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Thai Red Cross Emerging Infectious Diseases Clinical Center

ChulaIDWeekend 2022
Towards Educational Excellence

Advanced Issues on HIV/AIDS

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Disclosures

Opass Putcharoen, MD., MSc.

- Consulting fees from BMS
- Non-CME/CE services: Gilead Sciences, BMS, Merck, Siam Pharmaceutical, ViiV, Hetero laboratory and Mylan
- Advisory board: BMS, GSK

Agenda

- New drugs and Long-acting ART
- HIV Cure
- New strategies: 2-drug versus 3-drug regimens
- Specific populations: pregnancy, co infections

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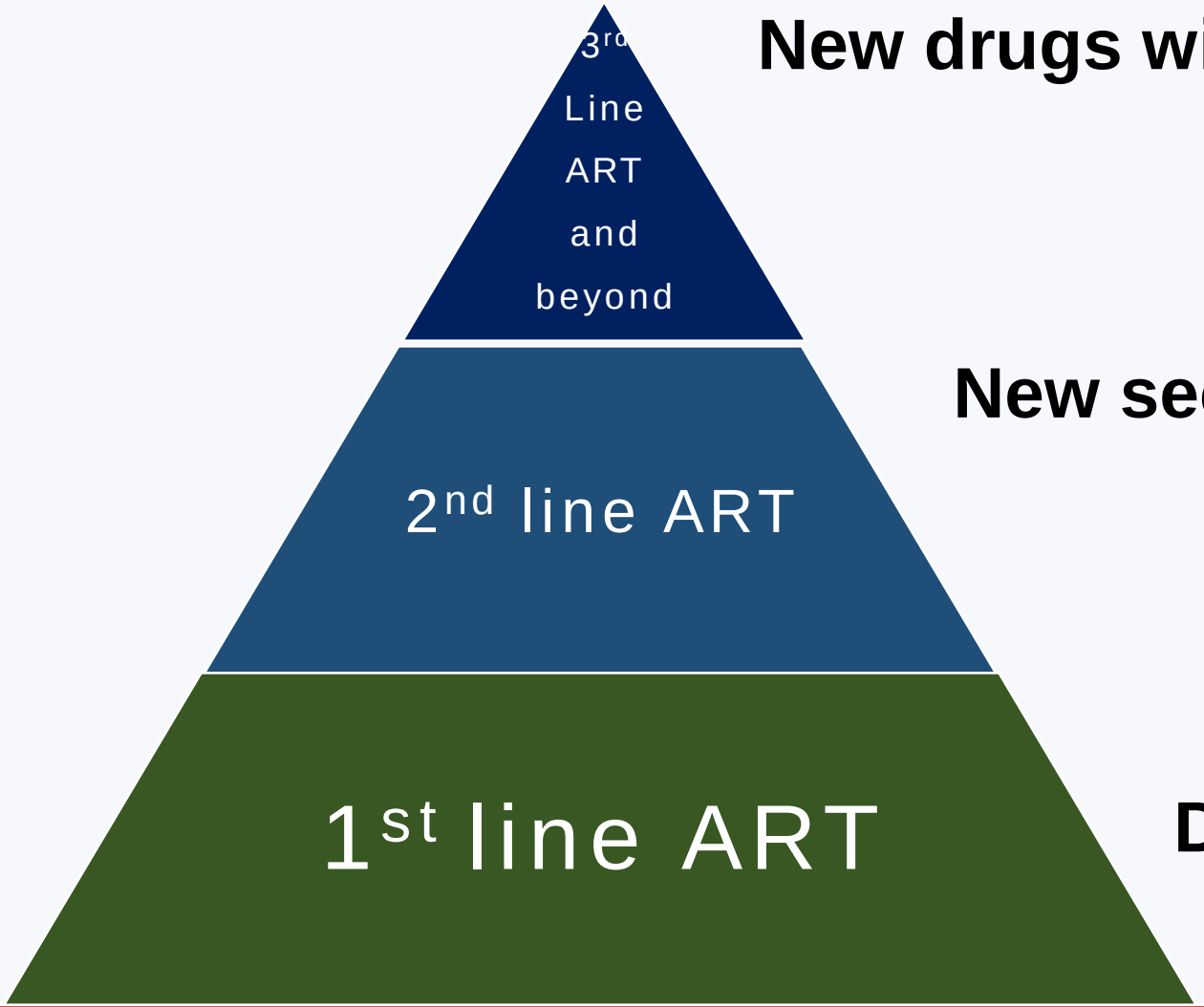
Why do we need new drugs?

- **Reduced dosing frequency**
- **Active against drug resistant HIV**
- **High barrier to resistance**
- **Reduced stigma**

HIV Treatment Strategies



New drugs with new mechanism of action

New second-line ART regimen

Long-term efficacy of INSTI
DTG and TAF for pregnant women
New two-drug regimens

Investigational agents

Entry inhibitor
Broadly neutralizing antibicy (BNAb): Ibalizumab

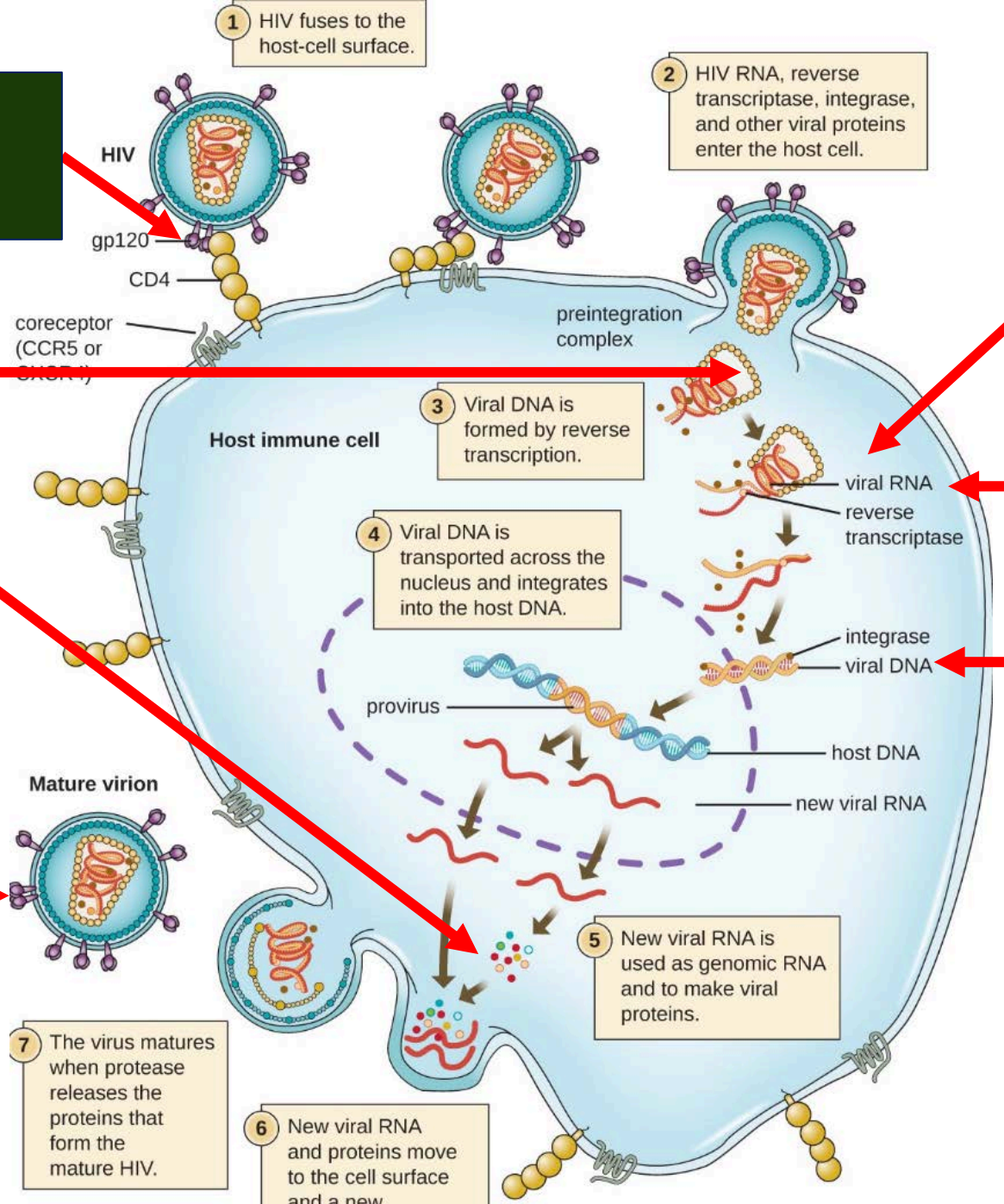
Capsid inhibitor
Lenacapavir

Maturation inhibitor
GSK 3640254

Nucleoside RT translocation inibitor
Islatravir

NNRTI
MK-8507

Integrase inhibitor
Cabotegravir (long-acting INSTI)



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DHHS 2021 June

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV

DTG

Botswana Tsepamo study have shown that the prevalence of neural tube defects (NTD) associated with DTG use during conception is much lower than previously reported. **Based on these new data, the Panel now recommends that a DTG-based regimen can be prescribed for most people with HIV who are of childbearing potential.**

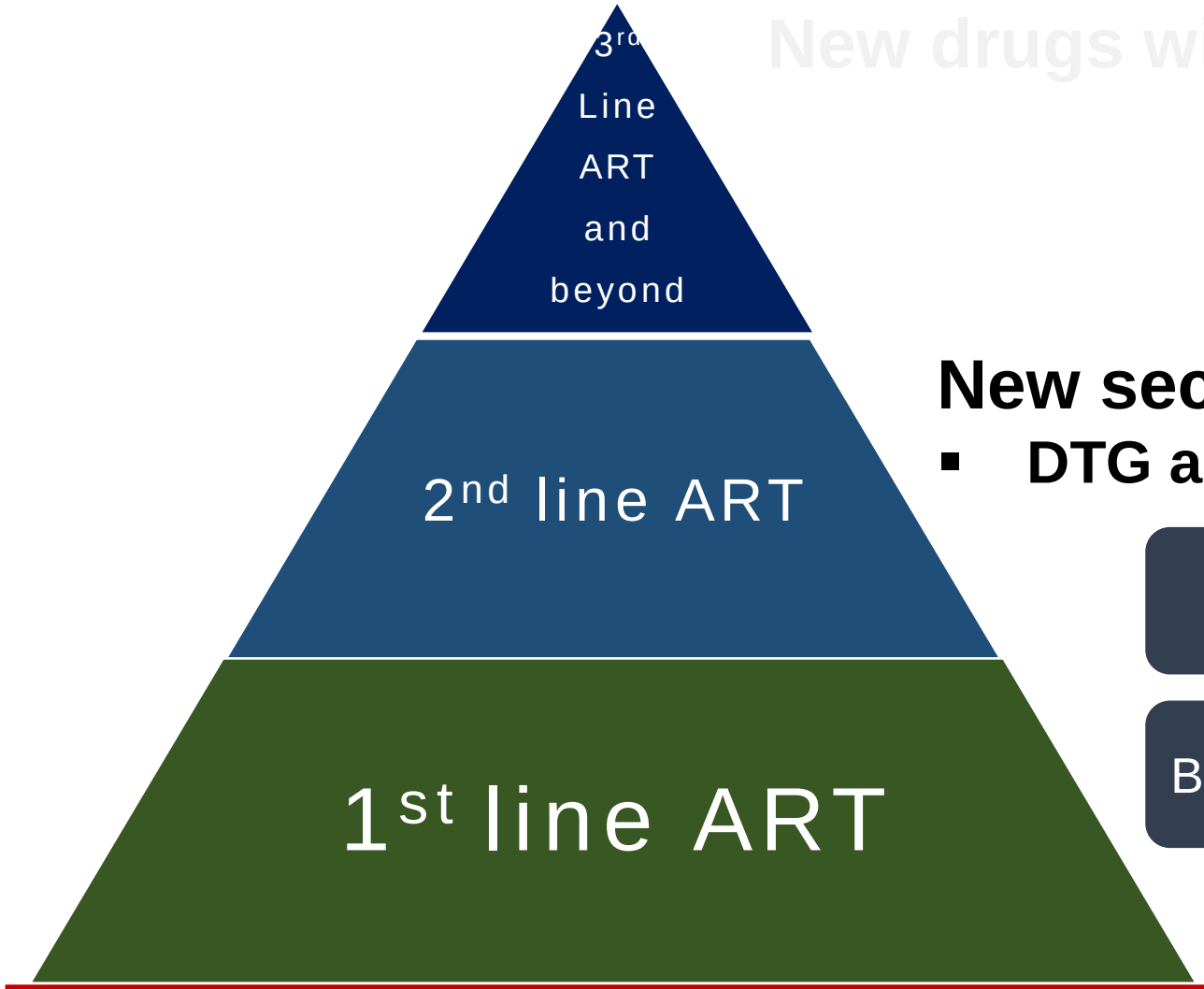
2nd line ART

A new regimen can **include two fully active** drugs if at least one with a high resistance barrier is included (e.g., **DTG or boosted darunavir) (AI)**."

Switching

The update to this section primarily focuses on the role of the **new long-acting injectable (LAI) regimen of intramuscular cabotegravir (CAB) plus rilpivirine (RPV) in this setting.**

HIV Treatment Strategies



New second-line ART regimen

- **DTG as a component of 2nd line ART**

New agent; DTG or DRV/r

Backbone: AZT/3TC or TDF/FTC

Investigational agents

Concepts

- 2NRTI+NNRTI failure
- Next options:
  - Recycling NRTI + New Agents (Integrase Inhibitor or PI)– Genotypic resistance
  - 2 New Agents (Integrase inhibitor + PI)

"Genotypic resistance and VL monitoring are limited in some countries"

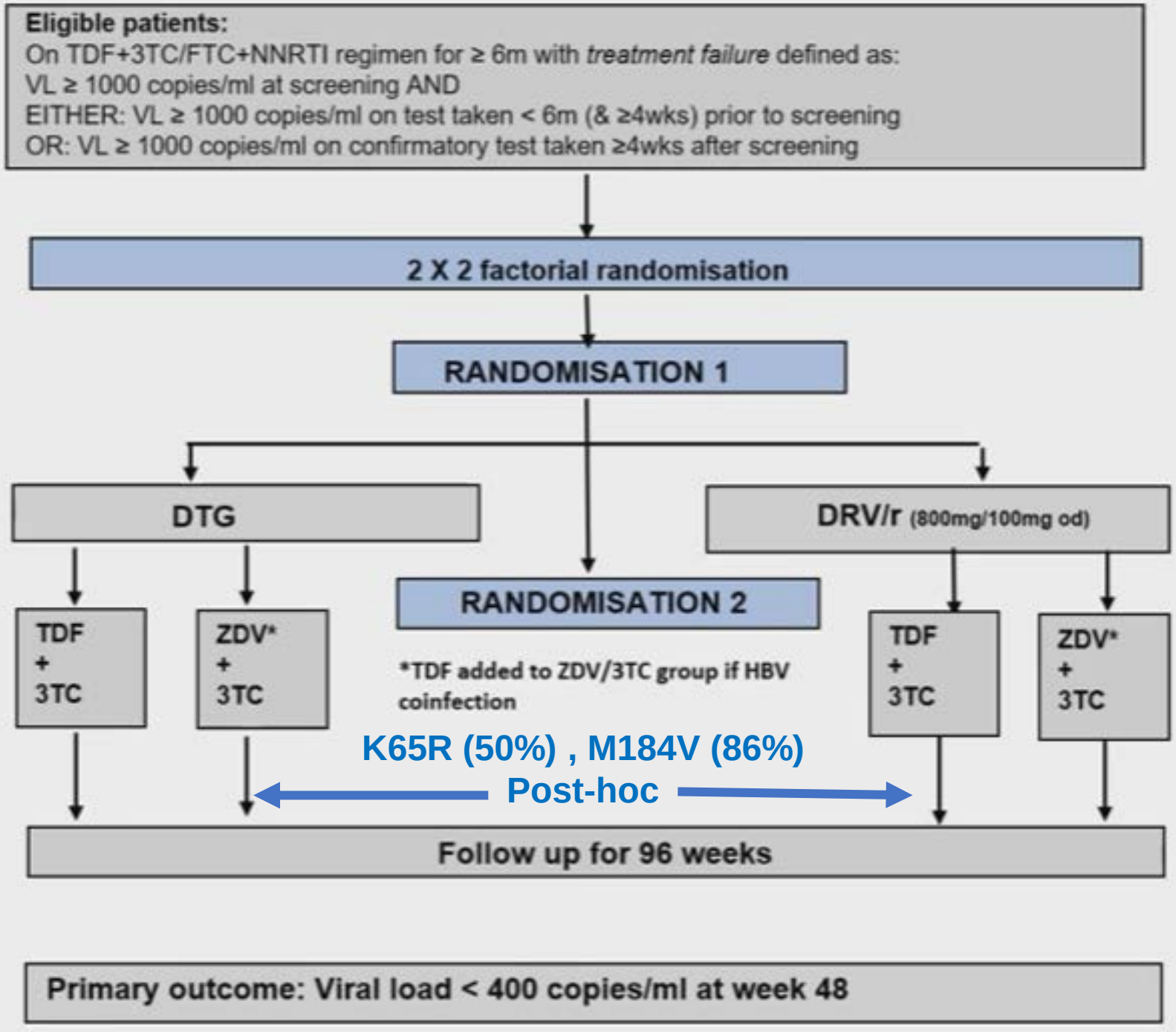
Design:

Two by two factorial randomization

Outcomes:

- FDA snapshot analysis: % with VL < 400 copies/mL at 48 weeks
- 12% margin for no-inferiority
- Sites: Uganda, Kenya and Zimbabwe

Abs#94



Outcome	Dolutegravir Group (N=235)	Darunavir Group (N=229)	Difference (95% CI) %	P
HIV-1 RNA level (primary outcome) – no (%)				
< 400 copies/ml (ITT)	212(90.2)	210 (91.7)	-1.49 (-6.7 to 3.7)	0.576
≥ 400 copies/ml	20 (8.5)	16 (7.0)	-	
No virological data	3 (1.3)	3 (1.3)	-	
- Withdrew because of AE/death	2 (0.9)	3 (1.3)		
- Withdrew for other reasons	1 (0.4)	0		
HIV-1 RNA level (sensitivity analyses, secondary, other outcomes) – no (%)				
< 400 copies/ml (adjusted)	88.2	89.8	- 1.6 (-6.9 to 3.6)	0.541
VL < 400 copies (per protocol)	205 (92.3)	204 (93.2)	-0.8 (-5.6 to 4.0)	0.744
VL < 1000 c/ml (ITT)	217 (92.3)	213 (93.0)	-0.7 (-5.4 to 4.1)	0.781
VL< 50 c/ml (ITT)	190 (80.9)	182 (79.5)	1.4 (-5.9 to 8.6)	0.710
Rebound (secondary outcome) – no (%)				
VL rebound ≥ 1000 c/ml, confirmed (ITT)	14 (6.0)	13 (5.7)	0.3 (-4.0 to 4.5)	0.897
VL rebound ≥ 1000 c/ml, confirmed with ≥1 major RM to DTG or DRV*	4*	0	-	-

* ≥1 major DTG mutation: 4 (1) T66TA, G118R, E138K, G149GA, G163GR (high-level); (2) E138K, G140A, Q148R (high-level); (3) T66I, G118R, E138K, G149GA (high-level); (4) R263K, M50I (intermediate level).

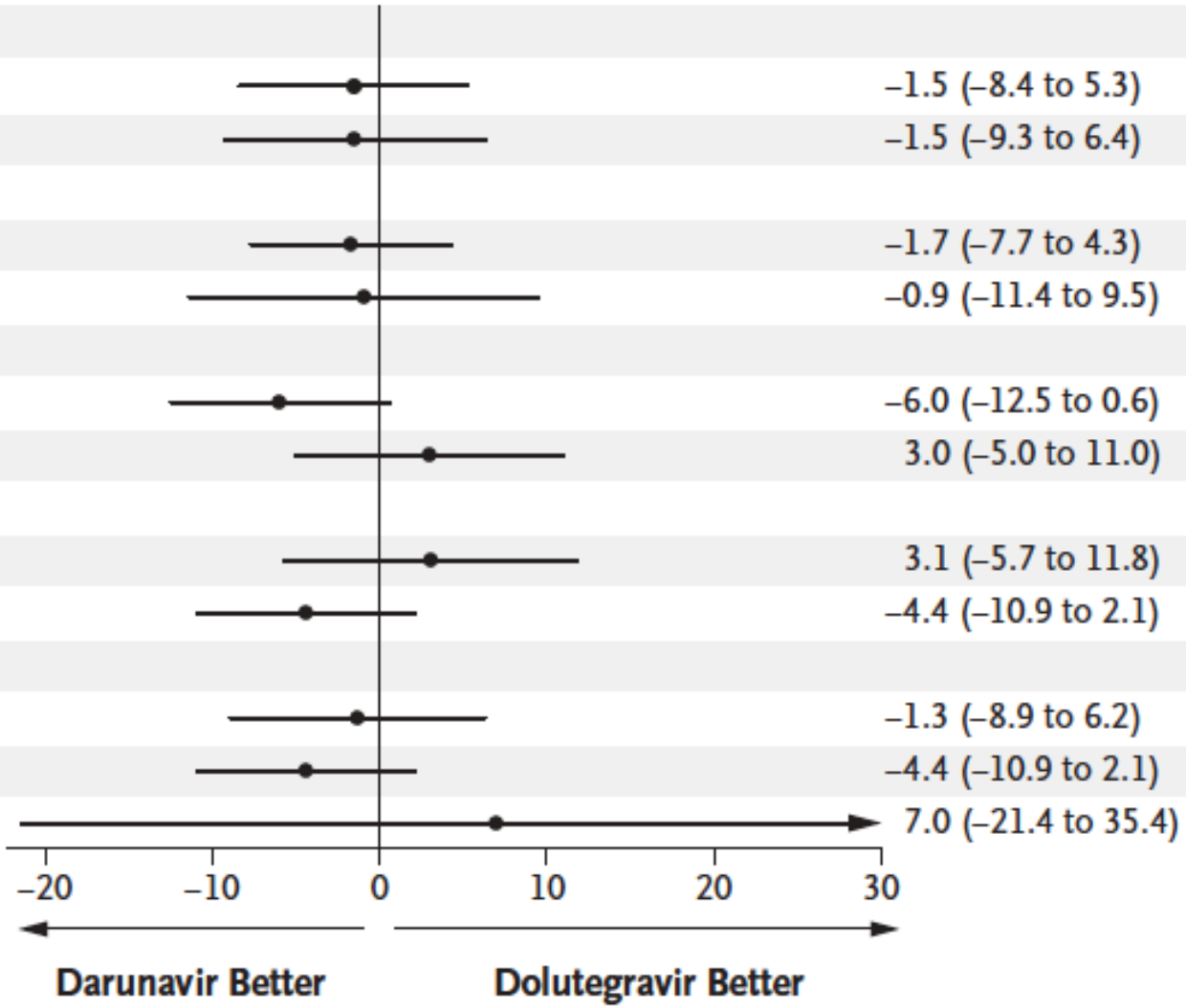
≥1 major DRV mutation: 0

Outcome	Tenofovir Group (N= 233)	Zidovudine Group (N= 231)	Difference (95% CI) %	P
HIV-1 RNA level (primary outcome) – no (%)				
< 400 copies/ml (ITT)	215 (92.3)	207 (89.6)	2.7 (-2.6 to 7.9)	0.317
≥ 400 copies/ml	15 (6.4)	21 (9.1)	-	
No virological data	3 (1.3)	3 (1.3)	-	
- Withdrew because of AE/death	3 (1.3)	2 (0.9)		
- Withdrew for other reasons	0	1 (0.4)		
HIV-1 RNA level (sensitivity analyses, secondary, other outcomes) – no (%)				
< 400 copies/ml (adjusted)	88.2	85.4	2.8 (-2.5 to 8.0)	0.304
VL < 400 copies (per protocol)	209 (93.7)	200 (91.7)	2.0 (-2.9 to 6.8)	0.423
VL < 1000 c/ml (ITT)	219 (94.0)	211 (91.3)	2.6 (-2.1 to 7.4)	0.274
VL< 50 c/ml (ITT)	188 (80.7)	184 (79.7)	1.0 (-6.2 to 8.3)	0.780
Rebound (secondary outcome) – no (%)				
VL rebound ≥ 1000 c/ml, confirmed (ITT)	11 (4.7)	16 (6.9)	-2.2 (-6.5 to 2.1)	0.310
VL rebound ≥ 1000 c/ml, confirmed with ≥1 major RM to DTG or DRV*	1	3	-	-

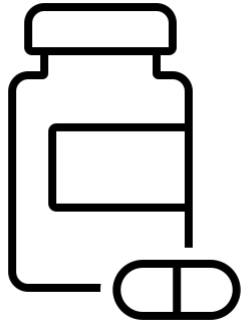
* ≥1 major DTG mutation: 4
≥1 major DRV mutation: 0

Dolutegravir in combination with NRTIs was effective in treating patients with HIV-1 infection, including those with extensive NRTI resistance in whom no NRTIs were predicted to have activity. Tenofovir was noninferior to zidovudine as second-line therapy.

Subgroup	Dolutegravir	Darunavir	Difference in Percentage Points (95% CI)
	no. of patients/total no. (%)		
NRTI randomization group			
Tenofovir	108/118 (91.5)	107/115 (93.0)	–1.5 (–8.4 to 5.3)
Zidovudine	104/117 (88.9)	103/114 (90.4)	–1.5 (–9.3 to 6.4)
Viral load at baseline			
<100,000 copies/ml	153/169 (90.5)	154/167 (92.2)	–1.7 (–7.7 to 4.3)
≥100,000 copies/ml	59/66 (89.4)	56/62 (90.3)	–0.9 (–11.4 to 9.5)
CD4+ cell count at baseline			
<200 cell/mm^3	112/125 (89.6)	108/113 (95.6)	–6.0 (–12.5 to 0.6)
≥200 cell/mm^3	100/110 (90.9)	102/116 (87.9)	3.0 (–5.0 to 11.0)
Sex			
Male	87/95 (91.6)	77/87 (88.5)	3.1 (–5.7 to 11.8)
Female	125/140 (89.3)	133/142 (93.8)	–4.4 (–10.9 to 2.1)
No. of predicted active NRTIs			
0	85/92 (92.4)	75/80 (93.8)	–1.3 (–8.9 to 6.2)
1	107/118 (90.7)	116/122 (95.1)	–4.4 (–10.9 to 2.1)
≥2	13/18 (72.2)	15/23 (65.2)	7.0 (–21.4 to 35.4)



≥ 1 month



≥ 1 week

≥ 6 months

Long-acting ART

Long-acting ART

SCIENCE NEWS

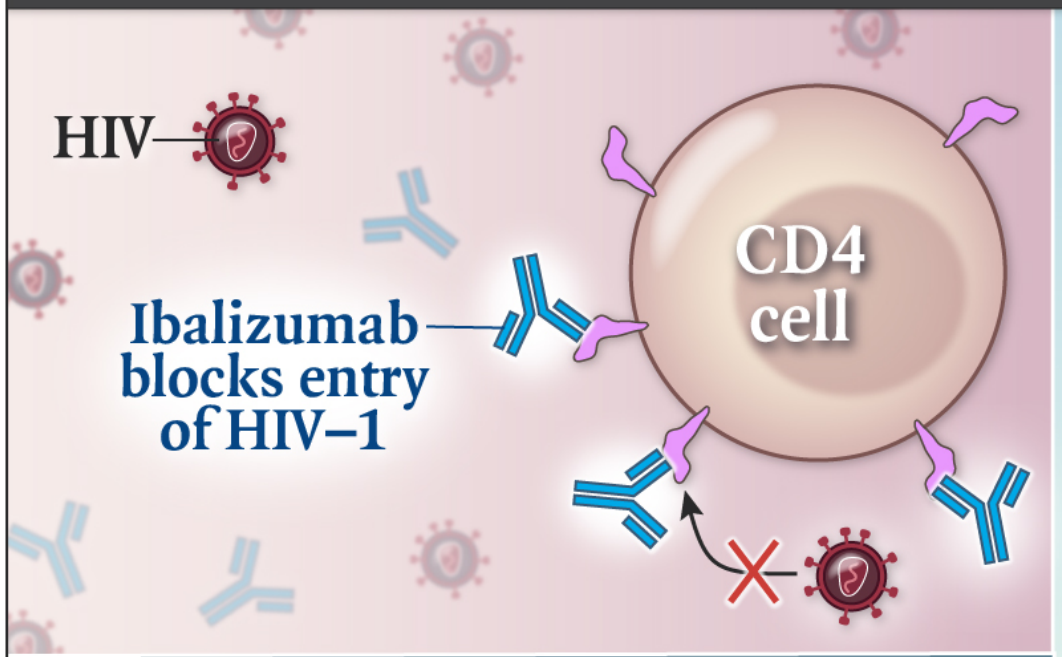
FDA Approves Cabenuva, the First Complete Long-Acting Injectable HIV Treatment

Injectable cabotegravir and rilpivirine are approved for people with viral suppression who would prefer monthly injections to daily pills.

January 21, 2021 · By Liz Highleyman

Ibalizumab for Multidrug-Resistant HIV-1

SINGLE-GROUP, OPEN-LABEL, MULTICENTER, PHASE 3 TRIAL



Patients with viral load decrease ≥0.5 $\log_{10}$ copies per milliliter from baseline

Control Period (Days 0–6)

Current therapy

3% (1/40)

Functional Monotherapy (Days 7–13)

Current therapy

+

Ibalizumab (Day 7, 2000 mg)

P < 0.001

83% (33/40)

Maintenance Period (Day 14–wk 25)

Optimized background regimen

+

Ibalizumab (800 mg every 14 days)

63% (25/40)

Ibalizumab had significant antiviral activity, reducing viral load over 24 weeks

The NEW ENGLAND JOURNAL of MEDICINE

Emu et al. 2018

Studies of Long-acting (LA) cabotegravir

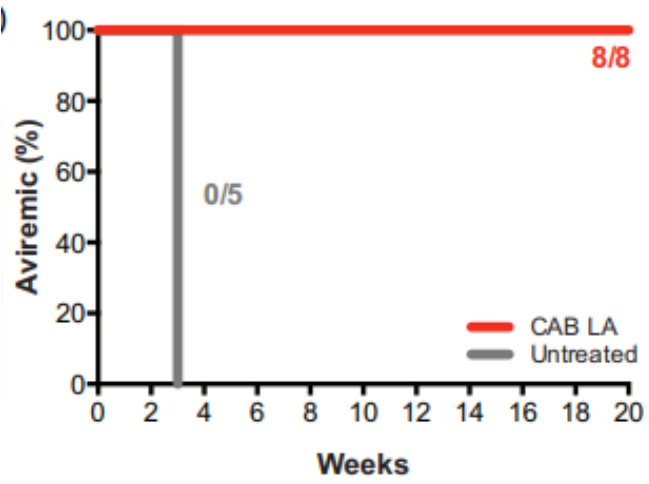
Prevention

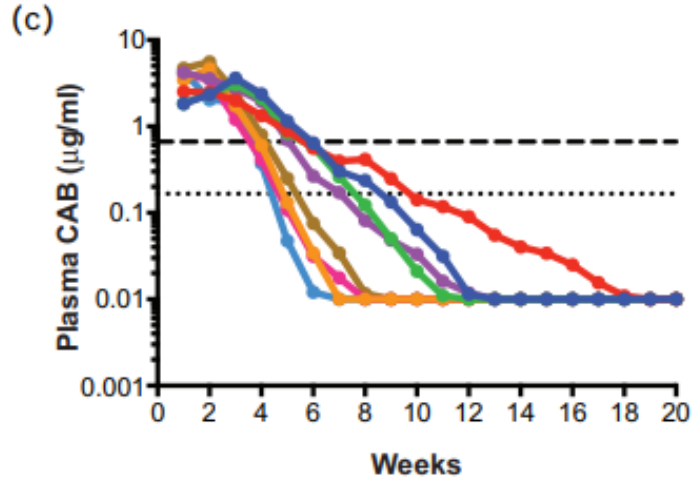
- HPTN 083
  - CAB-LA *versus* TDF/FTC

Treatment

- FLAIR: Tratment-naïve
  - CAB-LA + RPV–LA *versus* ABC/3TC/DTG
- ATLAS: Switching study
  - Patients with stable ART then switched to CAB-LA +RPV-LA *versus* continuing oral ART

Cabotegravir long acting injection protects macaques against intravenous challenge with SIVmac251





CROI 2021

HPTN 083

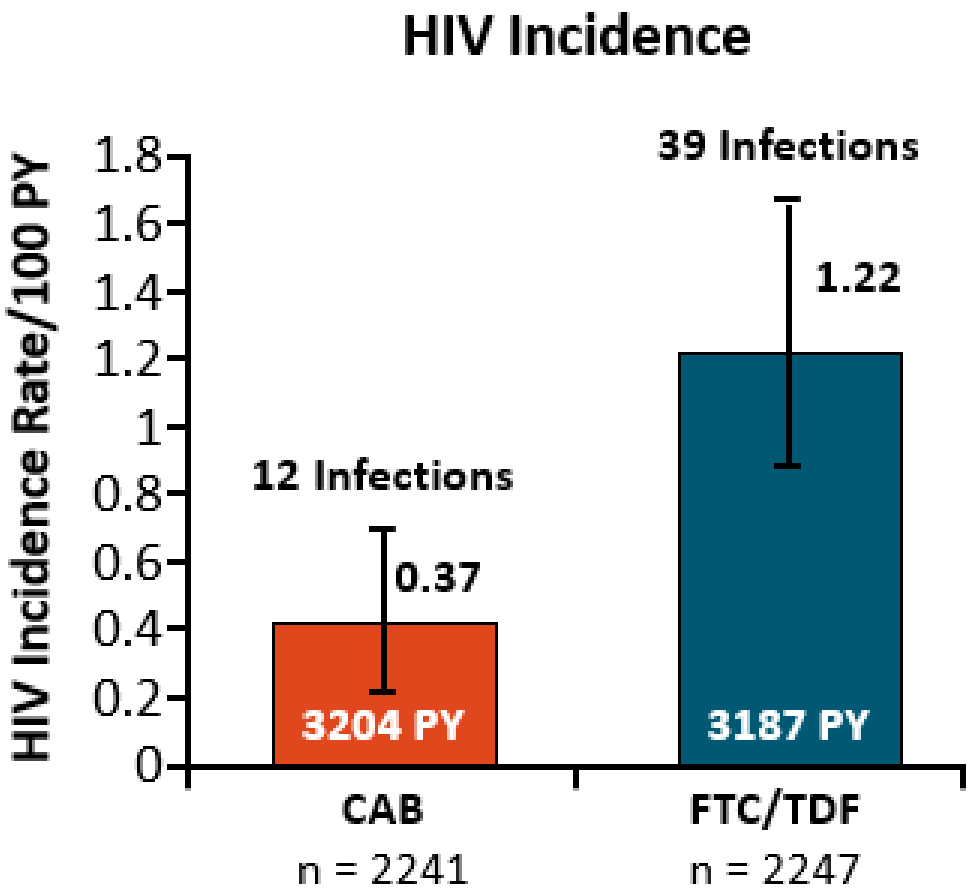
Long-acting cabotegravir proves to be highly effective for prevention of HIV acquisition in cisgender men and transgender women

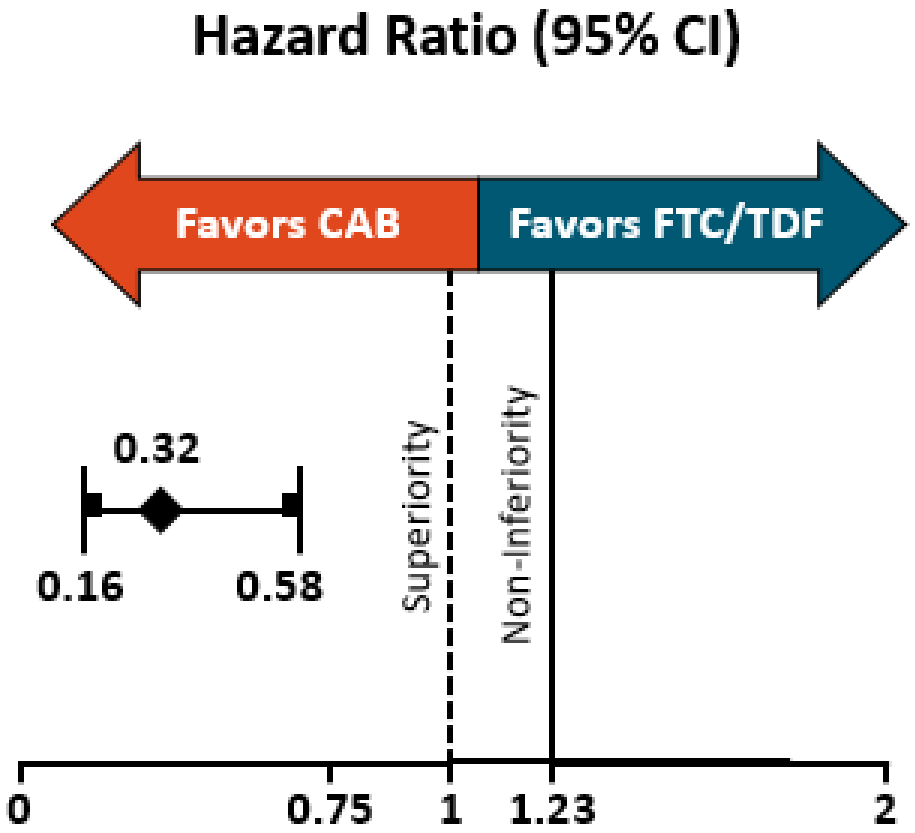
HIV-uninfected MSM and TGW aged ≥ 18 yrs at high risk of HIV infection*; no HBV/HCV infection, contraindication to gluteal injection, seizures, or gluteal tattoos/skin conditions (N = 4566)

Step 1	Wk 5	Step 2	Step 3
CAB 30 mg PO QD + **PBO** PO QD (n = 2282)		**CAB** LA 600 mg IM Q2M† + **PBO** PO QD for ~ 3 yrs	**FTC/TDF** PO QD for 1 yr
FTC/TDF PO QD + **PBO** PO QD (n = 2284)		**FTC/TDF** PO QD + **PBO** IM Q2M†‡ for ~ 3 yrs	

*Any noncondom receptive anal intercourse, > 5 partners, stimulant drug use, incident rectal or urethral STI or incident syphilis in past 6 mos; or SexPro Score ≤ 16 (US only). †First 2 doses given in Wks 5 and 9, then every 2 mos thereafter. ‡PBO for CAB injection was a 20% intralipid solution.

HPTN 083: HIV Incidence

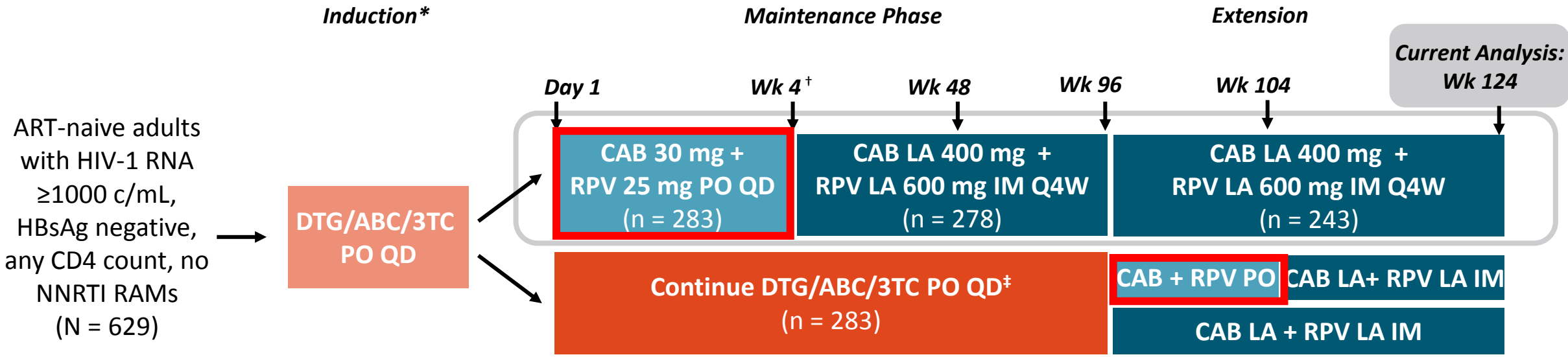




Source: 2021 Conference on Retroviruses and Opportunistic Infections*

FLAIR Wk 124: Long-Acting Cabotegravir + Rilpivirine for Treatment-Naive PWH

- Multicenter, randomized, open-label phase III non-inferiority trial



*Patients with HIV-1 RNA <50 c/mL at end of induction continued to maintenance phase. † Loading dose: CAB LA 600 mg IM + RPV LA 900 mg IM; regular dosing begun at Wk 8.

- **Previous analysis demonstrated noninferiority of switching virologically suppressed participants from daily oral DTG/ABC/3TC to monthly injections of CAB + RPV LA IM over 96 wk[1,2]**
- **Wk 124 endpoints: HIV-1 RNA ≥50 and <50 c/mL, confirmed virologic failure, safety/tolerability[3]**

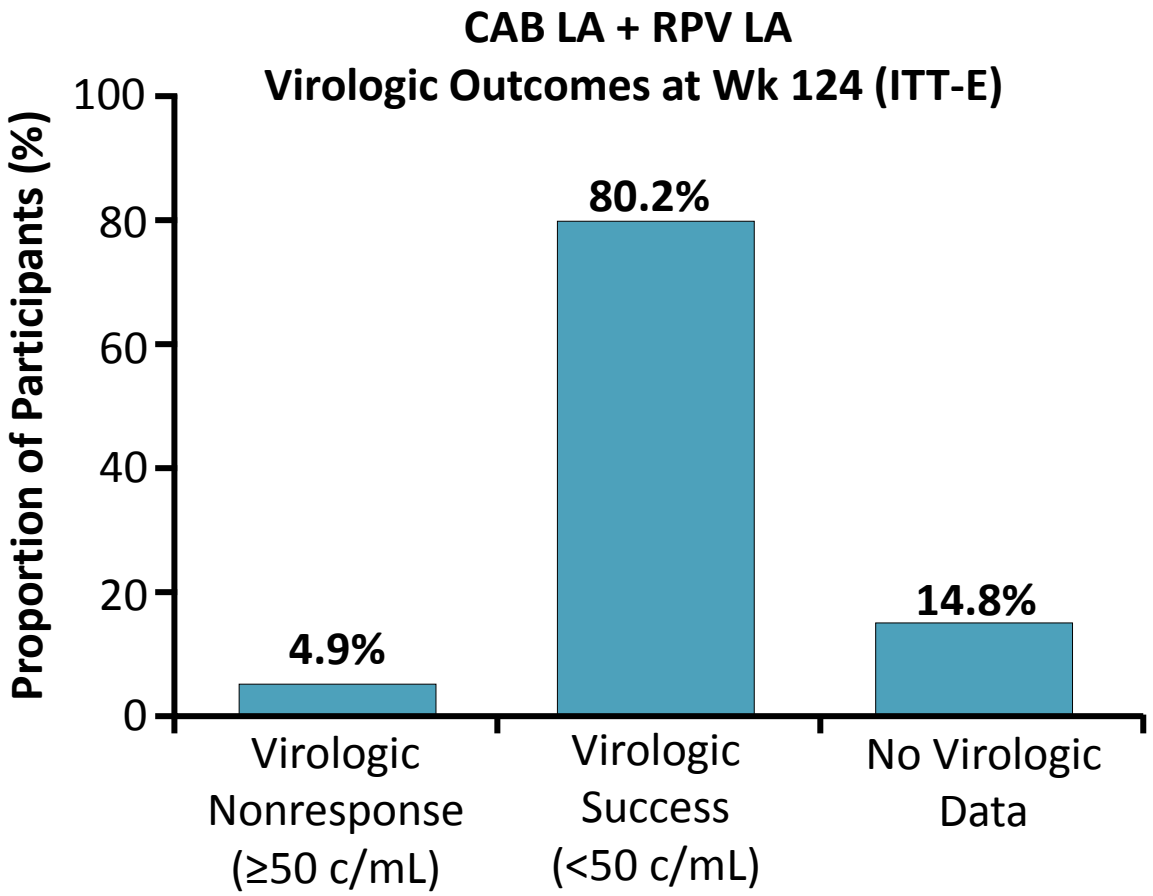
1. Orkin. NEJM. 2020;382:1124. 2. Orkin. Lancet HIV. 2021;8:e185. 3. Orkin. IAS 2021. Abstr OAB0302.

FLAIR: Wk 124 Virologic Snapshot Outcomes With CAB LA + RPV LA

- 229 participants ongoing
- Since Wk 96 analysis
  - 5 additional participants had HIV-1 RNA ≥50 c/mL
  - 1 additional participant had CVF
  - 13 additional participants not recorded as suppressed, most due to non-virologic reasons

Virologic Outcome, n (%)	Wk 96	Wk 124
Nonresponse (≥50 c/mL)	9 (3.2)	14 (4.9)
Success (<50 c/mL)	245 (86.6)	227 (80.2)
No virologic data	29 (10.2)	42 (14.8)
Confirmed virologic failure*	4 (1.4)	5 (1.8)

*2 consecutive plasma HIV-1 RNA ≥200 c/mL; 1 additional patient since Wk 96 analysis



Orkin. IAS 2021. Abstr OAB0302.

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FLAIR: Wk 124 Safety and Tolerability

- Safety profile at Wk 124 consistent with earlier analyses

Adverse event, n (%)	CAB LA + RPV LA Wk 124 (n = 283)	Increase Since Wk 96
Any AE	271 (96)	7 (2)
Grade 3/4 AE	38 (13)	9 (3)
Drug-related AE ▪ Pyrexia ▪ Headache ▪ Fatigue	102 (36) 18 (6) 15 (5) 10 (4)	7 (2) 1 (<1) 0 3 (1)
Drug-related grade 3/4 AE	5 (2)	1 (<1)
AE leading to withdrawal	15 (5)	1 (<1)
Any serious AE	33 (12)	2 (1)
Drug-related serious AE	1 (<1)	0
Fatal AE	0	0

- Injection site reactions (ISR) were most common AE; mostly low-grade
- 17,392 injections; 3,732 ISR events

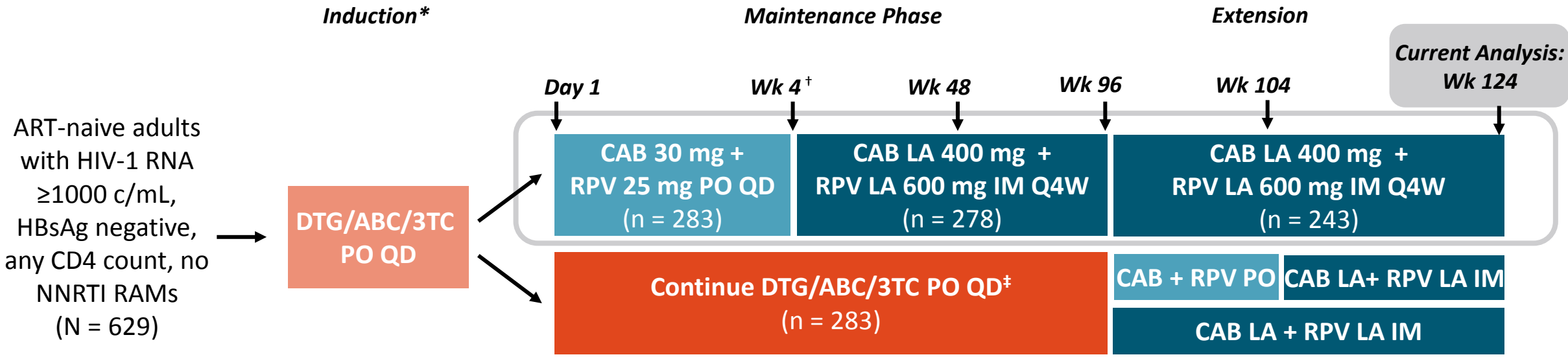
ISR outcome	CAB LA + RPV LA Wk 124 (n = 283)
No. injections	17,392
ISR events	3732
Pain, n (% of injections)	3131 (18)
Nodule, n (% of injections)	162 (<1)
Induration, n (% of injections)	158 (<1)
Median duration of ISR, days	3
Withdrawals due to ISR, n (% of participants)	7 (2)

Orkin. IAS 2021. Abstr OAB0302.

Slide credit: clinicaloptions.com

"Direct to Inject": Switching to CAB/RPV Without an Oral Lead-in

- Multicenter, randomized, open-label phase III non-inferiority trial



*Patients with HIV-1 RNA <50 c/mL at end of induction continued to maintenance phase. † Loading dose: CA[illegible] 600 mg IM + RPV LA 900 mg IM; regular dosing begun at Wk 8.

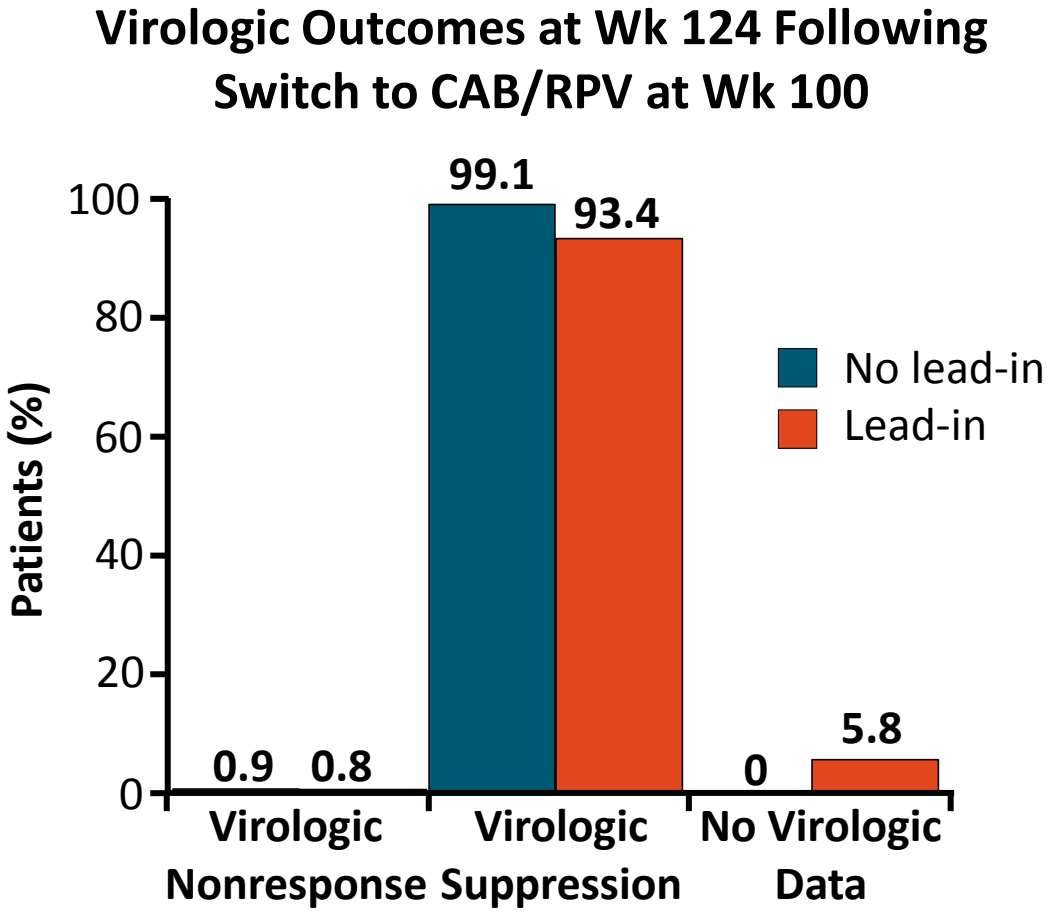
- Previous analysis demonstrated noninferiority of switching virologi[illegible]pressed participants from daily oral DTG/ABC/3TC to monthly injections of CAB + RPV LA IM[illegible]96 wk[1,2]
- **Wk 124 endpoints: HIV-1 RNA ≥50 and <50 c/mL, confirmed vi[illegible]gic failure, safety/tolerability[3]**

1. Orkin. NEJM. 2020;382:1124. 2. Orkin. Lancet HIV. 2021;8:e185. 3. Orkin. IAS 2021. Abstr OAB0302.

Slide credit: clinicaloptions.com

"Direct to Inject": Switching to CAB/RPV Without an Oral Lead-in

- FLAIR extension study
  - Participants on DTG/ABC/3TC arm achieving virologic suppression (HIV-1 RNA <50 copies/mL) in 20-wk induction phase could switch to monthly CAB/RPV at Wk 100
  - Switchers randomized to groups with (n = 121) or without (n = 111) an oral CAB + RPV lead-in

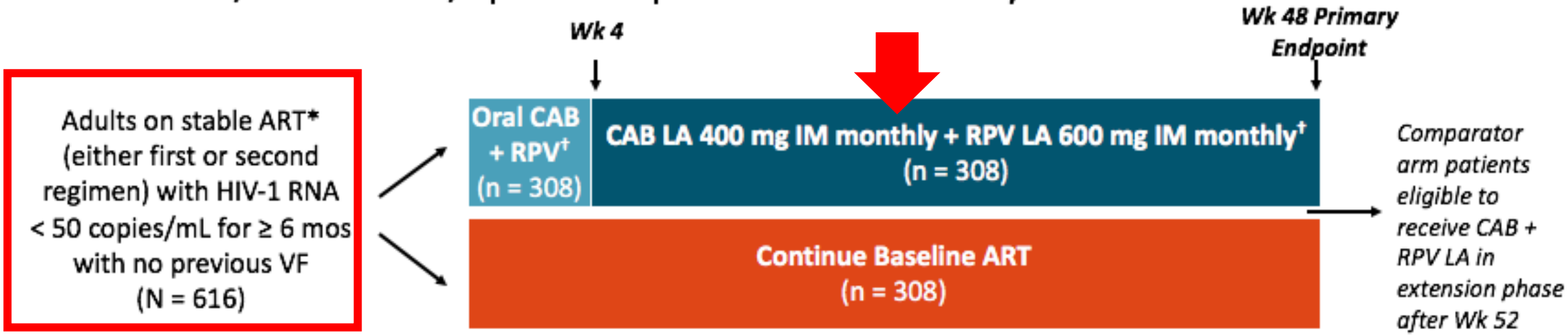


D'Amico. J Int AIDS Soc. 2020;23(suppl 7):15.

Slide credit: clinicaloptions.com

ATLAS: Study Design Switching study

- Multicenter, randomized, open-label phase III noninferiority trial



*Permitted baseline regimens: 2 NRTIs + INSTI (except DTG/ABC/3TC), NNRTI, or boosted PI (or unboosted ATV).
†CAB 30 mg + RPV 25 mg orally QD for 4 wks, followed by CAB LA 600 mg IM + RPV LA 900 mg IM at first injection, then CAB LA 400 mg IM + RPV LA 600 mg IM at Wk 8 and every 4 wks thereafter until withdrawal.

- Primary endpoint: HIV-1 RNA ≥ 50 copies/mL at Wk 48 (FDA snapshot) in ITT-E
  - 6% noninferiority margin for difference in efficacy between arms
- Secondary endpoints: HIV-1 RNA < 50 or < 200 copies/mL at Wk 48, VF, safety, resistance, patient-reported outcomes

Long-Acting Cabotegravir and Rilpivirine for HIV-1

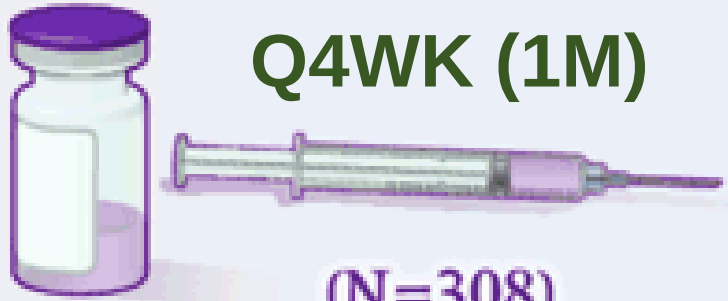
PHASE 3, OPEN-LABEL, MULTICENTER, RANDOMIZED TRIAL

616

Participants receiving antiretroviral therapy without virologic failure

Long-acting therapy

(cabotegravir and rilpivirine intramuscular injections every 4 wk)



Q4WK (1M)

(N=308)

Current oral therapy

(N=308)

HIV-1 RNA ≥50 copies/ml at 48 wk

1.6%

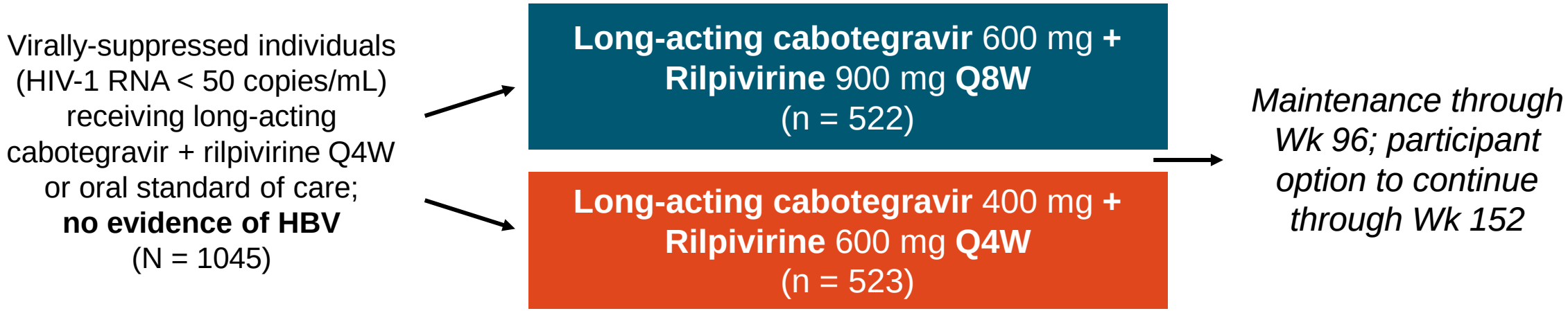
1.0%

Adjusted difference, 0.6 percentage points; 95% CI, −1.2 to 2.5

83% of participants who received long-acting therapy reported injection-site reactions

ATLAS-2M: Long-Acting Injectable CAB + RPV Q4W vs Q8W in Patients With Viral Suppression

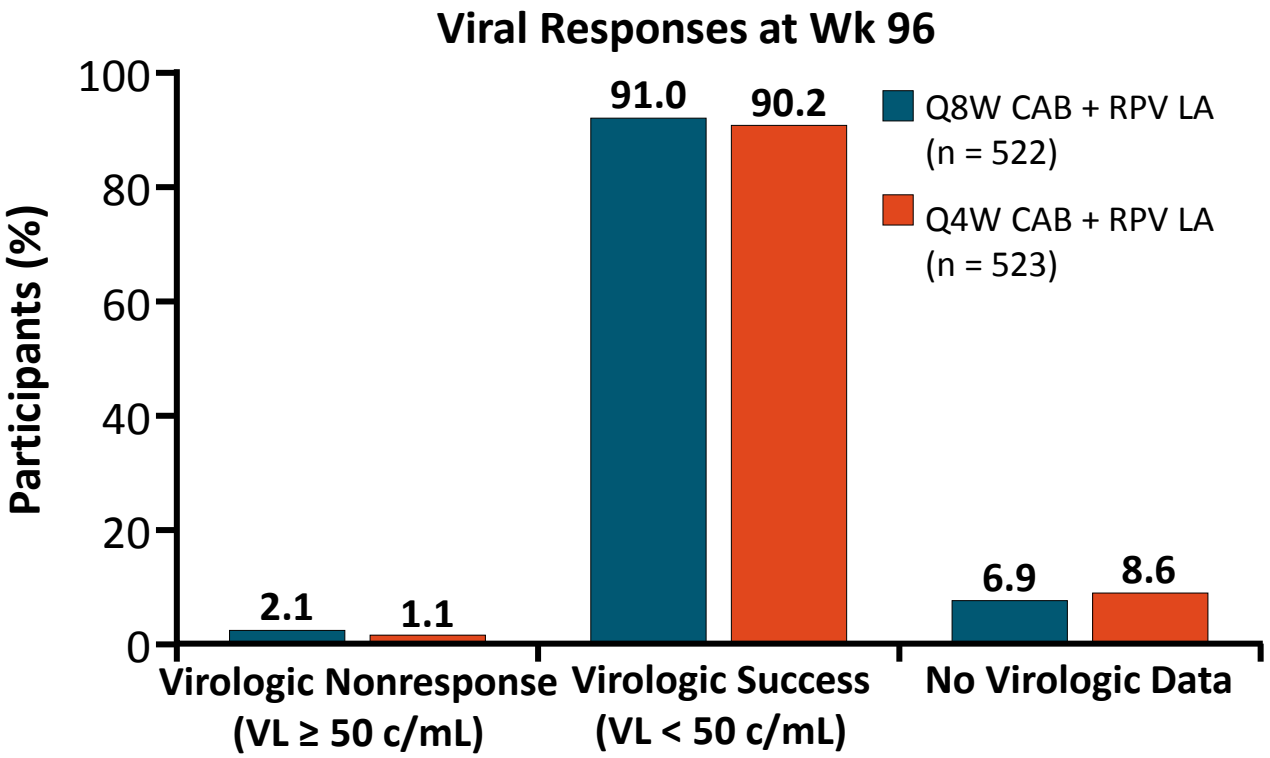
- Randomized, multicenter, open-label phase IIIb noninferiority trial

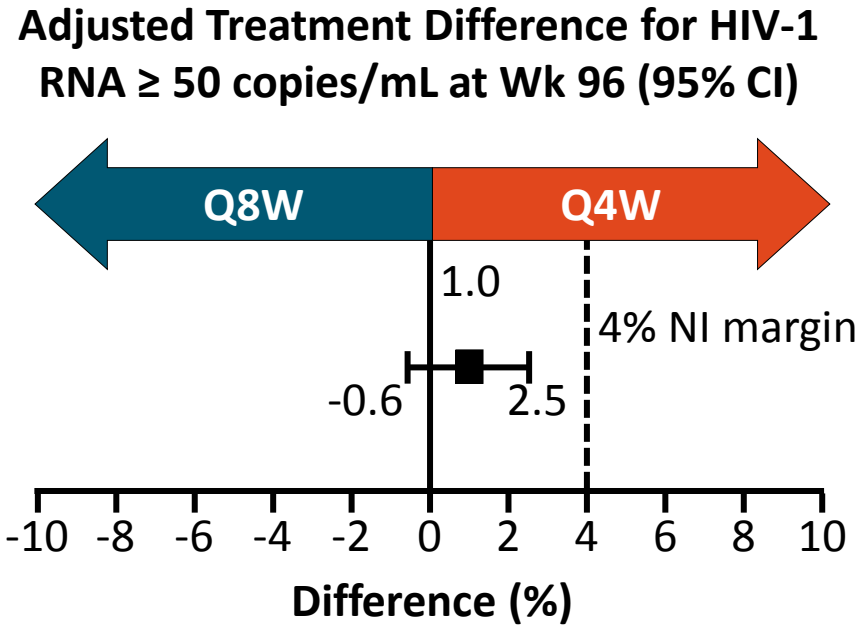


- **Analysis of primary endpoint (HIV-1 RNA ≥ 50 copies/mL at Wk 48 in ITT-E) showed Q8W dosing was noninferior to Q4W[1]**
- Secondary endpoints: HIV-1 RNA ≥ 50 or < 50 copies/mL at Wk 96 (ITT-E); CVF; viral resistance in patients with CVF; safety[2]

1. Overton. Lancet. 2020;396:1994. 2. Jaeger. CROI 2021. Abstr 401.

ATLAS-2M: Wk 96 Viral Suppression and Resistance Outcomes (ITT-E)





- CVF: n = 2 in Q4W arm, n = 9 in Q8W arm, with 1 case between Wks 48 and 96
  - RPV RAMs: n = 7 of 9 in Q8W arm, n = 1 of 2 in Q4W arm
  - INSTI RAMs: n = 5 of 9 in Q8W arm, n = 2 of 2 in Q4W arm

Jaeger. CROI 2021. Abstr 401.

Slide credit: clinicaloptions.com

ATLAS-2M: Wk 96 Safety and Tolerability

- AE profiles similar between Q8W, Q4W dosing; consistent from Wk 48 to Wk 96

AE, n (%)	Q8W (n = 522)	Δ From Wk 48	Q4W (n = 523)	Δ from Wk 48
Any AE	488 (93)	+15	499 (95)	+17
Drug-related AE	415 (80)	+15	413 (79)	+14
▪ Excluding ISRs	122 (23)	+13	146 (28)	+21
Any grade ≥ 3	57 (11)	+4	65 (12)	+16
▪ Drug related (not ISRs)	8 (2)	+6	10 (2)	+5
AE leading to withdrawal	18 (3)	+6	19 (4)	+6
▪ Drug related (not ISRs)	8 (2)	+3	12 (2)	+4
Any serious AE	33 (6)	+6	28 (5)	+9
▪ Drug related (not ISRs)	3 (< 1)	+1	3 (< 1)	+2

ISRs	Q8W (n = 522)	Q4W (n = 523)
Number of injections, n	12,832	23,855
▪ ISR events, n	3400	4157
▪ Injection site pain, n (%)	2662 (21)	3295 (14)
▪ Injection site nodule, n (%)	188 (1)	297 (1)
▪ Injection site discomfort, n (%)	134 (1)	148 (<1)
Grade 3 ISRs, n	54	50
Median duration, days (IQR)	3 (2-5)	3 (2-5)
Withdrawals related to injections, n (%)	7 (1)	11 (2)
Participants with ISR at each visit, n (%)		
▪ Wk 48	115/493 (23)	100/488 (20)
▪ Wk 96	74/473 (16)	54/468 (12)

Jaeger. CROI 2021. Abstr 401.

Slide credit: clinicaloptions.com

Factors That May Contribute to Risk of Treatment Failure With Long-Acting CAB/RPV

- Post hoc analysis of phase III data (Wk 48)
  - ATLAS and FLAIR (Q4W dosing)
  - ATLAS-2M (Q4W and Q8W dosing)
- Backwards elimination model (10 covariates)
- **Factors associated with increased odds of confirmed virologic failure:**
  - **RPV RAMs at baseline (OR: 40.36; *P* <.001)**
  - **Log_2 of post hoc Wk 8 RPV trough concentration (OR: 5.00; *P* = .002)**
  - **Baseline HIV-1 subtype A6/A1 (OR: 5.92; *P* = .008)**
  - **BMI ≥30 kg/m^2 at baseline (OR: 1.13; *P* = .020)**
- **Q8W dosing was not a significant factor**

Baseline Factors	Patients, % (n)*	CVF, % (n)	HIV-1 RNA <50 c/mL, % (n)
None	70.5 (732)	0.41 (3)	94.8 (694)
1	26.2 (272)	0.37 (1)	96.0 (261)
≥2	3.37 (35)	25.71 (9)	71.4 (25)

*For CVF analysis, N = 1039

Cutrell. AIDS. 2021;[Epub].

Slide credit: clinicaloptions.com

Nucleoside RT translocation inhibitor

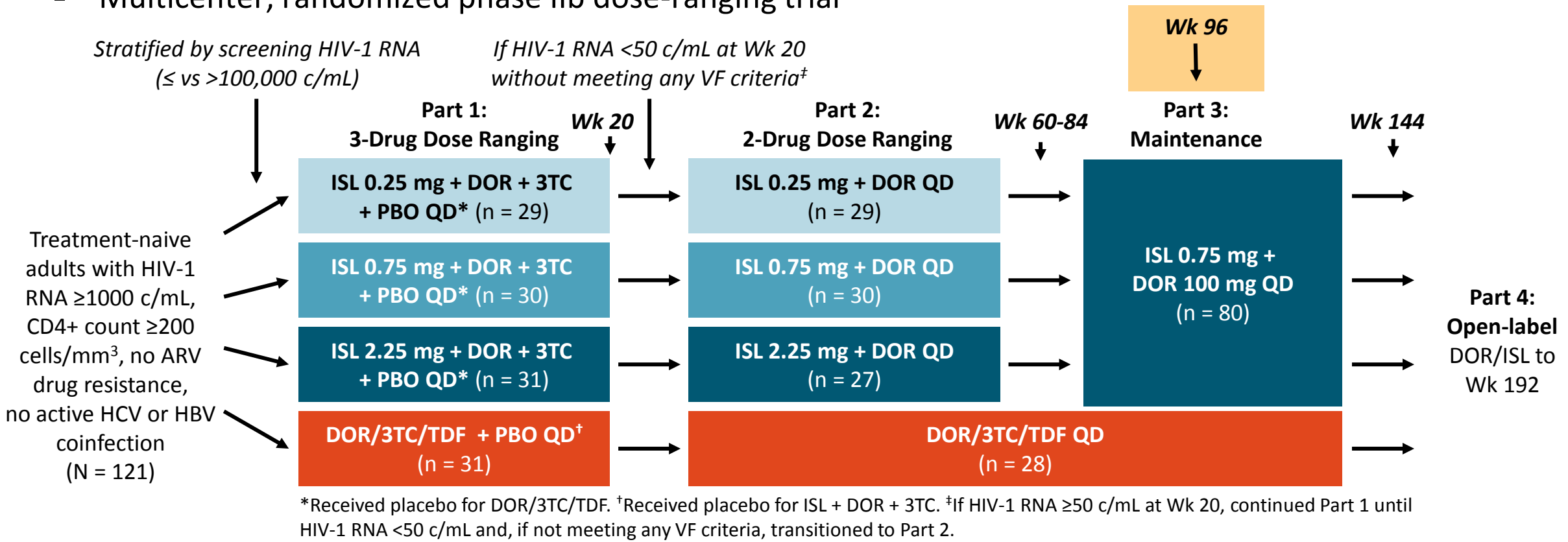
Islatravir

- Two phase 3 studies comparing **oral monthly islatravir** for PrEP (using the 60-mg dose) to FDA-approved daily PrEP are in process, one in cisgender women (**IMPOWER-022**) and one in men and transgender women who have sex with men (**IMPOWER-024**).
- **Islatravir is also being investigated in a subdermal implant** form with annual dosing and the potential to be combined with contraceptive medication

TheBodyPro
FOR THE HIV/AIDS WORKFORCE

Protocol 011 Islatravir + Doravirine in Treatment Naive Adults (Two-drug regimen): Wk 96 Safety Analysis

- Multicenter, randomized phase IIb dose-ranging trial



*Received placebo for DOR/3TC/TDF. †Received placebo for ISL + DOR + 3TC. ‡If HIV-1 RNA ≥50 c/mL at Wk 20, continued Part 1 until HIV-1 RNA <50 c/mL and, if not meeting any VF criteria, transitioned to Part 2.

- Baseline participant characteristics (ISL combined groups vs DOR/3TC/TDF)[2]: male (93.3% vs 90.3%), White race (75.6% vs 77.4%), Black race (21.1% vs 16.1%), median age (28.5 vs 27.0 yr)

1. Cunningham. IAS 2021. Abstr OAB0304. 2. Molina. Glasgow 2020. Abstr P0415.

Slide credit: clinicaloptions.com

Islatravir for two-drug regimen

Randomized, double-blind, comparator-controlled, dose-ranging trial.

Treatment-naive adults

Treatment:

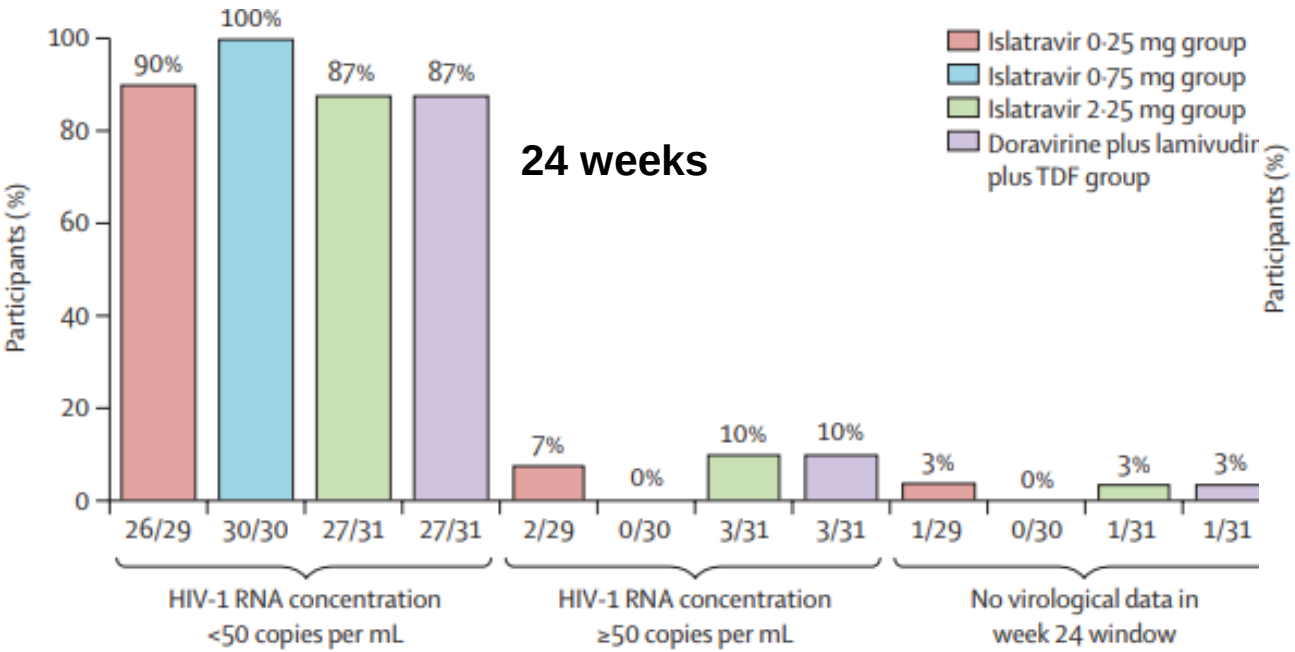
- Islatravir (0·25 mg, 0·75 mg, or 2·25 mg) plus DOR and 3TC

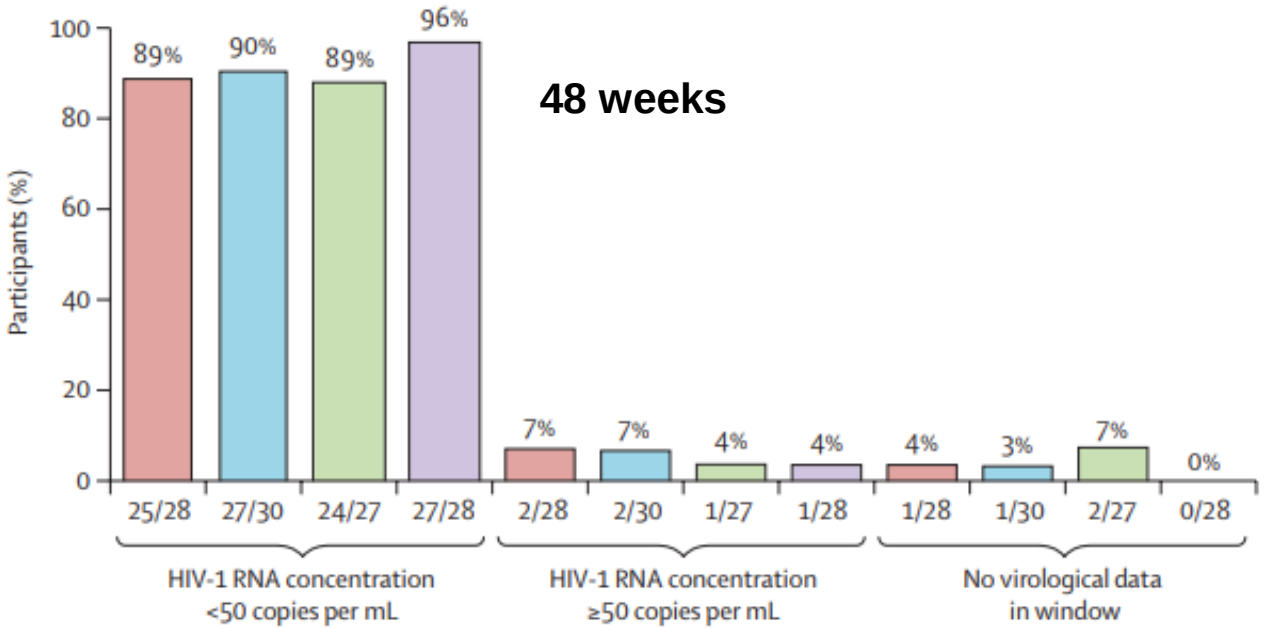
or

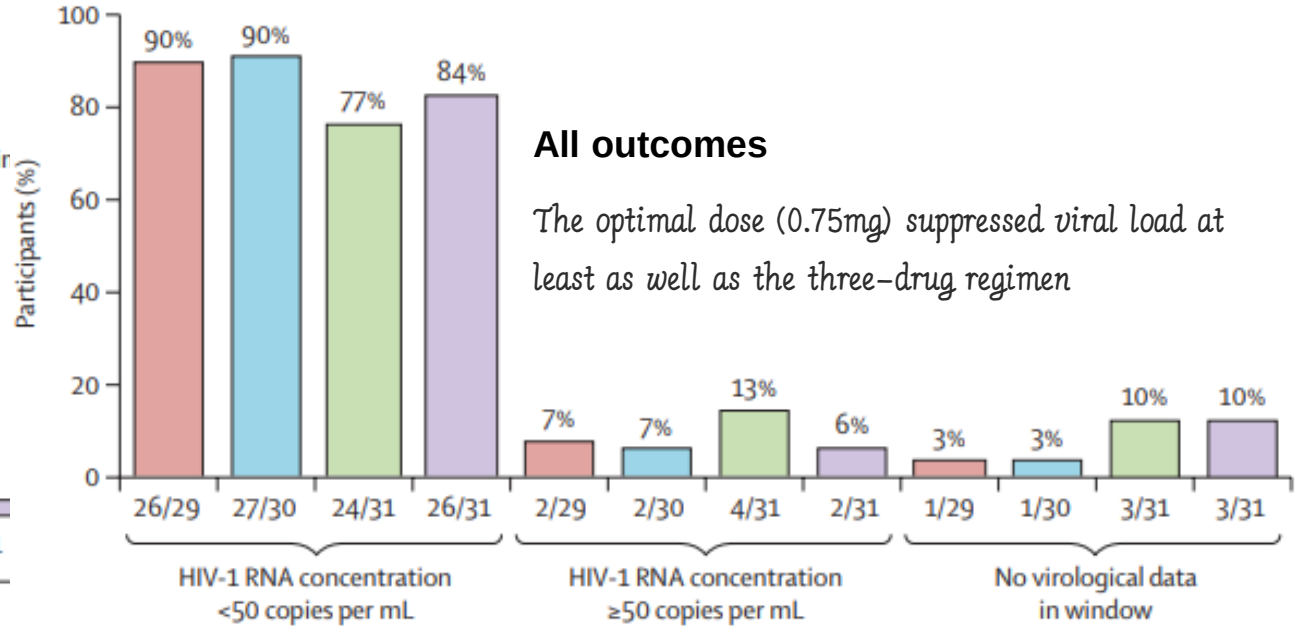
- DOR plus 3TC plus TDF once daily with placebo

for 24 weeks

Then islatravir plus DOR if VL <50 copies/mL

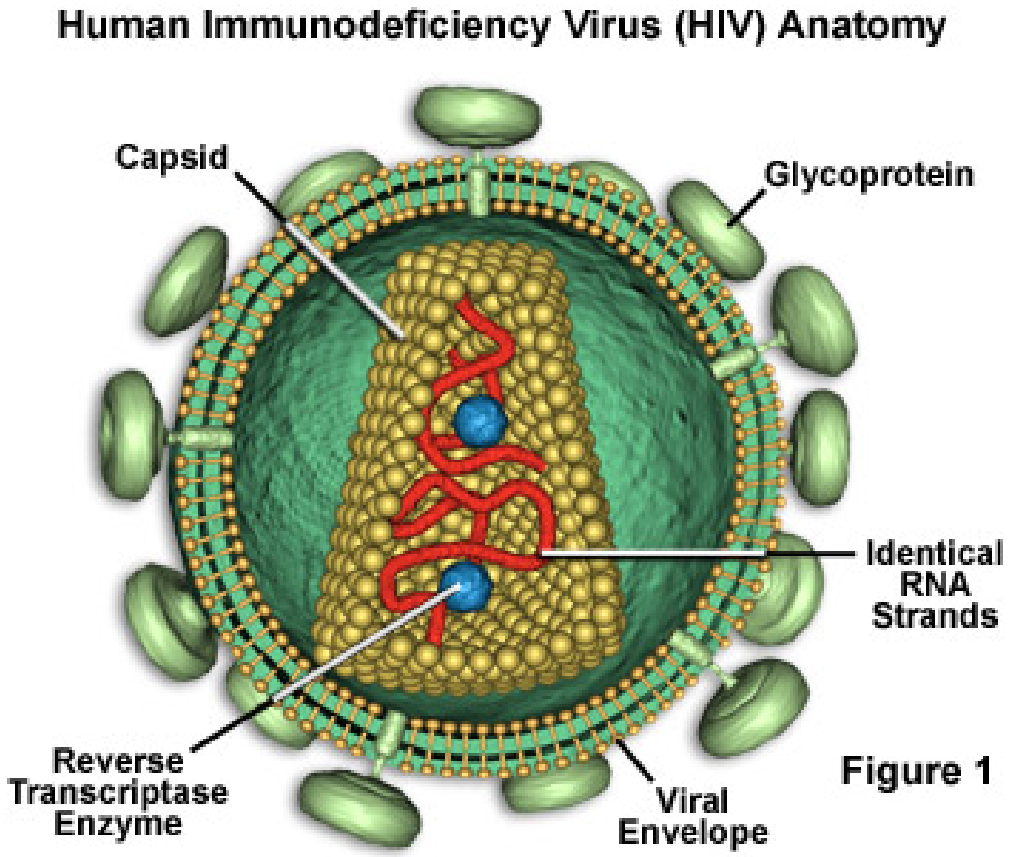


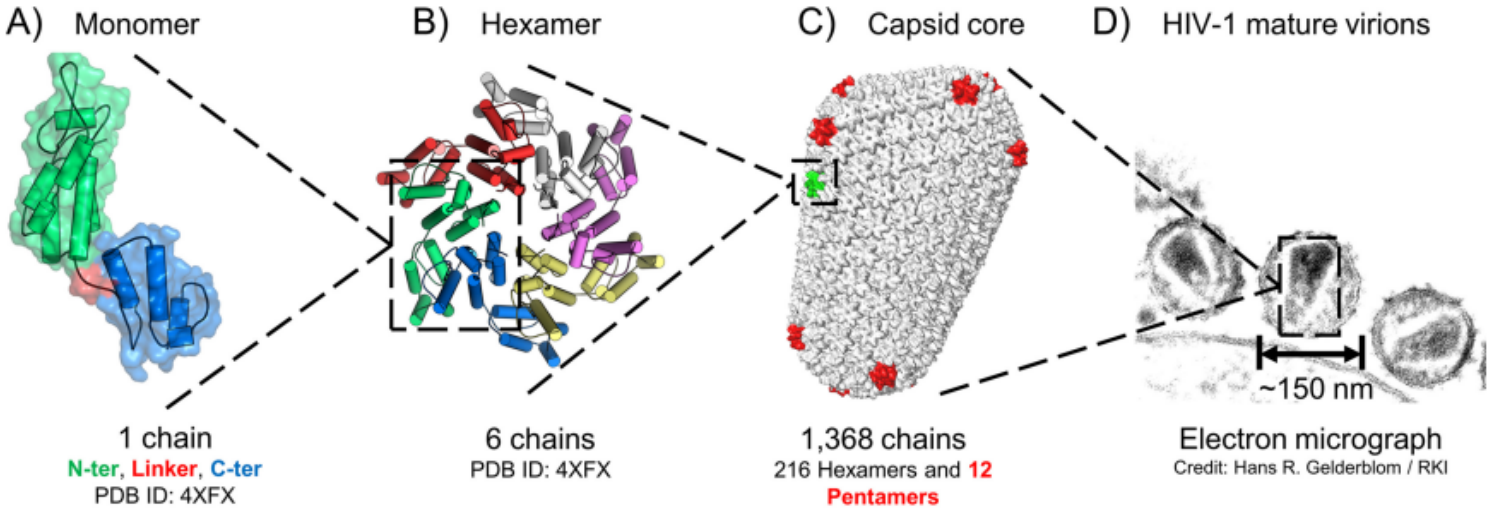


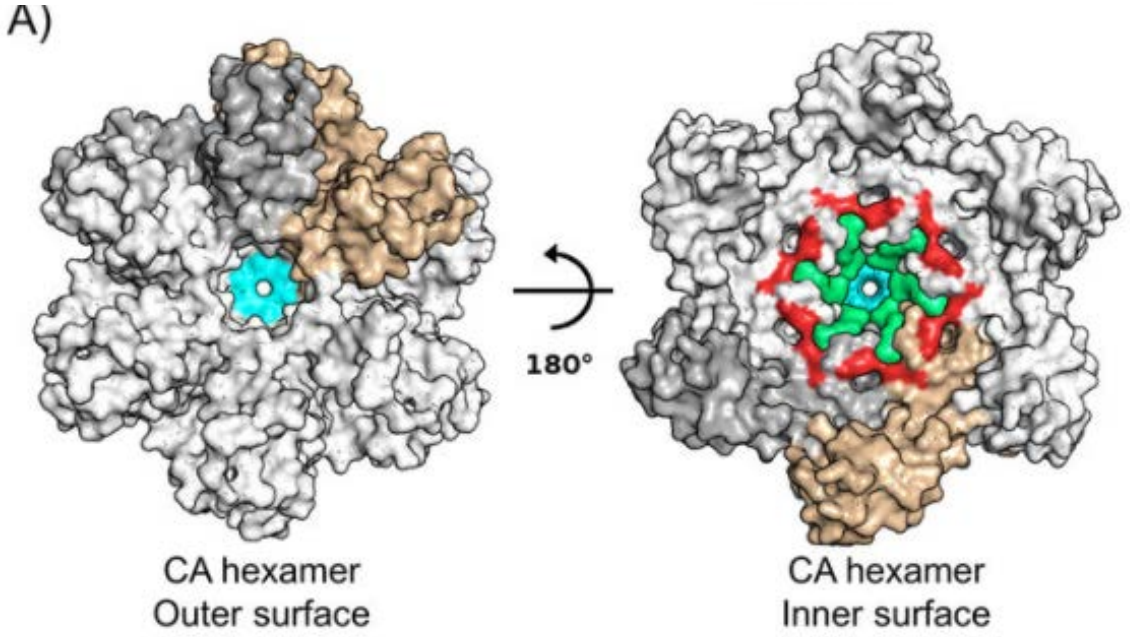


Lancet HIV 2021; 8: e324–33

HIV capsid





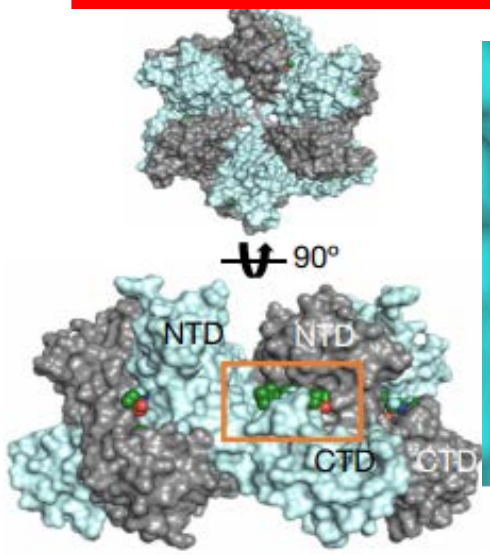


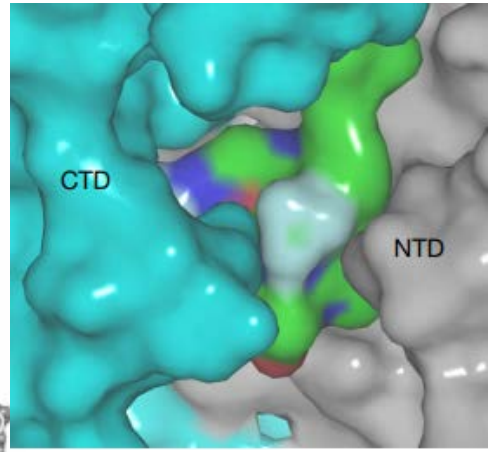
AMERICAN SOCIETY FOR MICROBIOLOGY | mBio®

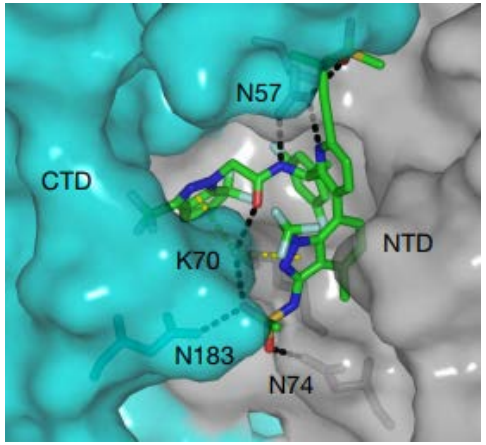
mBio 10:e02858-18.

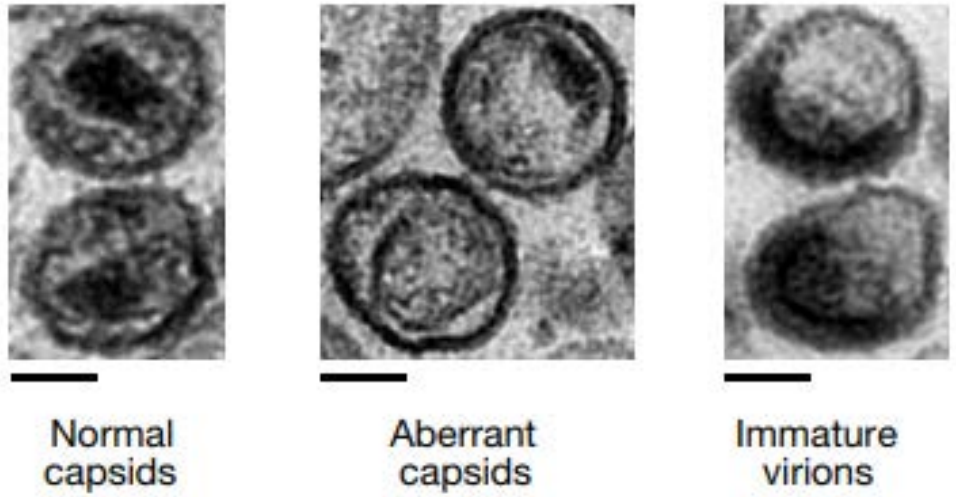
Clinical targeting of HIV capsid protein with a long-acting small molecule

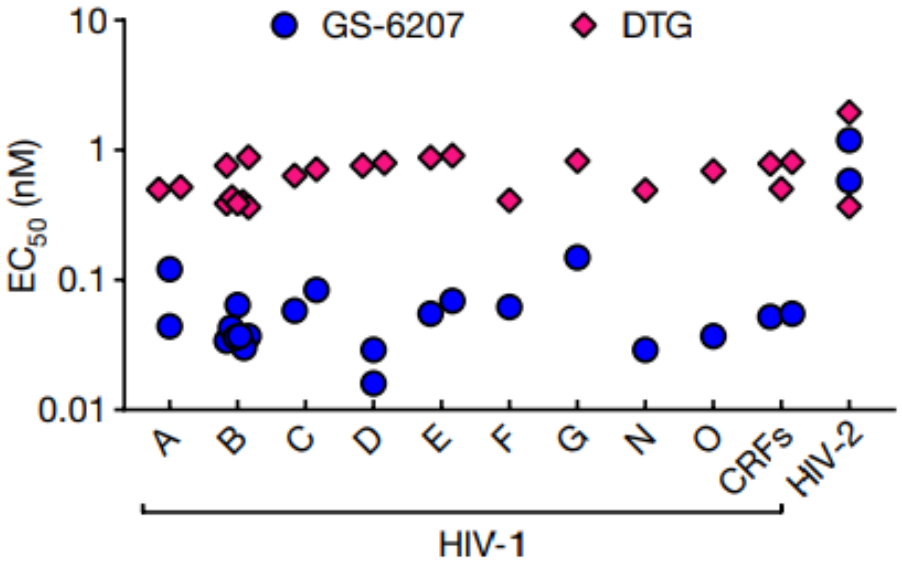
Nature | Vol 584 | 27 August 2020

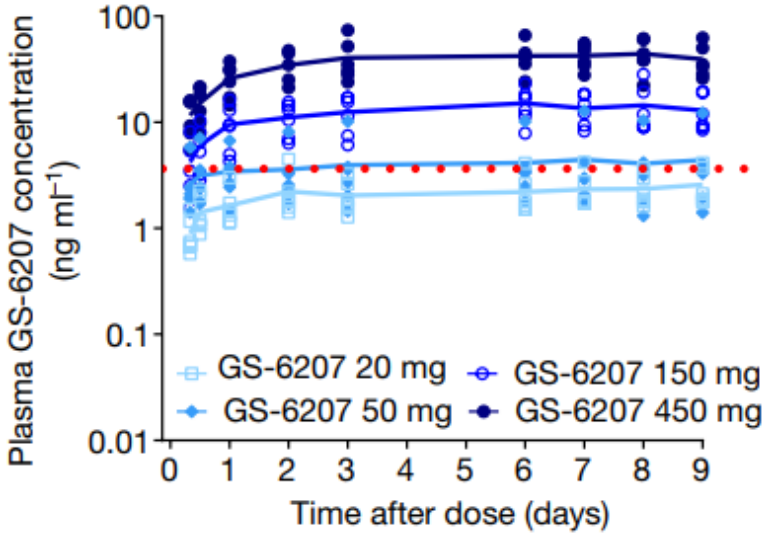


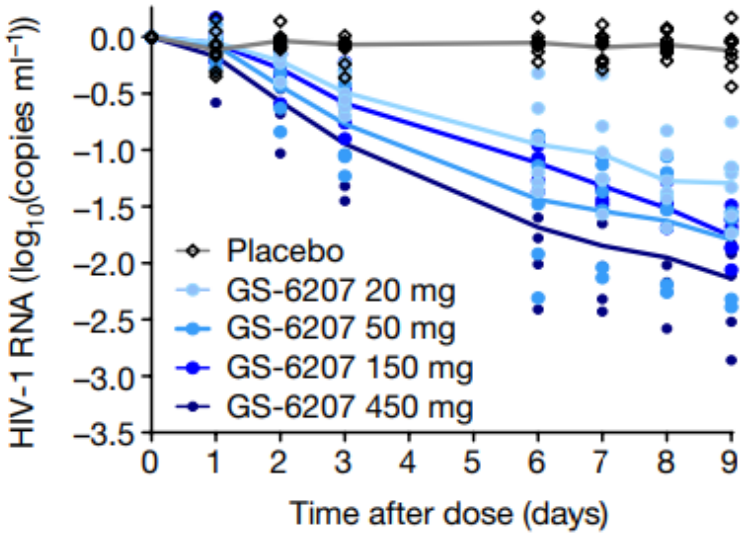






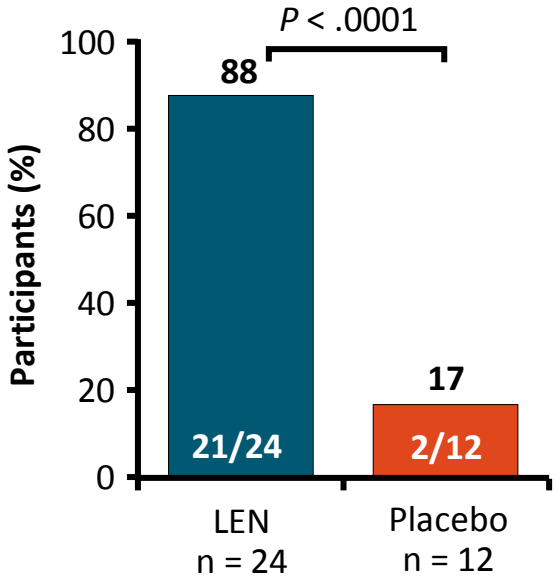




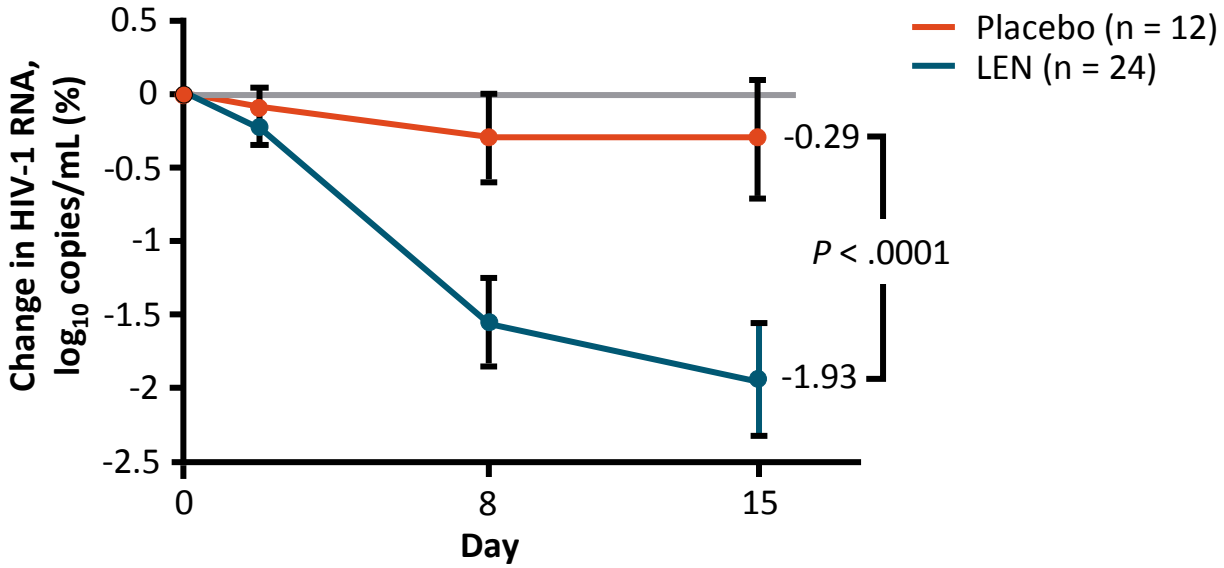


Lenacapavir in Heavily ART-Experienced PWH: Efficacy and Treatment-Emergent Resistance

Proportion of Participants on Functional Monotherapy With Decline in HIV-1 RNA ≥ 0.5 log_{10} copies/mL at Day 15



Mean Change in HIV-1 RNA by Visit

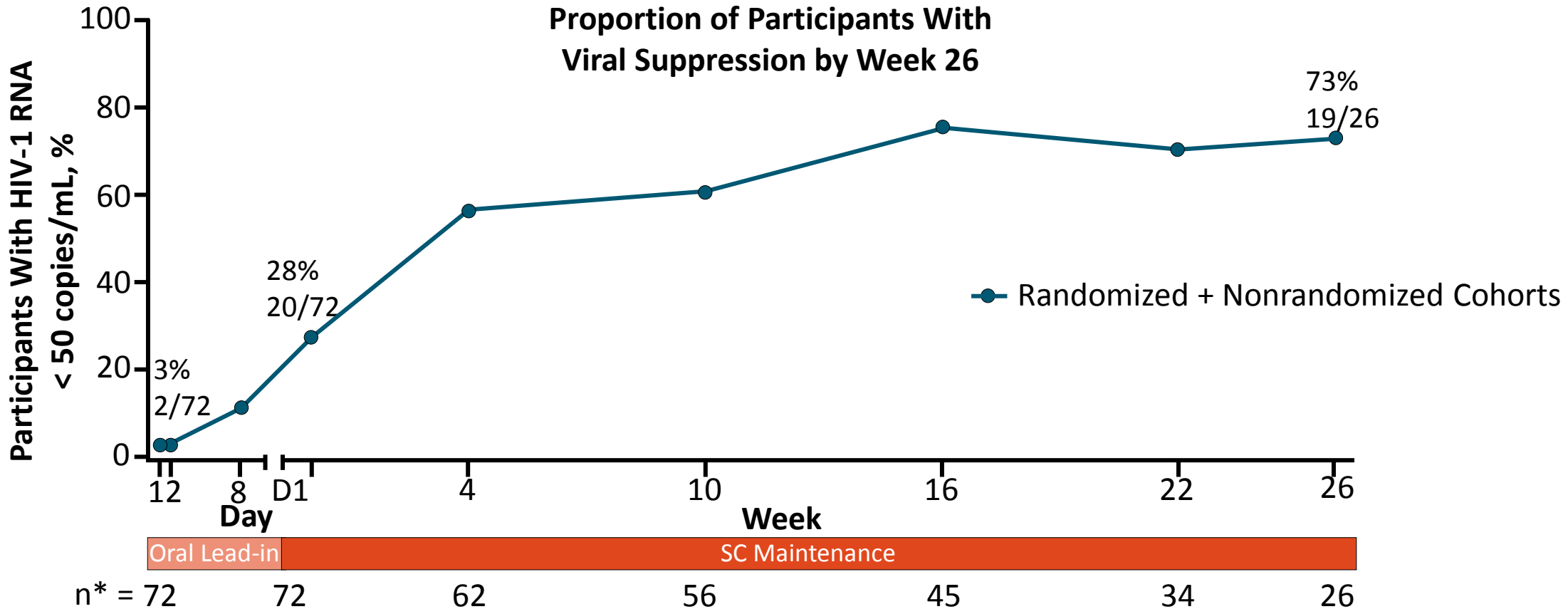


- 2 of 72 patients had emergent capsid mutations conferring high level LEN resistance: M66I and N74D at Wk 10; M66I at Wk 26
  - Both resuppressed (1 with, 1 without OBR change), but M66I significantly impairs viral replication

Segal-Maurer. CROI 2021. Abstract 127.

Slide credit: clinicaloptions.com

Lenacapavir in Heavily ART-Experienced PWH: Interim Data From SC Maintenance Phase



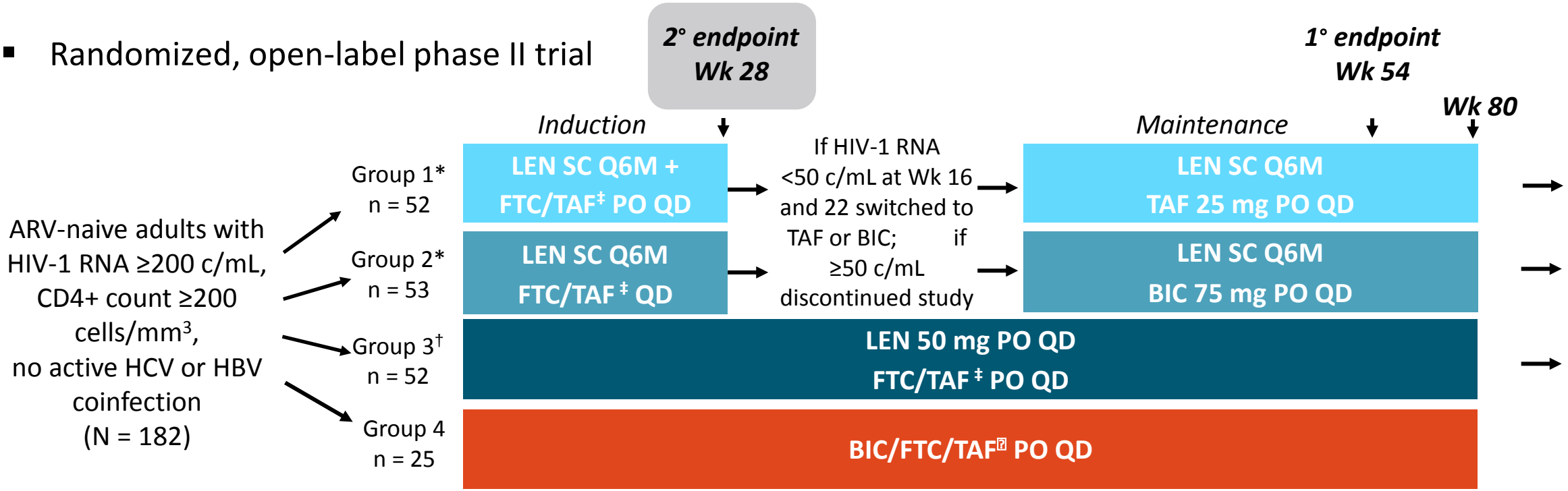
*Patient denominators are participants at each time period who received ≥ 1 dose of LEN SC and had an HIV-1 RNA result at time of data cut in Feb 2021 (study ongoing). †2 patients in open-label cohort had HIV-1 RNA < 50 copies/mL by Day 2 of oral lead-in phase, presumed to be due to improved adherence.

Segal-Maurer. CROI 2021. Abstract 127.

Slide credit: clinicaloptions.com

CALIBRATE: Lenacapavir in Treatment-Naive PWH

- Randomized, open-label phase II trial



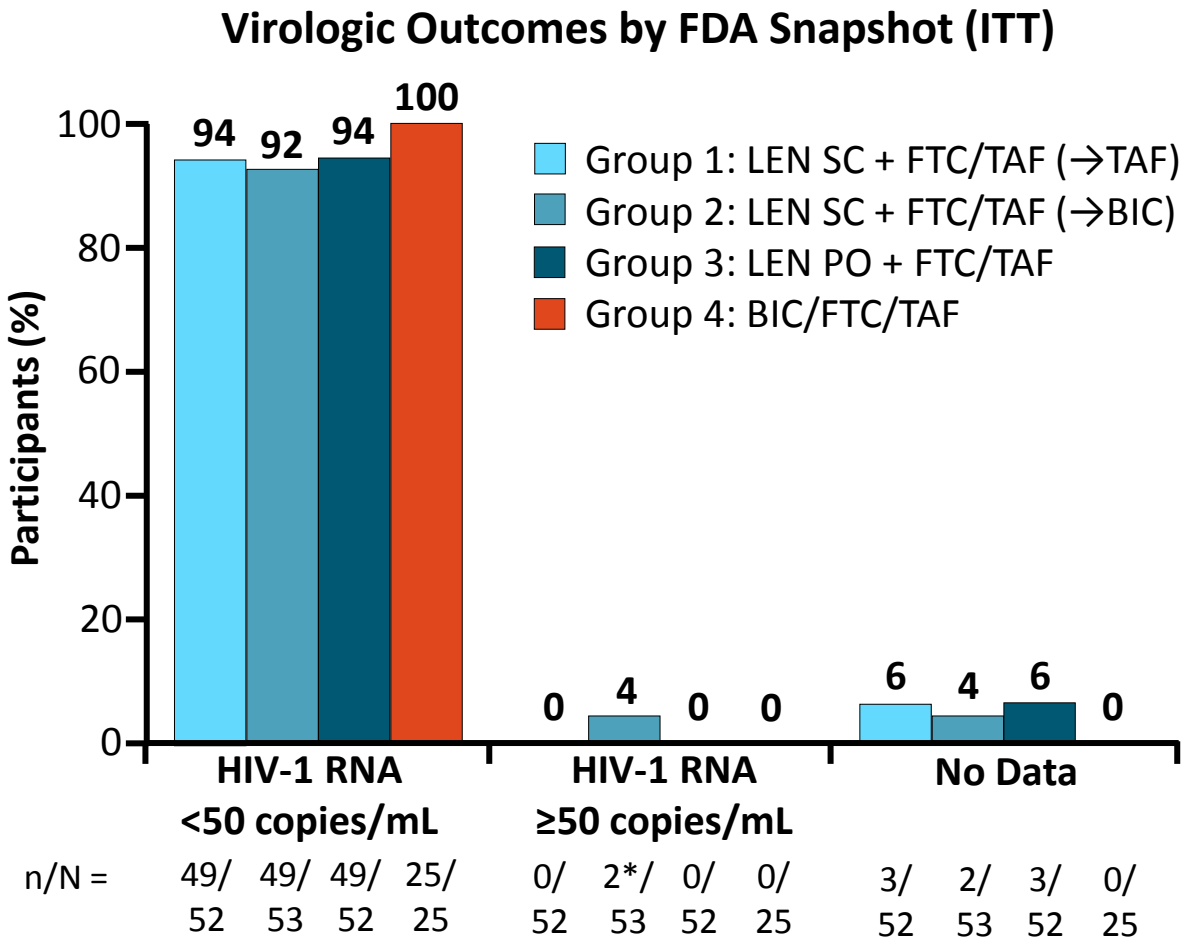
*LEN oral lead-in 600 mg Days 1 and 2, 300 mg Day 8; LEN 927 mg SC Day 15 and then Q6M.
†LEN 600 mg Days 1 and 2, then 50 mg from Day 3. ‡FTC/TAF 200/25 mg. ⍰BIC/FTC/TAF 50/200/25 mg.

- Participants at baseline: median age 29 yr; 93% male; 52% Black race; 45% Latinx ethnicity
- Primary outcome: proportion with HIV-1 RNA <50 c/mL at Wk 54; **secondary outcomes: proportion with HIV-1 RNA <50 c/mL at Wk 28**, 38, and 80; change from baseline in $\log_{10}$ HIV-1 RNA and CD4+ cell count at Wk 28, 38, 54, and 80

Gupta. IAS 2021. Abstr OALB0302.

Slide credit: clinicaloptions.com

CALIBRATE: Wk 28 Virologic Outcomes



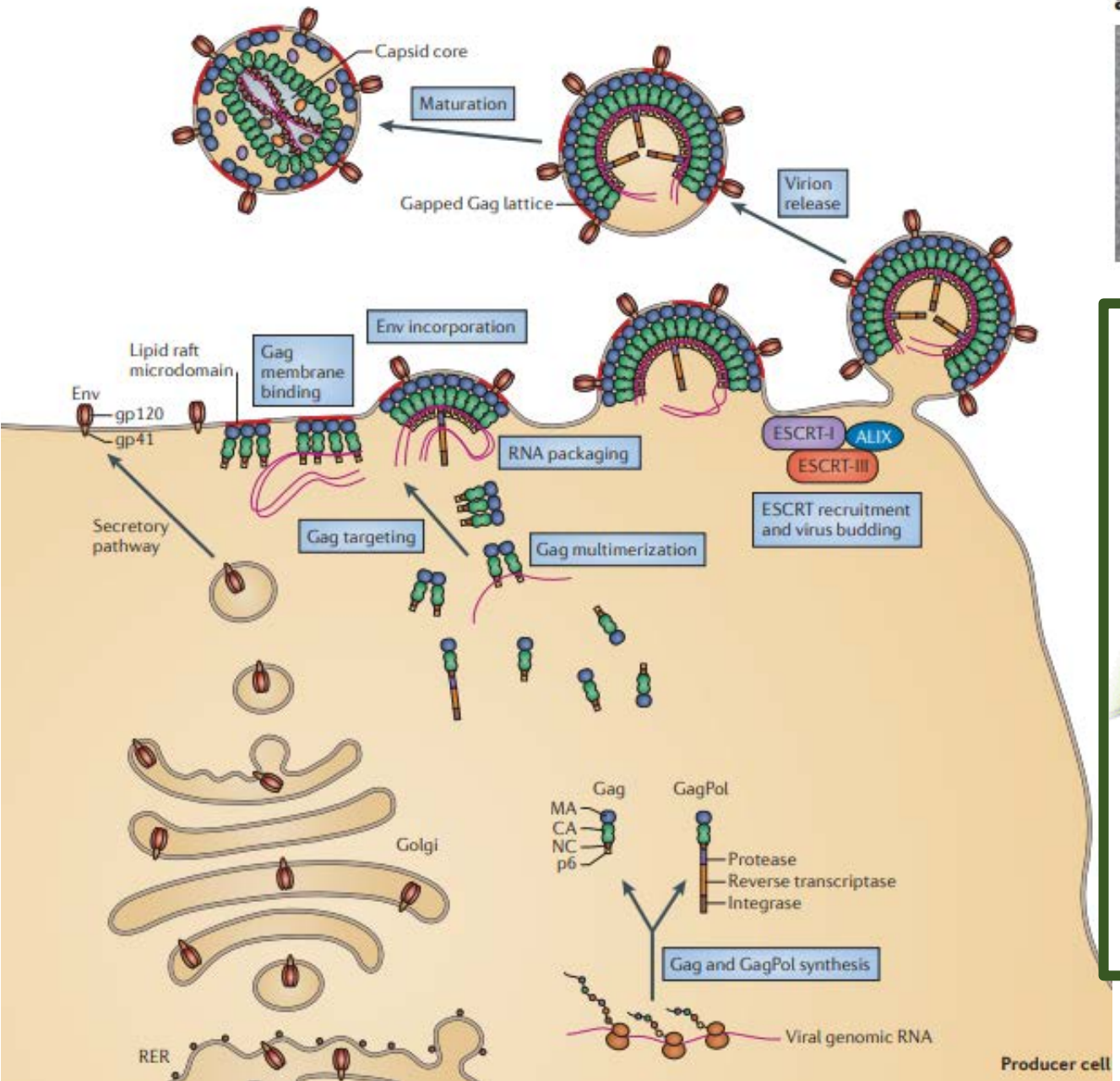
*1 discontinuation due to not meeting a protocol criterion of HIV-1 RNA <50 c/mL prior to Wk 28; 1 participant discontinued on Day 2.

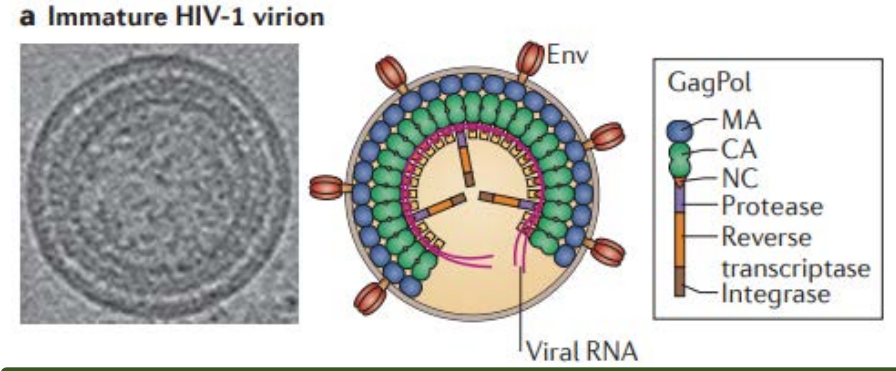
- One participant in **LEN SC + FTC/TAF → BIC** arm had emergent resistance mutations at Wk 10
  - CA: Q67H + K70R (LEN fold change = 20)
  - RT: M184M/I
- Plasma LEN concentrations consistently in target range

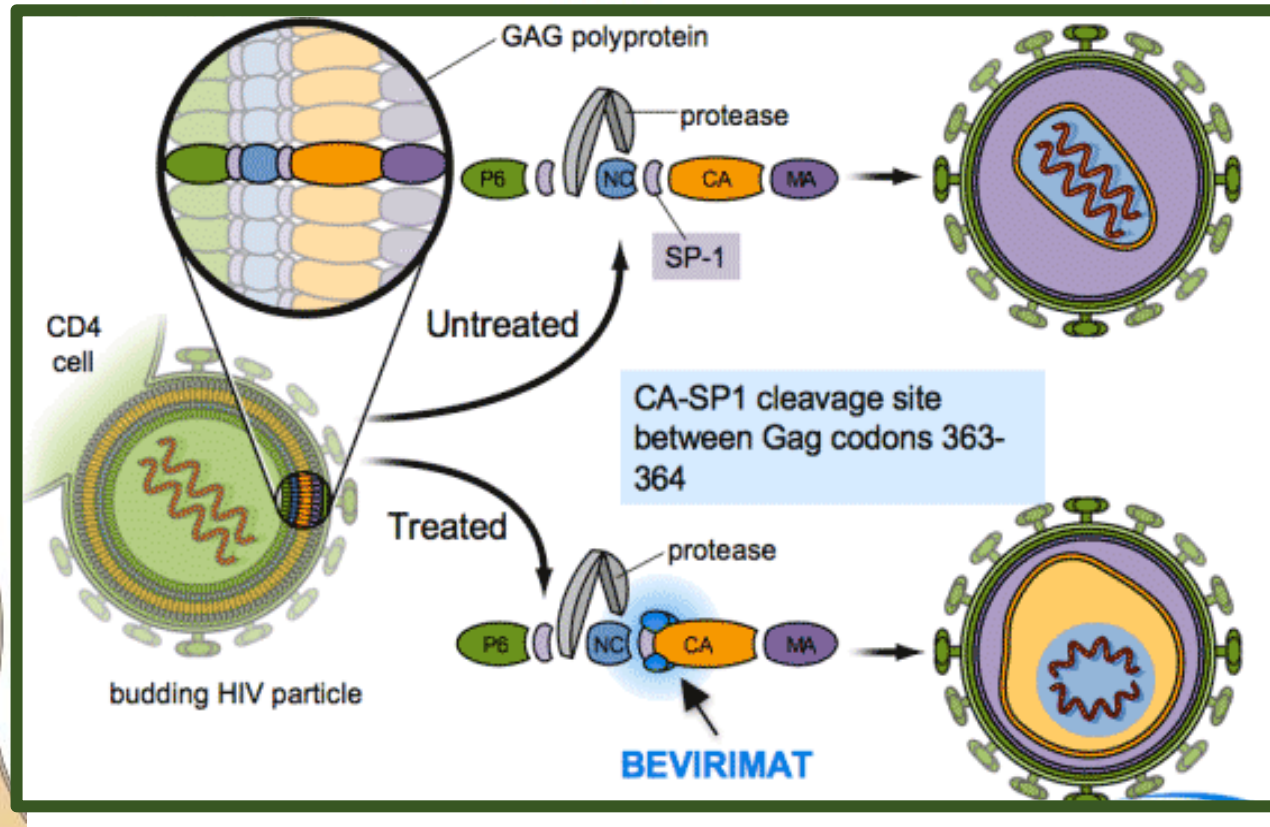
Gupta. IAS 2021. Abstr OALB0302.

Slide credit: clinicaloptions.com

HIV Maturation

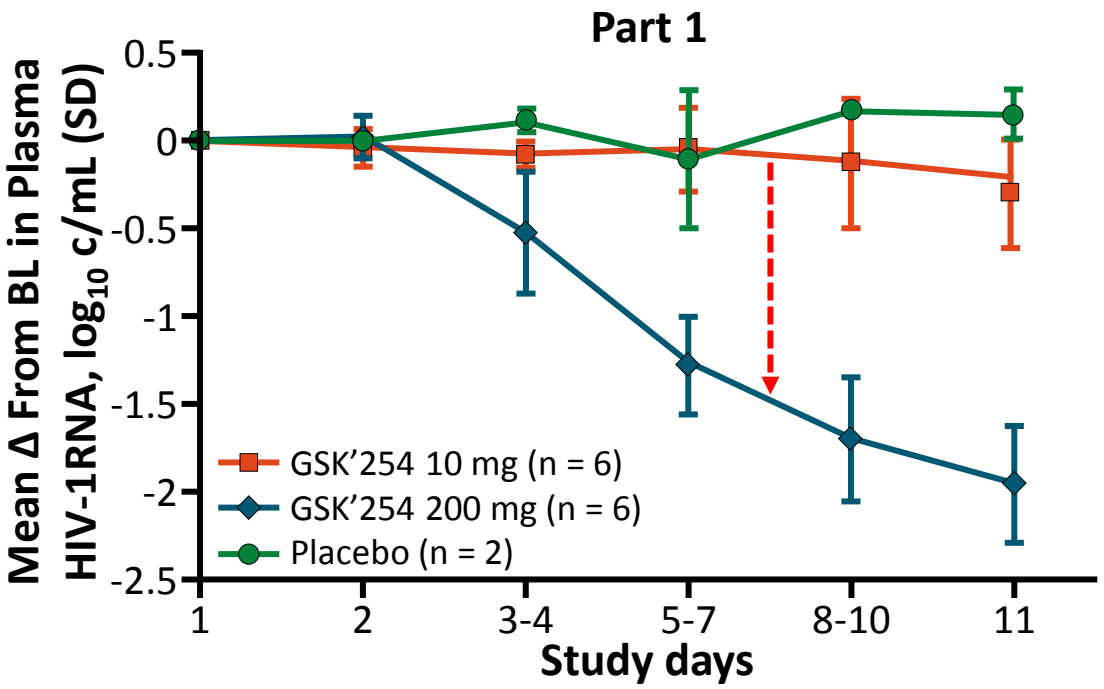


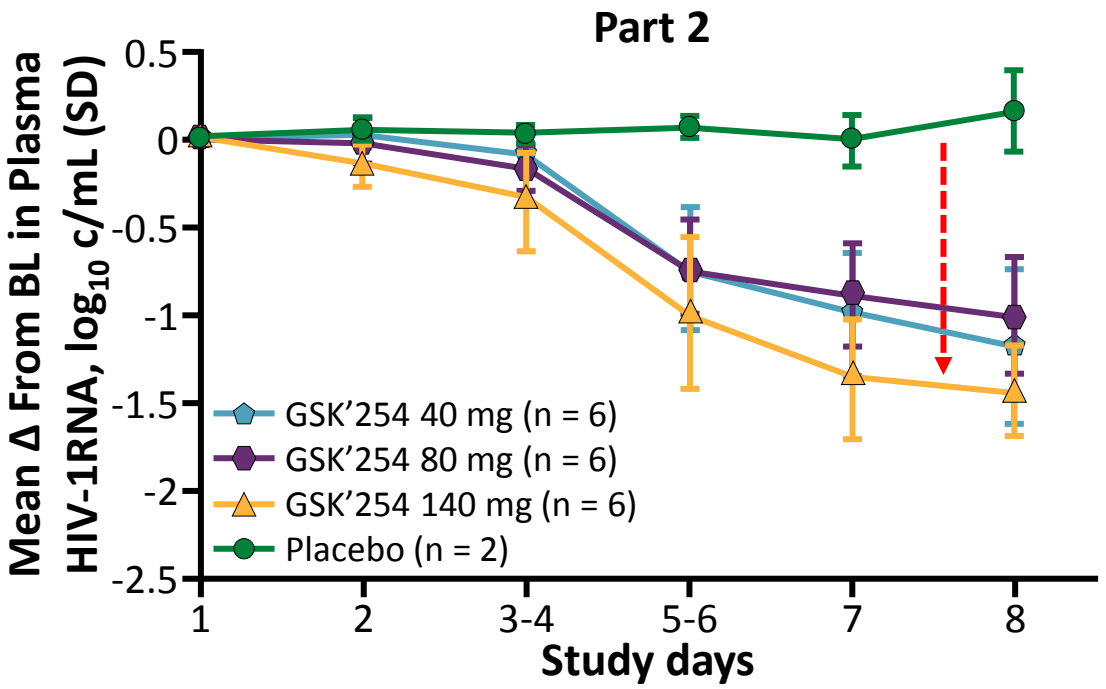




Nature 517, 505–508 (2015)

Phase IIa Study of GSK3640254: Antiviral Activity





Spinner. CROI 2021. Abstr 126. Reproduced with permission.

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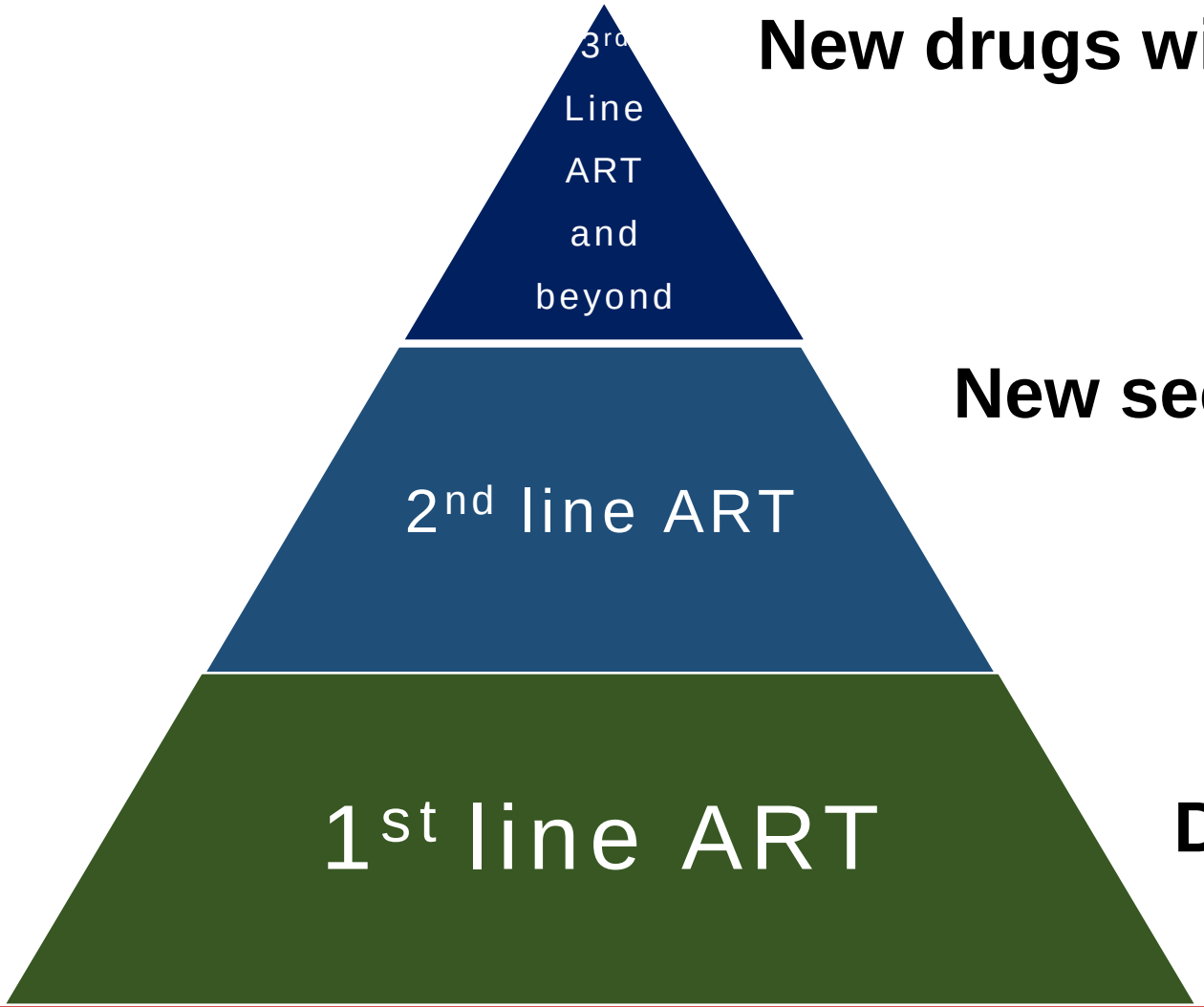
Summary



New drugs with new mechanism of action

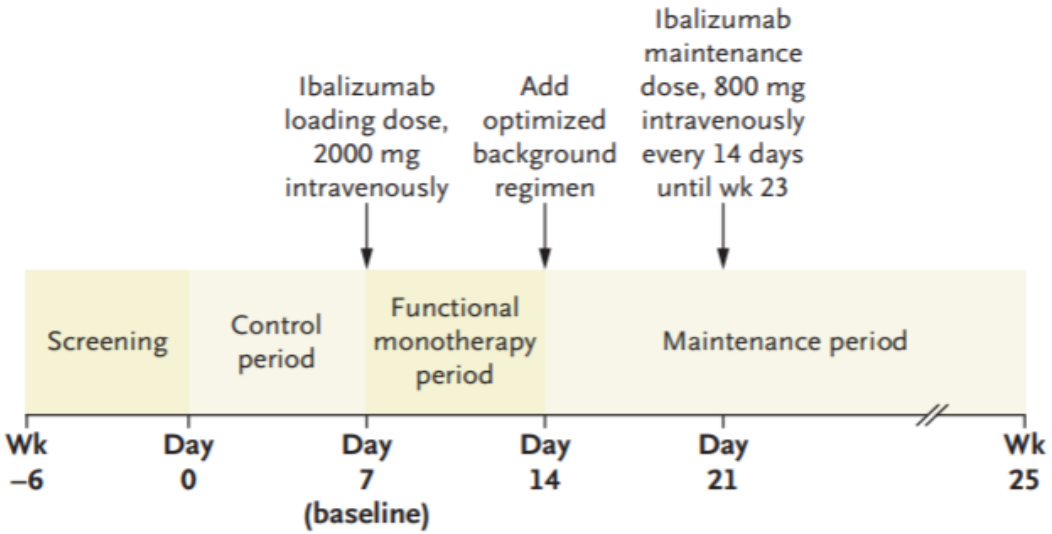
New second-line ART regimen

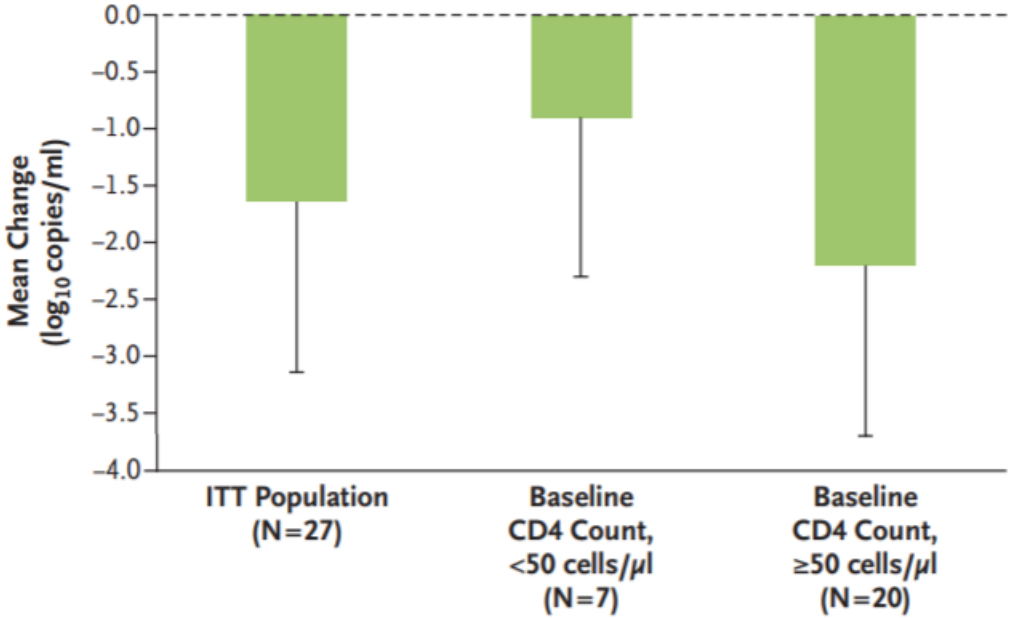
Long-term efficacy of INSTI
DTG and TAF for pregnant women

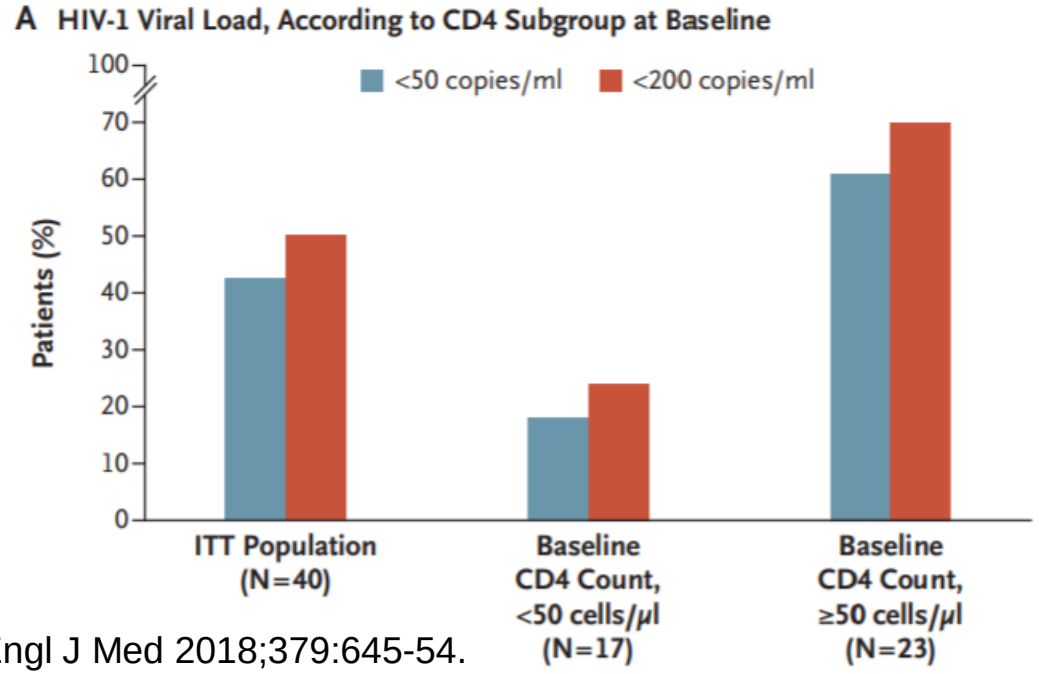
Investigational agents

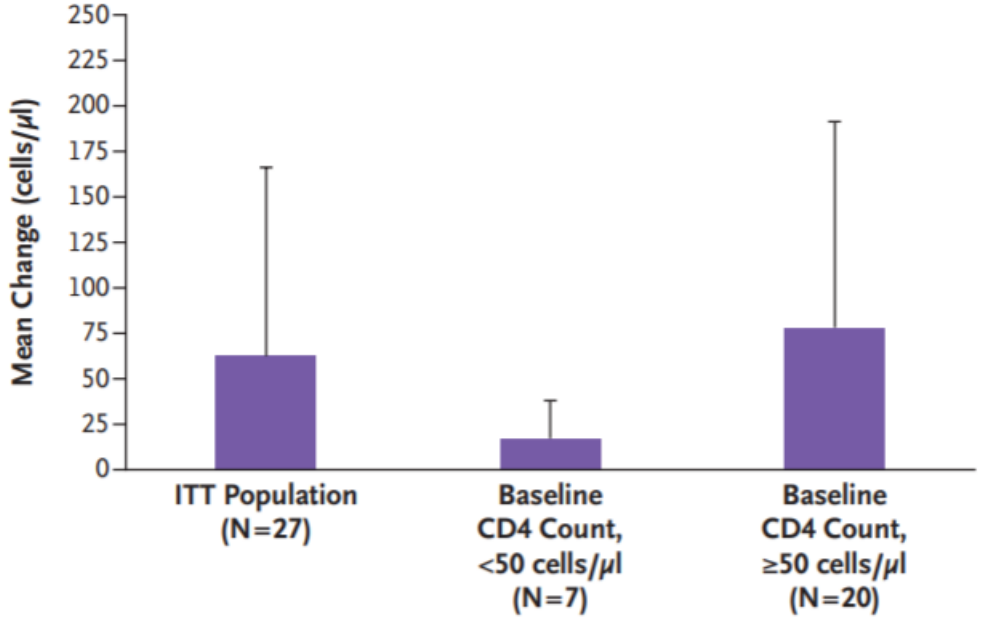

LET'S STOP
HIV
TOGETHER™

In patients with MDR HIV-1 infection who had advanced disease and limited treatment options, ibalizumab had significant antiviral activity during a 25-week study









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

Table 1. Baseline Characteristics of the Patients (Intention-to-Treat Population).*

Characteristic	Dolutegravir (N=235)	Darunavir (N=229)	Tenofovir (N=233)	Zidovudine (N=231)	Overall (N=464)
Female sex — no (%)	140 (59.6)	142 (62.0)	140 (60.1)	142 (61.5)	282 (60.8)
Median age (IQR) — yr	33 (28–40)	35 (28–42)	34 (28–43)	35 (28–40)	34 (28–41)
Age group — no (%)					
12–17 yr	1 (0.4)	2 (0.9)	0	3 (1.3)	3 (0.6)
18–34 yr	138 (58.7)	121 (52.8)	128 (54.9)	131 (56.7)	259 (55.8)
35–49 yr	82 (34.9)	82 (35.8)	87 (37.3)	77 (33.3)	164 (35.3)
≥50 yr	14 (6.0)	24 (10.5)	18 (7.7)	20 (8.7)	38 (8.2)
Country of birth — no (%)					
Uganda	181 (77.0)	170 (74.2)	176 (75.5)	175 (75.8)	351 (75.6)
Kenya	25 (10.6)	26 (11.4)	25 (10.7)	26 (11.3)	51 (11.0)
Zimbabwe	29 (12.3)	30 (13.1)	29 (12.4)	30 (13.0)	59 (12.7)
Other†	0	3 (1.3)	3 (1.3)	0	3 (0.6)
Median body-mass index (IQR)‡	21.2 (19.3–23.9)	21.6 (20.0–24.7)	21.8 (19.8–24.4)	21.1 (19.5–24.1)	21.4 (19.7–24.3)
HBV surface antigen positive — no./total no. (%)§	9/234 (3.8)	13/229 (5.7)	9/233 (3.9)	13/230 (5.7)	22/463 (4.8)
Median CD4+ cell count (IQR) — per mm^3	189 (58–388)	202 (84–357)	200 (77–388)	191 (58–340)	194 (68–367)
CD4+ cell-count group — no. (%)					
<50 per mm^3	54 (23.0)	39 (17.0)	45 (19.3)	48 (20.8)	93 (20.0)
50–199 per mm^3	71 (30.2)	74 (32.3)	70 (30.0)	75 (32.5)	145 (31.2)
200–349 per mm^3	43 (18.3)	56 (24.5)	47 (20.2)	52 (22.5)	99 (21.3)
≥350 per mm^3	67 (28.5)	60 (26.2)	71 (30.5)	56 (24.2)	127 (27.4)
Median HIV-1 viral load (IQR) — log_{10} copies/ml	4.5 (3.9–5.1)	4.4 (3.8–5.1)	4.4 (3.9–5.1)	4.4 (3.9–5.1)	4.4 (3.9–5.1)
HIV-1 viral load group — no. (%)					
<100,000 copies/ml	169 (71.9)	167 (72.9)	171 (73.4)	165 (71.4)	336 (72.4)
≥100,000 copies/ml	66 (28.1)	62 (27.1)	62 (26.6)	66 (28.6)	128 (27.6)
Median time receiving first-line ART (IQR) — yr	3.6 (1.4–6.3)	3.7 (1.7–5.9)	3.7 (1.6–6.1)	3.7 (1.7–6.4)	3.7 (1.6–6.2)
Previously received zidovudine — no. (%)	14 (6.0)	14 (6.1)	15 (6.4)	13 (5.6)	28 (6.0)

FLAIR: Additional CVF Patient Characteristics

Characteristic (Wk 108)	
Sex at birth	Male
BMI, kg/m^2	24.7
HIV-1 subtype	A6
Baseline RAMs	None
Viral load at suspected/confirmed virologic failure, copies/mL	887/1112
Treatment-emergent NNRTI RAMs	V106V/A, V108V/I, E138G, M230L
Treatment-emergent INSTI RAMs	N155H, R263K
Wk 8 troughs: CAB µg/mL/RPV ng/mL	1.05/24.6*
Wk 108 troughs: CAB µg/mL/RPV ng/mL	1.73/79.5

- Resuppressed to HIV-1 RNA <50 c/mL at 3 mo on EFV/FTC/TDF

*By comparison, Wk 8 CAB and RPV geometric mean (5th, 95th percentile) for the FLAIR population was 1.56 µg/mL (0.551, 3.61) and 41.2 ng/mL (17.9, 92.7), respectively.

Orkin. IAS 2021. Abstr OAB0302.

Slide credit: clinicaloptions.com

Protocol 011 Safety Analysis: Cumulative AE Summary From Wk 0-96

AE, n (%)	ISL 0.25 mg + DOR QD (n = 29)	ISL 0.75 mg + DOR QD (n = 30)	ISL 2.25 mg + DOR QD (n = 31)	DOR/3TC/TDF QD (n = 31)
≥1 AE	25 (86.2)	27 (90.0)	22 (71.0)	27 (87.1)
Drug-related AE	0	3 (10.0)	4 (12.9)	7 (22.6)
Serious AE	1 (3.4)	3 (10.0)	1 (3.2)	3 (9.7)
Drug-related serious AE	0	0	0	1 (3.2)
Discontinued due to AE	0	0	2 (6.5)	1 (3.2)
Discontinued due to drug-related AE	0	0	2 (6.5)	1 (3.2)
Deaths	0	0	0	0

- No new drug-related AEs or discontinuations due to AEs in any ISL+DOR group Wk 48-96
- Most common AE in ISL+DOR groups: headache (11%); in DOR/3TC/TDF: diarrhea (19%)
  - Most events mild, transient, and not related to study treatment; incidence of both AEs similar at Wk 48 and 96

Cunningham. IAS 2021. Abstr OAB0304.

Protocol 011 Safety Analysis: Grade 3/4 Laboratory Abnormalities From Wk 0 to 96

Laboratory abnormality in ≥2 participants in any group, n/N (%)*	ISL 0.25 mg + DOR QD	ISL 0.75 mg + DOR QD	ISL 2.25 mg + DOR QD	DOR/3TC/TDF QD
Fasting triglycerides (mg/dL)				
▪ Grade 3: >500-1000	2/29 (6.9)	0/30 (0)	1*/29 (3.4)	0/26 (0)
Alanine aminotransferase (IU/L)				
▪ Grade 3: 5.0 to <10.0 x ULN	0/29 (0)	1/30 (3.3)	2/31 (6.5)	1/31 (3.2)
Creatinine kinase (IU/L)				
▪ Grade 3: 10.0 to <20.0 x ULN	4*/29 (13.8)	0/30 (0)	0/31 (0)	1/31 (3.2)
▪ Grade 4: ≥20.0 x ULN	1*/29 (3.4)	2/30 (6.7)	3/31 (9.7)	1/31 (3.2)

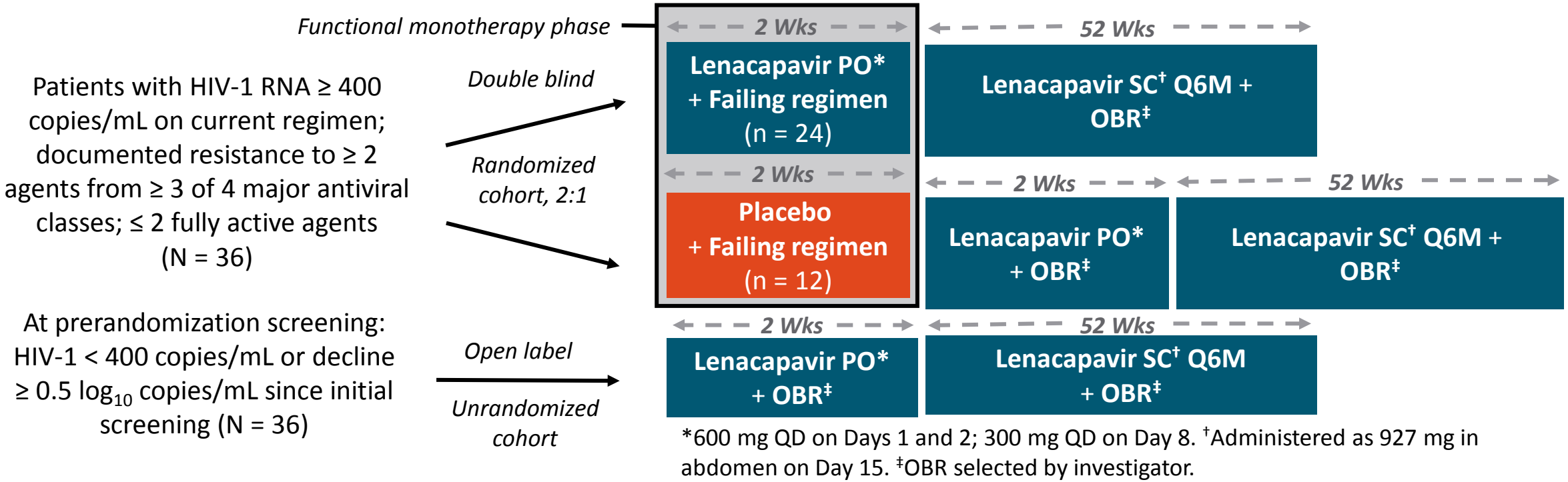
*1 laboratory abnormality occurred after Wk 48

- Laboratory abnormalities at Wk 96 similar to those reported at Wk 48
  - No dose-related trends observed
  - Most common laboratory change in all groups: elevated creatine kinase
    - Associated with physical exertion in 11 of 12 cases; all resolved

Cunningham. IAS 2021. Abstr OAB0304. DeJesus. AIDS 2020. Abstr OAB0302.

CAPELLA Phase II/III: Lenacapavir in Heavily ART-Experienced PWH

- Lenacapavir: potent, long-acting, first-in-class HIV capsid inhibitor (EC_{50} = 50 pM) with in vitro activity against strains resistant to NRTI, NNRTI, INSTI, or PI class



*600 mg QD on Days 1 and 2; 300 mg QD on Day 8. †Administered as 927 mg in abdomen on Day 15. ‡OBR selected by investigator.

- Primary objective: ≥ 0.5 log_{10} copies/mL reduction of HIV-1 RNA at Day 15 (end of functional monotherapy phase) in randomized cohort; secondary objectives: efficacy and safety through Wk 16 from both cohorts

Segal-Maurer. CROI 2021. Abstr 127.

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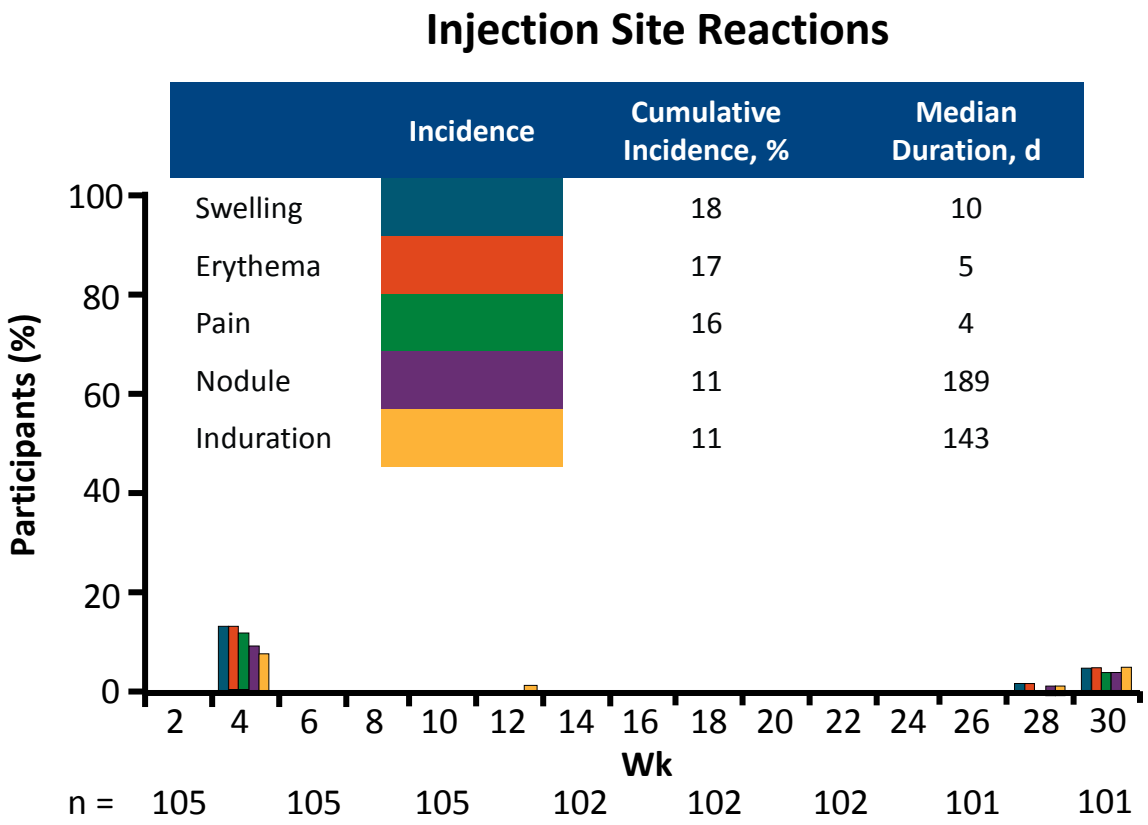
CALIBRATE: Adverse Events and Injection Site Reactions

- LEN was well tolerated with favorable safety profile
  - No SAEs or grade 4 AEs related to study drug
  - Most common AEs: headache and nausea (11% each)
  - GI AEs in SC vs oral LEN:
    - Nausea: 12% vs 8%
    - Diarrhea: 6% vs 8%
- ISRs in 39% of participants; 83% were grade 1 and generally resolved in days
- 2 discontinuations due to ISRs (grade 1 injection site induration)



Gupta. IAS 2021. Abstr OALB0302.

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Lenacapavir in Heavily ART-Experienced PWH: Safety

- No treatment-related serious AEs or discontinuation

Adverse Event, n (%)	Randomized (n = 36)	Nonrandomized (n = 36)	Total (N = 72)
AE frequency ≥ 5%, any grade			
▪ Headache	8	8	8
▪ Nausea	14	3	8
▪ Cough	11	3	7
▪ Diarrhea	11	3	7
▪ Back pain	3	8	6
▪ Pyrexia	6	6	6
▪ Rash	8	3	6
▪ Urinary tract infection	6	6	6
Grade 3/4 lab abnormality	31	11	21
▪ Low creatinine clearance	11	3	7
▪ Nonfasting hyperglycemia	12	0	7
▪ High creatinine	8	3	6
▪ Glycosuria	8	3	6
▪ Fasting hyperglycemia	11	0	6

- 46% (33/72) had ≥ 1 drug-related injection site reactions; 82% were grade 1
- No discontinuations due to ISRs

ISR to SC LEN	Cumulative Incidence (%)	Median Duration (d)
Swelling	22	11
Erythema	18	6
Nodule	18	116
Pain	14	4

Segal-Maurer. CROI 2021. Abstract 127.

Slide credit: clinicaloptions.com

CUSTOMIZE: Implementation-Effectiveness of Long-Acting Cabotegravir and Rilpivirine Injection

- Phase IIIb, hybrid III implementation-effectiveness study of monthly CAB LA + RPV LA injection
  - Quantitative and qualitative data collected from July 2019 to October 2020 to examine barriers to, facilitators of, and effective strategies for regimen delivery
  - Clinic types included universities, private practices, AIDS healthcare foundations, HMOs, and federally qualified health centers across the United States
  - 26 providers (physicians, injectors, administrators) from 8 clinics completed surveys and interviews at baseline, interim (Mo 4), and Mo 12
  - 109 patients received monthly CAB LA + RPV LA (following 1-mo oral lead-in) and completed surveys
    - 86% men, 57% white, 37% black, median BMI 27 (17-55) kg/m^2

Czarnogorski. IAS 2021. Abstr OAD0705.

Slide credit: clinicaloptions.com

CUSTOMIZE: HCP and Patient Implementation Barriers

Perceived Barriers to CAB LA + RPV LA Implementation Among HCPs Over Time, %	Baseline (N = 26)	Mo 4 (N = 24)	Mo 12 (N = 23)
Patient ability to keep monthly appointment	81	38	39
Patient transportation for monthly appointment	77	38	43
Flagging/awareness of missed visits	73	46	22
Staff resourcing for clinic flow	54	38	17
Rescheduling missed visits	50	21	26
Patients failing treatment due to missed dose/visit	50	17	13
Management of patients with other needs	50	33	22
Injection-site soreness	46	42	48

- 74% of patients reported no interference with monthly injection visits
- **Perceived barriers to monthly injectable CAB LA + RPV LA implementation inconsistent between patients and providers**

Perceived Barriers to CAB LA + RPV LA Implementation at Mo 12, %	Patients (N = 102)	HCPs (N = 23)
Injection pain/soreness	15	48
Patient transportation	3	43
Rescheduling missed visits	1	26
Scheduling injection visits	2	17

Czarnogorski. IAS 2021. Abstr OAD0705.

Slide credit: clinicaloptions.com

CUSTOMIZE: Clinical Outcomes at Mo 12 and Time Spent in Clinic

Virologic Outcome at Mo 12, n (%)	Patients (N = 115)
Virologic success (<50 copies/mL)	101 (88)
Virologic nonresponse (≥50 copies/mL)	0
No virologic data ▪ Discontinued due to AE or death ▪ Discontinued for other reasons ▪ On study but missing data in window	14 (12) 5 (4)* 8 (7) 1 (1)†
Scheduling injection visits	2

* 2 deaths, both unrelated to study treatment.
† Due to COVID-19.

- Tolerability and safety of monthly CAB LA + RPV LA through Mo 12 consistent with phase III data
  - Fatigue (5%) and headache (5%) were most common non-ISR drug-related AEs
  - 2 (2%) patients withdrew due to ISRs
- 93% of patients thought time spent in clinic for CAB LA + RPV LA injection was extremely/very acceptable
- Median duration of visit length decreased over time
  - Mo 1: 57 min
  - Mo 11: 34 min

Czarnogorski. IAS 2021. Abstr OAD0705.

Slide credit: clinicaloptions.com

CUSTOMIZE: Impact of COVID-19

- 93% of patients maintained monthly CAB LA + RPV LA dosing schedule despite COVID-19 disruptions; remainder used temporary oral therapy (7%; CAB + RPV or alternative ART) or rescheduled LA injections (<1%)
- 19% of study patients (19/102) had a COVID-19–impacted visit (missed/rescheduled visit, quarantine, COVID-19 diagnosis, clinic closure)
  - CAB + RPV LA acceptability and treatment preference remained high among these individuals
- At Mo 12, 97% of study patients reported they will continue to use monthly CAB LA + RPV LA

Patient Perspectives of CAB LA + RPV LA at Mo 12, %	Impacted by COVID-19 (n = 19)	Not Impacted by COVID-19 (n = 83)	Total (N = 102)
Acceptability	97	98	98
Treatment preference			
▪ CAB LA + RPV LA	95	92	92
▪ Daily oral tablet regimen	5	2	3
▪ No preference	0	6	5

Czarnogorski. IAS 2021. Abstr OAD0705.

Slide credit: clinicaloptions.com

Next-Generation Maturation Inhibitor GSK3640254: Phase IIa Proof-of-Concept Trial

- New antiretrovirals with unique mechanisms of action needed for patients who fail existing ART options
- GSK3640254: investigational, next-generation HIV-1 maturation inhibitor
  - Demonstrated in vitro activity against panel of clinical HIV-1 isolates including diverse Gag sequences[1]
  - Phase I study in healthy volunteers found treatment was well tolerated with PK supportive of QD, unboosted dosing[2]
- Current analysis reports final results from dose-ranging phase IIa study of GSK3640254 antiviral activity in ART-naive patients with HIV[3]

1. Jeffrey. CROI 2021. Abstr 421. 2. Joshi. Pharmacol Res Perspect. 2020;8:e00671. 3. Spinner. CROI 2021. Abstr 126.

Phase IIa Study of GSK3640254: Safety

AEs, n (%)	GSK3640254					Placebo (n = 4)	Total (N = 34)
	10 mg (n = 6)	40 mg (n = 6)	80 mg (n = 6)	140 mg (n = 6)	200 mg (n = 6)		
Any, n (%)	3 (50)	5 (83)	4 (67)	5 (83)	5 (83)	0	22 (65)
▪ Headache	0	1 (17)	0	1 (17)	2 (33)	0	4 (12)
▪ Diarrhea	1 (17)	1 (17)	0	0	1 (17)	0	3 (9)
▪ Oropharyngeal pain	0	0	0	1 (17)	2 (33)	0	3 (9)
▪ Abdominal pain	0	0	2 (33)	0	0	0	2 (6)
▪ Nasopharyngitis	0	0	0	0	2 (33)	0	2 (6)
▪ Lymphadenopathy	1 (17)	0	0	0	1 (17)	0	2 (6)
▪ Vomiting	1 (17)	0	0	0	1 (17)	0	2 (6)
Any drug related, n (%)	2 (33)	2 (33)	2 (33)	1 (17)	2 (33)	0	9 (26)
▪ Diarrhea	1 (17)	1 (17)	0	0	1 (17)	0	3 (9)
▪ Abdominal pain	0	0	2 (33)	0	0	0	2 (6)
▪ Vomiting	1 (17)	0	0	0	1 (17)	0	2 (6)

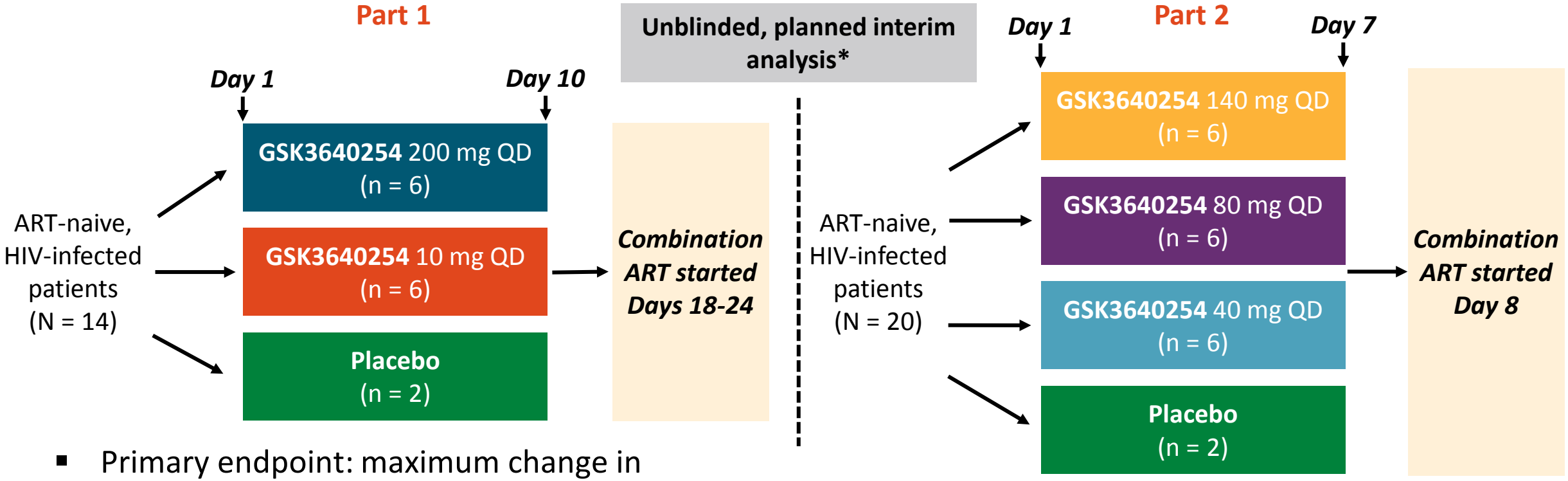
- No grade 3 or 4 AEs, no AEs leading to d/c, and no deaths
- 2 serious AEs occurred (grade 1 anal abscess; grade 3 congestive cardiomyopathy); neither considered related to study drug

Spinner. CROI 2021. Abstr 126.

Slide credit: clinicaloptions.com

Phase IIa Study of GSK3640254: Study Design

- Multicenter, randomized, double-blind (sponsor-unblinded), placebo-controlled, adaptive trial



- Primary endpoint: maximum change in HIV-1 RNA vs Day 1 during parts 1 and 2
- Secondary endpoints: resistance, PK, safety

*Detection of resistance mutations at interim analysis resulted in protocol amendment, reducing duration of monotherapy from 10 days to 7 days in Part 2.

Spinner. CROI 2021. Abstr 126.