BHIVA
British HIV Association

BHIVA 'Best of CROI' feedback webinars 2023: ANTIRETROVIRALS

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GILEAD Creating Possible MSD ViiV Healthcare

With thanks to those presenting research for permission to use slides for 'Best of CROI'

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Conflict of Interest

Speaker/advisory fees: ViiV, MSD, Janssen, Gilead, Pfizer

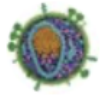
Investigator on trials: Gilead, ViiV, & Janssen

Important to note

Extra slides (e.g. baseline demographics, additional results) will be available online

Small gripe(s)

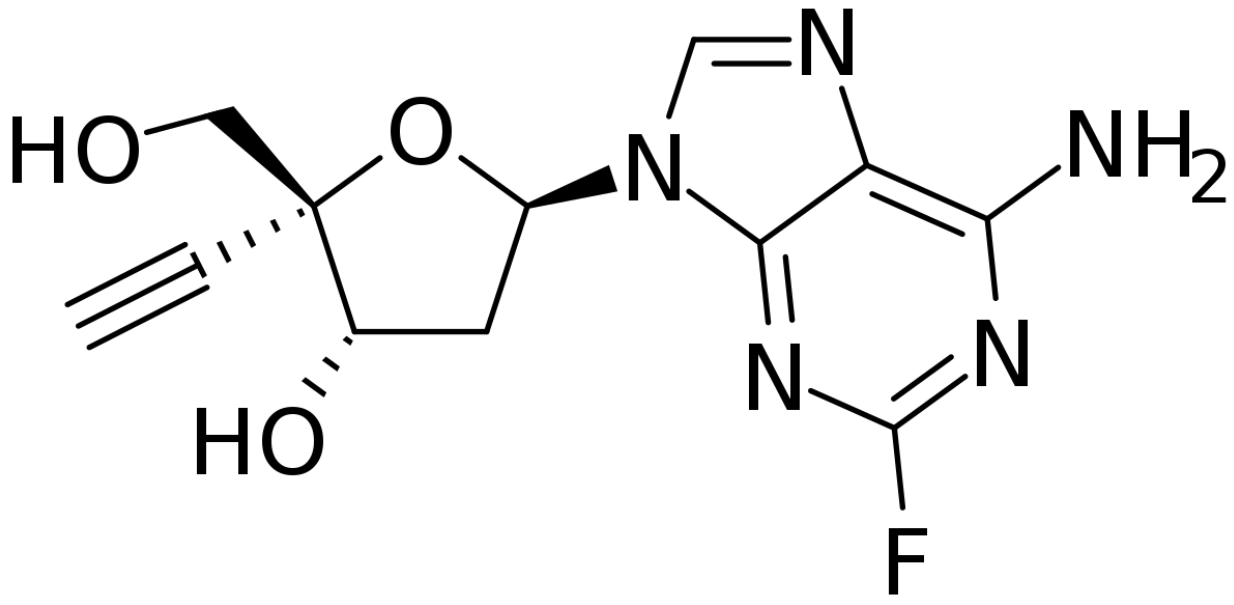
The influencers of #CROI2023

	Laura Waters @drlaurajwaters	100
	Liz Highleyman @LizHighleyman	91
	Carlos del Rio @CarlosdelRio7	85
	CROI 2023 @CROI_Official	74
	BK Titanji #IAmAScientist @Boghuma	70
	Sidd Kogilwaimath @HIVDocSK	65
	Monica Gandhi MD, MPH @MonicaGandhi9	61

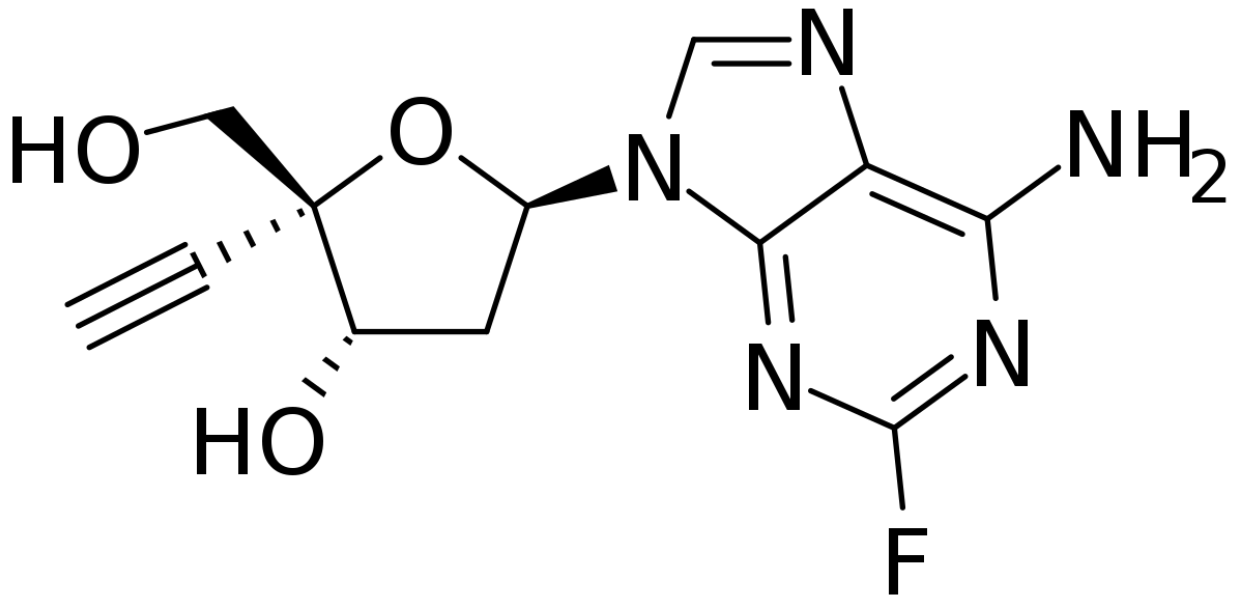
Content

- **Renaissance** the rebirth of islatravir
- **Reassurance** a head-to-head of injectable CAB/RPV vs Biktarvy
- **Rethink** DTG+DRV/r after 1st line NNRTI failure
- **Reality?** bNABs + lenacapavir

RENAISSANCE: islatravir



TOTAL LYMPHOCYTE COUNTS +/- CD4 IN ART & PREP TRIALS
MONTHLY ORAL FOREVER NO MORE
ANNUAL IMPLANT HOPEFUL?
BACK IN TRIALS: **DAILY ORAL** (WITH DOR)
BACK IN TRIALS: **WEEKLY ORAL** (WITH LEN)



WHAT WAS NEW AT CROI 2023? NOT MUCH. VERY DETAILED ANALYSIS ACROSS MANY TRIALS CONFIRMING DOSE RELATED CELL COUNT CHANGES + CONFIRMING 0.25MG DAILY IS PREDICTED TO BE SAFE + EFFECTIVE

Assessment of lymphocytes across programmes

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

Summary

- ISL dose-dependent decreases from baseline were observed in mean total lymphocyte counts and CD4+ T-cell counts, with greater decreases observed at the higher ISL doses administered QW (20 mg) and QM (60 mg) compared with QD (0.75 mg) administration
- Among participants who discontinued ISL in PrEP studies, the percent change in total lymphocyte counts have returned to levels similar to the control group
- In the DOR/ISL (100/0.75mg) QD studies, decreases in total lymphocyte counts and CD4+ T-cell counts stabilized between Weeks 48 and 72
- Incidence of infection was not increased in ISL-treated participants compared to control groups
- These investigations, together with clinical and modelling data identified an ISL-TP threshold level (and subsequently ISL clinical doses) below which decreases in lymphocyte cell counts are not expected to be observed

ISL development: next steps

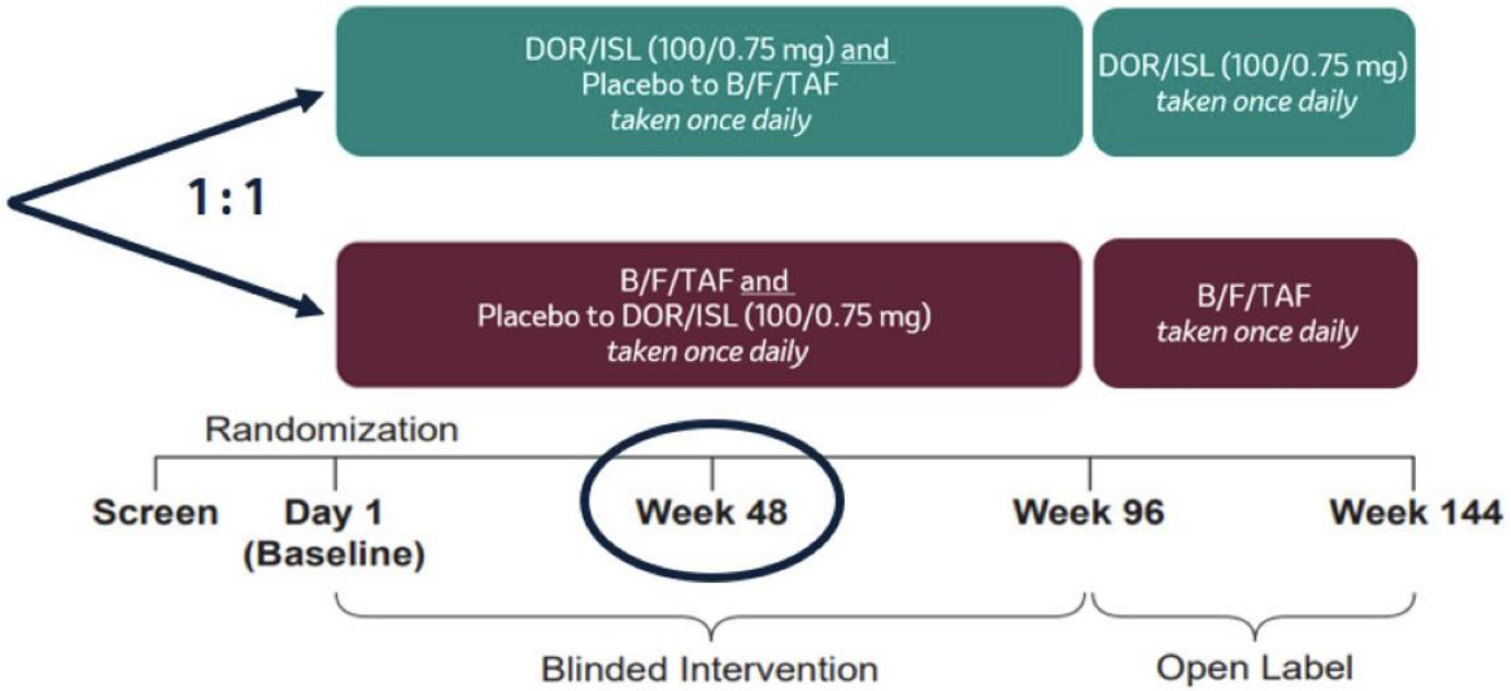
- ISL-Triphosphate Sub-study
  - Objective: to evaluate intracellular exposure in PWH receiving long-term (e.g. greater than 1 year) ISL 0.75 mg QD
- Immune function of ISL-exposed cells Sub-study
  - Objective: To assess the functionality of lymphocytes (CD4+ T-cells and B cells) obtained from PWH receiving ISL 0.75 mg QD
- Clinical development of ISL for treatment of HIV-1 has resumed
  - Doravirine/ISL 100/0.25 mg orally once daily
  - ISL 2 mg plus lenacapavir 300 mg orally once weekly

DOR/ISL (100/0.75mg) vs BIC/FTC/TAF

Population

- PLWH ≥18 years of age
- Virologically suppressed (plasma RNA <50 copies/mL) for ≥3 months on B/F/TAF
- Documented HIV-1 RNA <50 copies/mL at screening
- No history of treatment failure on any regimen
- No known resistance to DOR*
- No active HBV infection

*V106A/M, V108I, Y188L, H221Y, P225H, F227C/L, M230I/L, L234I, P236L or Y318F

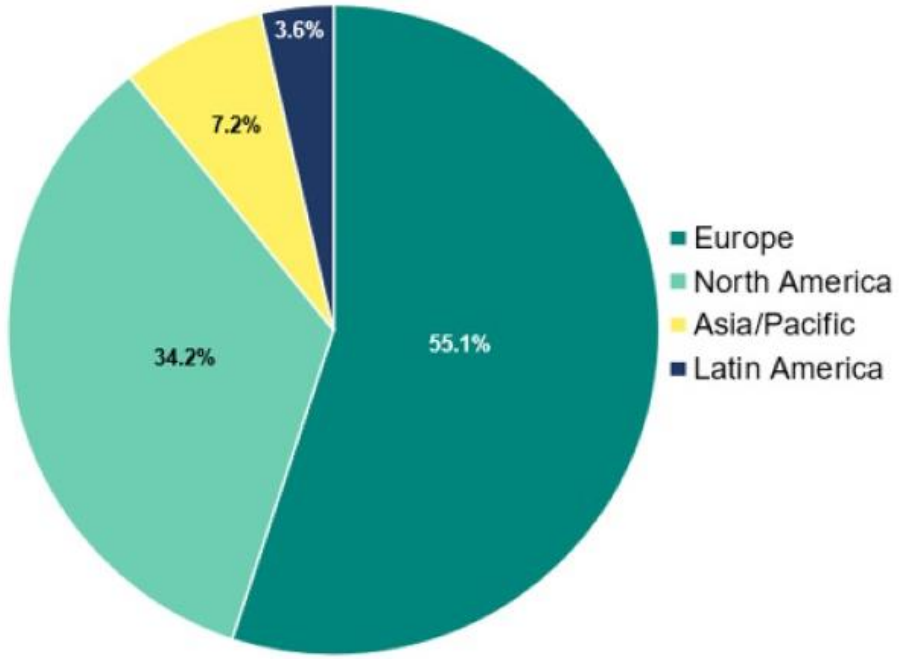


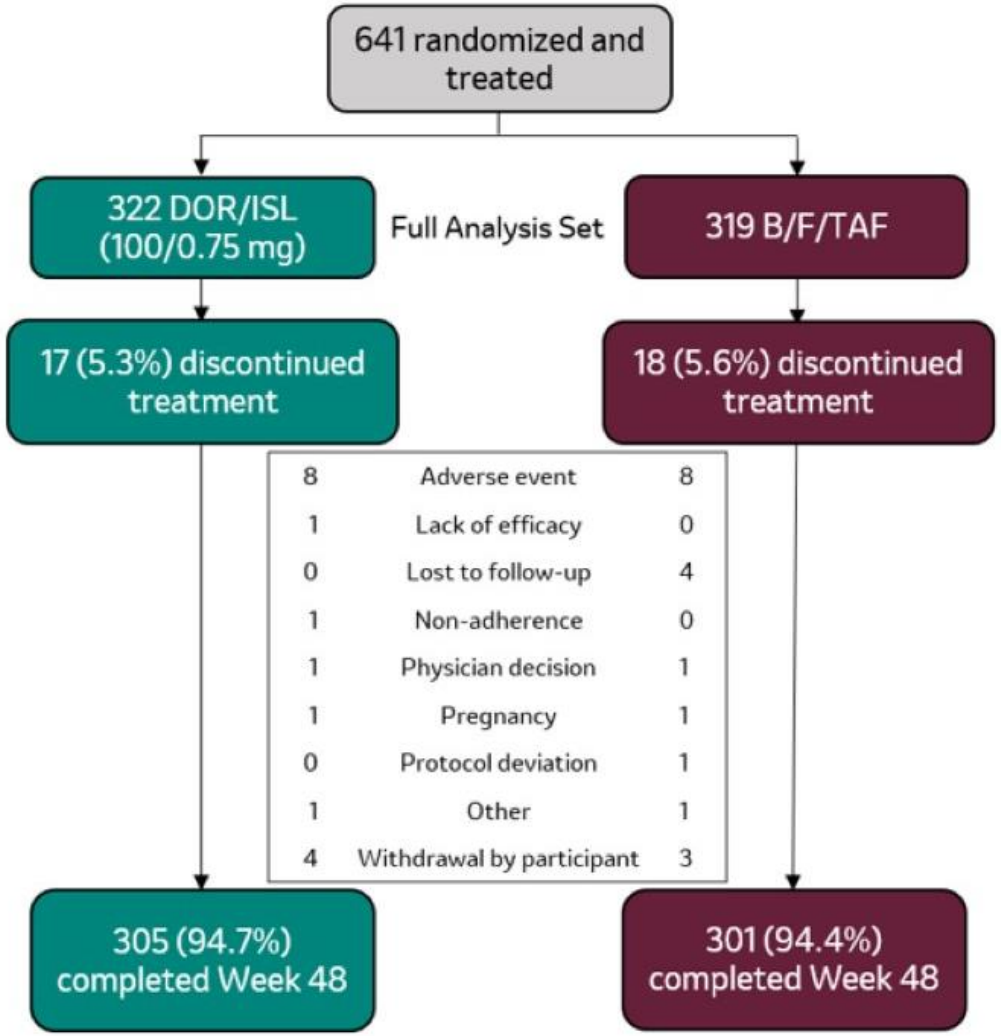
Primary Efficacy Endpoint: HIV-1 RNA ≥50 copies/mL at Week 48 (FDA snapshot approach), non-inferiority margin 4%

Study population

- 89 study sites in 11 countries
- Recruitment Feb 18, 2020 - Sept 3, 2020
  - 726 individuals screened
  - 83 not randomized (39 screen failures)

Enrollment by Region

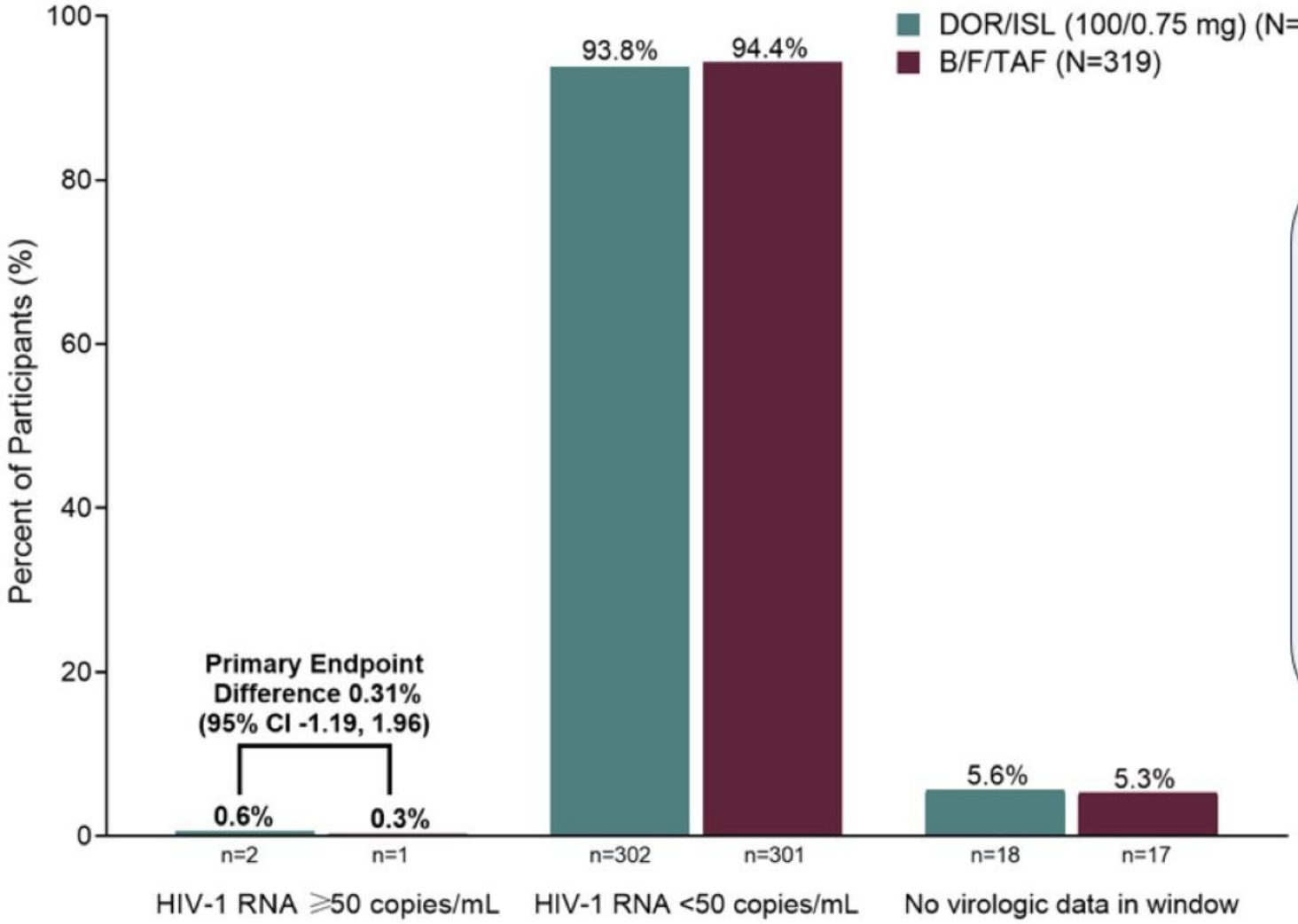




Demographics & baseline characteristics

Characteristic	DOR/ISL (100/0.75 mg) (N=322)	B/F/TAF (N=319)
Female sex at birth, n (%)	105 (33)	77 (24)
Age (years), median (range)	48.0 (20.0 – 76.0)	48.0 (19.0 – 77.0)
Race, n (%)		
White	240 (75)	239 (75)
Black or African American	58 (18)	55 (17)
Asian	14 (4)	13 (4)
Hispanic or Latino Ethnicity, n (%)	64 (20)	55 (17)
Years since HIV-1 diagnosis, median (range)	10.2 (0.6 – 37.6)	9.4 (0.6 – 38.1)
Months of B/F/TAF prior to enrollment, median (range)	14.4 (3.5 – 59.2)	15.3 (3.4 – 57.9)
CD4+ T-cell count (cells/mm^3)		
Median (range)	645 (147 - 3035)	704 (62 - 1856)
>350 cells/mm^3, n (%)	287 (89)	294 (92)
≥200 and ≤350 cells/mm^3, n (%)	31 (10)	21 (7)
<200 cells/mm^3, n (%)	4 (1)	4 (1)

W48 virologic outcomes: FDA snapshot

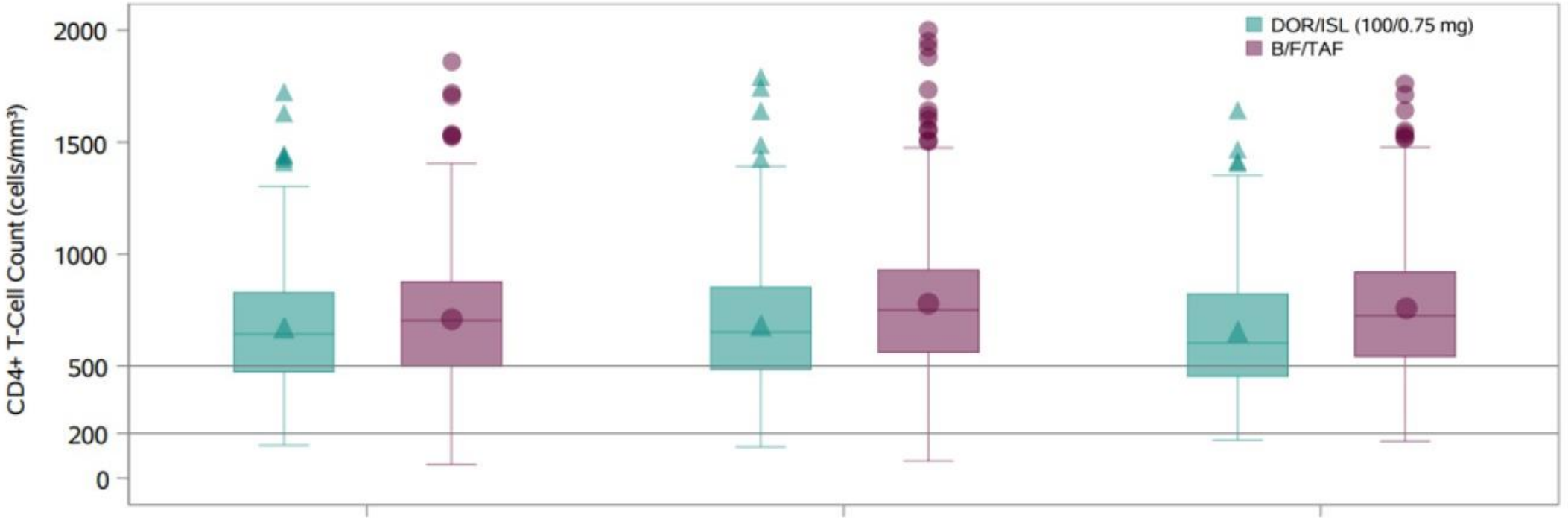


One participant taking DOR/ISL had virologic failure (confirmed plasma HIV-1 RNA ≥200 copies/mL) at Week 12

- No resistance detected to DOR or ISL in plasma samples
- ISL was not detected in plasma samples collected at Week 12

Mills A et al. CROI 2023. Oral abstract 197

CD4 changes

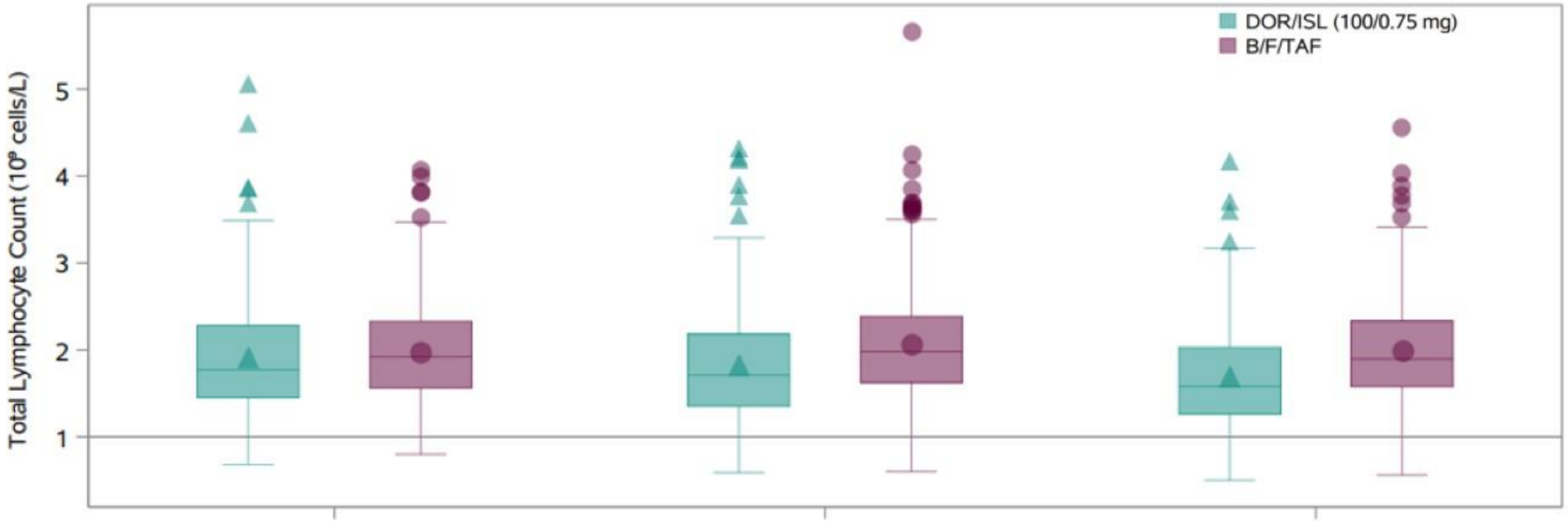


	Baseline		Week 24		Week 48	
N	322	319	304	302	301	298
Mean (cells/mm³)	679	715	687	782	661	761
Mean Change (cells/mm³)	-	-	10.9	67.6	-19.7	40.5
Mean % Change	-	-	5.2%	15.7%	0.9%	12.8%

Difference -68.1, 95% CI -94.7, -41.4

Figure key: box represents the IQR (Q3-Q1), horizontal line represents the median, and symbol represents the mean.
One DOR/ISL participant, with a CD4+ T-cell count >2300 cells/mm³ at all timepoints, is not shown in the figure.

Lymphocyte changes



	Baseline		Week 24		Week 48	
N	322	319	309	300	291	288
Mean (10^9 cells/L)	1.91	1.98	1.82	2.06	1.69	2.00
Mean Change (10^9 cells/L)	-	-	-0.08	0.08	-0.20	0.02
Mean % Change	-	-	-2.4%	5.9%	-8.4%	3.3%

*Difference -0.24, 95% CI -0.31, -0.18

*Post-hoc analysis.

Figure key: box represents the IQR (Q3-Q1), horizontal line represents the median, and symbol represents the mean.

Adverse events

n (%) of participants	DOR/ISL (100/0.75 mg) (N=322)	B/F/TAF (N=319)	Difference (95% CI)[a]
≥1 AE	229 (71)	238 (75)	-3.5 (-10.4, 3.4)
Drug-related[b] AE	32 (10)	38 (12)	-2.0 (-6.9, 2.9)
Toxicity grade 3-4 AE	28 (9)	27 (9)	0.2 (-4.2, 4.7)
Serious AE	13 (4)	15 (5)	-0.7 (-4.0, 2.6)
Serious drug-related AE	0 (0)	0 (0)	0.0 (-1.2, 1.2)
Deaths	0 (0.0)	0 (0.0)	0.0 (-1.2, 1.2)
Discontinued due to an AE	8 (3)	8 (3)	-0.0 (-2.7, 2.6)
Discontinued due to a drug-related AE	6 (2)	5 (2)	0.3 (-2.0, 2.6)
Discontinued due to a serious AE	1 (<1)	0 (0)	0.3 (-0.9, 1.7)

[a]Based on Miettinen & Nurminen method.
[b]Considered by the investigator to be related to the study drug.
AE=adverse event.

Most common adverse events

n (%) of participants	DOR/ISL (100/0.75 mg) (N=322)	B/F/TAF (N=319)	Difference (95% CI)
All causality events (≥5% incidence in either group)			
Headache	25 (8)	23 (7)	0.6 (-3.6, 4.8)
COVID-19	19 (6)	18 (6)	0.3 (-3.5, 4.0)
Arthralgia	17 (5)	19 (6)	-0.7 (-4.4, 3.0)
Back pain	13 (4)	17 (5)	-1.3 (-4.8, 2.1)
Diarrhea	8 (3)	20 (6)	-3.8 (-7.3, -0.7)
Drug-related events (≥5 participants in either group)			
Nausea	8 (3)	2 (1)	1.9 (-0.1, 4.3)
Dizziness	1 (0)	5 (2)	-1.3 (-3.3, 0.3)
Myalgia	0 (0)	5 (2)	-1.6 (-3.6, -0.4)

Infection Related AEs

- Infection rates were comparable between treatment groups (DOR/ISL 31.4% vs B/F/TAF 30.7%)
- 1 CDC AIDS-Defining Category C event in each group
  - DOR/ISL: esophageal candidiasis
  - B/F/TAF: recurrent Kaposi sarcoma

Conclusions

In PLWH who are virologically suppressed for ≥3 months on B/F/TAF

- DOR/ISL (100/0.75 mg) was non-inferior to continued B/F/TAF in maintaining virological suppression of HIV-1 RNA <50 copies/mL through 48 weeks of treatment
  - No DOR or ISL resistance was observed through Week 48
- DOR/ISL (100/0.75 mg) was generally well tolerated with a comparable adverse event profile to that of continued B/F/TAF through 48 weeks of treatment
- Decreases in CD4+ T-cells and total lymphocytes in the DOR/ISL group were modest
  - These decreases were not associated with infection-related AEs
- Phase 3 clinical development of DOR/ISL has resumed with DOR/ISL (100/0.25 mg) QD in treatment-naive and virologically suppressed participants

DOR/ISL (100/0.75mg) vs baseline ART

Population

- Adults with HIV-1
- Virologically suppressed on stable, oral 2- or 3-drug ART for ≥3 months
- HIV-1 RNA <50 copies/mL at screening
- No history of treatment failure on any regimen
- No known resistance to DOR*
- No active HBV infection

* V106A/M, V108I, Y188L, H221Y, P225H, F227C/L, M230I/L, L234I, P236L or Y318F

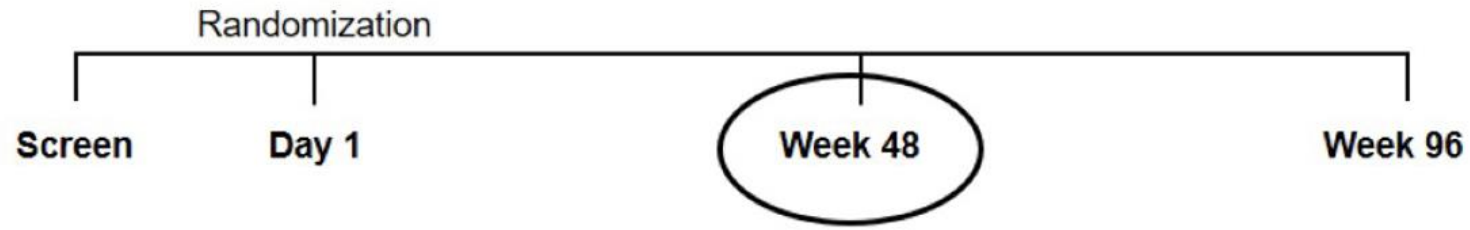
Stratified by bART regimen: PI-based, InSTI-based, Other (mainly NNRTI)

1:1

Open-label DOR/ISL (100/0.75 mg) *taken once daily*

Baseline ART (bART) *taken per label*

Open-label DOR/ISL (100/0.75 mg) *taken once daily*

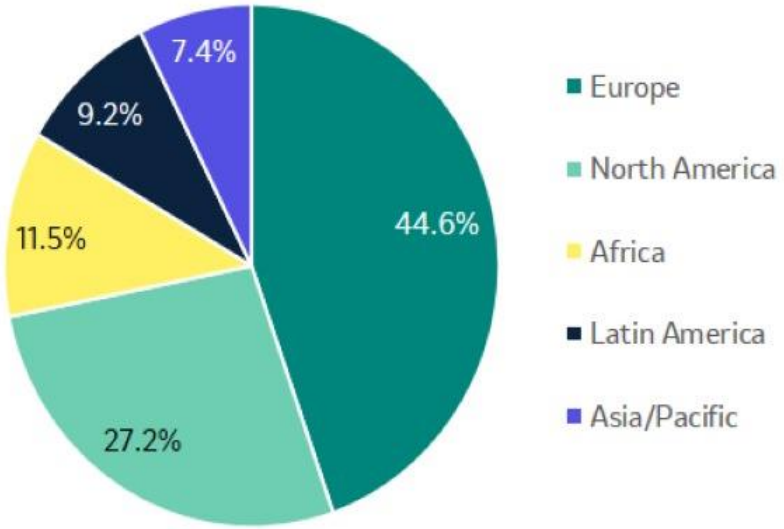


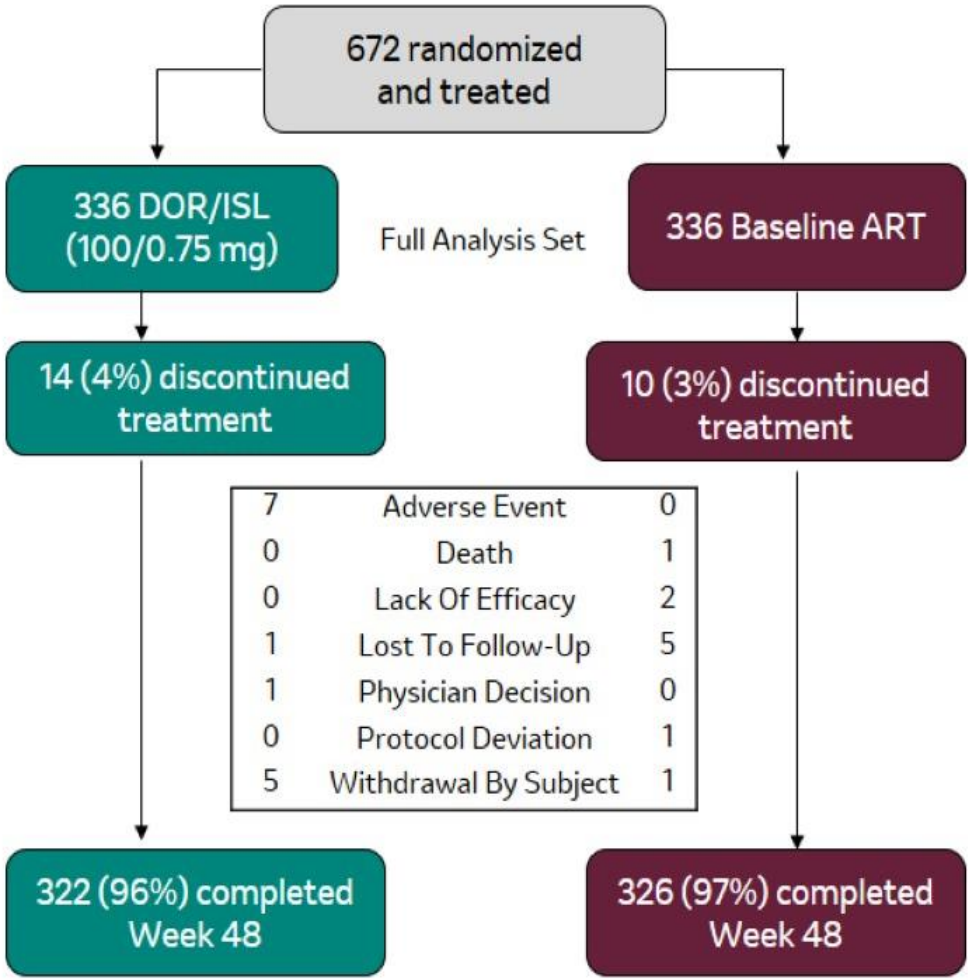
Primary Efficacy Endpoint: HIV-1 RNA ≥50 copies/mL at Week 48 (FDA snapshot approach), non-inferiority margin 4%

Study population

- 79 study sites in 15 countries
- Recruitment 18-Feb-2020 to 02-Oct-2020
  - 740 individuals screened
  - 68 not randomized (45 screen failures)

Enrollment by Region

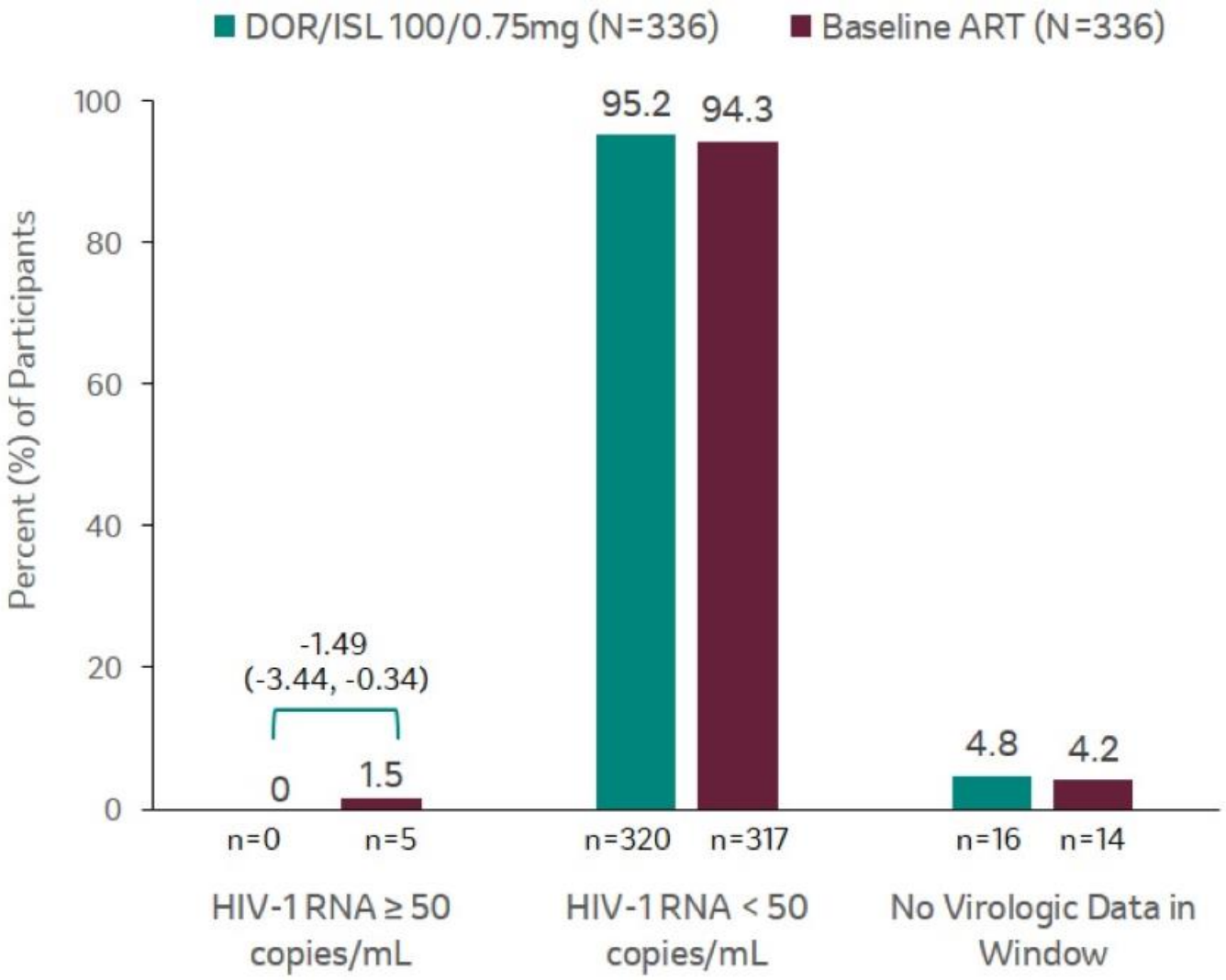




Demographics & baseline characteristics

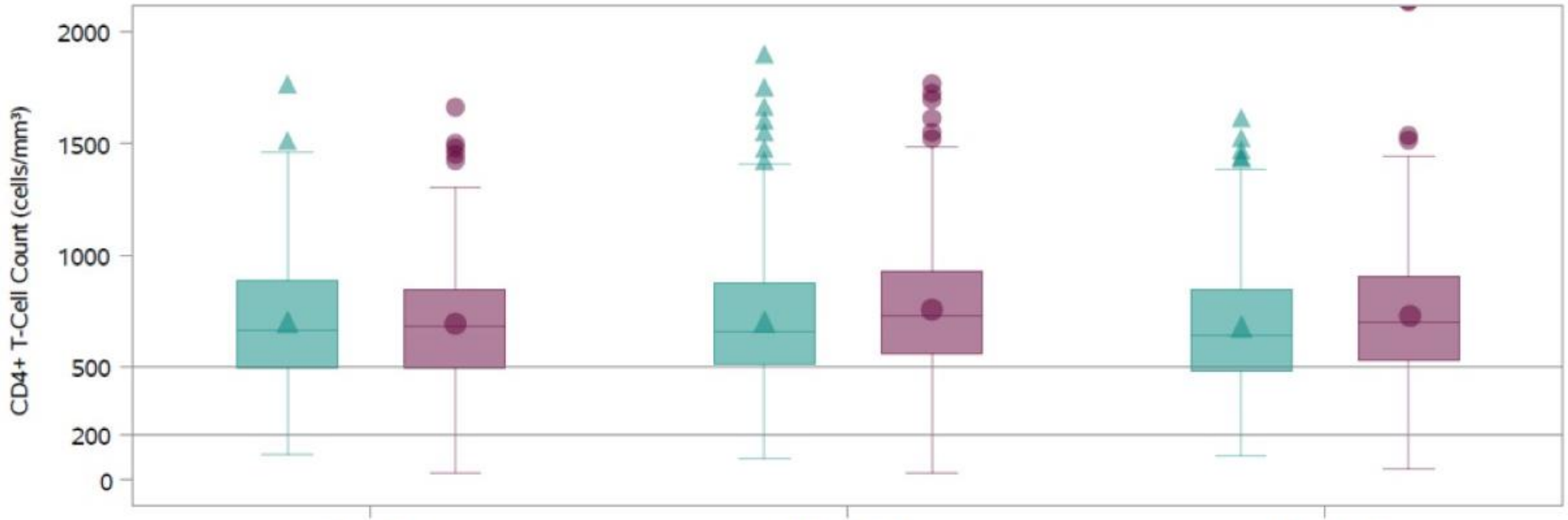
Characteristic	DOR/ISL 100/0.75mg (N=336)	Baseline ART (N=336)
Female sex at birth, n (%)	123 (36.6)	126 (37.5)
Age (years), median (range)	46 (20 to 76)	45 (19 to 79)
Race, n (%): White	210 (62.5)	198 (58.9)
Black or African American	88 (26.2)	91 (27.1)
Asian	19 (5.7)	19 (5.7)
Ethnicity, Hispanic or Latino, n (%)	67 (19.9)	64 (19.0)
Years since HIV-1 diagnosis, median (range)	9.9 (0.6 to 36.7)	8.8 (0.4 to 38.3)
Years on current ART before study, median (range)	2.7 (0.1 to 23.0)	2.8 (0.1 to 16.7)
Baseline ART Strata, n (%): PI-based	46 (13.7)	46 (13.7)
InSTI-based	174 (51.8)	174 (51.8)
Other (NNRTI-based)	116 (34.5)	116 (34.5)
CD4+ T-cell Count, median (range)	665 (111 to 1766)	685 (31 to 1666)
>350 cells/mm^3, n (%)	308 (91.7)	308 (91.7)
200 to 350 cells/mm^3, n (%)	19 (5.7)	19 (5.7)
<200 cells/mm^3, n (%)	4 (1.2)	6 (1.8)

W48 virologic outcomes: FDA snapshot



- **Switching to DOR/ISL is non-inferior to continuing Baseline ART**:
  0% vs 1.5% with HIV-1 RNA ≥50 c/mL (difference -1.49; 95% CI -3.44, -0.34)
- No participant on DOR/ISL had virologic failure (confirmed HIV-1 RNA ≥200 c/mL)
- 3 participants (1%) on Baseline ART (1 InSTI-based; 2 NNRTI-based) had virologic failure, with resistance to ≥1 component of the regimen

CD4 count changes

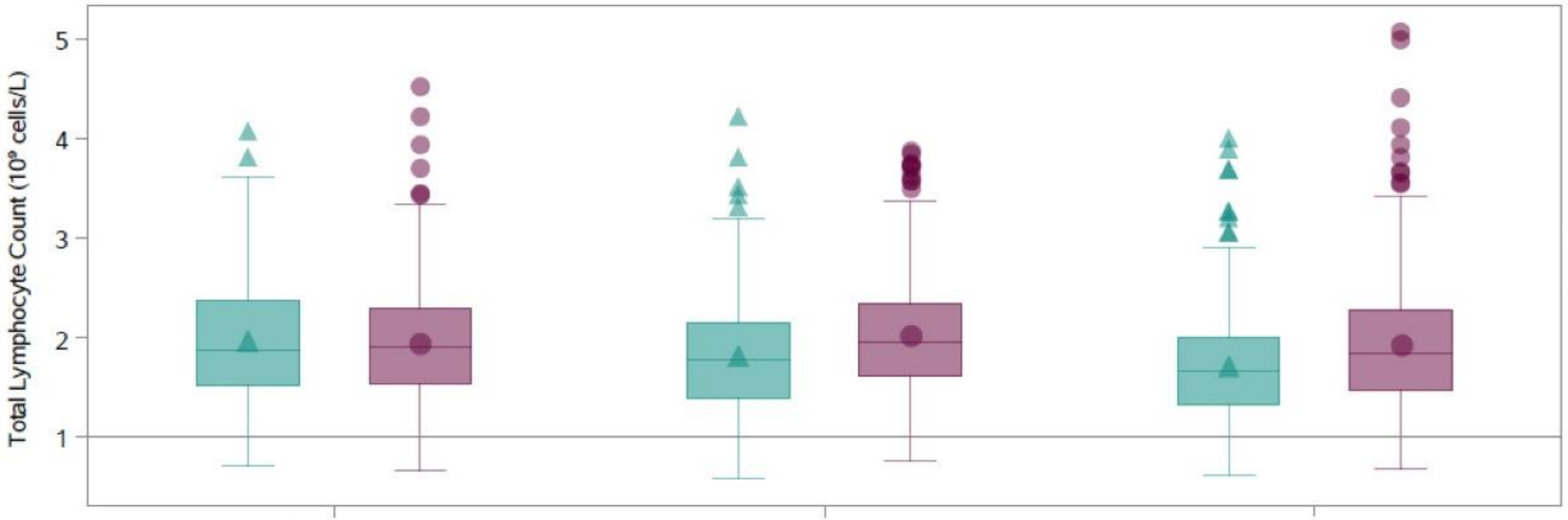


	Baseline		Week 24		Week 48	
N	331	333	315	316	313	311
Mean (cells/mm³)	703	700	701	763	677	732
Mean Change			-3.6	59.5	-30.3	38.8
Mean % Change			2.3%	11.5%	-0.7%	8.7%

Difference -66.7, 95% CI -95.8, -37.7

Figure key: box represents the IQR (Q3-Q1), horizontal line represents the median, and symbol represents the mean.

Total lymphocyte count changes



	Baseline		Week 24		Week 48	
N	332	335	303	313	297	302
Mean (10^9 cells/L)	1.97	1.95	1.81	2.03	1.71	1.94
Mean Change			-0.15	0.08	-0.26	0.01
Mean % Change			-5.4%	6.1%	-10.7%	2.3%

→ Difference -0.27, 95% CI -0.34, -0.19

Figure key: box represents the IQR (Q3-Q1), horizontal line represents the median, and symbol represents the mean.

Adverse events

n (%) of participants	DOR/ISL 100/0.75mg (N=336)	Baseline ART (N=336)	Difference (95% CI)[a]
One or more adverse events (AE)	269 (80.1)	236 (70.2)	9.8 (3.3, 16.3)
Drug-related AE[b]	66 (19.6)	30 (8.9)	10.7 (5.5, 16.1)
Toxicity grade 3-4 AE	23 (6.8)	25 (7.4)	-0.6 (-4.6, 3.4)
Serious AE	14 (4.2)	13 (3.9)	0.3 (-2.8, 3.5)
Serious drug-related AE	1 (0.3)	0 (0.0)	0.3 (-0.8, 1.7)
Deaths	0 (0.0)	1 (0.3)	-0.3 (-1.7, 0.8)
Discontinued due to an AE	7 (2.1)	1 (0.3)	1.8 (0.2, 4.0)
Discontinued due to a drug-related AE	5 (1.5)	0 (0.0)	1.5 (0.3, 3.4)
Discontinued due to a serious AE	2 (0.6)	0 (0.0)	0.6 (-0.5, 2.1)

[a] Based on Miettinen & Nurminen method. [b] Determined by the investigator to be related to the study drug.

- Five discontinued due to drug-related AEs: paranoia (serious); fatigue/headache/nausea; abnormal dreams/disorientation/disturbance in attention; increased weight; and headache/nasopharyngitis/ocular discomfort/depressed mood.
- Two discontinued due to non-drug-related AEs: Hodgkin's disease (serious), and new hepatitis B infection (not serious).

Molina J-M et al. CROI 2023. Oral abstract 196

Most common adverse events

	DOR/ISL 100/0.75mg (N=336)	Baseline ART (N=336)	Difference (95% CI)
All Causality (≥5% incidence), n (%)			
Headache	35 (10.4)	16 (4.8)	5.7 (1.7, 9.9)
COVID-19	18 (5.4)	16 (4.8)	0.6 (-2.8, 4.1)
Drug-related (≥5 participants), n (%)			
Insomnia	7 (2.1)	1 (0.3)	1.8 (0.2, 4.0)
Abnormal dreams	6 (1.8)	1 (0.3)	1.5 (-0.1, 3.6)
Headache	6 (1.8)	2 (0.6)	1.2 (-0.6, 3.3)
Nausea	5 (1.5)	1 (0.3)	1.2 (-0.3, 3.2)
Pruritus	5 (1.5)	0 (0.0)	1.5 (0.3, 3.4)
Weight increase	5 (1.5)	0 (0.0)	1.5 (0.3, 3.4)

Infection-related AEs

- Incidence of infections 33.6% in both treatment groups.
- No CDC AIDS-defining Category C events occurred in either group.

Conclusions

In adults with HIV-1 who are virologically suppressed for ≥3 months on stable oral ART

- DOR/ISL (100/0.75mg) was non-inferior to continued baseline ART in maintaining virologic suppression of HIV-1 RNA <50 c/mL through 48 weeks of treatment
  - No virologic failure (HIV-1 RNA ≥200 c/mL) observed with DOR/ISL through Week 48
- DOR/ISL (100/0.75mg) was generally well tolerated with a safety profile similar to that of continued baseline ART through 48 weeks of treatment
- Decreases in CD4+ T-cells and total lymphocytes in the DOR/ISL group were modest
  - These decreases were not associated with infection-related AEs
- Phase 3 clinical development of DOR/ISL has resumed with DOR/ISL (100/0.25 mg) QD in treatment-naive and virologically suppressed participants

Other key points, conclusions & implications

- **CD4 & TLC**
  - small increase on continued ART, small drop on DOR/ISL
- **Adverse events**
  - nothing standout; more total AE & discontinuations on DOR/ISL in 2nd study

DOR/ISL non-inferior for suppressed switch BUT this is with the 0.75g ISL dose

Will 0.25mg fare as well?

Will there be metabolic advantages?

REASSURANCE: IM-CAB/RPV

Baseline Characteristics

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

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

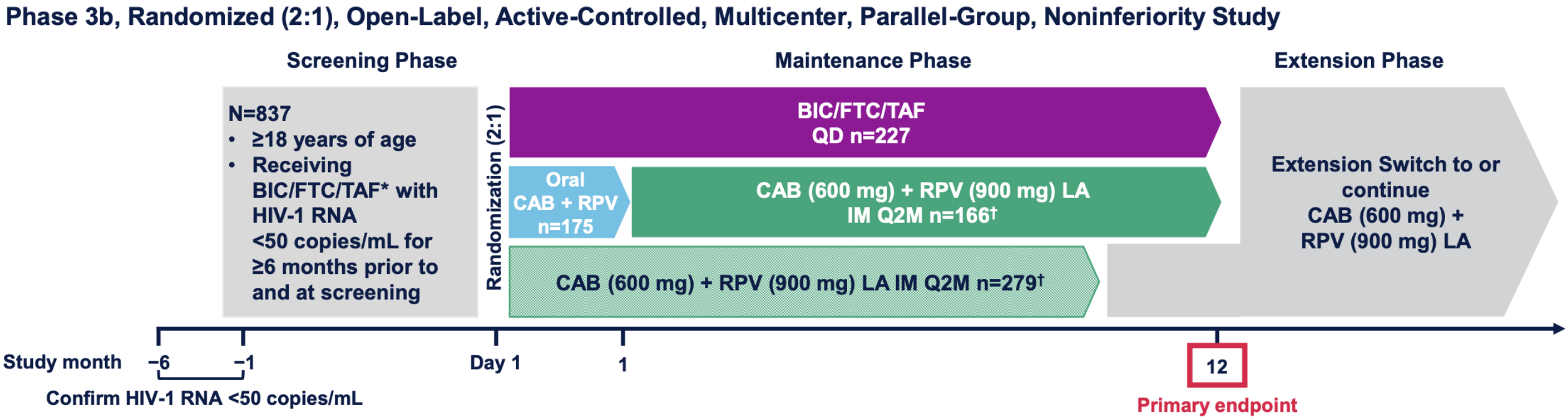
*Other race participants: American Indian or Alaska Native, n=14 (CAB + RPV LA Q2M) and n=2 (BIC/FTC/TAF); Native Hawaiian or other Pacific Islander, n=1 (BIC/FTC/TAF); multiple, n=8 (CAB + RPV LA Q2M) and n=4 (BIC/FTC/TAF).
BMI, body mass index; IQR, interquartile range; LA, long-acting; mITT-E, modified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

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

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

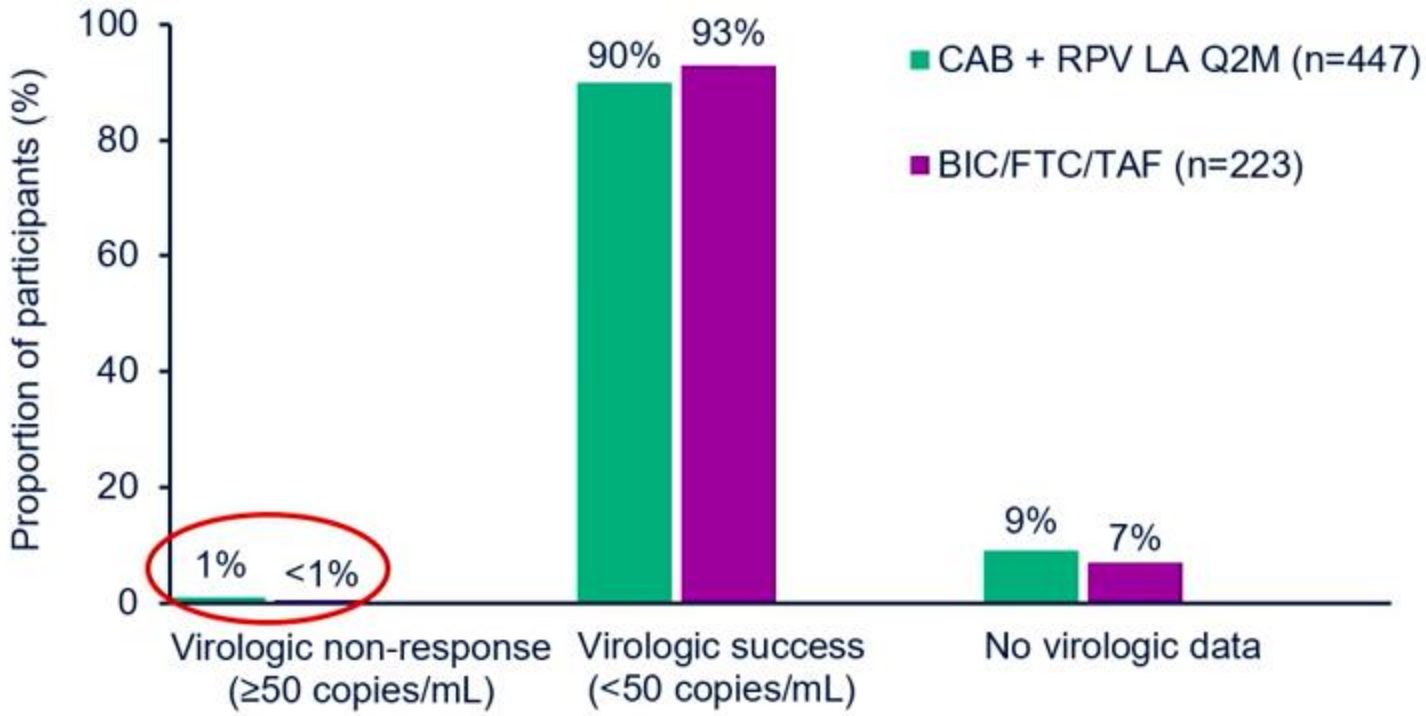
Ramgopal et al. CROI 2023; Virtual and Seattle, WA. Oral presentation 191.

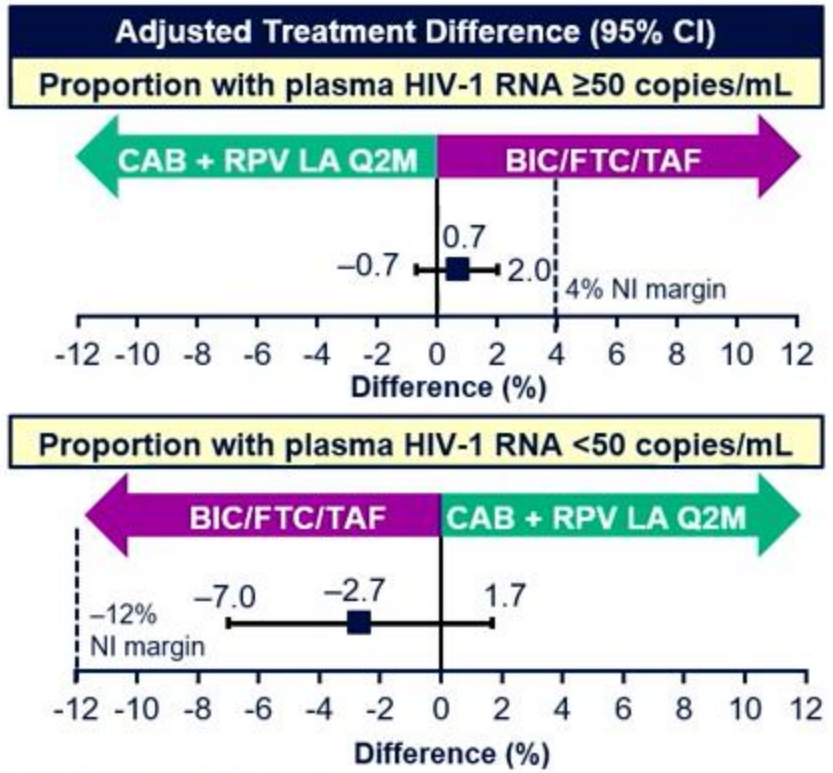
SOLAR: IM-CAB/RPV vs continued BIC/FTC/TAF



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

M12 virological outcomes





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

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

Month 12 Snapshot Outcomes (mITT-E Population)

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

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

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

SOLAR: Confirmed virological failure

Participants With CVF in the mITT-E Population									
Sex at birth, country	**Baseline BMI (kg/m²)**	**HIV-1 subtype at baseline**	**Viral load at SVF/CVF (copies/mL)**	**RPV RAMs observed at baseline (proviral DNA)**	**INI RAMs observed at baseline (proviral DNA)**	**RPV RAMs observed at failure (viral RNA)**	**INI RAMs observed at failure (viral RNA)**	**Phenotypic resistance (fold-change) to RPV/CAB**	**SVF timepoint (month)**
Male, Italy*	21.5	B	1327/1409	None	None	M230L	Q148R	3.2/3.1	6
Male, Spain†	22.9	AE	6348/419	None	G140G/R	K101E	G118R	1.9/8.4	11
Participant With CVF in the ITT-E Population‡									
Male, United States	30.5	C§	3797/928	Assay failed	Assay failed	E138E/K + Y181Y/C	None	4.2/assay failed	3

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

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

Safety Summary (Excluding Injection Site Reactions [ISRs])

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

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

*OLI period: dysesthesia/limb discomfort/paresthesia/peripheral swelling, n=1; dizziness, n=1; fatigue, n=1; deafness/ear congestion/fatigue, n=1; blood pressure fluctuation (participant reported)/depression, n=1; diarrhea/joint stiffness, n=1; Injection period: myocardial infarction, n=1; alanine aminotransferase increase, n=1; fatigue/pyrexia, n=1. †Increased alanine aminotransferase, n=2; acute myocardial infarction, n=1.
AE, adverse event; BIC/FTC/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CAB, cabotegravir; LA, long-acting; OLI, oral lead-in; Q2M, every 2 months; RPV, rilpivirine.

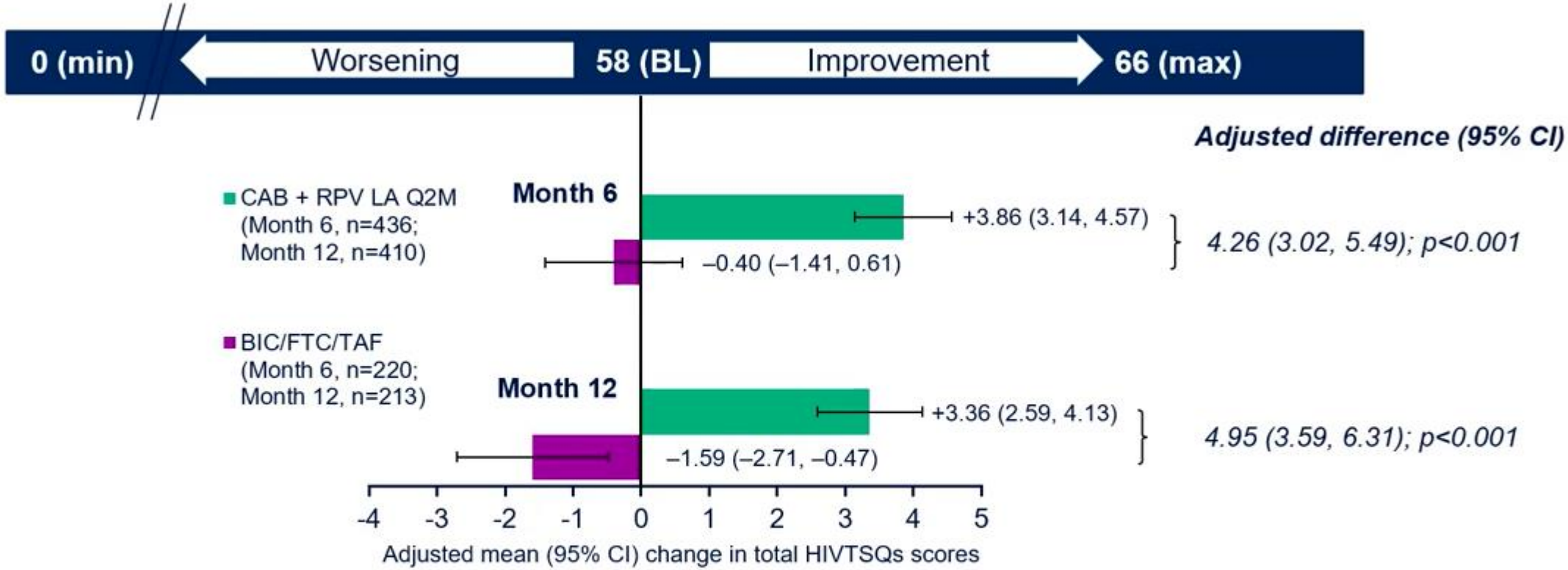
ISR Summary (Event-Level)

Parameter, n (%)	CAB + RPV LA Q2M (with OLI; n=166)*	CAB + RPV LA Q2M (SWI; n=279)*	Total (n=445)*
Number of injections, n	2228	3724	5952
ISR events, n†	734	1181	1915
Pain, n (% of injections)	507 (23)	887 (24)	1394 (23)
Discomfort, n (% of injections)	56 (3)	65 (2)	121 (2)
Nodule, n (% of injections)	28 (1)	56 (2)	84 (1)
Grade 3, n (% of ISR events)‡	19 (3)	10 (<1)	29 (2)
Median duration (IQR), days	3 (2, 5)	3 (2, 5)	3 (2, 5)
Participant withdrawal due to injection-related reasons, n (% of participants with injections)§	3 (2)	8 (3)	11 (2)

- Most ISRs were Grade 1 or 2 (98%), short-lived (median 3 days), with few participants discontinuing due to injection-related reasons

*Represents the number of participants who received an injection. †A single injection could result in more than one ISR. Grading was missed for one ISR event in the CAB + RPV LA SWI group.
‡There were no Grade 4 or Grade 5 ISRs. §Includes participants who discontinued due to ISR AEs, and an additional participant who withdrew from the study citing injection intolerability. This also includes one participant who was excluded from the primary analysis (mITT-E) population.
AE, adverse event; CAB, cabotegravir; IQR, interquartile range; ISR, injection site reaction; LA, long-acting; mITT-E, modified intention-to-treat exposed; OLI, oral lead-in; Q2M, every 2 months; RPV, rilpivirine; SWI, starting with injections.

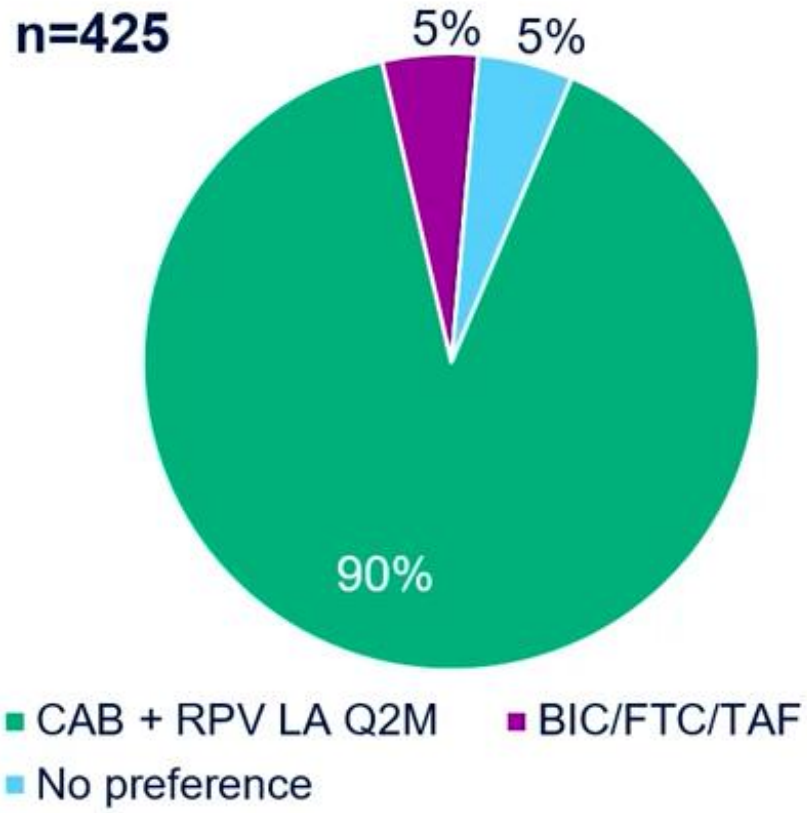
Treatment Satisfaction

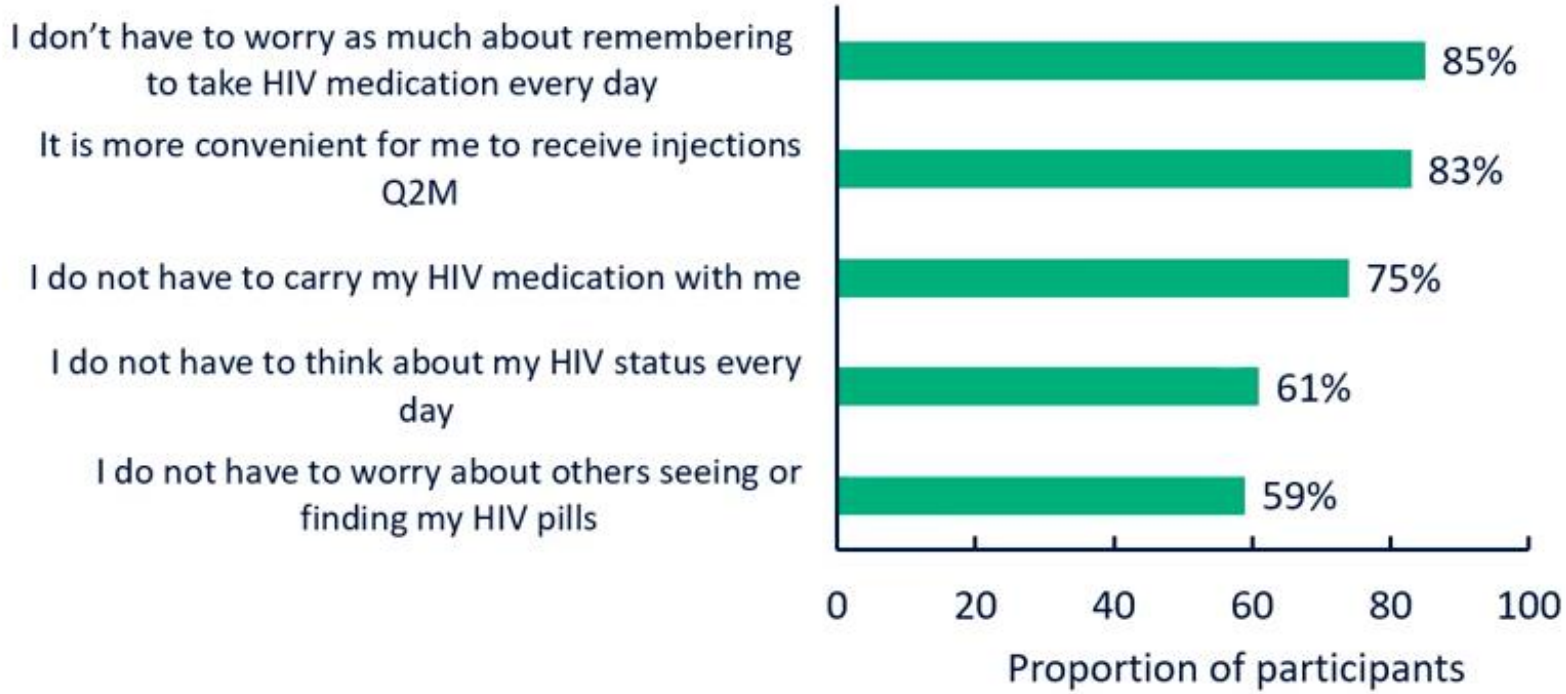


- Mean adjusted HIVTSQs scores improved significantly for CAB + RPV LA vs. BIC/FTC/TAF participants from baseline (LA, 57.88; BIC/FTC/TAF, 58.38) to Month 6 (LA, +3.86; BIC/FTC/TAF, –0.40) and Month 12 (LA, +3.36; BIC/FTC/TAF, –1.59) demonstrating greater improvement from baseline in HIV treatment satisfaction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

HIVTSQs, HIV Treatment Satisfaction Questionnaire status version.

Treatment preference & why





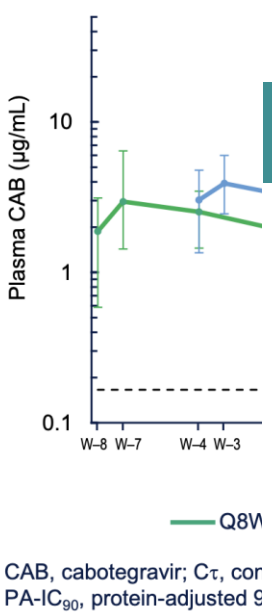
- Overall, at the time of study withdrawal or at Month 12, 90% (n=382/425) of participants preferred CAB + RPV LA compared with 5% (n=21/425) who preferred daily oral BIC/FTC/TAF therapy

*Top five most frequently reported reasons for preference.

Conclusions

- At baseline, 47% of participants on BIC/FTC/TAF reported psychosocial challenges with their daily oral therapy
- At Month 12, CAB + RPV LA Q2M demonstrated noninferior virologic efficacy vs. BIC/FTC/TAF
  - The overall CVF rate was low (<1%) in the population receiving CAB + RPV LA; all re-suppressed on alternative oral ART
- CAB + RPV LA was well tolerated, with most (98%) ISRs being mild to moderate in severity, short in duration (median 3 days), and rarely leading to withdrawal (2%)
- 90% of participants in the LA arm preferred CAB + RPV LA after switch from BIC/FTC/TAF
- Participants who switched to CAB + RPV LA from BIC/FTC/TAF had significant improvement in treatment satisfaction
- These data demonstrate that CAB + RPV LA addresses important unmet needs for people living with HIV who are virally suppressed on oral daily therapy

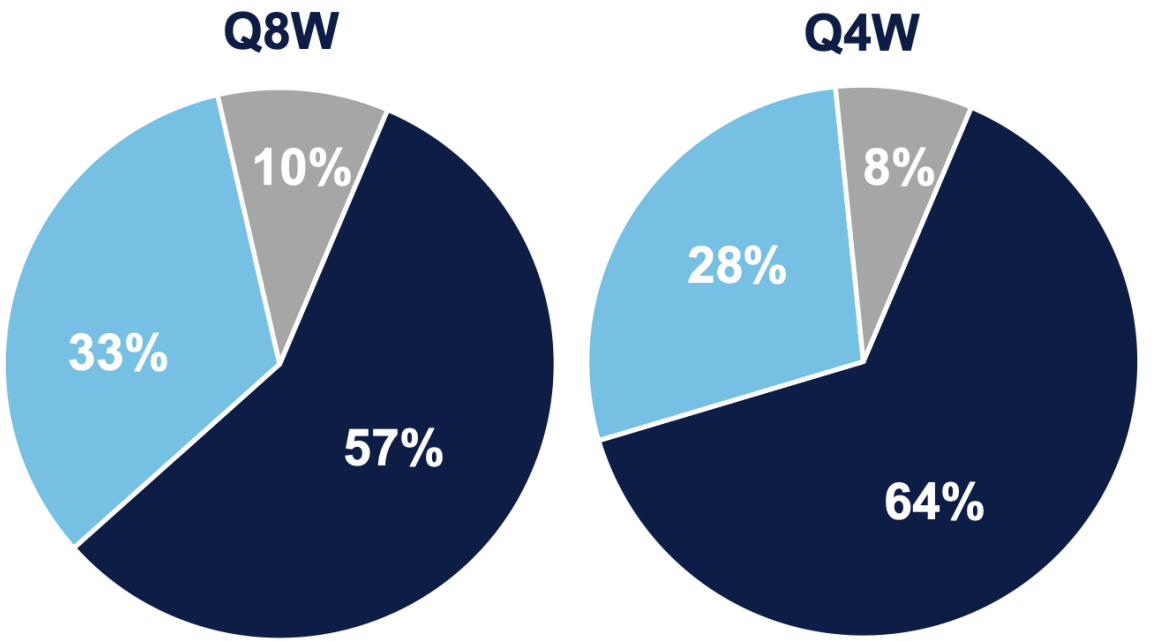
Thigh IM-CAB/RPV injections



CAB, cabotegravir; Cτ, cor
PA-IC$_{90}$, protein-adjusted 9

CAB 1000 RPV

Preference



*Return to gluteal injection phase.
Q4W, every 4 weeks; Q8W, every 8 weeks.

Good PK but not OK (for many)

OLI? Or no OLI? French cohort n=58

- **Cabotegravir:**

Characteristics	M1 cabotegravir trough level				M3 cabotegravir trough level		
	< 1120 ng/mL (n=35)	≥ 1120 ng/mL (n=23)	p	p*	< 1120 ng/mL (n=43)	≥ 1120 ng/mL (n=13)	p
Median age, years (IQR)	29 (26 – 34)	31 (28 – 34)	0.7		29 (26 – 34)	31 (30 – 36)	0.1
Male, n (%)	29 (83)	22 (96)	0.2		38 (88)	11 (85)	0.7
European origin, n (%)	25 (71)	15 (65)	0.8		32 (74)	8 (62)	0.5
Median BMI, kg/m^2 (IQR)	24 (22 – 27)	22 (20 – 25)	**0.01**	**0.009**	24 (22 – 26)	24 (22 – 27)	0.5
No lead-in, n (%)	29 (83)	13 (57)	**0.04**	**0.02**	35 (81)	6 (46)	**0.03**

* Multivariate analysis

- **Rilpivirine:** no risk factor for low trough levels at M1 and M3

IM-CAB/RPV outside the license

- **San Francisco Ward 86 clinic**
  - Substance use, unstable housing & mental health issues common
- **N=133 treated 06/2021-11/2022:**
  - No history of RPV or INSTI RAMs
  - No viral suppression requirement
  - Willing to come to clinic **Q4W**
  - 68% non-white, 66% unstably housed
  - On-time injections 74%
  - 57% virally suppressed on oral ART, **ALL STAYED SUPPRESSED**

57 (43%) viraemic at switch

55 virally suppressed after a median of 33 days

2 (3.5%) experienced VF:
Neither experienced 2log drop
1 baseline V179I: VF with Y181C+L100I
1 baseline T97A: VF with R263K+E138K

NEITHER ABLE TO TAKE PO ART SINCE

Implications for practice

- IM-CAB/RPV cuts it for most, not all, & until we can reliably identify people at risk of rebound, we must counsel all
- In England we cannot prescribe beyond NICE guidance, which is based on the SmPC
  - If we can save lives with IM-CAB/RPV…..we should be able to?

RETHINK: 2nd line DTG+DRV/r

History of D²EFT

- Originally a 2 arm RCT utilising 1 innovative 2DR vs SOC commencing April 2017
- 3rd arm added May 2018 (changing ART landscape, extensive stakeholder consultation)

STANDARD OF CARE	INTERVENTION ARM	INTERVENTION ARM
DRV/r+2N	DRV/r+DTG	DTG + XTC/TDF
Nucleosides Selected - Genotyping or WHO Algorithm	No Nucleosides	Recycled Nucleosides
Drug Class But Not Drug Recycled	No Genotyping Required	No Genotyping Required
No Coformulation Possible	No Drug or Drug Class Recycled	Drugs and Class Recycled
	Potential Coformulation	Coformulated
ARM 1	ARM 2	ARM 3

XTC= FTC or 3TC

- Adults with VF on 2NRTI+NNRTI (VL >500 at least 7 days apart after at least 24W ART)
- Exclusions: prior PI/INSTI, HBV sAg+, sig co-morbidity/active coinfection, pregnancy/BF
- Modified ITT excluding any participant randomised who did not commence ART

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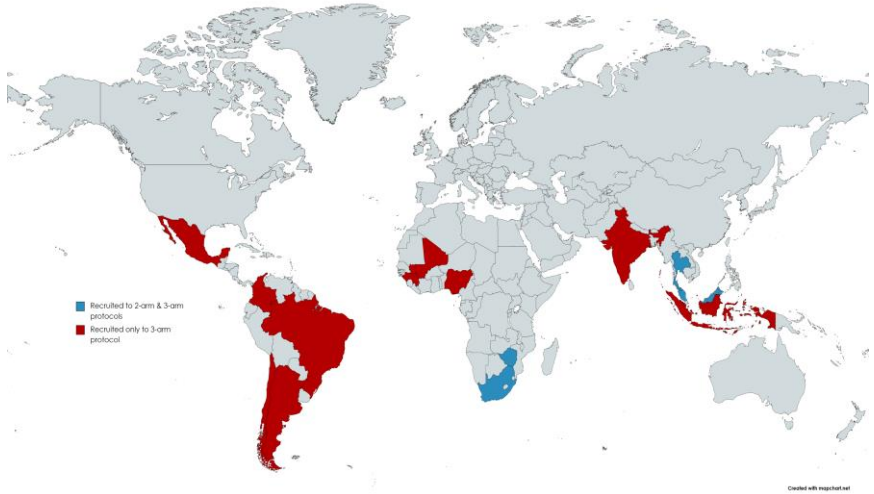
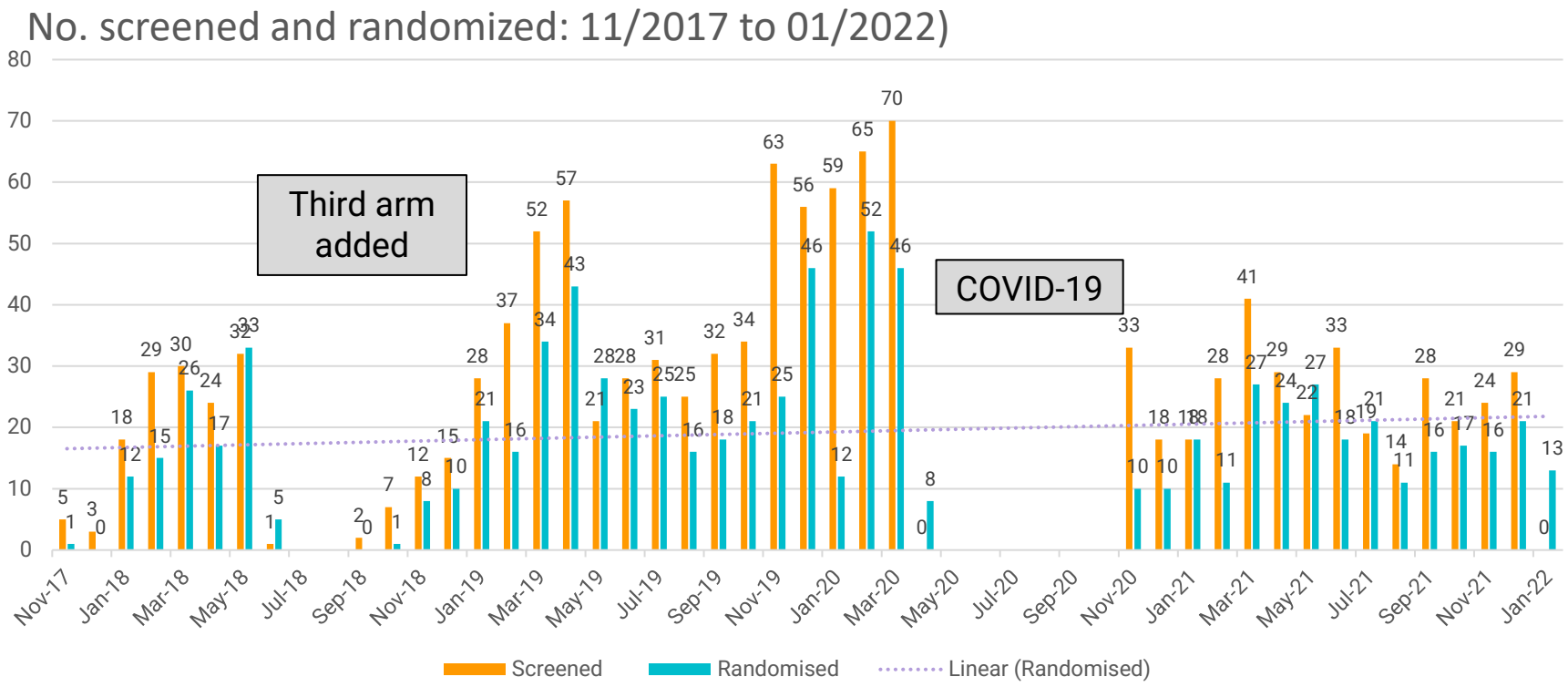
Recruitment

Sample size increased from 610 to 1010
Recruited 831 participants over 14 countries
(722 in Stage 2)





Despite external challenges retention and engagement of participants was exceptional:
7 withdrawals
3 LTFU

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Baseline characteristics

Characteristic	Stage 1 (n=109)		Stage 2 (n=722)			Total
	DRV/r + 2NRTI (n=53)	DTG + DRV/r (n=56)	DRV/r + 2NRTI (n=210)	DTG + DRV/r (n=216)	DTG + TDF/XTC (n=296)	(n=831)
Age (years) Mean (SD)	39.4 (9.6)	39.6 (10.8)	39.6 (9.6)	39.0 (9.6)	39.5 (10.6)	39.4 (10.0)
Male (n, %)	24 (45.3)	29 (51.8)	97 (46.2)	94 (43.5)	136 (45.0)	380 (45.7)
Ethnicity (n,%)						
Asian	20 (37.7)	20 (35.7)	51 (24.3)	51 (23.6)	69 (23.3)	211 (25.4)
Black	32 (60.4)	36 (64.3)	145 (69.1)	149 (69.0)	208 (70.3)	570 (68.6)
CD4 cells/mm^3 (median, IQR)	188 [101, 350]	166 [59, 297]	195 [85, 355]	213 [93, 350]	226 [113, 373]	206 [93, 357]
HIV VL log_{10}c/ml (median, IQR)	4.2 [3.3, 4.7]	4.3 [3.7, 4.9]	4.2 [3.5, 4.9]	4.1 [3.6, 4.9]	4.2 [3.6, 4.8]	4.2 [3.6, 4.8]
BMI (median, IQR)	22.6 [20.1, 24.6]	21.6 [19.2, 25.0]	23.6 [21.0, 27.4]	22.5 [19.8, 26.7]	23.5 [20.4, 27.0]	23.0 [20.3, 26.8]

- NNRTI at first line failure : 82.7% Efavirenz, 11.4% Nevirapine
- NRTIs used in second line with DRV/r: 76% ZDV/3TC, 19% TDF/XTC

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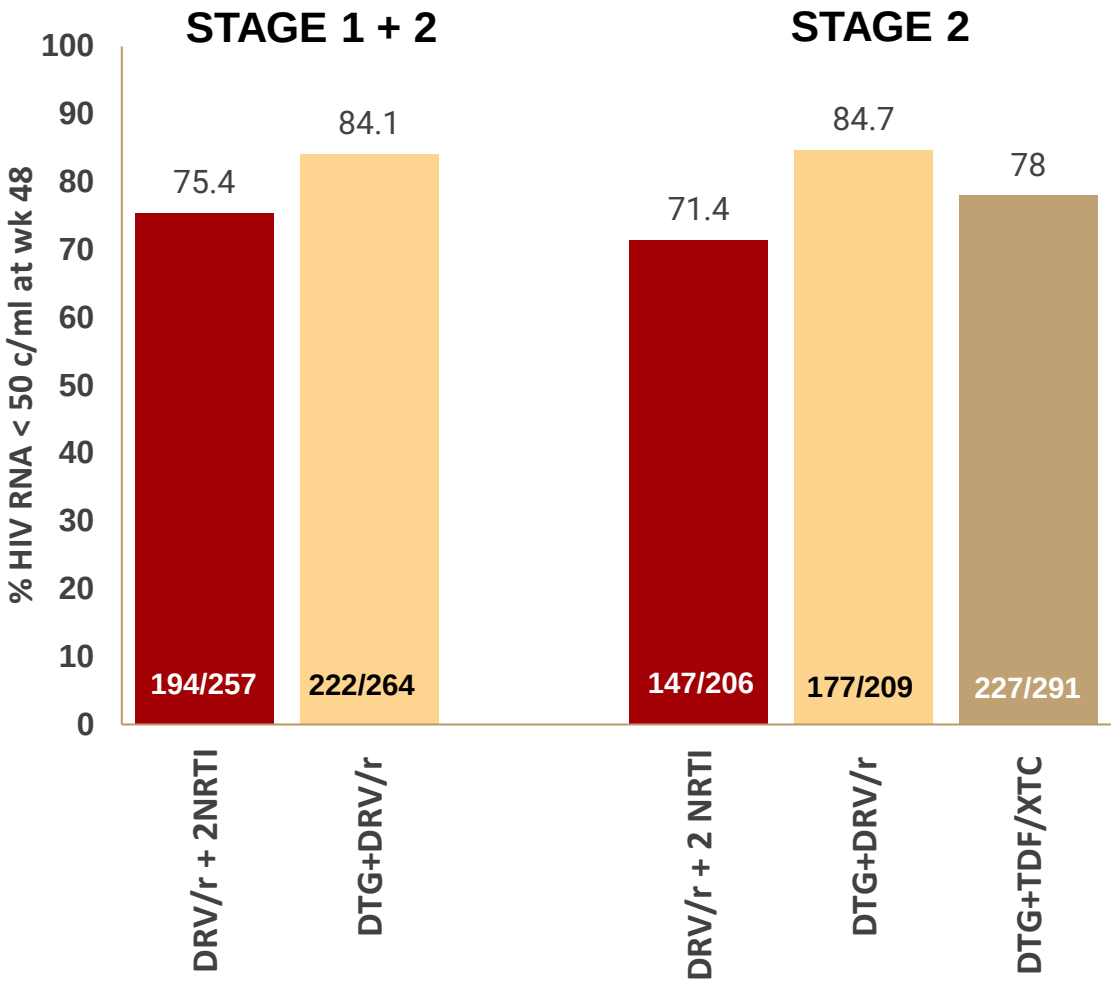
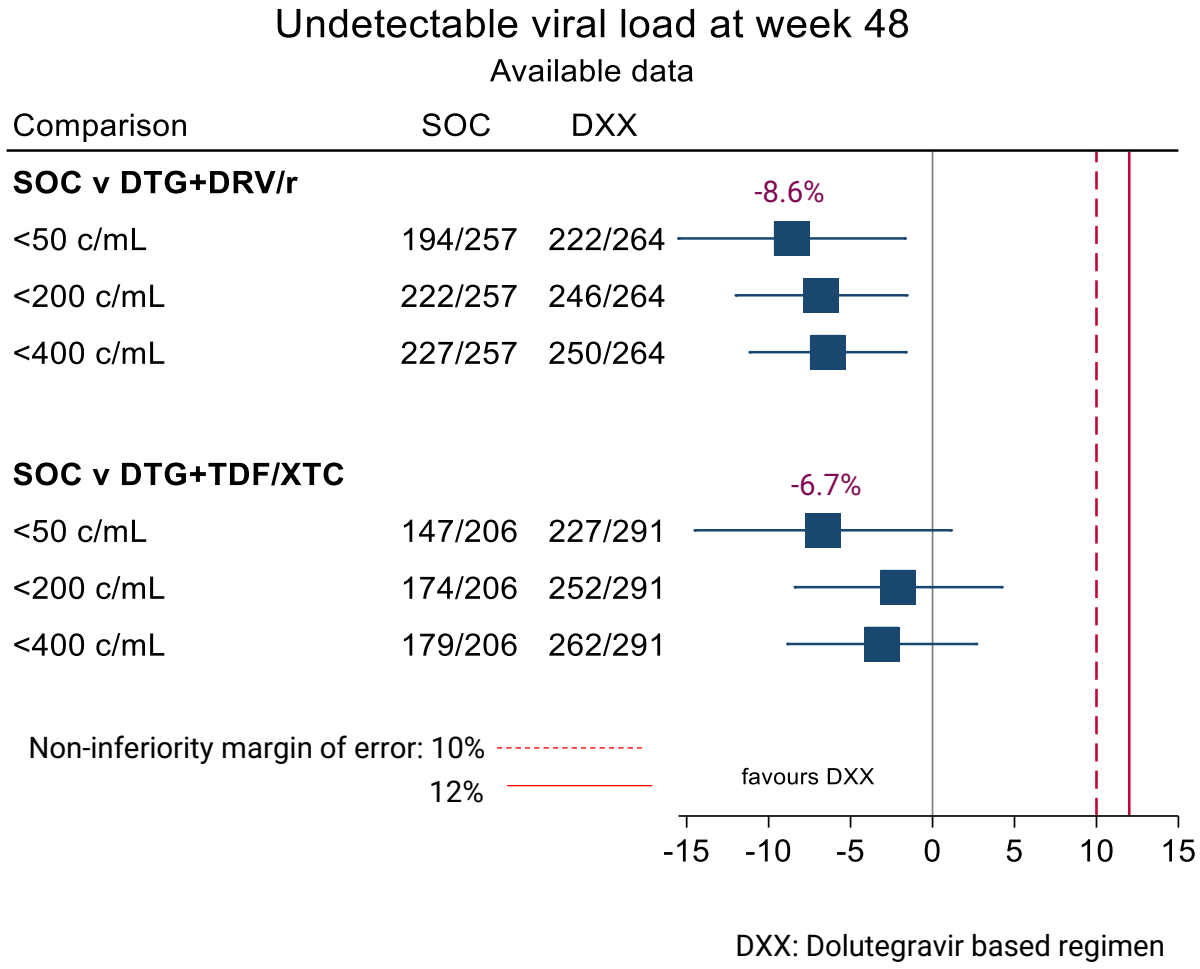
Primary outcome





DXX: Dolutegravir based regimen

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Conclusions & implications

- Both intervention arms non-inferior to SOC (2NRTI+DRV/r)
- CD4 increase + weight gain both greater in DTG arms
- 2DR superior but availability of TLD as a **low cost FDC** is relevant from a programme perspective
- Note, most people in DRV/r arm were on ZDV/3TC backbone

Have we become too complacent post-NADIA?

Is 2NRTI+INSTI enough for people with NRTI RAMs*?

What is the tipping point?

*in the context of HIC funding/access

REALITY? LEN + bNAbs

LEN with bNAbs, Teropavimab and Zinlirvimab, Dosed Every 6 Months in PLWH

N = 21

Virologically suppressed PLWH, aged ≥ 18 years

Outcomes

Primary: Safety and tolerability

Secondary: HIV-1 RNA < 50 and ≥ 50 c/mL at W26 (FDA snapshot); PK

2021-Ongoing

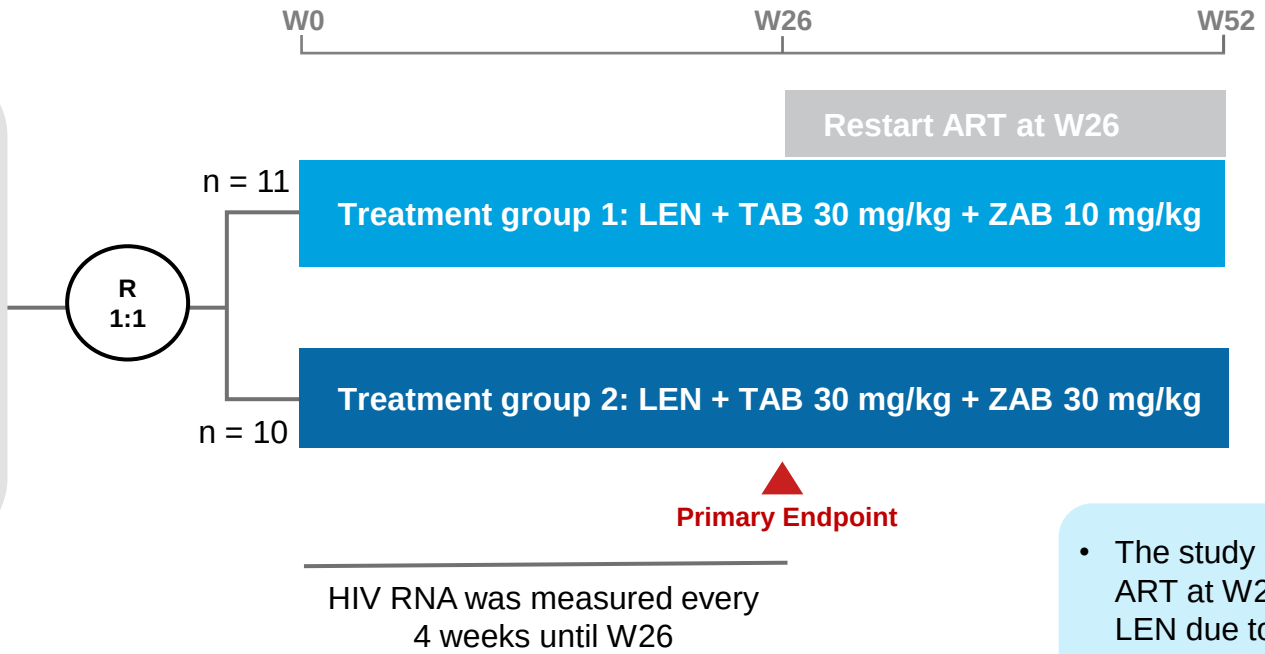
Adults living with HIV1

Virologically suppressed ≥ 18 months[a]

Met susceptibility criteria for TAB and ZAB[b]

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 W26 after the FDA clinical hold on investigational LEN due to stability issues in borosilicate vials

[a]Previous virologic failure was allowed as long as participants had been suppressed for at least 18 months prior to screening.
[b]Susceptibility defined as IC90 ≤ 2 μg/mL to each antibody by PhenoSense mAb Assay (Monogram Biosciences).
IC, inhibitory concentration; PK, pharmacokinetics; TAB, teropavimab; VS, virologically suppressed; ZAB, zinlirvimab

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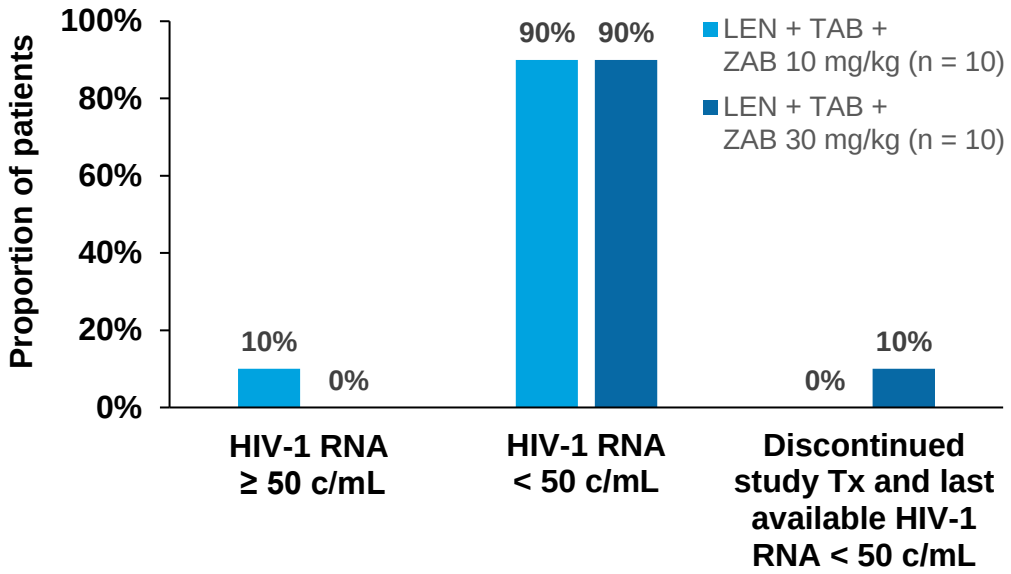
Week 26: Efficacy and Safety

Virologic Outcomes at Week 26



- One participant withdrew at W12 with HIV-1 RNA < 50 c/mL
- One participant had a confirmed virologic rebound at W16
- CD4 cell counts remained stable over the course of the study period

Safety and Tolerability

- There were no serious AEs, no Grade 4 AEs and no AEs that led to study treatment discontinuation
- There were two Grade 3 AEs:
  - One injection-site cellulitis on D1, which resolved with antibiotics
  - One injection-site erythema on D3, which resolved without intervention by D10
- AEs occurring in ≥3 participants:
  - Injection site pain
  - Erythema
  - Nodule
  - Induration
  - Mass
  - COVID-19
  - Upper respiratory tract infection

Combination of the bNAbs, teropavimab & zinlirvimab, with LEN can sustain viral suppression 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; Tx, treatment; VS, virologically suppressed; ZAB, zinlirvimab

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Results & implications

- 90% in each arm maintained viral suppression
  - 1 discontinued at W12 while suppressed
  - 1 experienced viral rebound at W16
- Good PK & safety; AEs as expected (ISR)

55% were not susceptible to the bNAbs at baseline

30% of the remainder not eligible for other reasons

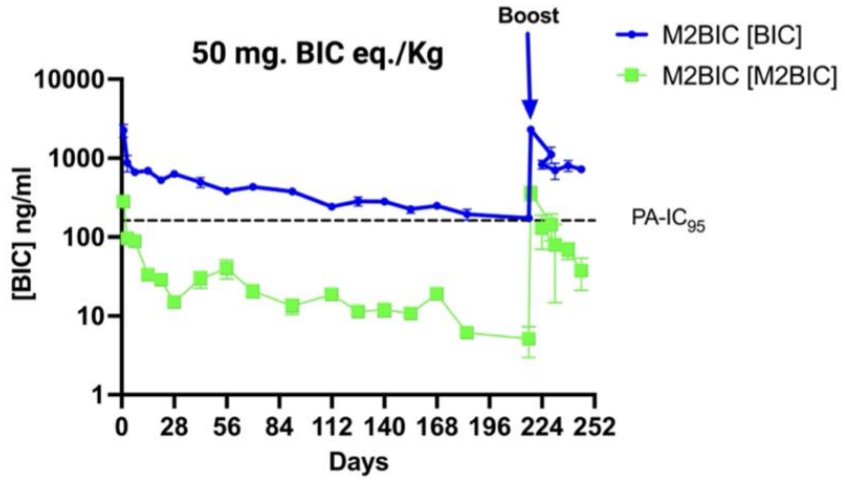
This + likely significant cost may limit usefulness

PHASE 2 TRIALS PLANNED

Poster 540

Nayan MU et al

Nanoformulations of bictegravir that could support 6-monthly parenteral dosing



Thank you for listening!

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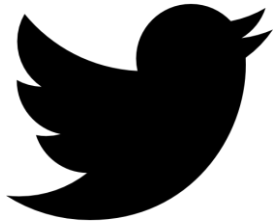

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