22 (HR: 0.34; 95% CI 0.18 to 0.62)
HPTN 084	Cisgender women (3224)	CAB LA (every 8 weeks) versus TDF/FTC (daily)	3 (+1*) versus 36	0.15 versus 1.85 (HR 0·09; 95% CI 0.04 to 0.27]

LA: Long Acting, CAB: cabotegravir, FTC/TDF: emtricitabine + tenofovir disoproxil fumarate.
(*) HIV infection already present at baseline

Inclusion criteria:

HIV negative
High risk individuals

EMA positive opinion for cabotegravir 24th July 2023

Landovitz RJ, Donnell D, Clement ME, et al. **N Engl J Med. 2021** Aug 12; 385(7): 595–608
Eshleman SH, Fogel JM, Piwowar-Manning E, et al. HPTN 084. **J Infect Dis. 2022** May 15; 225(10): 1741–1749.

Injectable LEN for PrEP (every 6 months)

Purpose 1

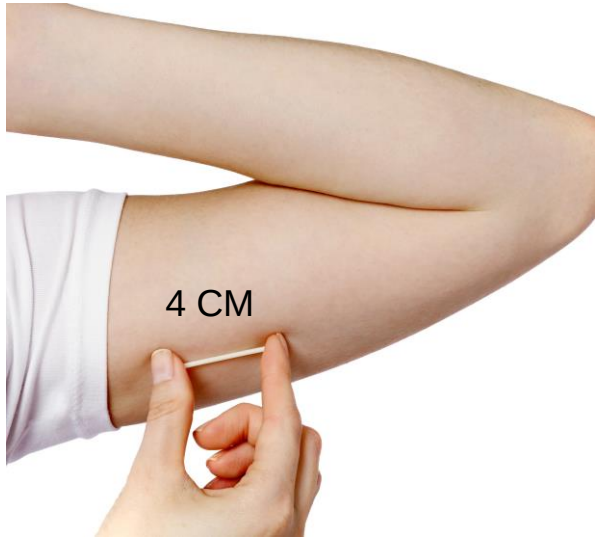
- Approx 5,000 cisgender women in South Africa
- Designed to test efficacy of injectable LEN, every six months, vs F/TAF OD in preventing HIV acquisition
- Scheduled to run until June 2027. More details here.

Purpose 2

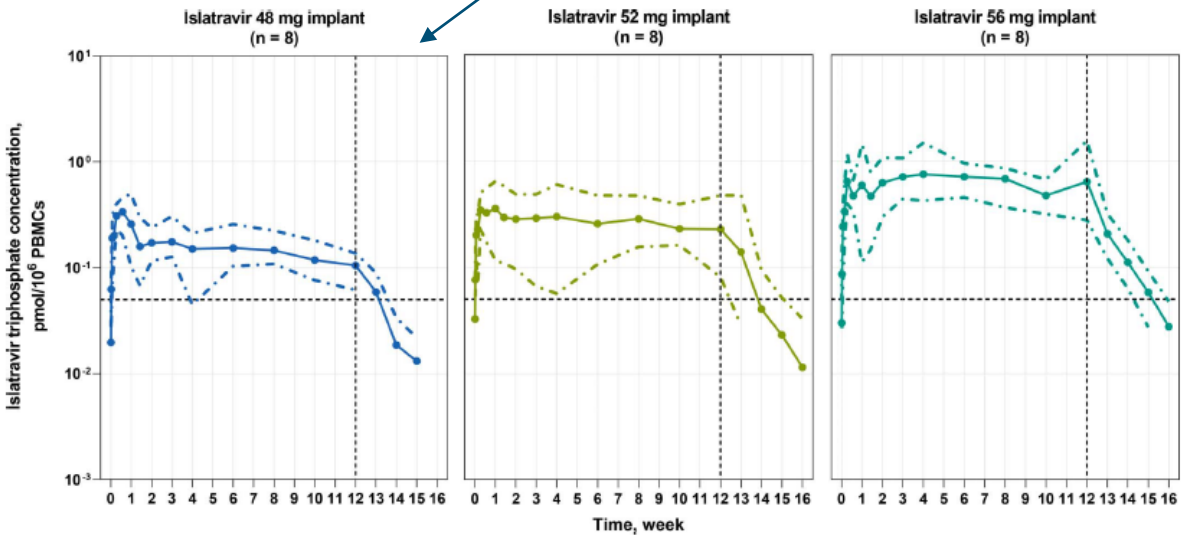
- Approx 3,000 MSM, transgender men and women, and gender non-binary people in Puerto Rico, South Africa and the USA
- Efficacy of LEN as PrEP given as an injection every 6 months
- Scheduled to run until April 2027.

Temporarily witheld, ongoing since May 2022

A Randomized, Double-Blind, Placebo-Controlled, Phase 1 Trial of Radiopaque Islatravir-Eluting Subdermal Implants for Pre-exposure Prophylaxis Against HIV-1 Infection



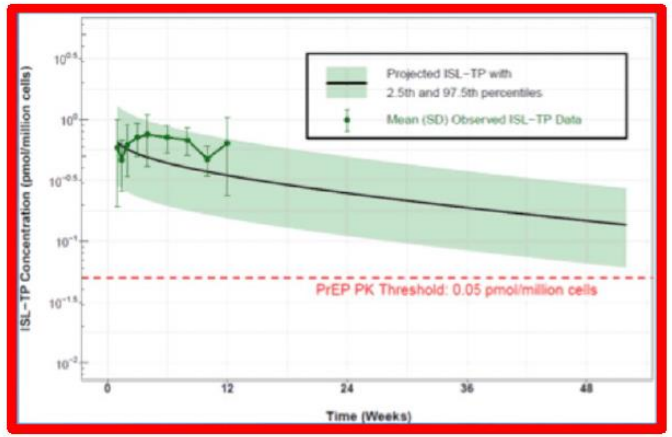
line corresponds to implant removal.



JAIDS 2023 Apr 1;92(4):310-316.

Long acting – Implants

Next-generation ISL implants projected to provide yearly HIV prophylaxis



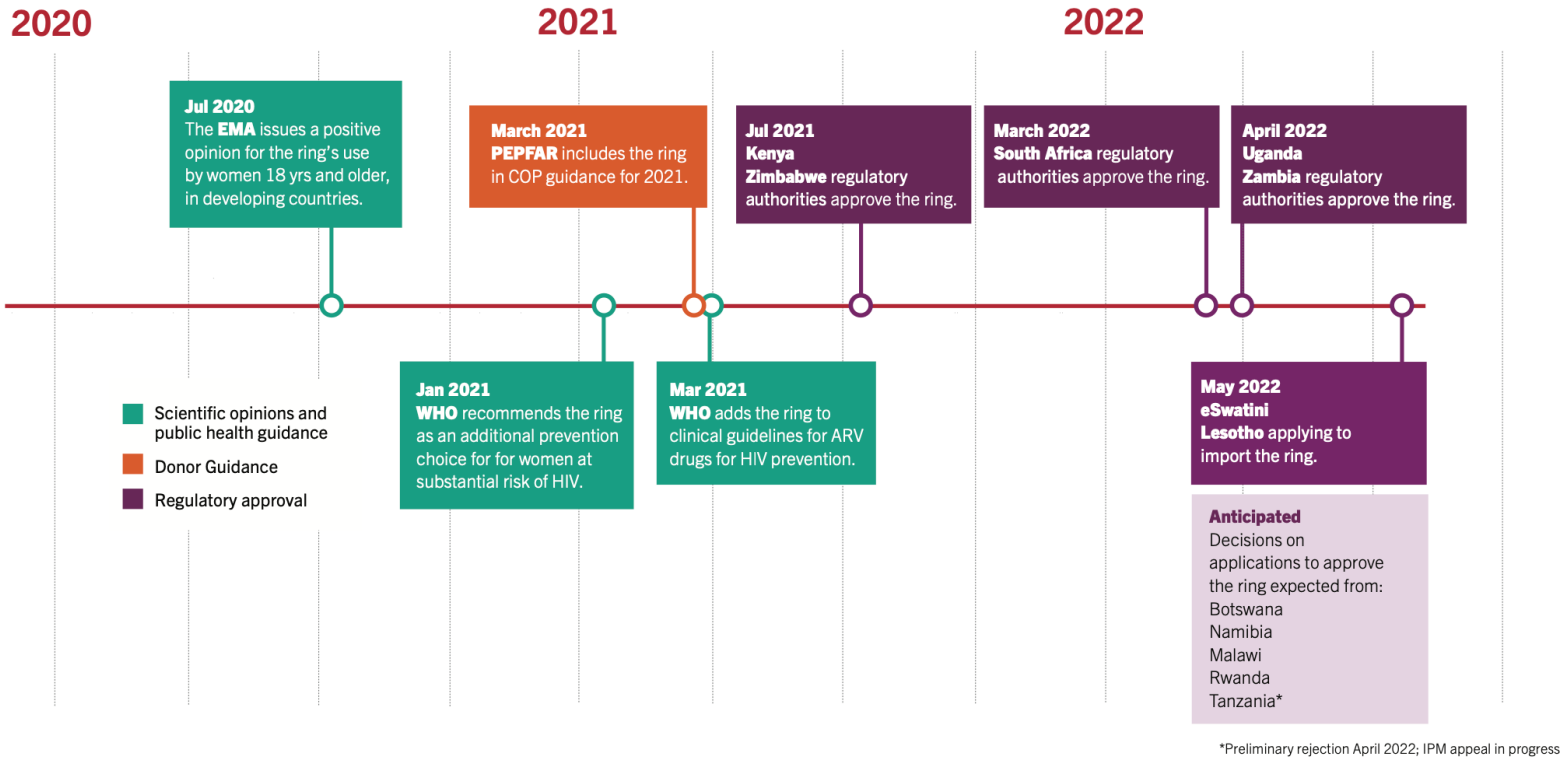
56mg implant projected to release adequate ISL-TP (above the PK threshold) for almost all individuals for > 52 weeks

Randolph et al. CROI 2021

Summary

Background The Ring Study, a phase 3 trial in 1959 sexually active women (randomised 2:1), showed a favourable safety profile and a 31% HIV-1 infection risk reduction for a vaginal ring containing 25 mg of dapivirine, compared with a placebo ring. We report here the DREAM study, which aimed to evaluate safety, adherence, and HIV-1 incidence in those using the dapivirine vaginal ring (DVR) in open-label use.

Access to the Dapivirine Vaginal Ring: A timeline on progress



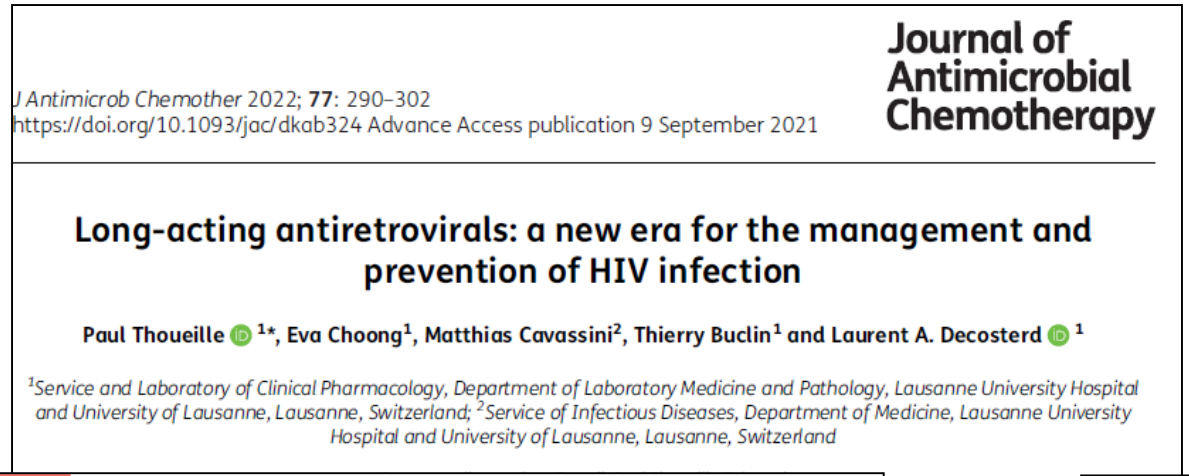
*Preliminary rejection April 2022; IPM appeal in progress

AVAC
Global Advocacy for HIV Prevention

For more information go to PrEPWatch.org

September 2022

The future for HIV Prevention and Treatment is long-acting



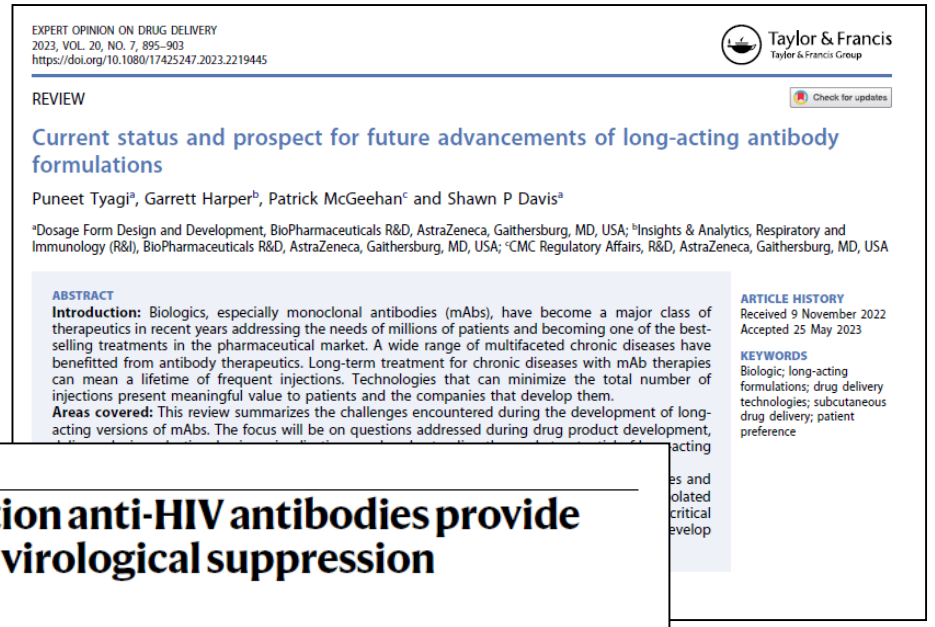
J Antimicrob Chemother 2022; **77**: 290–302
https://doi.org/10.1093/jac/dkab324 Advance Access publication 9 September 2021

Journal of Antimicrobial Chemotherapy

Long-acting antiretrovirals: a new era for the management and prevention of HIV infection

Paul Thoueille [1]*, Eva Choong[1], Matthias Cavassini[2], Thierry Buclin[1] and Laurent A. Decosterd [1]

[1]*Service and Laboratory of Clinical Pharmacology, Department of Laboratory Medicine and Pathology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland;* [2]*Service of Infectious Diseases, Department of Medicine, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland*



EXPERT OPINION ON DRUG DELIVERY
2023, VOL. 20, NO. 7, 895–903
https://doi.org/10.1080/17425247.2023.2219445

Taylor & Francis
Taylor & Francis Group

REVIEW

Check for updates

Current status and prospect for future advancements of long-acting antibody formulations

Puneet Tyagi[a], Garrett Harper[b], Patrick McGeehan[c] and Shawn P Davis[a]

[a]Dosage Form Design and Development, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, MD, USA; [b]Insights & Analytics, Respiratory and Immunology (R&I), BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, MD, USA; [c]CMC Regulatory Affairs, R&D, AstraZeneca, Gaithersburg, MD, USA

ABSTRACT

Introduction: Biologics, especially monoclonal antibodies (mAbs), have become a major class of therapeutics in recent years addressing the needs of millions of patients and becoming one of the best-selling treatments in the pharmaceutical market. A wide range of multifaceted chronic diseases have benefitted from antibody therapeutics. Long-term treatment for chronic diseases with mAb therapies can mean a lifetime of frequent injections. Technologies that can minimize the total number of injections present meaningful value to patients and the companies that develop them.

Areas covered: This review summarizes the challenges encountered during the development of long-acting versions of mAbs. The focus will be on questions addressed during drug product development,

ARTICLE HISTORY
Received 9 November 2022
Accepted 25 May 2023

KEYWORDS
Biologic; long-acting formulations; drug delivery technologies; subcutaneous drug delivery; patient preference

REVIEW

Long-acting implants to treat and prevent HIV infection

Ethel D. Weld[a] and Charles Flexner[a,b]

Purpose of review
Subcutaneous implants are a promising technology to enable long-acting parenteral delivery of antiretroviral drugs (ARV) because they may be able to provide protective drugs concentrations for a year or longer following a single implant. The present review covers the current status of preclinical and clinical development of antiretroviral implants.

Recent findings
Over the past three decades, subcutaneous implants have been widely used for long-acting hormonal contraception and the treatment of hormonally-driven malignancies. They are economical and scalable to manufacture, but require special procedures for insertion and removal. They are generally well tolerated, and can remain in place for up to five years. As long-acting delivery of ARV would confer significant advantages, a few investigational implants are under development for the delivery of ARV; most remain at preclinical stages of development. Islatravir, a potent nucleoside analog reverse transcriptase translocation inhibitor that shows particular promise, has entered clinical testing in implant form. Investigational implants containing tenofovir alafenamide and nevirapine, and entecavir (for hepatitis B virus) have been developed and tested in animal models, with varying degrees of success. There is also burgeoning interest in bioerodable implant formulations of established ARVs.

DA, EMA and Health
of people living with
addition, islatravir, a
ulated as an implant
A-ARTs) are given at

Article

Combination anti-HIV antibodies provide sustained virological suppression

https://doi.org/10.1038/s41586-022-04797-9
Received: 25 October 2021
Accepted: 25 April 2022
Published online: 1 June 2022
Check for updates

Michael C. Sneller[1,10], Jana Blazkova[1,10], J. Shawn Justement[1], Victoria Shi[1], Brooke D. Kennedy[1], Kathleen Gittens[2], Jekaterina Tolstenko[1], Genevieve McCormack[1], Emily J. Whitehead[1], Rachel F. Schneck[1], Michael A. Proschan[3], Erika Benko[4], Colin Kovacs[4], Cihan Oguz[5,6], Michael S. Seaman[7], Marina Caskey[8], Michel C. Nussenzweig[8,9], Anthony S. Fauci[1], Susan Moir[1,10] & Tae-Wook Chun[1,10]✉

Antiretroviral therapy is highly effective in suppressing human immunodeficiency virus (HIV)[1]. However, eradication of the virus in individuals with HIV has not been possible to date[2]. Given that HIV suppression requires life-long antiretroviral therapy, predominantly on a daily basis, there is a need to develop clinically effective alternatives that use long-acting antiviral agents to inhibit viral replication[3]. Here we report the results of a two-component clinical trial involving the passive transfer of two HIV-specific broadly neutralizing monoclonal antibodies, 3BNC117 and 10-1074. The first component was a randomized, double-blind, placebo-controlled trial that enrolled participants who initiated antiretroviral therapy during the acute/early phase of HIV infection. The second component was an open-label single-arm trial that enrolled individuals with viraemic control who were naive to antiretroviral therapy. Up to 8 infusions of 3BNC117 and 10-1074, administered over a period of 24 weeks, were well tolerated without any serious adverse events related to the infusions. Compared with the placebo, the combination broadly neutralizing monoclonal antibodies maintained complete suppression of plasma viraemia (for up to 43 weeks) after analytical treatment interruption, provided that no antibody-resistant HIV was