Nuove strategie terapeutiche in HIV

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Disclosures

I received support for travel meetings from Janssen, Merck Sharp & Dohme, ViiV Healthcare and Gilead Sciences

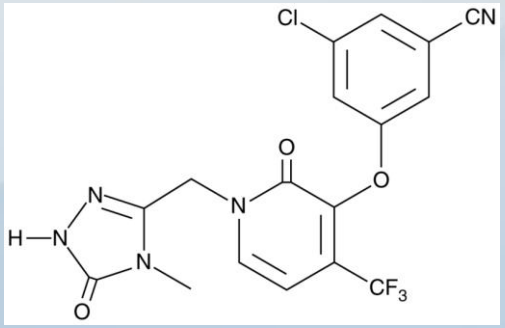
New but…already in use

Doravirine (DOR) was Designed to Address Limitations of Other Approved NNRTIs

DOR has been shown to be **effective against WT viruses and most common NNRTI-associated mutants** including K103N, Y181C and K103N/Y181C[1]
(NNRTI resistance)

DOR has a **low potential for DDIs** [4]
(Cytochrome P450 CYP3A substrate)

DOR dosed once daily provides **virologic suppression regardless of HIV-1 RNA baseline level**[2,3]
(Efficacy in high VL)



DOR has a **favorable CNS safety profile** with a lower proportion of drug-related neuropsychiatric adverse events versus efavirenz.[2]
(CNS toxicity)

DOR has shown to have a **superior lipid profile versus Efavirenz and ritonavir-boosted Darunavir**[2,3]
(Lipid profile)

DOR can be taken **with or without food**[5]
(Food restrictions)

DOR in combination with 3TC/TDF has demonstrated **modest weight gain, similar to the average yearly weight changes** in adults without HIV-1[6]
(Weight)

1. Feng M, et al. Antimicrob. Agents and Chemother. 2016
2. Orkin C, et al. CID. 2019
3. Molina JM, et al. Lancet HIV. 2018
4. Colombier MA, et al. Curr Opin HIV AIDS. 2018
5. Behm MO, et al. Clin Drug Investig. 2017
6. Orkin C, et al. Oral presentation at AIDS 2020

DRIVE-FORWARD and DRIVE-AHEAD Combined Analyses

Virologic Efficacy: Proportion with HIV-1 RNA <50 c/mL (FDA Snapshot Analysis)*

Study	Week 48 (Primary Analysis Endpoint)	Week 96
DRIVE-FORWARD		
Doravirine + 2 NRTIs	84%	73%
Darunavir+r + 2 NRTIs	80%	66%
DRIVE-AHEAD		
Doravirine/3TC/TDF	84%	78%
Efavirenz/FTC/TDF	81%	74%

*Due to differences in study design, efficacy between clinical trials should not be compared

Molina JM, Squires K, Sax PE, et al. DRIVE-FORWARD: 48-Week results of a randomized, double-blind, phase 3, non-inferiority trial. Lancet HIV. 2018;5(5):e211-e220. https://www.ncbi.nlm.nih.gov/pubmed/29592840
Orkin C, Squires KE, Molina JM, et al. DRIVE-AHEAD Week 48 Results. Clin Infect Dis. 2019;68(4):535-544. https://www.ncbi.nlm.nih.gov/pubmed/30184165

DRIVE-FORWARD and DRIVE-AHEAD Combined Analyses

Virologic Efficacy: Baseline Viral Load (Observed Failure Analysis)*

	HIV-1 RNA < 50 copies/mL, % (N) Week 48	
Study	**>100,000 HIV RNA copies/mL**	**≤100,000 HIV RNA copies/mL**
DRIVE-FORWARD		
Doravirine + 2 NRTIs	81% (79)	90% (285)
Darunavir+r + 2 NRTIs	76% (72)	89% (282)
DRIVE-AHEAD		
Doravirine/3TC/TDF	81% (69)	91% (277)
Efavirenz/FTC/TDF	81% (73)	91% (258)

*Due to differences in study design, efficacy between clinical trials should not be compared

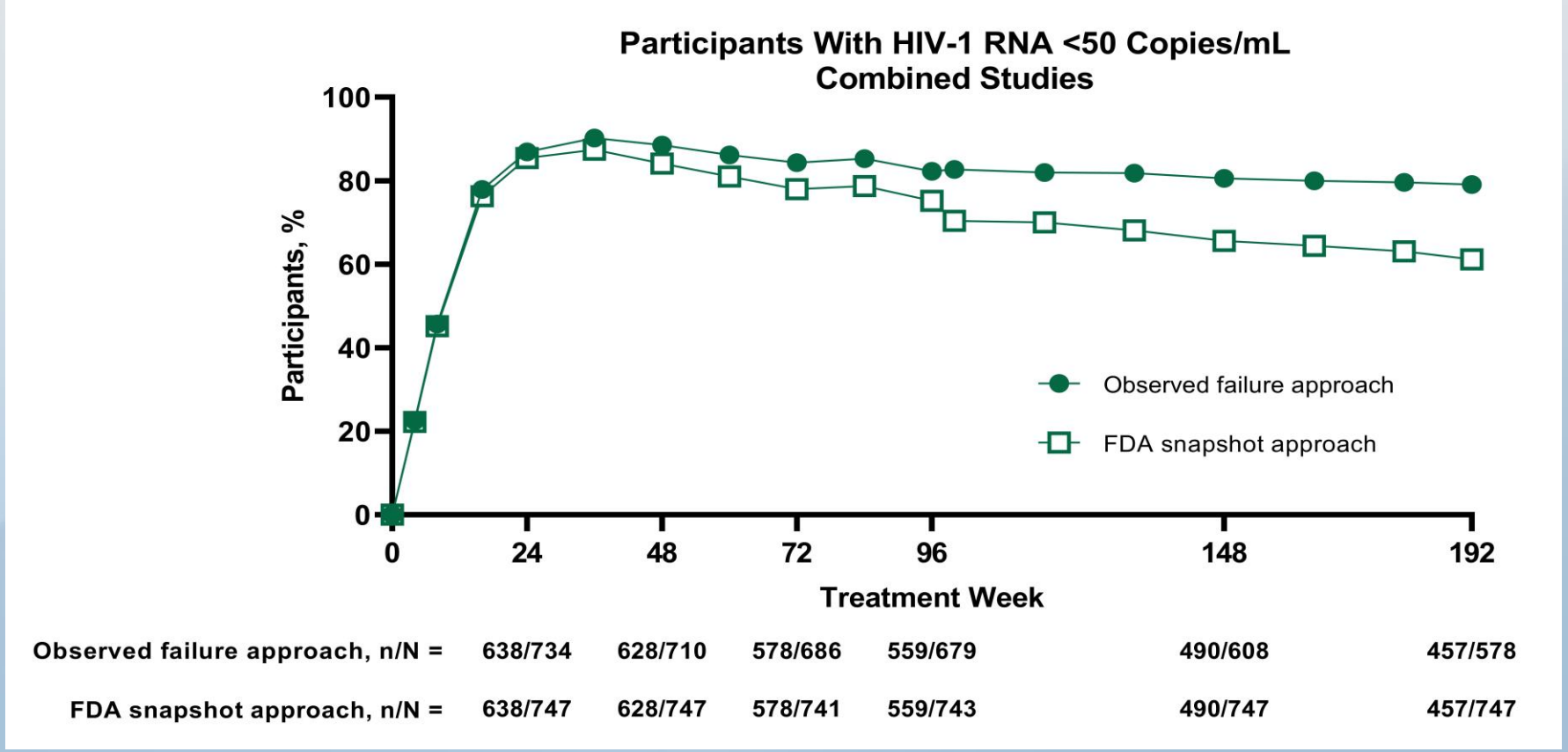
Molina JM, Squires K, Sax PE, et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomized, double-blind, phase 3, non-inferiority trial. Lancet HIV. 2018;5(5):e211-e220. https://www.ncbi.nlm.nih.gov/pubmed/29592840

Orkin C, Squires KE, Molina JM, et al. Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate is Non-inferior to Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate in Treatment-naive Adults With Human Immunodeficiency Virus-1 Infection: Week 48 Results of the DRIVE-AHEAD Trial. Clin Infect Dis. 2019;68(4):535-544. https://www.ncbi.nlm.nih.gov/pubmed/30184165

DRIVE-FORWARD and DRIVE-AHEAD Combined Analyses wk 192

At Week 192, **HIV-1 RNA <50 copies/mL** was maintained in most participants: **79.1%** by observed failure approach and 61.2% by FDA snapshot approach

At Week 192, **the mean increase from baseline in CD4+ T-cell count was 236.2** cells/mm^3 (95% CI: 216.8, 255.6)



Molina JM – DRIVE-FORWARD and DRIVE-AHEAD 192-week Oral Presentation Data, EACS 2021

Real-life use of Doravirine in treatment experienced people living with HIV. A multicenter Italian study

Maria Mazzitelli, MD, PhDa * , Melania Degli Antoni, MDb, Francesco Castelli, MDb, Diego Ripamonti, MDc , Gianluca Zuglian, MDc , Giuseppe Lapadula, MDd, Massimiliano Fabbiani, MDe , Alice Ferraresi, MDf , Cristina Putaggio, MDa , Anna Maria Cattelan, MDa , Eugenia Quiros-Roldan, MDb

Abstract

Use of doravirine (DOR), a new nonnucleoside reverse-transcriptase inhibitors recently approved for HIV treatment, is still unclear in clinical practice and real-life data are scarce.

We retrospectively investigated the rationale for switching people with HIV to DOR-containing/-based regimens in a real-life cohort. Among 132 patients (68.9% males, median age 56 years), the main reasons to start DOR were prevention of toxicities (39.4%) and dyslipidemia (18.2%). DOR was combined with integrase inhibitors in 40.9% cases, and in 25.7% of patients, DOR was prescribed without availability of a genotypic resistance test.

Twenty-four weeks after the switch to DOR-containing/-based regimens, no significant changes in CD4+ T-cell count, CD4/CD8 ratio, detectable HIV-RNA, serum creatinine levels, and body weight were detected. By contrast, a significant reduction in lipids (both cholesterol and triglycerides) was observed in 52 patients for whom a follow-up assessment was available ($P = .008$ and .01, respectively).

Our data confirmed that switching to DOR-containing/-based regimens may have a favorable impact on lipid profile and a neutral impact on weight gain. However, more data are needed to support its use in patients who do not have a genotypic test available or have an extensive nonnucleoside reverse-transcriptase inhibitors-associated resistance, as well as its use in a dual regimen, especially in combination with second-generation integrase inhibitors.

Abbreviations: DOR = doravirine, INI = integrase inhibitor, NNRTI = nonnucleoside reverse-transcriptase inhibitors, NRTI = nucleoside reverse-transcriptase inhibitors, PI = protease inhibitor, PLWH = people living with HIV.

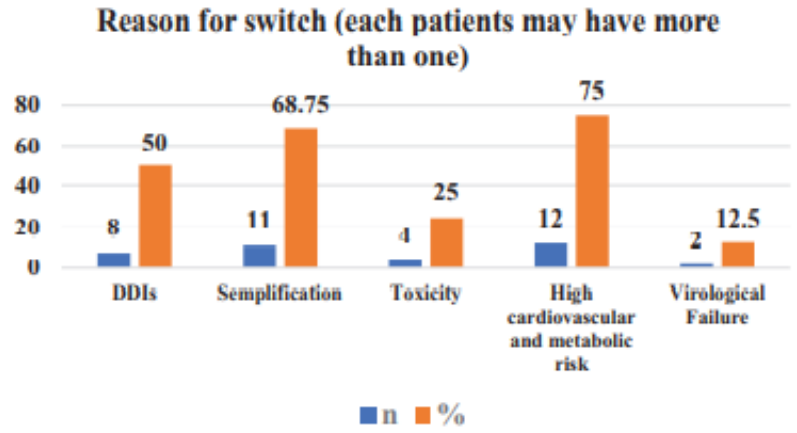
Keywords: doravirine, dyslipidemia, HIV, PLWH, real-life, switch

Real life use of dolutegravir doravirine dual regimen in experienced elderly PLWH with multiple comorbidities and on polypharmacy. A retrospective analysis

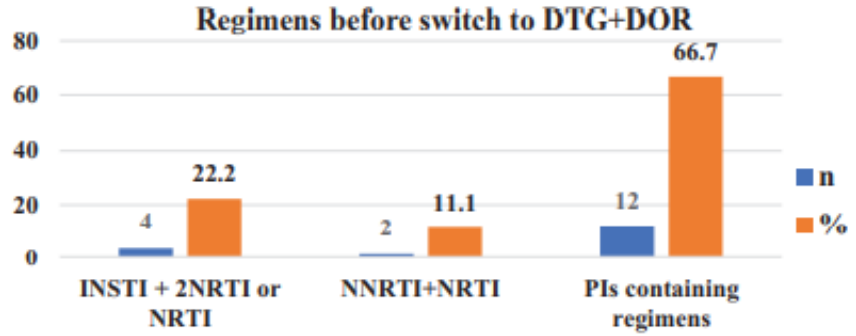
A

Comorbidity *each patient had more than 1	Overall 18 n (%)
Dyslipidaemia	16 (88.8)
Hypertension	14 (77.7)
Depression	7 (38.9)
COPD	6 (33.3)
Diabetes	5 (27.8)
Osteoporosis	5 (27.8)
Obesity	3 (16.7)
Cirrhosis	2 (1.1)
Ischaemic heart disease	2 (1.1)

B



C



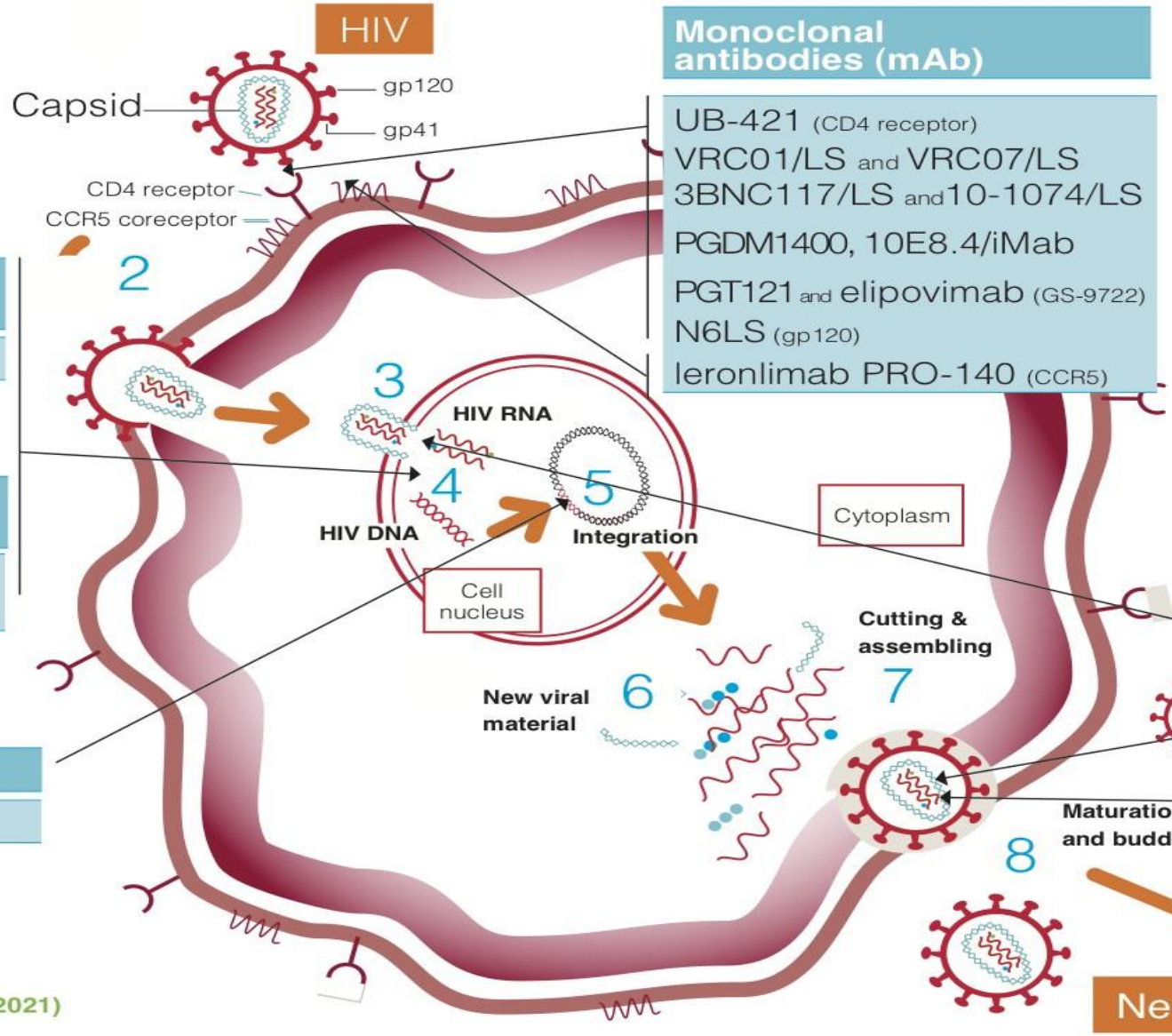
D

Parameter	Before switch, n(%)	After switch n (%)	p value
Undetectable HIV-RNA (Yes)	15 (88.2)	17 (100)	-
CD4+, cell/mm³, mean (SD)	607 (240)	629 (232)	0.37
Cholesterol, mmol/L, mean (SD)	5.1 (3.3)	4.8 (1.4)	0.1
HDL, mmol/L, mean (SD)	1.5 (0.7)	1.1 (0.4)	0.75
LDL, mmol/L, mean (SD)	3.1 (1)	2.9 (1.1)	0.49
Triglycerides, mmol/L, mean (SD)	1.41 (0.7)	1.5 (0.7)	0.2
Fasting glucose, mmol/L, mean (SD)	6.2 (1.7)	5.5 (1.4)	0.08
BMI, kg/m², mean (SD)	25.4 (3.2)	24.7 (3.3)	<0.01
Body weight, kg, mean (SD)	75.2 (11.6)	73.1 (11.6)	<0.01
Waist circumference, cm, mean (SD)	98.1 (10)	95.9 (9.8)	<0.01
Creatinine, umol/L	86.1 (22)	90.7 (23.4)	0.04
eGFR, ml/min, mean (SD)	79.4 (21)	75.2 (20.9)	0.03

Maria Mazzitelli, Lolita Sasset, Davide Leoni, Cristina Putaggio, Anna Maria Cattelan
Medicine (Baltimore). 2021 Dec 30; 100(52): e28488

Novel initial therapies

HIV pipeline 2021: targets in the HIV lifecycle



Monoclonal antibodies (mAb)

UB-421 (CD4 receptor)
VRC01/LS and VRC07/LS
3BNC117/LS and 10-1074/LS
PGDM1400, 10E8.4/iMab
PGT121 and elipovimab (GS-9722)
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islatravir (EFdA)

NNRTIs (non-nukes)

elsulfavirine
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INIs (INSTIs)

cabotegravir LA

Capsid inhibitors

lenacapavir (GS-6207)
GSK (pre-clinical)

Maturation inhibitors

GSK'254 (oral)
GSK '937 (LA)

Stages in the HIV lifecycle

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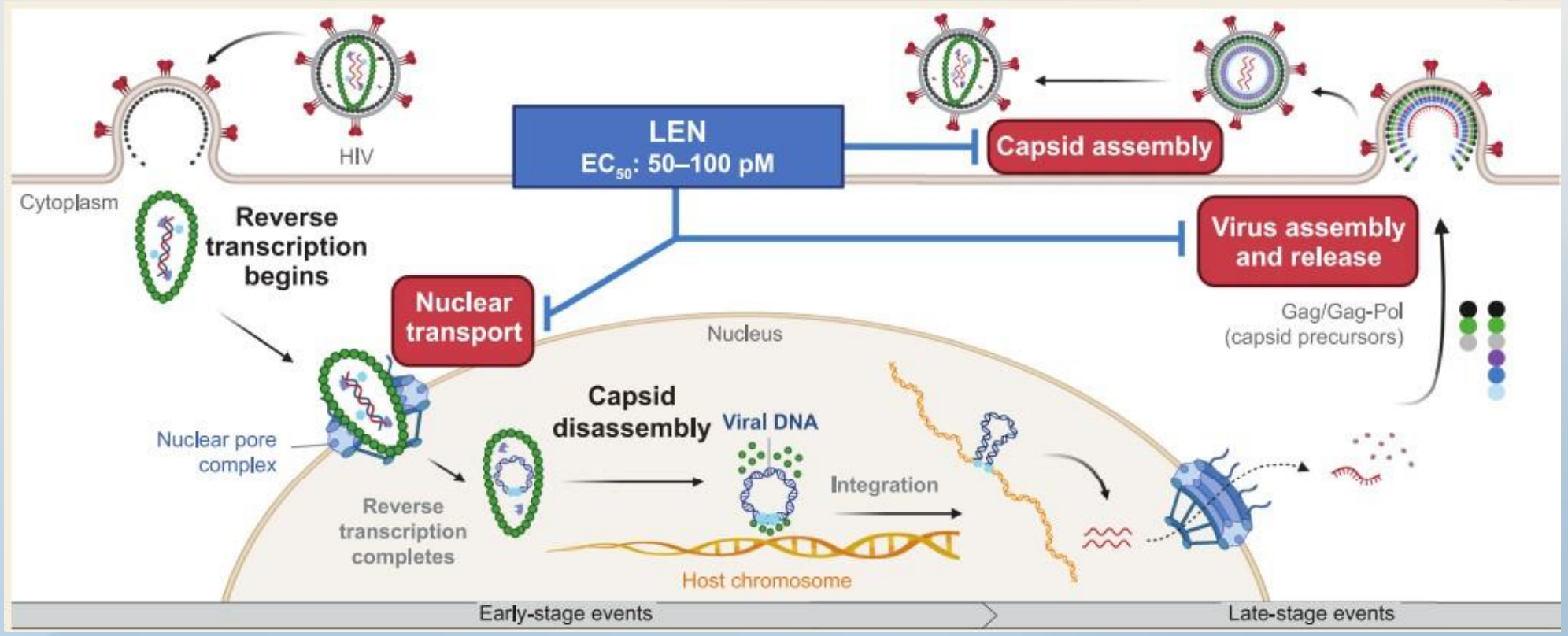
7. Protease cuts and reassembles new HIV.
8. Each cell produces hundreds of new virions.

** Updated in 2021.*

i-base.info (March 2021)

Lenacapavir: mechanism of action



- First-in-class capsid (CA) inhibitor
- Picomolar potency (EC50 = 50-100 pM)
- LEN inhibits early stage nuclear entry of HIV DNA, HIV assembly and proper capsid formation

Stellbrink, EACS 2021

CALIBRATE Interim Analysis: Background

- **Lenacapavir**: novel HIV-1 capsid inhibitor in clinical development for the treatment and prevention of HIV-1 infection[1]
  - Demonstrates high potency, low clearance, and slow-release kinetics[1]
  - Can be administered **PO or SC**

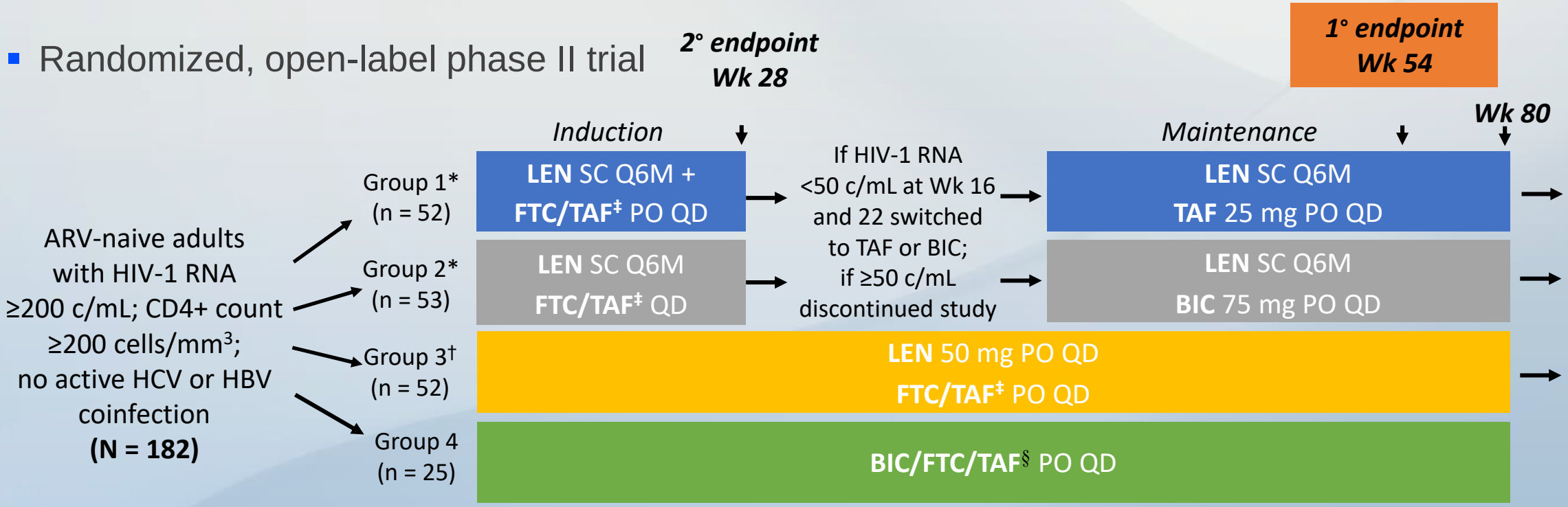
- **CALIBRATE**: ongoing, randomized phase II induction-maintenance study investigating **long-acting SC lenacapavir in treatment-naive patients**
  - Long-acting SC lenacapavir is dosed **every 6 mo**
  - Induction phase (baseline to Week 28): patients randomized to oral or long-acting SC lenacapavir also receiving FTC/TAF orally, daily

- Current interim analysis provides efficacy and safety data during induction phase at Week 28

1. Segal-Maurer. CROI 2021. Abstr 127. 2. Gupta. IAS 2021. Abstr OAB0302.

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.

- **Primary outcome:** proportion with HIV-1 RNA <50 c/mL at Wk 54

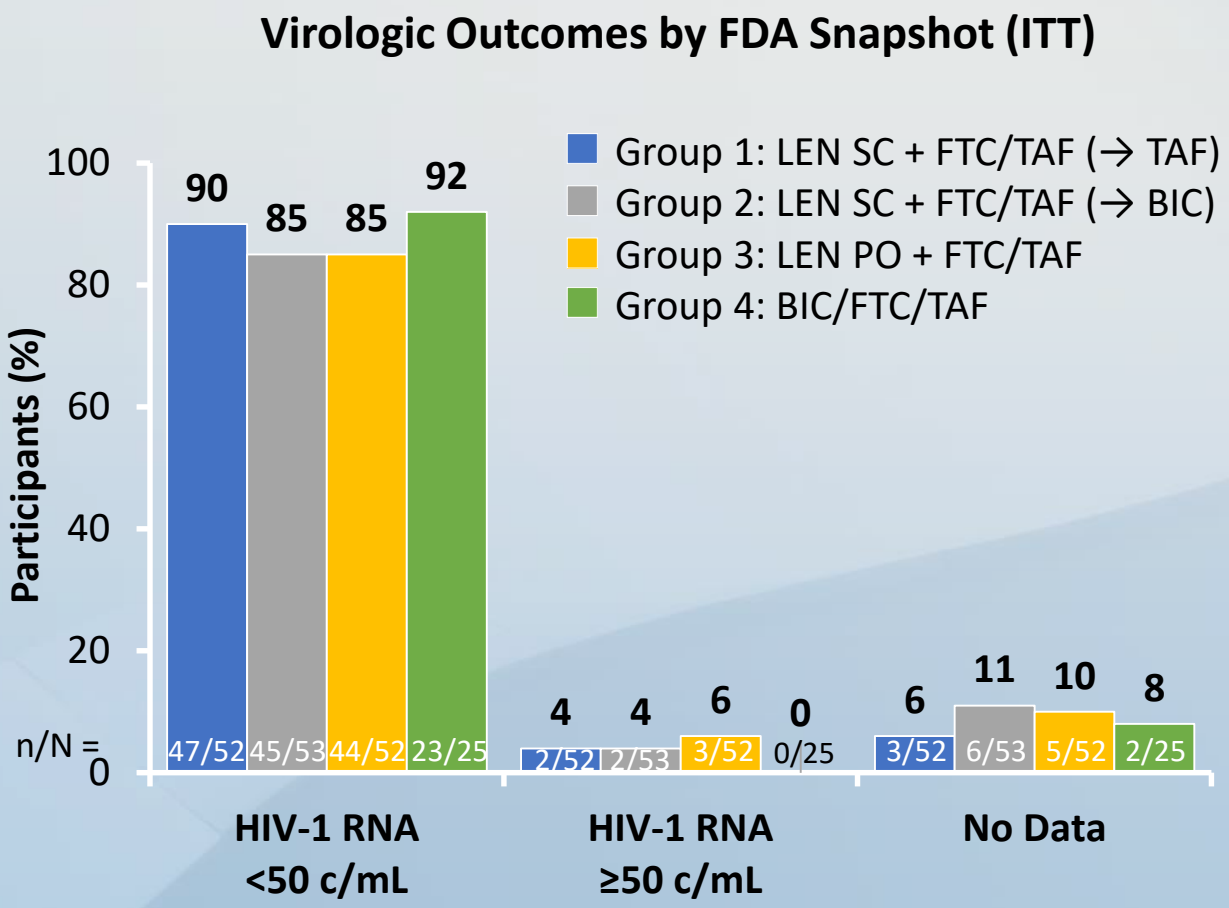
Gupta. CROI 2022. Abstr 138.

CALIBRATE: Baseline Characteristics

Characteristic	LEN SC + FTC/TAF → TAF (n = 52)	LEN SC + FTC/TAF → BIC (n = 53)	LEN Oral + FTC/TAF (n = 52)	BIC/FTC/TAF (n = 25)
Median age, yr (range)	31 (19-61)	28 (19-56)	28 (19-72)	29 (21-61)
Female sex at birth, %	10	2	12	0
Black, %	46	45	60	64
Hispanic/Latinx, %	48	40	46	48
Median HIV-1 RNA, log_{10} copies/mL ▪ Q1-Q3 ▪ >100 copies/mL	4.27 3.77-4.63 10	4.32 3.96-4.74 17	4.53 3.82-4.83 17	4.37 4.09-4.77 16
Median CD4+ cell count, cells/mm^3 ▪ Q1-Q3 ▪ <200 cells/mm^3	404 320-599 0	450 332-599 2	409 301-600 6	482 393-527 0

Gupta. IAS 2021. Abstr OAB0302.

CALIBRATE: Wk 54 Virologic Outcomes



- pooling lenacapavir arms 88% of the patients achieved and maintained virological suppression at Week 54

Gupta. CROI 2022. Abstr 138.

CALIBRATE: Safety and VF through Wk 54

LEN well tolerated with favorable safety profile

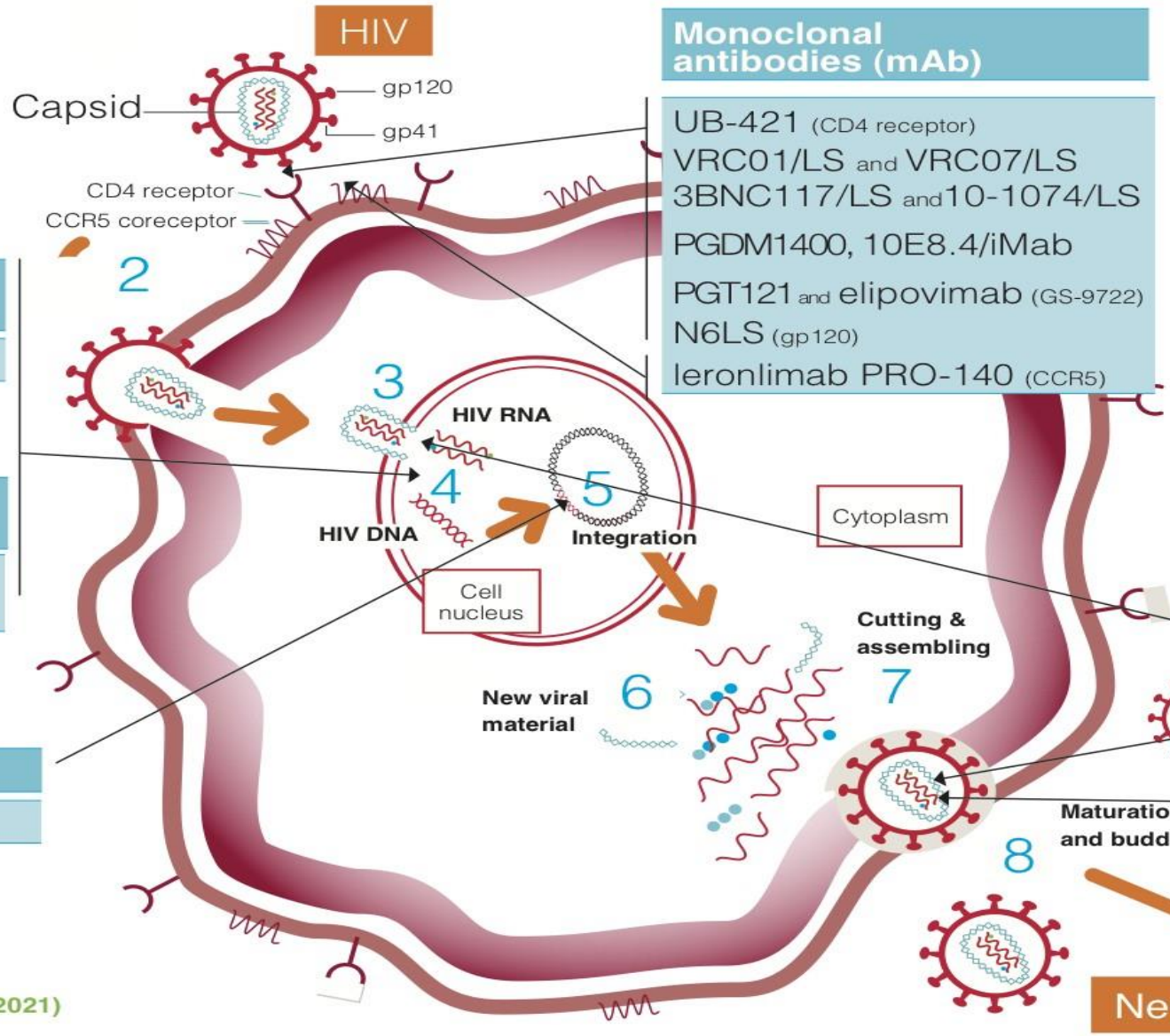
- No SAEs or grade 4 AEs related to study drug
- Most common AEs: headache and nausea (13% each)

3 discontinuations due to ISRs (due to grade 1 induration or erythema and swelling)

Emergent LEN resistance observed in 2/157 (1.5%) patients of Calibrate.

Both resuppressed on regimen of INSTI + 2 NRTIs

HIV pipeline 2021: targets in the HIV lifecycle



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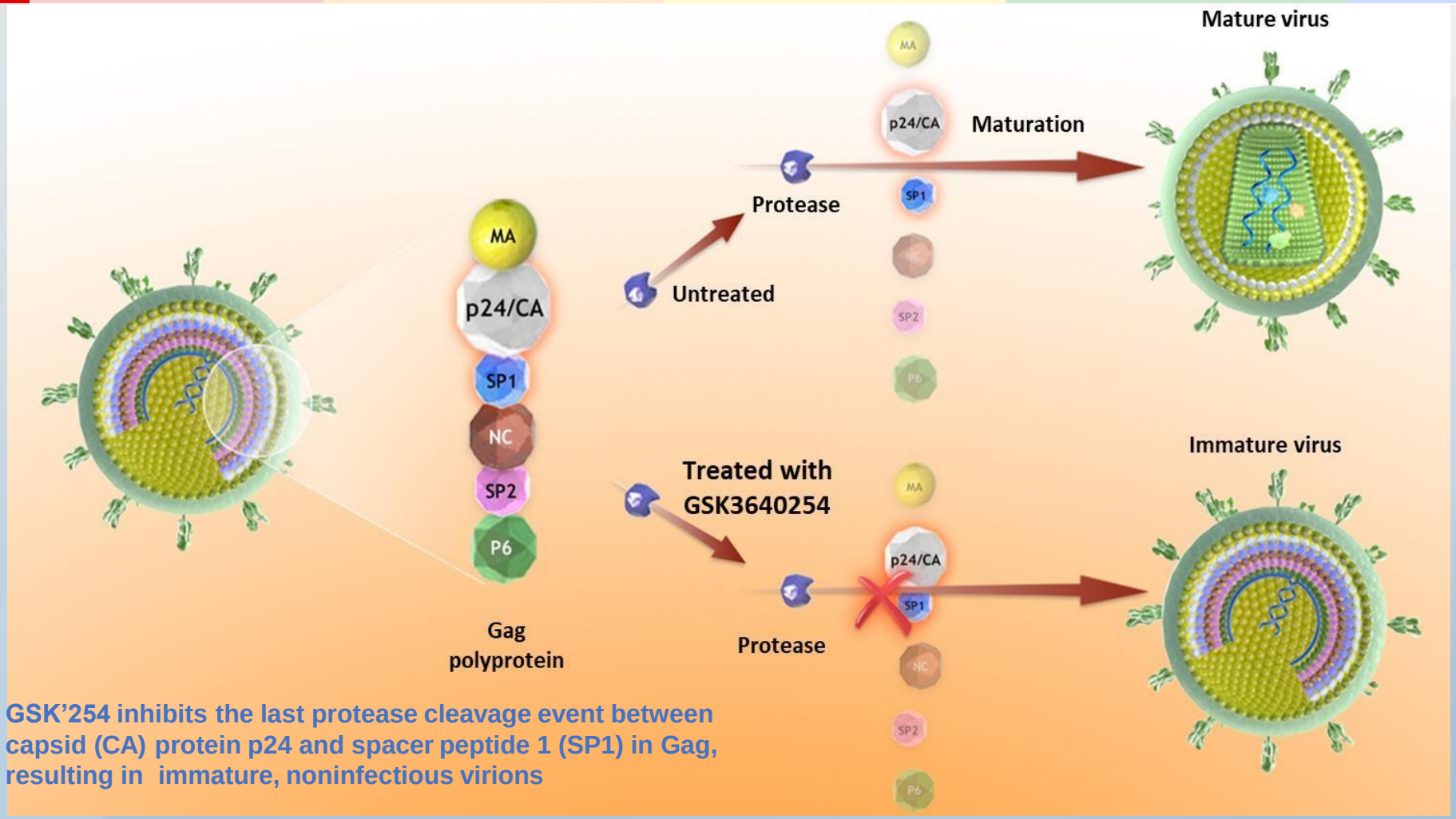
i-base.info (March 2021)

Maturation Inhibitors: mechanism of action



GSK'254 inhibits the last protease cleavage event between capsid (CA) protein p24 and spacer peptide 1 (SP1) in Gag, resulting in immature, noninfectious virions

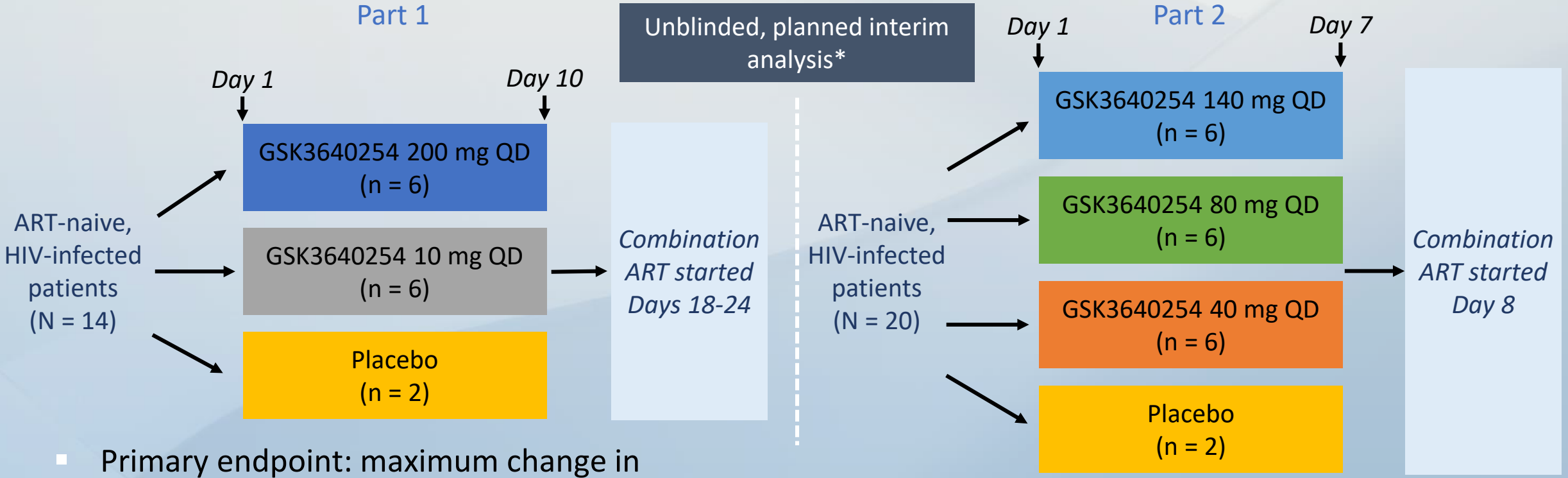
Maturation inhibitors (MIs) offer a novel mechanism of action by **blocking a late step in the virus life cycle to prevent the creation of infectious virions**. Specifically, MIs block the **cleavage of p25** into the p24 capsid protein and spacer peptide 1 (SP1), a step that normally permits protein restructuring to allow for development of mature infectious virions.

Figure adapted from Lataillade et al. Conceptualization of HIV-1 maturation inhibition, and design of the mode of action of GSK3532795. In: 22nd CROI; February 22-26, 2015; Seattle, WA. Oral presentation 114LB.

1. Adamson et al. *Expert Opin Ther Targets*. 2009;13:895-908. **2.** Hwang et al. *Clin Infect Dis*. 2017;65:442-452.

Phase IIa Study of GSK3640254: Study Design

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

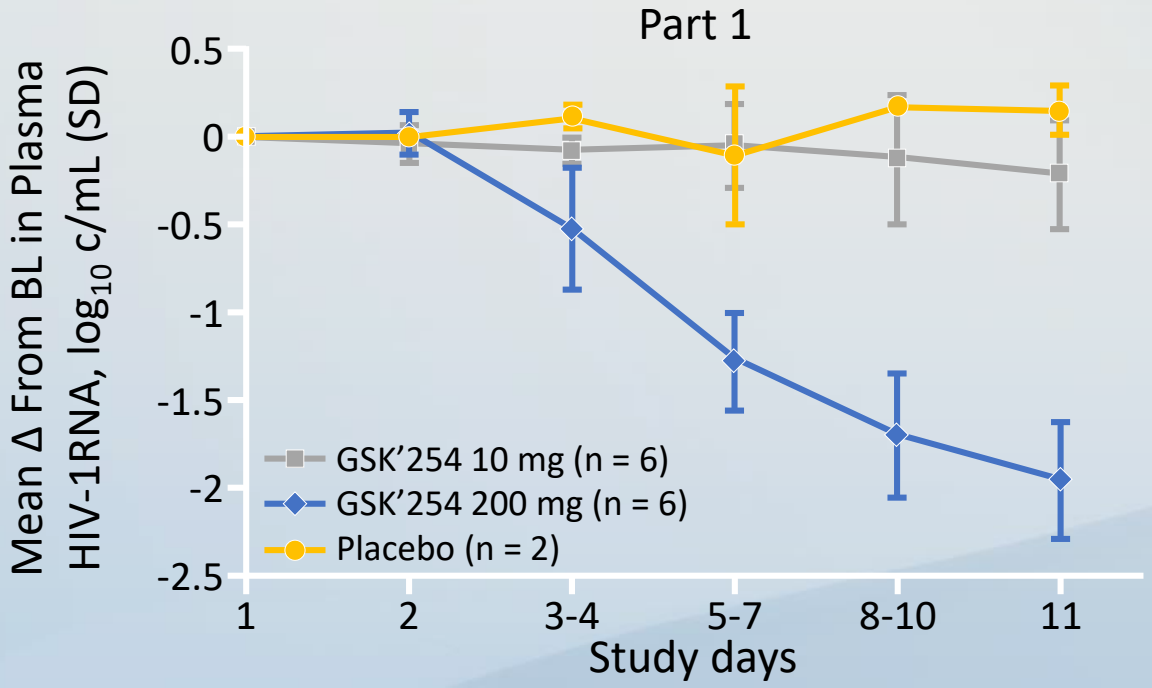


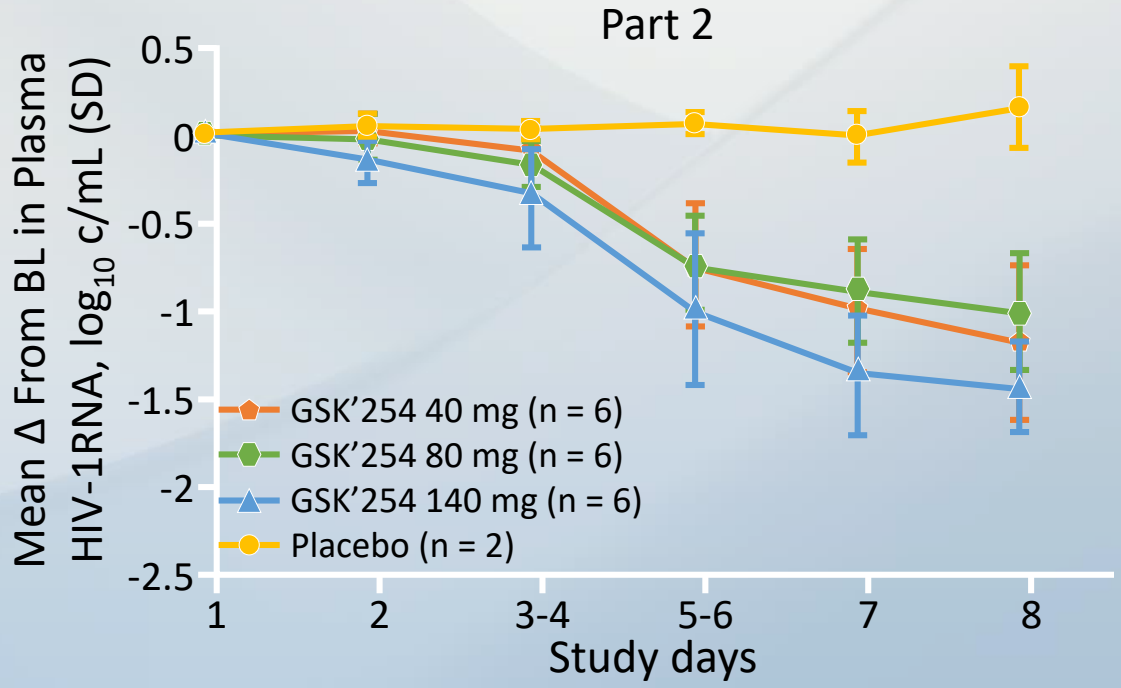
- Primary endpoint: maximum change in HIV-1 RNA vs Day 1 during parts 1 and 2
- Secondary endpoints: resistance, PK, safety

***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.

Phase IIa Study of GSK3640254: Antiviral Activity





Mean Change in HIV-1 RNA vs BL, log_{10} copies/mL (SD)	Part 1 (Day 11)			Part 2 (Day 8)			
	GSK3640254 10 mg (n = 6)	GSK3640254 200 mg (n = 6)	Placebo (n = 2)	GSK3640254 40 mg (n = 6)	GSK3640254 80 mg (n = 6)	GSK3640254 140 mg (n = 6)	Placebo (n = 2)
Primary endpoint	-0.22 (0.309)	**-1.96 (0.337)**	0.14 (0.134)	-1.18 (0.436)	-1.02 (0.330)	**-1.45 (0.235)**	0.15 (0.226)
Maximum change	-0.36 (0.252)	-2.01 (0.329)	-0.21 (0.262)	-1.18 (0.436)	-1.02 (0.330)	-1.49 (0.267)	-0.03 (0.127)

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

Maturation Inhibitor GSK254

Phase IIa Proof-of-Concept Evaluation of the Antiviral Efficacy, Safety, Tolerability, and Pharmacokinetics of the Next-Generation Maturation Inhibitor GSK3640254

Christoph D Spinner [1], et al.

Abstract

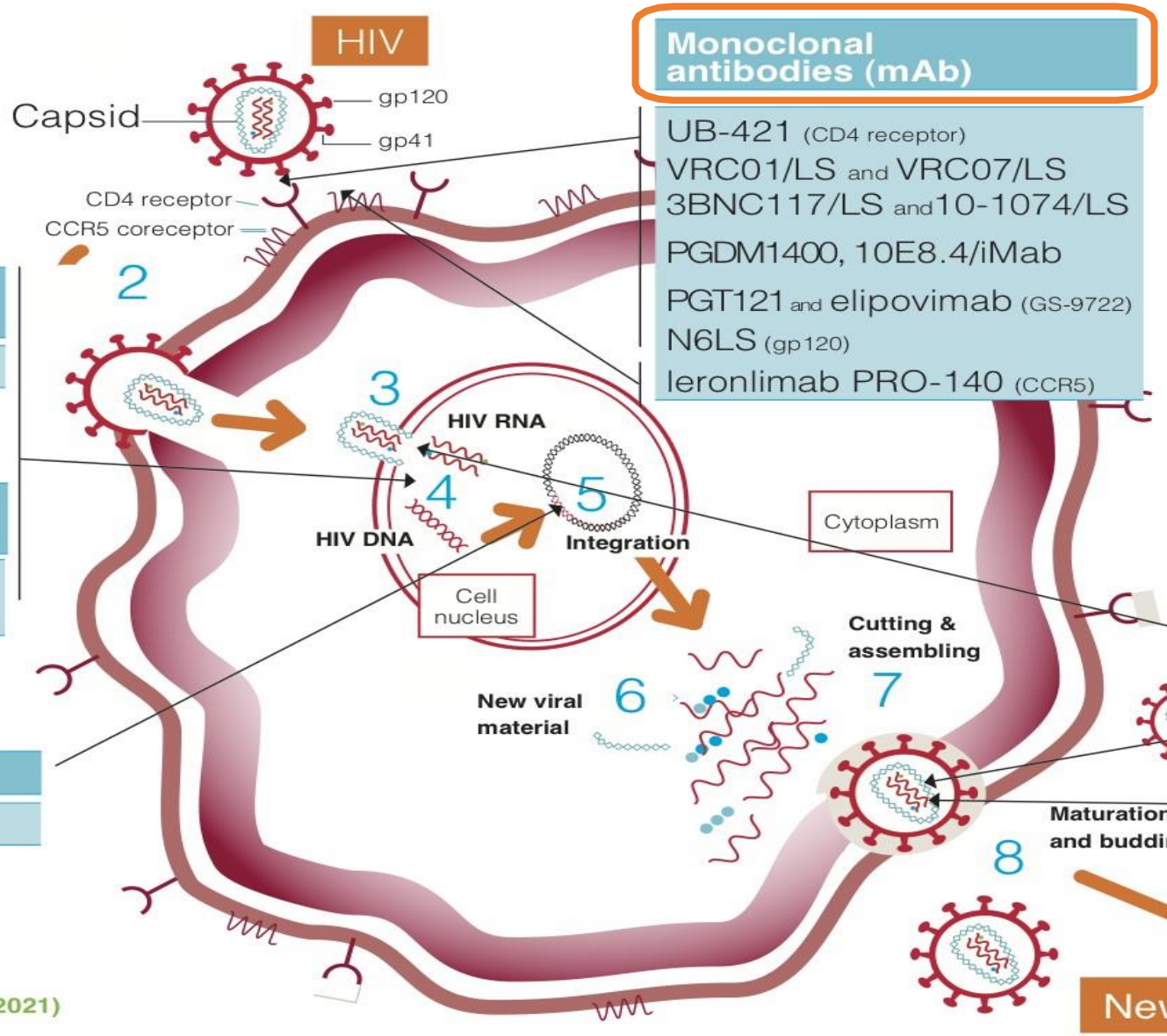
Background: GSK3640254 (GSK'254) is a next-generation human immunodeficiency virus type 1 (HIV-1) maturation inhibitor with pharmacokinetics (PK) supporting once-daily therapy.

Methods: This phase IIa double-blind (sponsor-unblinded), randomized, placebo-controlled, adaptive study evaluated antiviral effect, safety, tolerability, and PK of once-daily GSK'254 monotherapy administered with food (moderate-fat meal) in HIV-1-positive, treatment-naive adults. In part 1, participants received GSK'254 10 or 200 mg for 10 days. In part 2, participants received GSK'254 40, 80, or 140 mg for 7 days, modified from 10 days by a protocol amendment to decrease potential for resistance-associated mutations (RAMs). The primary endpoint was maximum change from baseline in HIV-1 RNA.

Results: Maximum changes in HIV-1 RNA of -0.4, -1.2, -1.0, -1.5, and -2.0 log10 occurred with GSK'254 10, 40, 80, 140, and 200 mg, respectively. Regardless of dosing duration, doses ≥40 mg resulted in ≥1-log10 declines in HIV-1 RNA. Plasma PK was generally dose proportional to 140 mg but non-proportional between 140 and 200 mg. Four participants in the 200-mg group developed RAMs on day 11 in part 1, 1 with phenotypic resistance. No RAMs occurred in part 2. Adverse events (AEs) were reported by 22 (65%) participants; headache was the most common (n = 4). Two non-drug-related serious AEs occurred. All AEs were of mild-to-moderate intensity, except for 2 grade 3 non-drug-related AEs in 1 participant.

Conclusions: This monotherapy study established a dose-antiviral response relationship for GSK'254. No safety or tolerability concerns were noted. These results supported dose selection for the ongoing phase IIb study (ClinicalTrials.gov: NCT04493216).

HIV pipeline 2021: targets in the HIV lifecycle



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** Updated in 2021.*

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IMPAACT 2008: Background

VRC01: human IgG_1 broadly neutralizing monoclonal antibody to CD4-binding site on HIV-1 envelope surface glycoprotein[1]

Current study assessed safety and efficacy of adding VRC01 (dosed 40 mg/kg SC at Wk 0, 2, 6, and 10) **to early ART in infants with HIV to promote viral reservoir clearance**[5]

1. Huang. EBioMedicine. 2021;64:103203. 5. Khaitan. AIDS 2022. Abstr OALBB0102.

IMPAACT 2008: Efficacy and Resistance

HIV-1 DNA Level	VRC01 + ART	ART Only	P Value
Median change at Wk 14 vs Wk 0, log_{10} copies/million PBMCs (IQR)	-0.41 (-0.94 to -0.30)	-0.53 (-0.70 to -0.33)	.42

- Similar decline in HIV-1 RNA and HIV-1 DNA in VRC01 + ART and ART-only groups during 14-wk treatment period
- VRC01 resistance

  5 of 17 (29%) of patients with available data had VRC01 resistance at Wk 0[1]

  HIV-1 RNA decline did not differ by presence of baseline VRC01 resistance
- VRC01 plasma concentrations

  28 days after dose, 31% had VRC01 concentrations below target level (<50 µg/mL)

Investigators concluded that more potent ART regimens combined with more potent or combination broadly neutralizing antibodies may be required to reduce viral reservoirs in infants with HIV

Khaitan. AIDS 2022. Abstr OALBB0102.

Strategies for HTE patients

How to Treat Multidrug Resistant HIV With LTO and Virologic Failure?

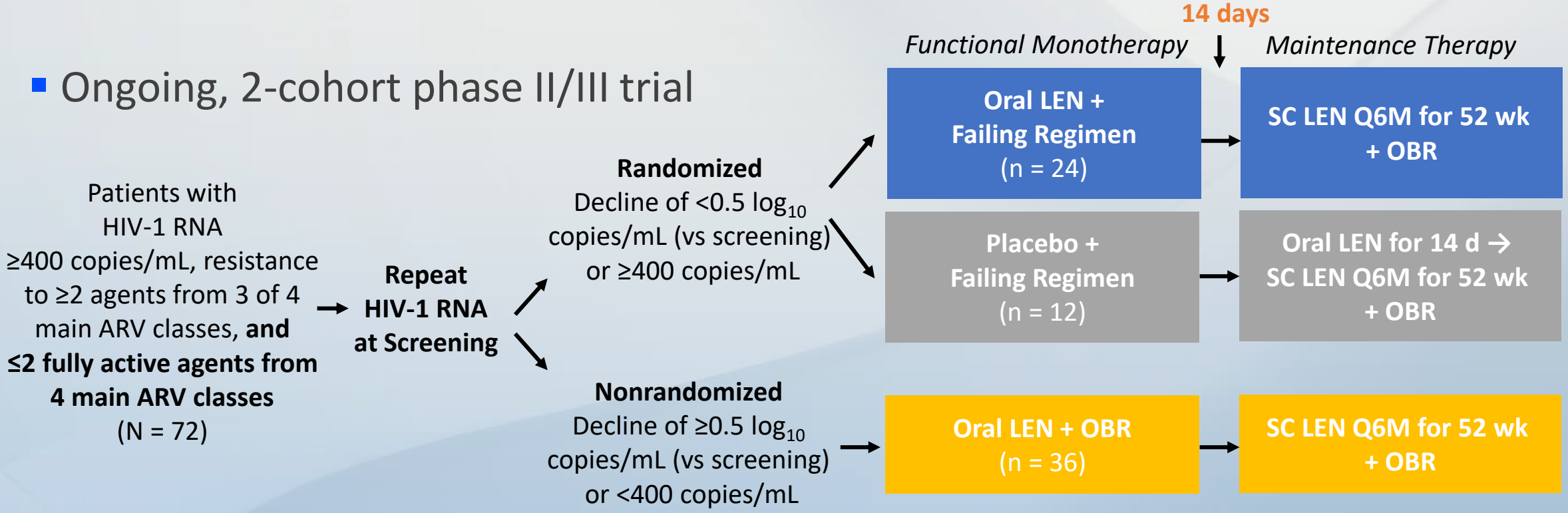
- **Construct an ART regimen with ≥2, preferably 3, active drugs or sum up equivalent with partially active drugs**[1]
  - Precise estimation of residual activity can be challenging (phenotype)
  - Choose best OBR (often among DRV/RTV BID + DTG BID + ETR BID ± TAF/FTC)
    - Avoid using a drug if full resistance: >60 points in HIVDB Stanford or history of treatment-limiting toxicity

- **Choose ≥1 active drug with new MoA and no cross resistance based on OBR:**
  - **Ibalizumab**: 800 mg IV every 14 days[2]
  - **Fostemsavir**: 600 mg BID PO[3]
  - **Lenacapavir**: 600 mg PO Days 1 and 2, 300 mg Days 8, then 927 mg SC Day 15 and every 6 mo[4]
  - Do not forget[1]: **enfuvirtide** (if no previous failure) and **maraviroc** (CCR5 tropic)
  - Islatravir,[5] bNAbs[6]: investigational
- Limited information (usually) in salvage ART trials due to limited number of subjects and study design (ethics)

1. DHHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV.
2. Ibalizumab PI. 3. Fostemsavir PI. 4. NCT04150068. 5. clinicalinfo.hiv.gov/en/drugs/islatravir/health-professional. 6. Hsu. Front Immuno. 2021;12:2771.

CAPELLA: Study Design

- Ongoing, 2-cohort phase II/III trial

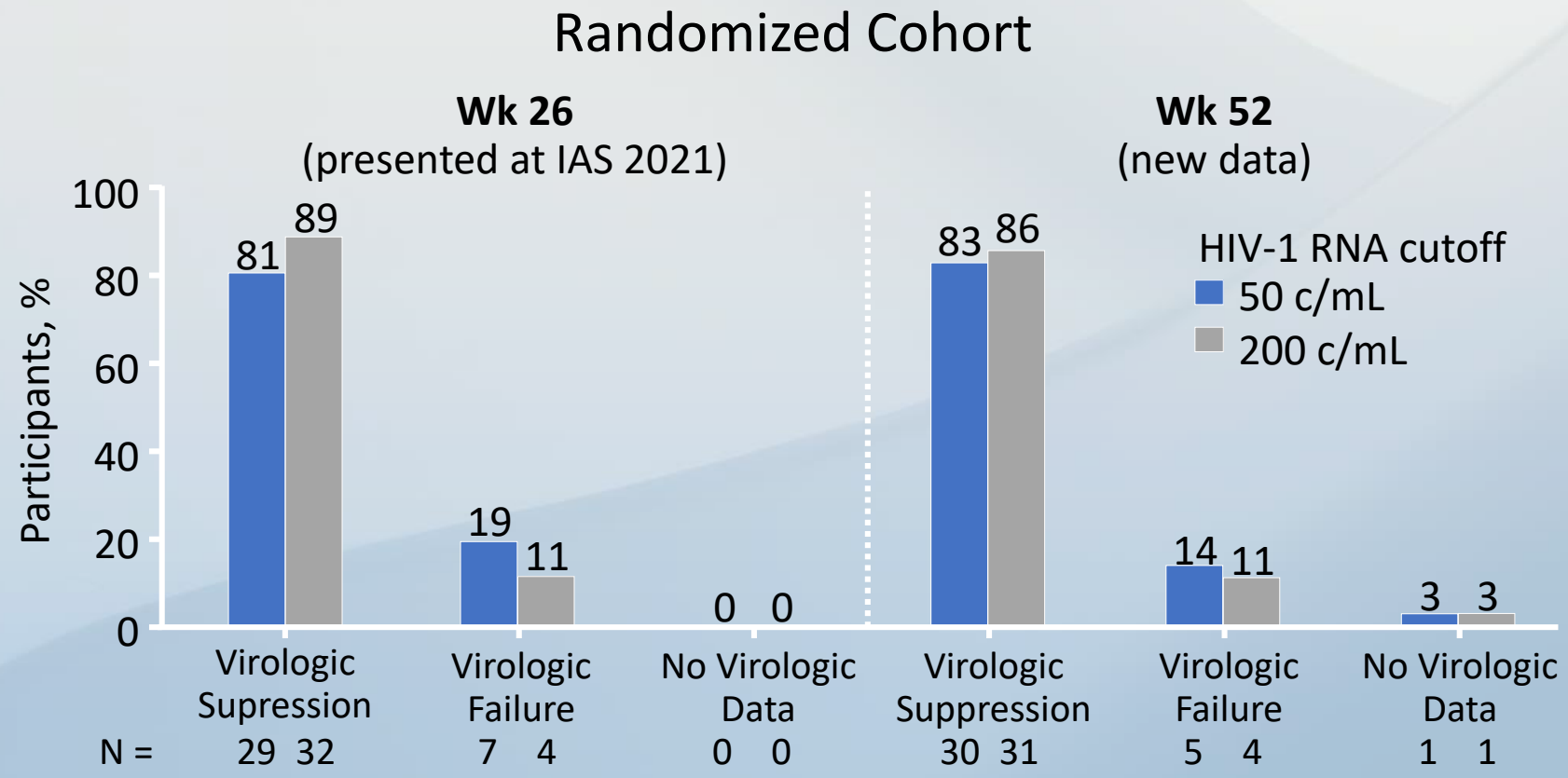


Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8; SC LEN administered as 927 mg (2 x 1.5 mL) in the abdomen on Day 15 and Q6M thereafter.

LEN + failing regimen (LEN functional monotherapy) associated with ≥0.5-log decline in HIV-1 RNA in 88% of patients vs 17% with placebo at Day 14

Ogbuagu. CROI 2022. Abstr 491.

CAPELLA: LEN Efficacy at Wk 26 and 52



- **CD4+ count increased by 83 cells/mm³ at Wk 52 in randomized cohort**
- **83% (30/36) achieved HIV-1 RNA <50 copies/mL by 52 wk in randomized cohort**

Ogbuagu. CROI 2022. Abstr 491.

CAPELLA: LEN Resistance

LEN RAMs emerged in 8/72 from randomized and nonrandomized cohorts

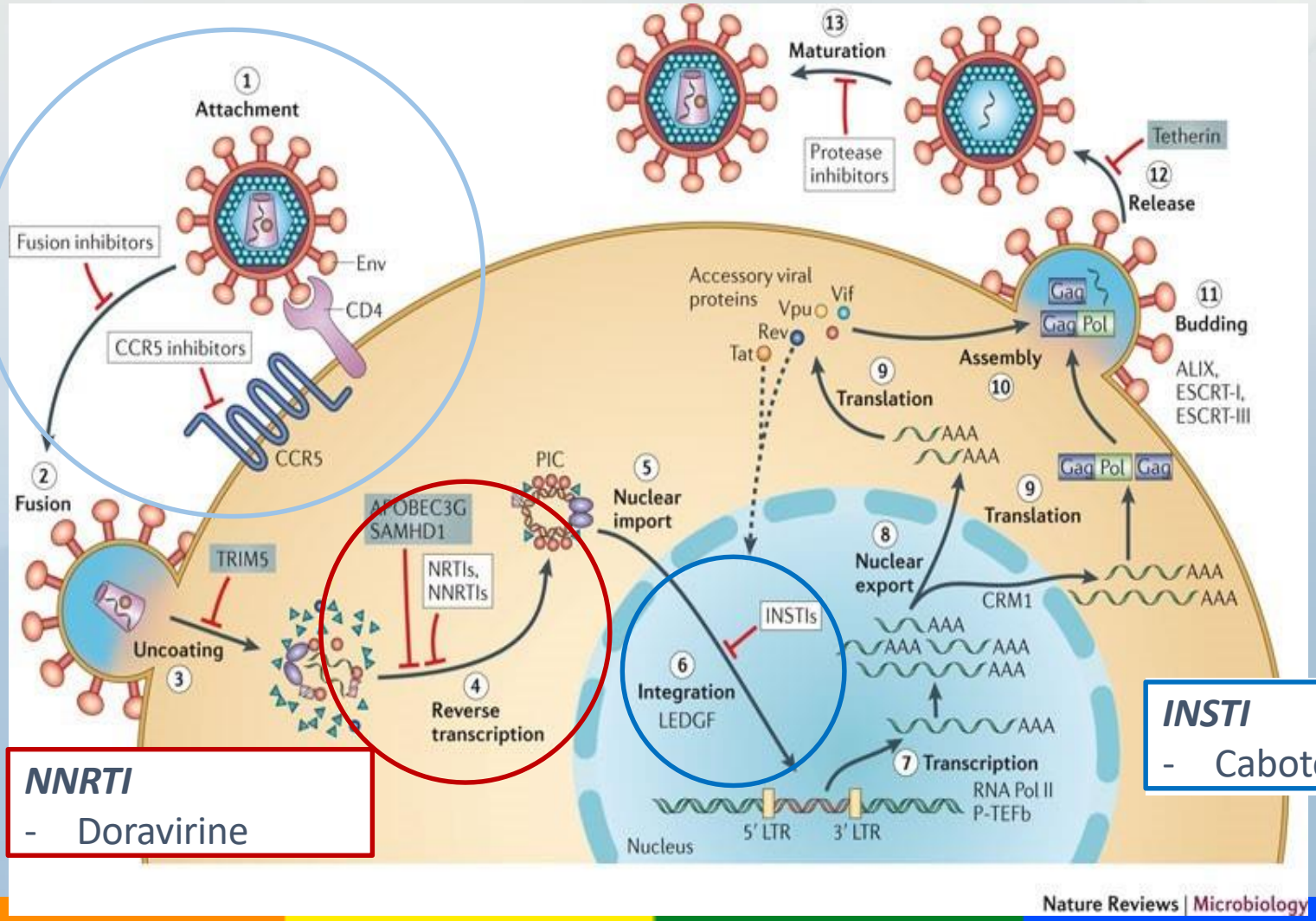
Emergent LEN Resistance, n (%)	Randomized Cohort (n=36)	Nonrandomized Cohort (n =36)
Participants meeting criteria for resistance testing	11 (31)	10 (28)
Emergent LEN resistance	4 (11)	4 (11)
▪ M661	4	2
▪ Q67H/K/N	1	2
▪ K70H/N/R/S	1	3
▪ N74D/H/S	3	0
▪ A105S/T	3	1
▪ T107A/C/N	1	3

- **All 8 persons with emergent LEN resistance were high risk for resistance** (0 active drugs in OBR, n = 4; inadequate adherence to OBR, n = 4)

Ogbuagu. CROI 2022. Abstr 491. Reproduced with permission

Recently approved drugs: Entry inhibitors

Entry inhibitors:
- Ibalizumab
- Fostemsavir

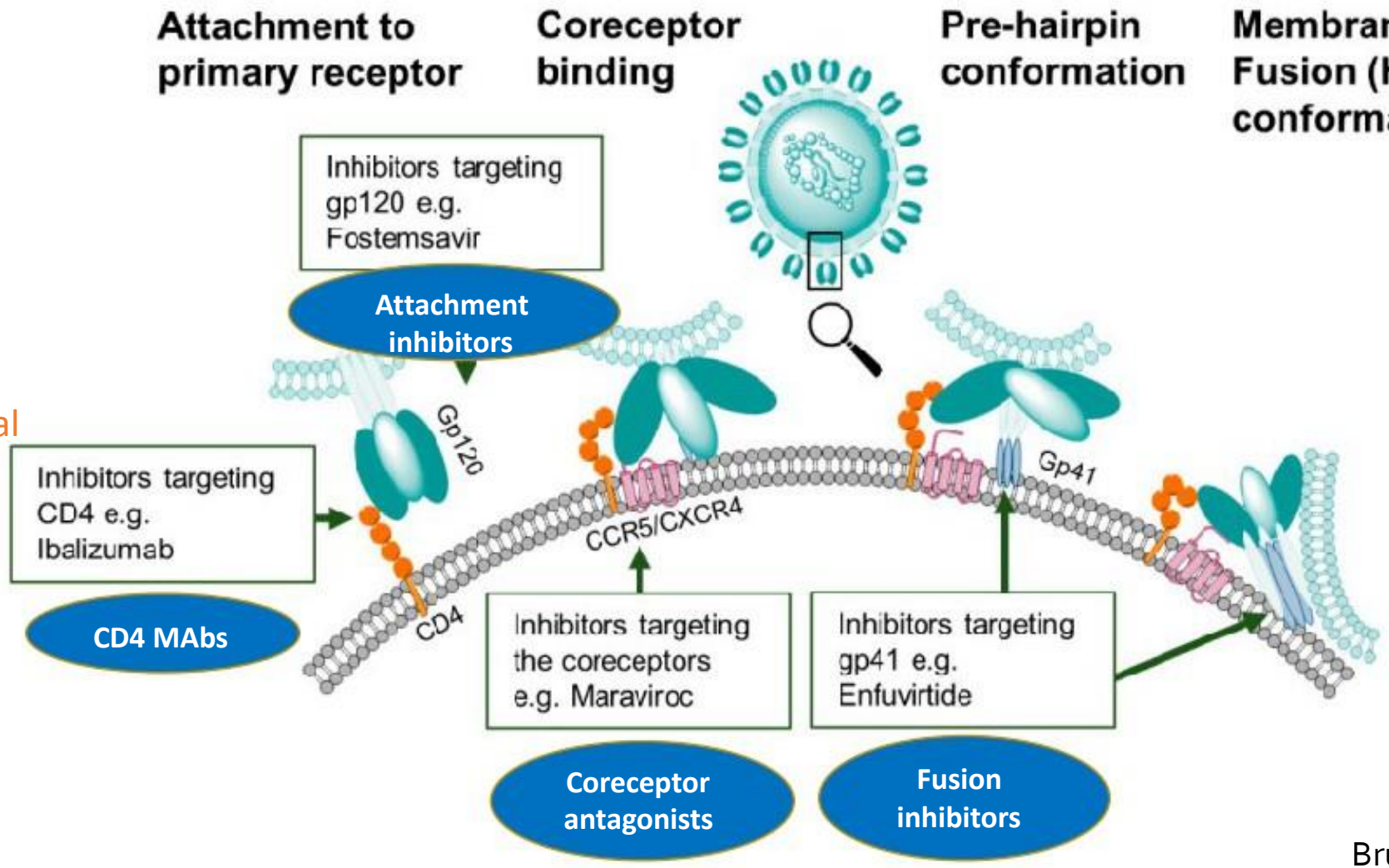


NNRTI
- Doravirine

INSTI
- Cabotegravir

Fostemsavir: active metabolite, temsavir, **binds to HIV-1 envelope glycoprotein 120 and prevents conformational changes** needed for viral interaction with CD4, thereby **blocking viral attachment and subsequent entry**

- **Ibalizumab**: monoclonal antibody that **binds to the T-cell CD4 receptor** and prevents conformational changes in CD4-gp120 complex, thereby **blocking viral entry**

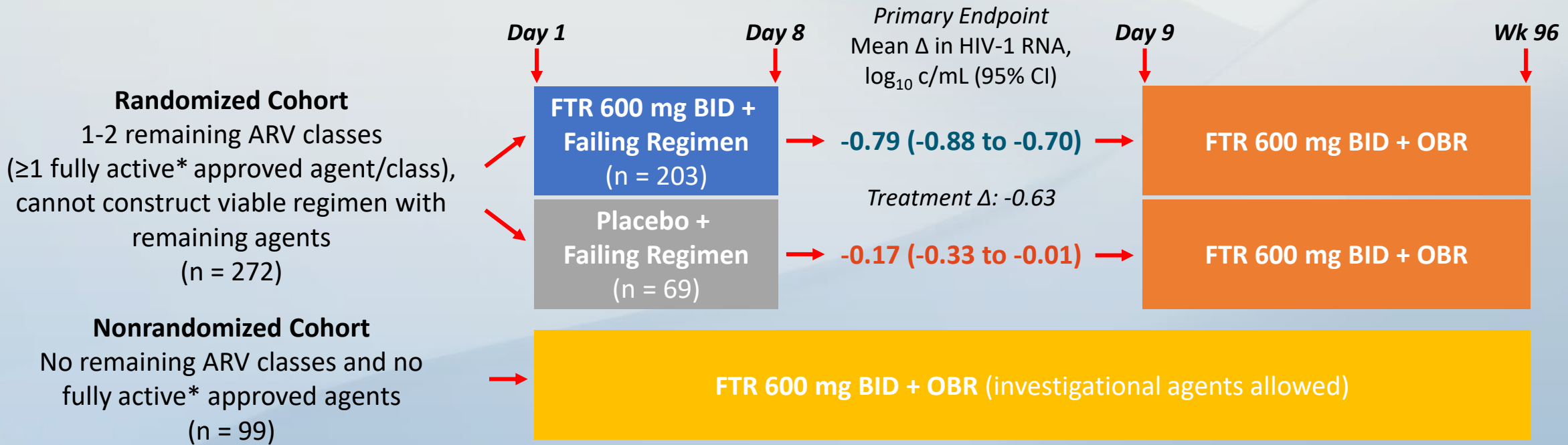


Bruxelle, Microorganisms 2021

Fostemsavir

- Oral extended-release tablets
- **One tablet taken twice daily, with or without food**
- Must be swallowed WHOLE; do not chew, crush, or split the tablets

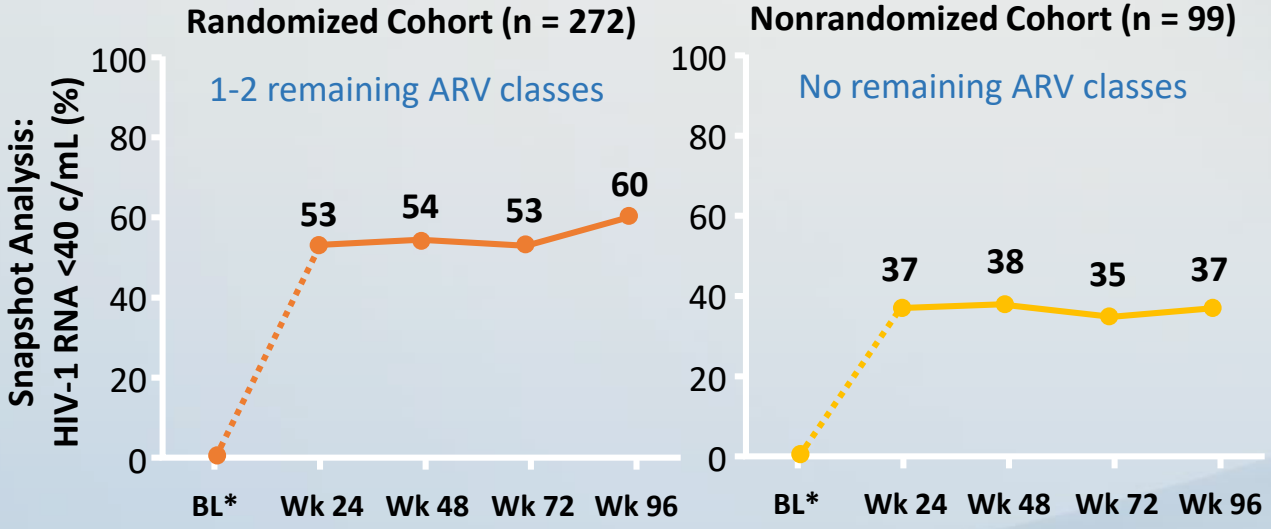
BRIGHTE: Fostemsavir in Heavily Treatment–Experienced Adults With Multidrug-Resistant HIV



*No evidence of resistance; patient eligible for, tolerant of, willing to receive the ARV.

Kozal. NEJM. 2020;382:1232. Pialoux. AIDS 2018. Abstr THPEB045.

BRIGHTE: Virologic and Safety Outcomes Through 96 Wk



Outcome at Wk 96, n (%)	Randomized (n = 272)	Nonrandomized (n = 99)
HIV-1 RNA <40 c/mL	163 (60)	37 (37)
HIV-1 RNA ≥40 c/mL	81 (30)	43 (43)
No virologic data	28 (10)	19 (19)
▪ D/c due to AE or death	15 (6)	14 (14)

*Snapshot analysis excluded BL data; 1 patient had BL HIV-1 RNA <40 c/mL.

- Cumulative safety outcomes through Wk 96 for all treated patients

Most common AE: **nausea (5%)**

Drug-related AEs: grade 2-4, 21%; serious, 3%

AEs leading to d/c: 7%

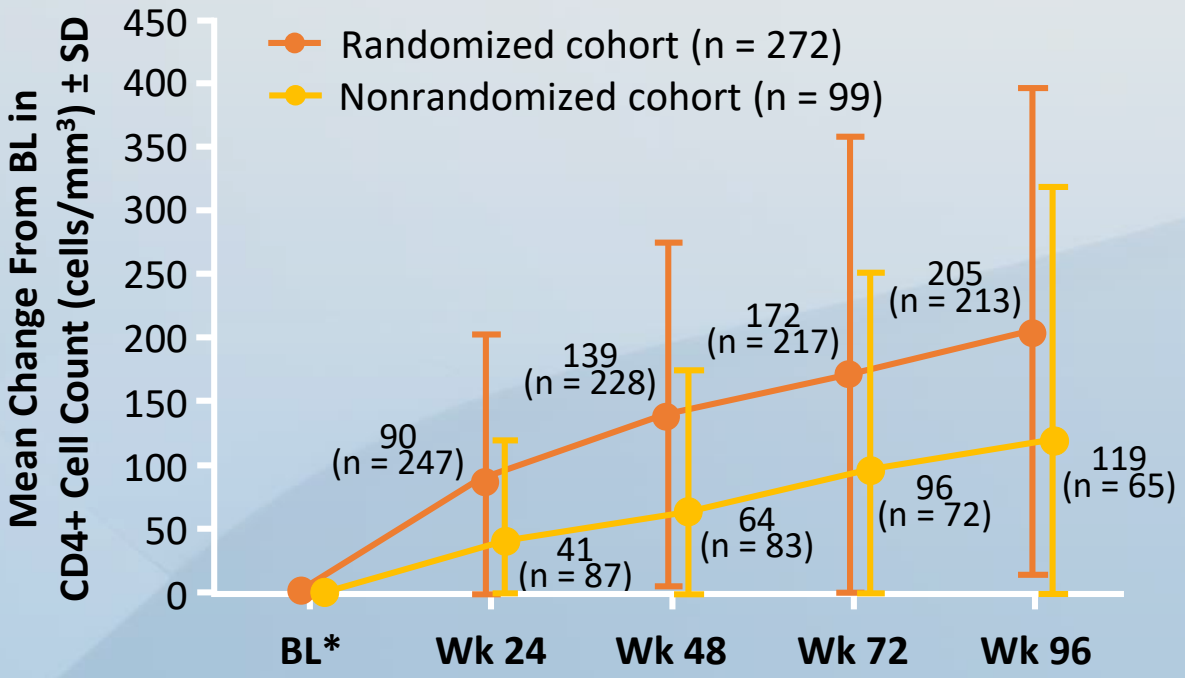
Death: 8%; most due to AIDS-related events or acute infections, 1 deemed treatment-related (IRIS)

1. Lataillade. IAS 2019. Abstr MOAB0102. 2. Lataillade. Lancet HIV. 2020;7:e740

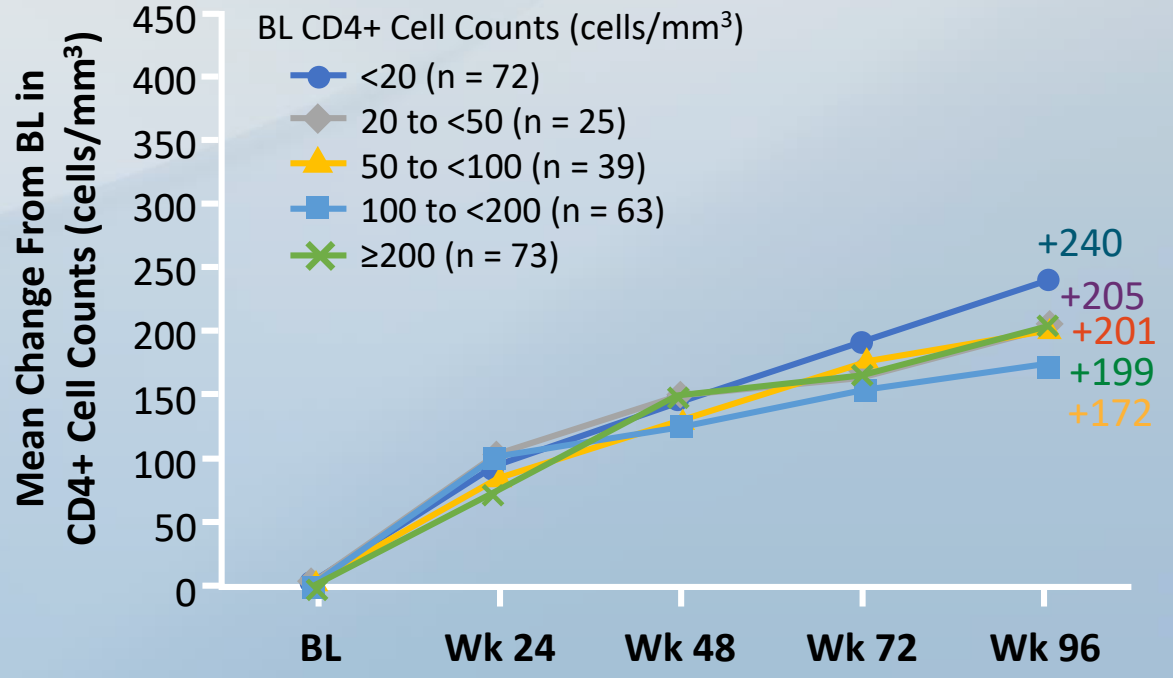
BRIGHTE: CD4+ Cell Counts Through Wk 96

- Among randomized patients with BL CD4+ cell count <50 cells/mm^3, **56% had a CD4+ cell count ≥200 cells/mm^3 at Wk 96**

By Cohort



By BL CD4+ Cell Count (Randomized Cohort)



*BL mean CD4+ cell count, cells/mm^3: randomized cohort, 153; nonrandomized cohort, 99.

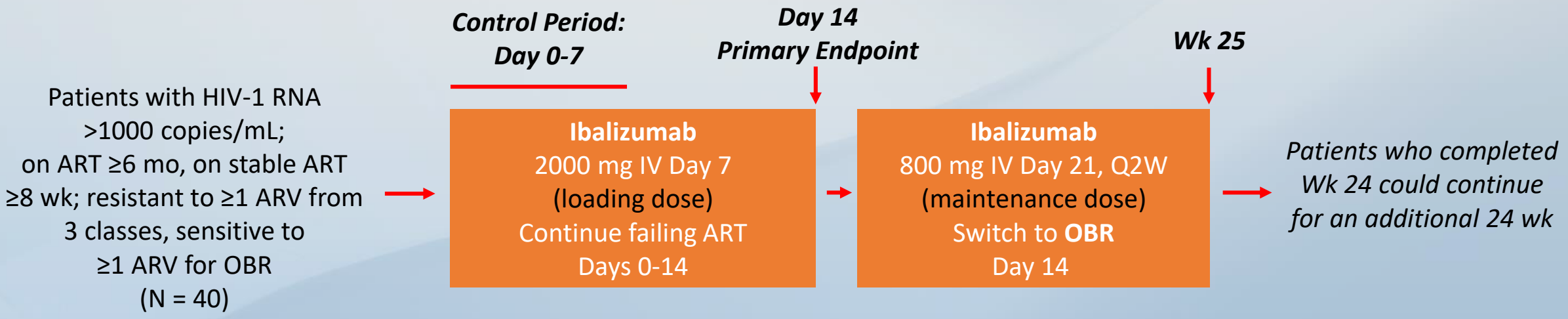
1. Lataillade. IAS 2019. Abstr MOAB0102. 2. Lataillade. Lancet HIV. 2020;7:e740

Ibalizumab

- Administered as an **IV infusion**
- Infusion given **every 2 wk** in cephalic vein of right or left arm
- First infusion ≥30 min followed by 1-hr observation; subsequent infusions can be decreased to ≥15 min followed by observation for 15 min if no Aes
- **It protects T-cell against the viral attachment**

TMB-301: Ibalizumab in Pretreated Patients Infected With Multidrug-Resistant HIV

- Single-arm, open-label phase III trial in patients with virologic failure
  - **Primary endpoint: HIV-1 RNA decrease ≥0.5 $\log_{10}$ copies/mL from baseline to Day 14**



- **53% with resistance to all drugs from ≥3 classes; 68% with INSTI resistance**
- **Mean BL VL 4.5 $\log_{10}$ copies/mL; mean BL CD4+ cell count: 150 cells/mm³**

Emu. NEJM. 2018;379:645.

TMB-301/-311: Ibalizumab in Heavily Treatment–Experienced Adults With Multidrug-Resistant HIV

- TMB-301: single-arm, open-label phase III trial in patients with virologic failure (53% with resistance to all drugs from ≥3 classes, 68% with INSTI resistance)
  - Control period (failing regimen only) on Days 0-7; ibalizumab 2000 mg IV loading dose on Day 7; failing regimen continued to Day 14 then switched to OBR; ibalizumab 800 mg IV on Day 21 then Q2W
- TMB-311: patients completing 25 wk in TMB-301 continue ibalizumab 800 mg Q2W for up to 96 wk

Virologic Outcome	Day 14[1] (N = 40)	Wk 25[1] (N = 40)	Wk 48[2,3] (N = 27)	Wk 96[4] (N = 27)
≥0.5 $\log_{10}$ HIV-1 RNA decrease, %	**83*†**	63	NR	NR
≥1.0 $\log_{10}$ HIV-1 RNA decrease, %	60	55	67	NR
Mean $\log_{10}$ HIV-1 RNA decrease	1.1	1.6	2.1	NR
Median $\log_{10}$ HIV-1 RNA decrease	NR	2.5	2.8	2.8
HIV-1 RNA <50 c/mL, %	NR	**43**	**59**	**56**
HIV-1 RNA <200 c/mL, %	NR	50	63	NR

*Primary endpoint; *P* <.0001 vs 3% at end of 7-day control period.
†3 patients without ≥0.5 $\log_{10}$ HIV-1 RNA decrease at Day 14 later reached HIV-1 RNA <50 c/mL with ibalizumab + OBR.[5]

1. Emu. NEJM. 2018;379:645. 2. Emu. IDSA 2017. Abstr 1686. 3. Emu. HIV Glasgow 2018. Abstr O345.
4. Emu. CROI 2019. Abstr 485. 5. DeJesus. HIV Glasgow 2018. Abstr P064.

TMB-301/-311: Safety and Immunologic Outcomes

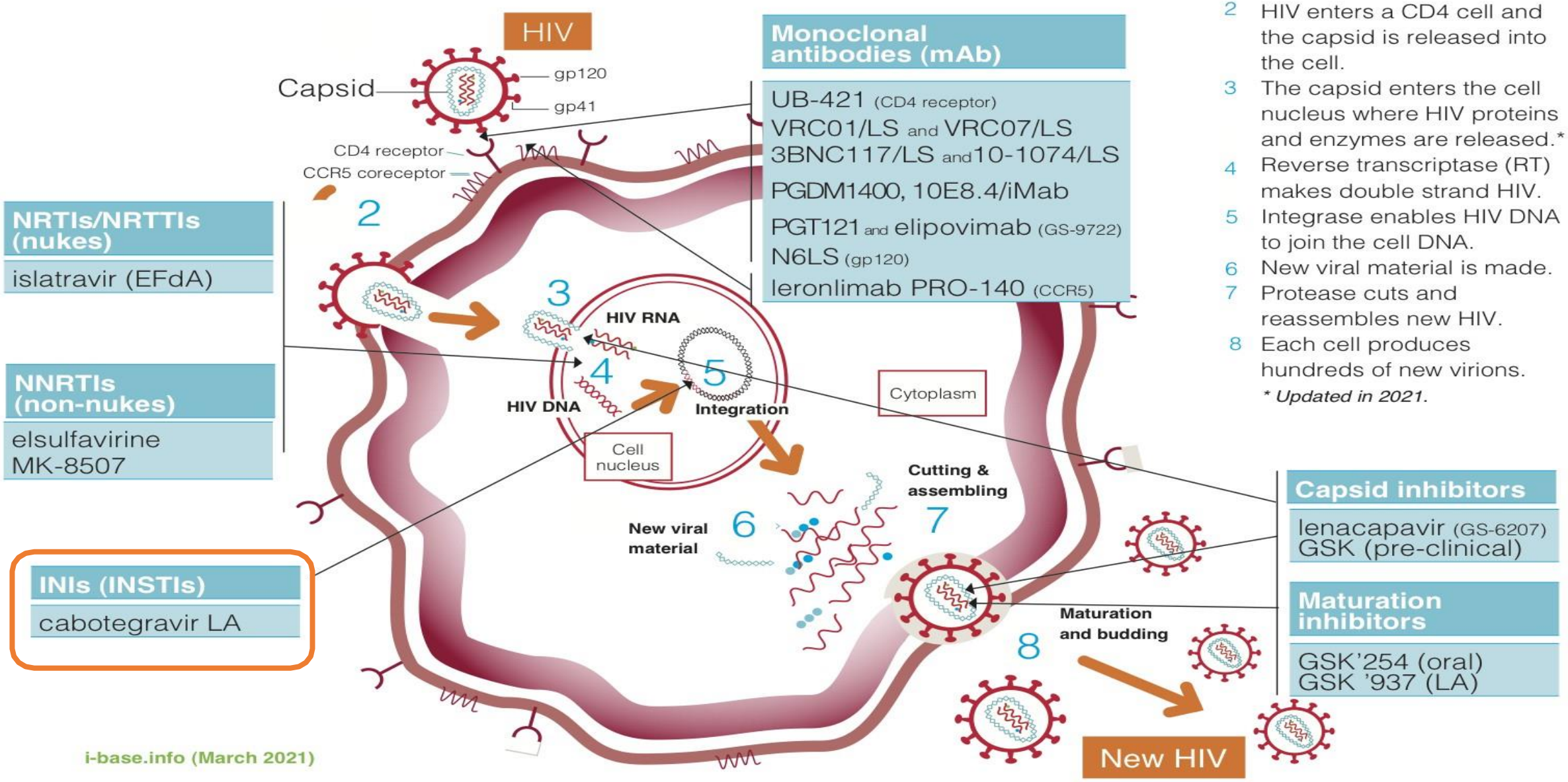
AEs Through Wk 25,[1] n (%)	Patients (N = 40)
Any AE	32 (80)
Assessed as related to ibalizumab	7 (18)
Leading to d/c of ibalizumab	5 (13)
Occurring in patients who died	4 (10)
Serious AE	9 (23)
AEs occurring in >10% of patients	
▪ Diarrhea	8 (20)
▪ Dizziness	5 (13)
▪ Fatigue	5 (13)
▪ Nausea	5 (13)
▪ Pyrexia	5 (13)
▪ Rash	5 (13)

- **Reasons for early d/c (none related to ibalizumab):**
  - Consent withdrawal: n = 2
  - Physician decision: n = 1
  - Death: n = 2 (advanced CVD, CMV progression)
- **Median CD4+ cell count increases from baseline[2]:**
  - Wk 25: 42 cells/mm^3 (n = 27)
  - Wk 96: 45 cells/mm^3 (n = 22)

1. Emu. NEJM. 2018;379:645. 2. Emu. CROI 2019. Abstr 485.

Novel switch strategies

HIV pipeline 2021: targets in the HIV lifecycle



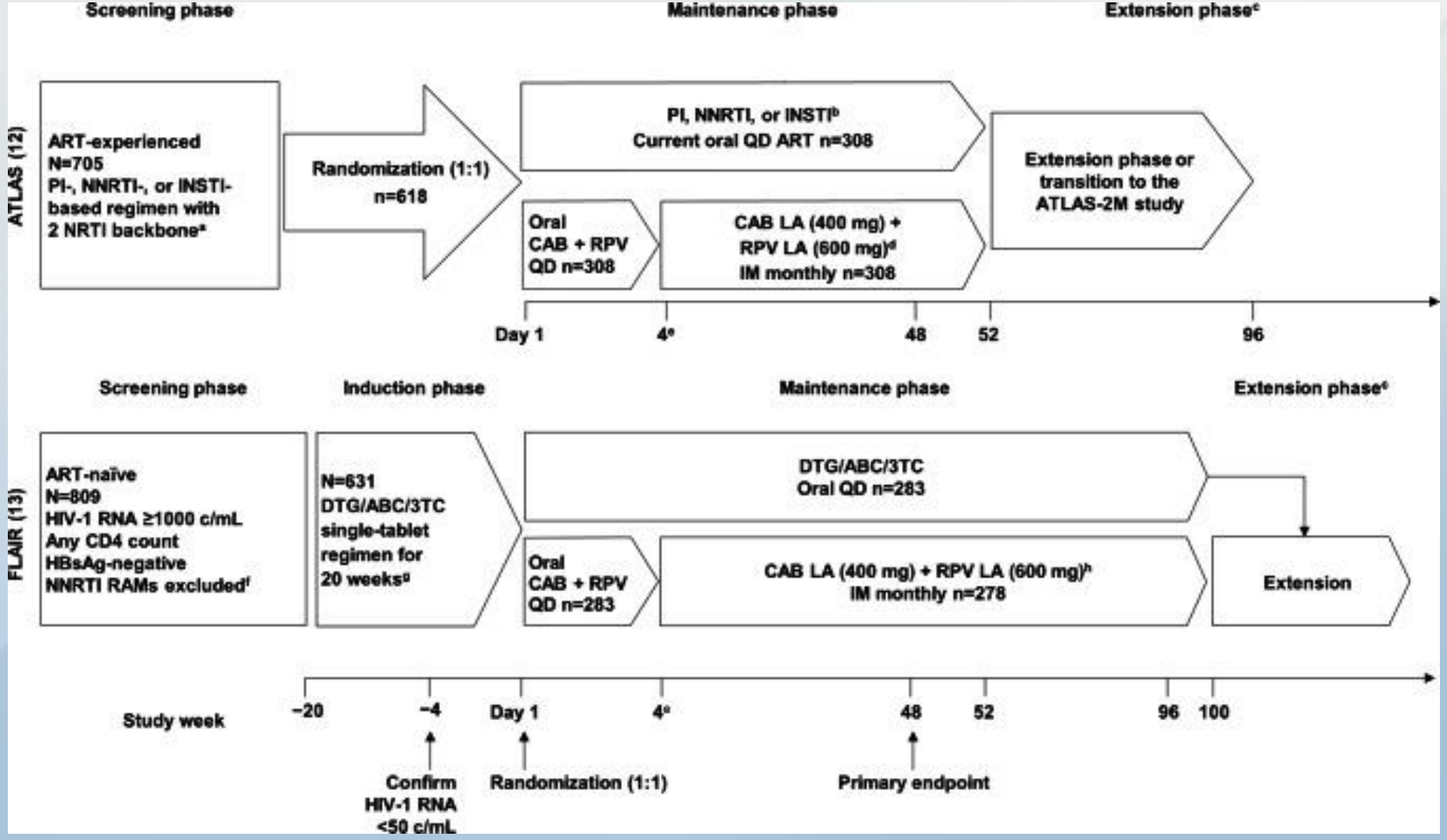
Stages in the HIV lifecycle

1. HIV attaches to a CD4 cell.
2. HIV enters a CD4 cell and the capsid is released into the cell.
3. The capsid enters the cell nucleus where HIV proteins and enzymes are released.*
4. Reverse transcriptase (RT) makes double strand HIV.
5. Integrase enables HIV DNA to join the cell DNA.
6. New viral material is made.
7. Protease cuts and reassembles new HIV.
8. Each cell produces hundreds of new virions.

** Updated in 2021.*

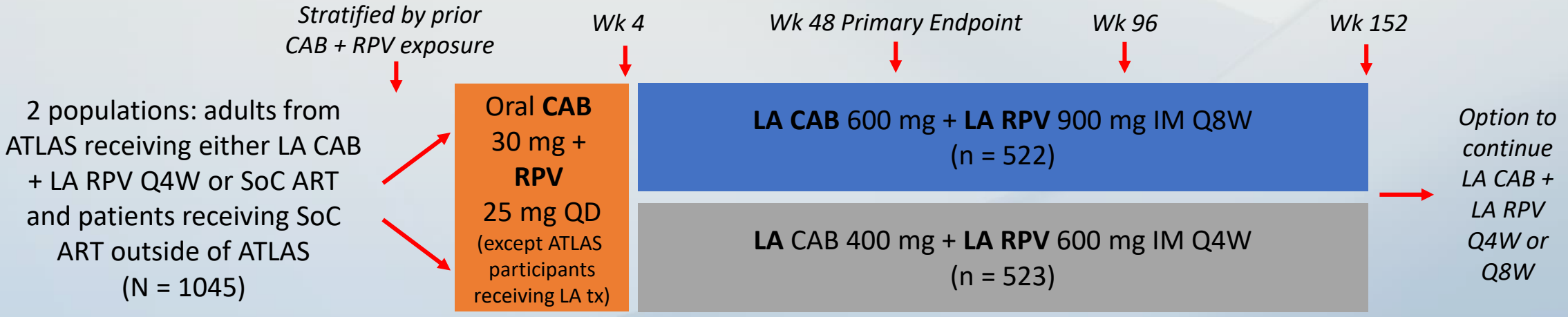
i-base.info (March 2021)

ATLAS and FLAIR studies



ATLAS-2M: LA CAB + RPV Q8W vs Q4W

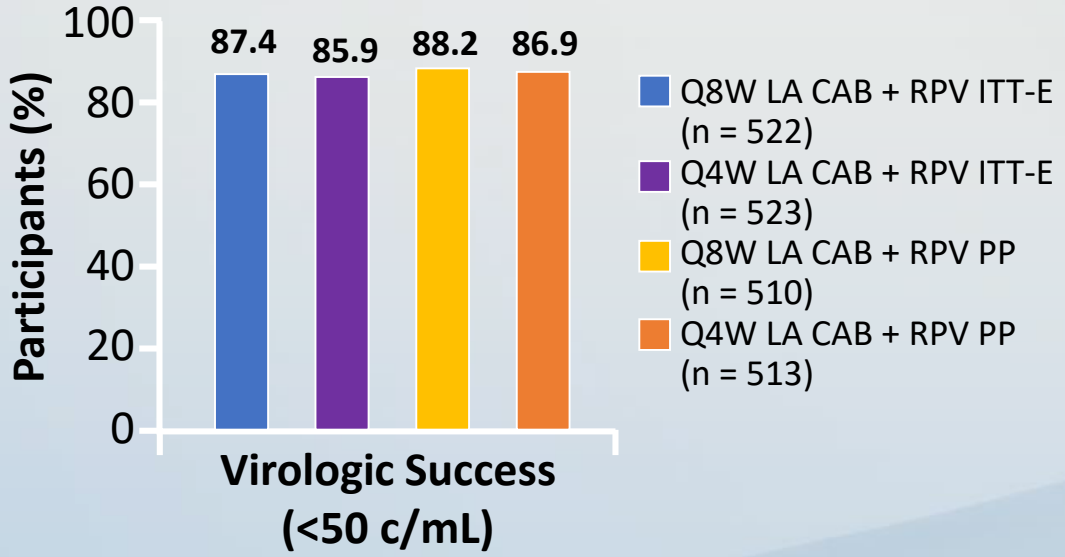
- Multicenter, randomized, open-label phase IIIb noninferiority trial



- Primary endpoint: HIV-1 RNA ≥50 c/mL at Wk 48 by FDA snapshot in ITT-E
  - Q8W found to be noninferior to Q4W at Wk 48
- Wk 152 endpoints: plasma HIV-1 RNA ≥50 or <50 c/mL at Wk 152 by FDA snapshot in ITT-E, CVF incidence, viral resistance in patients with CVF, safety and tolerability, treatment satisfaction

Overton. Lancet. 2021;396:1994. Overton. CROI 2022. Abstr 479. NCT03299049.

ATLAS-2M: Wk 152 Outcomes



- LA CAB + RPV well tolerated
  - 99% of ISRs were grade 1/2; median duration was 3 days
  - 8 (2%) Q8W and 13 (3%) Q4W withdrew due to ISRs
- Patient satisfaction scores significantly favored Q8W vs Q4W dosing at week 24, 48, 152

- 13 participants had CVF: Q8W, n = 11 (2%); Q4W, n = 2 (<1%)
  - None with injection >7 days late

Overton. Lancet. 2021;396:1994. Overton. CROI 2022. Abstr 479.

Risk Factors for Virologic Failure With LA CAB + RPV

- Post hoc analysis of **Wk 48 phase III data**[1]
  - ATLAS and FLAIR (Q4W dosing)
  - ATLAS-2M (Q4W and Q8W dosing)
- 13/1039 (1.25%) participants had CVF in ATLAS, FLAIR, ATLAS-2M
- Among 96.7% with 0 or 1 risk factor for CVF, 0.4% had CVF
- Q8W dosing was not a significant factor associated with CVF

--- INDICATIONS AND USAGE----------
CAB/RPV … is indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine.[2]

Factors Associated With CVF	OR
RPV RAS(s) at baseline	40.36
Wk 8 RPV trough concentration	5.00
Baseline HIV-1 subtype A6/A1	5.92
BMI (kg/m^2) at baseline	1.13

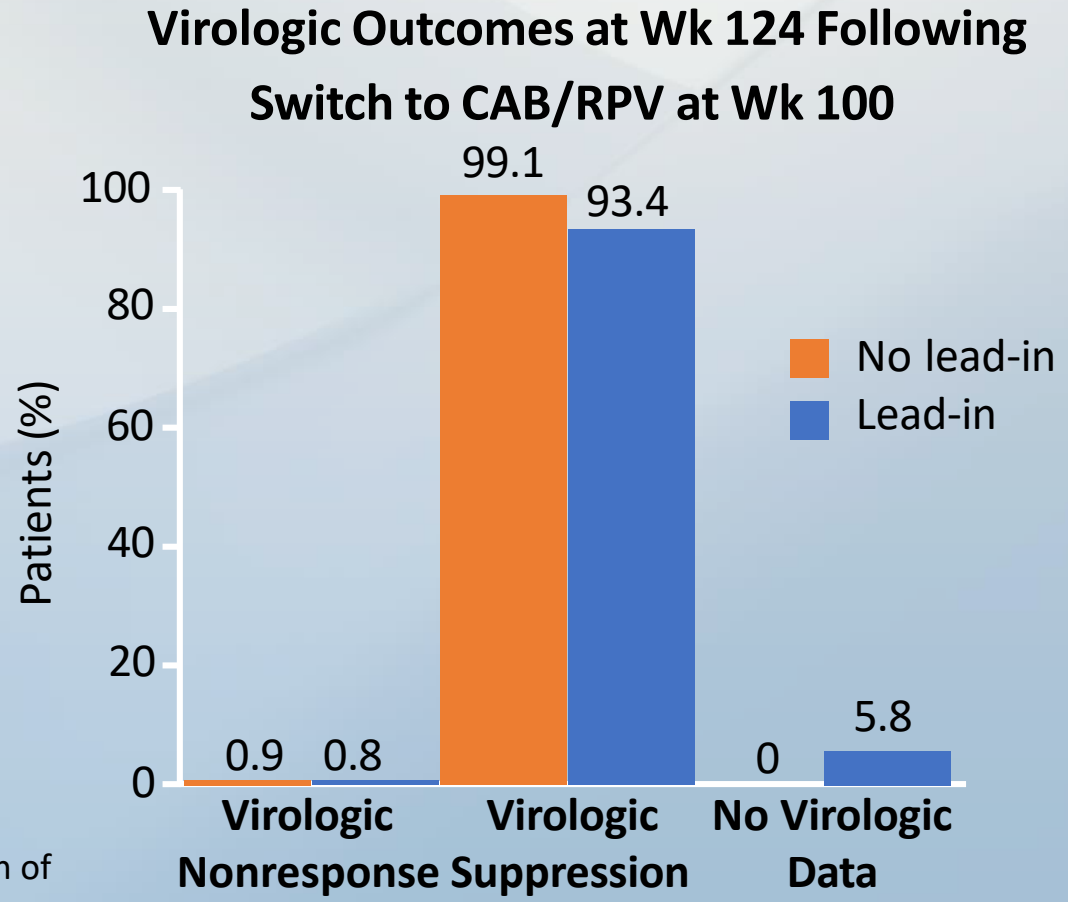
No. of Baseline Factors Associated With CVF	CVF, %	HIV-1 RNA <50 c/mL, %
None	0.4	95
1	0.4	96
≥2	26	71
Total	**1.3**	**94**

1. Cutrell. AIDS. 2021;35:1333. 2. Injectable CAB + RBV PI.

Slide credit: clinicaloptions.com

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

- FLAIR extension study[1]
  - Participants receiving DTG/ABC/3TC achieving virologic suppression (HIV-1 RNA <50 c/mL) could switch to monthly LA CAB + RPV at Wk 100
  - Switchers elected to start with (n = 121) or without (n = 111) oral CAB + RPV lead-in
    - **As of March 2022, the oral lead-in is optional according to the FDA approved prescribing information[2]**



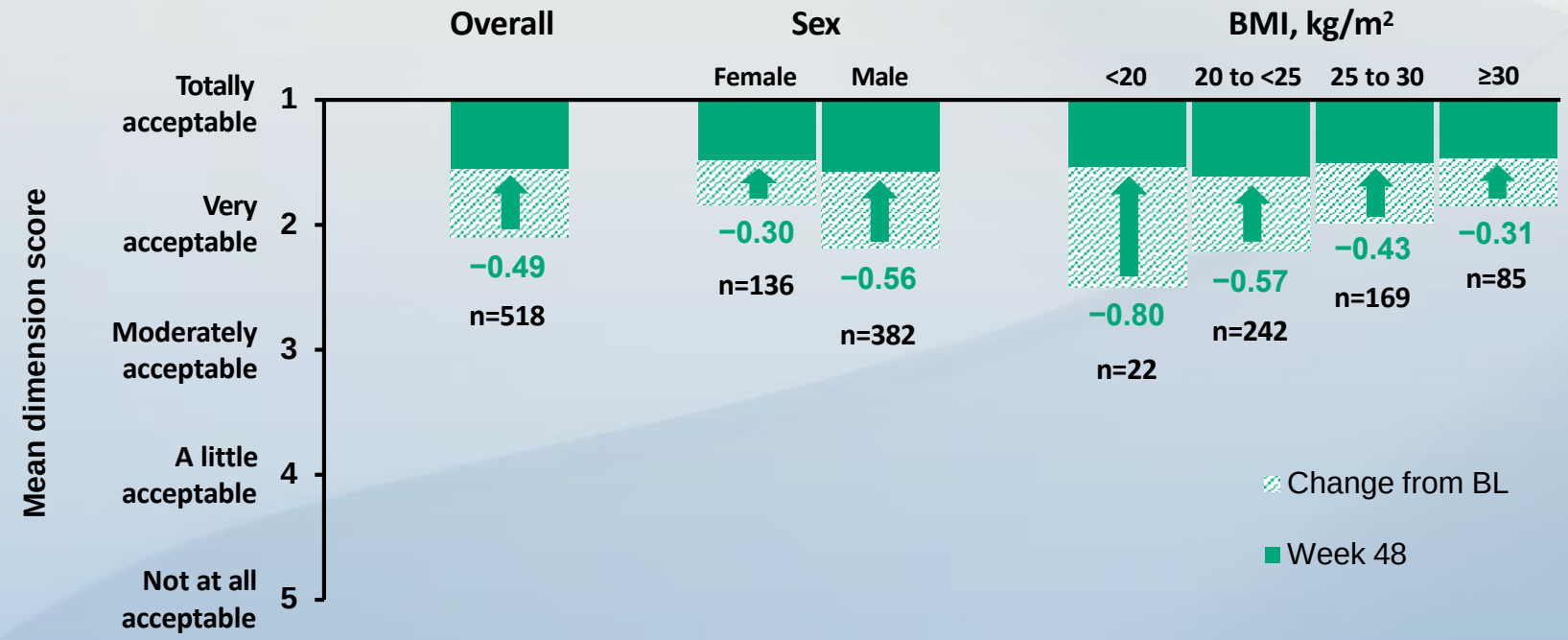
*Burden of travel, prohibited medication use, participant relocation, burden of procedures/intolerability of injections, and pregnancy.

1. Orkin. Lancet HIV. 2021;8:e668. 2. Cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension PI.

Slide credit: clinicaloptions.com

Pooled ATLAS and FLAIR sub-group analysis: Acceptance of ISRs improves over time regardless of sex or BMI (PIN)

Mean change in PIN acceptability of ISR scores from BL (Week 5) to Week 48



- Female participants and those with higher BMI were more accepting of pain and ISRs at Week 5 ($p<0.05$)
- Acceptability of ISRs with CAB + RPV LA was high at BL (Week 5) overall, and reached similar high levels at Week 48 for all subgroups, regardless of initial PIN scores

- Chounta V, et al. HIV Glasgow 2020. Poster P012

CARLOS: Patient and HCP Perspectives on Switching From Daily Oral ART to Long-Acting CAB + RPV

- Ongoing 3-yr, noninterventional, prospective cohort study in Germany
- Analysis includes 236 PWH who switched from daily ART to LA CAB + RPV Q2M injections May - December 2021
  - PWH and HCP treatment perspectives assessed through surveys conducted at baseline

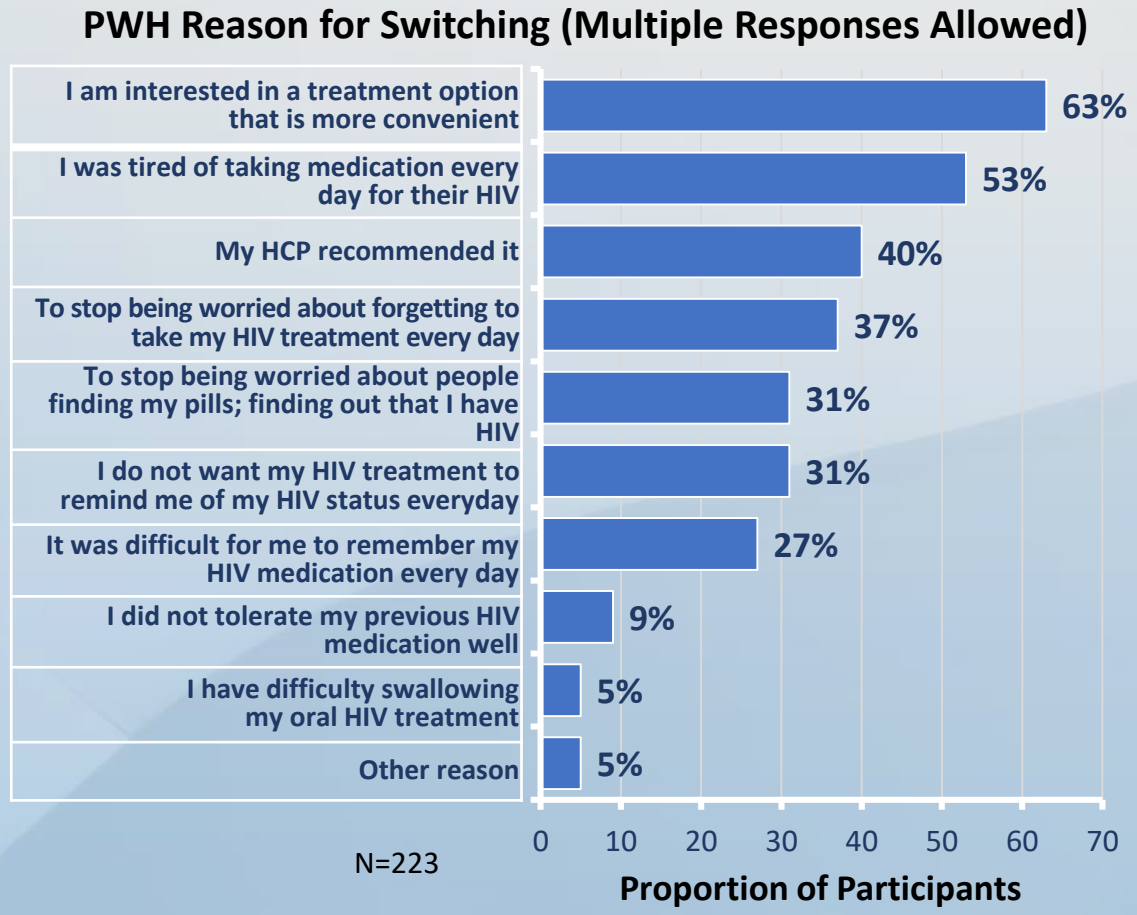
Most Common Patient-Reported Challenges With Daily HIV Medication, %	**N = 223**
Daily HIV med routine was inconvenient	40
Felt they had to hide daily HIV meds from others	34
Daily HIV meds reminded them of their HIV status	27
Problems remembering to take daily HIV meds	27

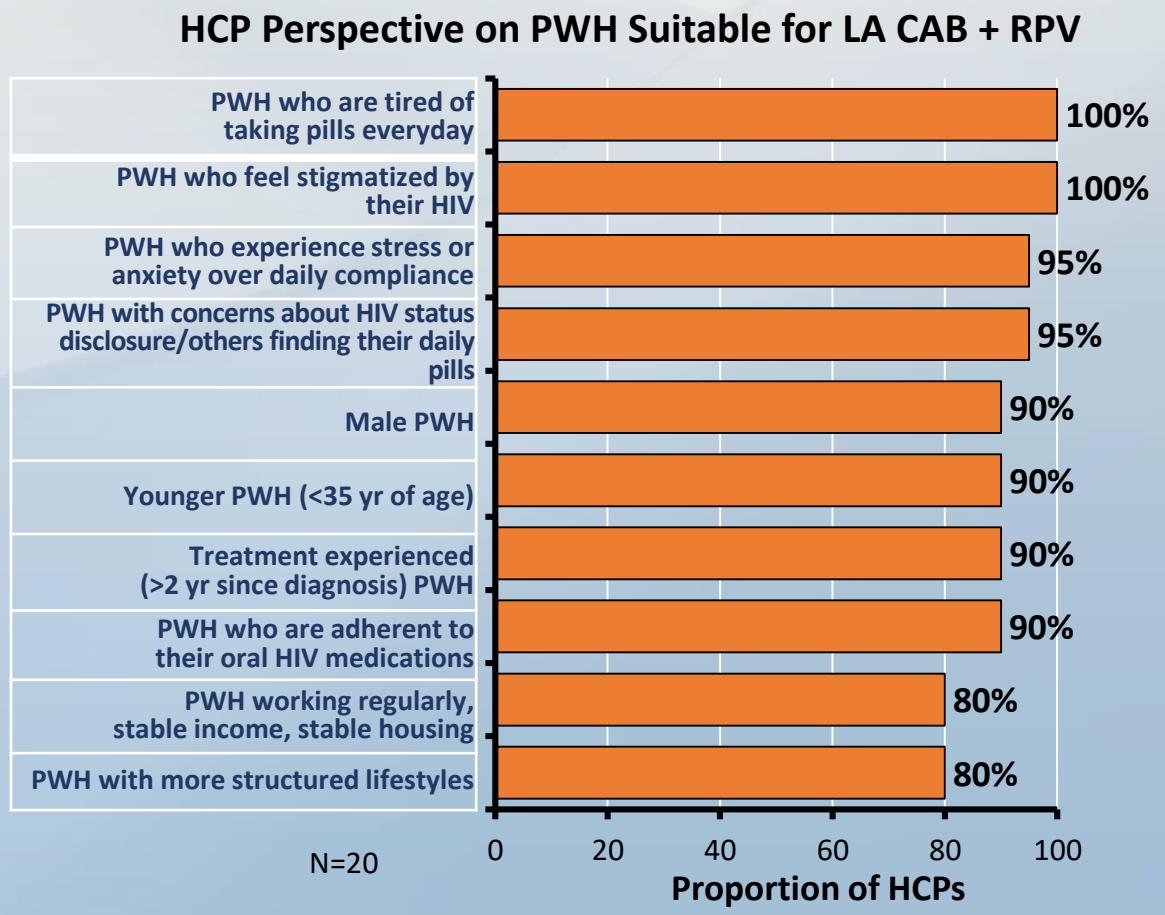
Most Common Patient-Reported Concerns About LA CAB + RPV, %	**N = 221**
Pain or soreness from the injection	33
Impact on HIV-1 RNA and/or CD4 counts	27
AEs from the injection	26
Scheduling travel/holiday to meet 2-wk injection window	23
No worries about LA CAB + RPV injection	32

Scherzer. AIDS 2022. Abstr EPB179.

CARLOS: Perspectives on Switching From Daily Oral ART to Long-Acting ART

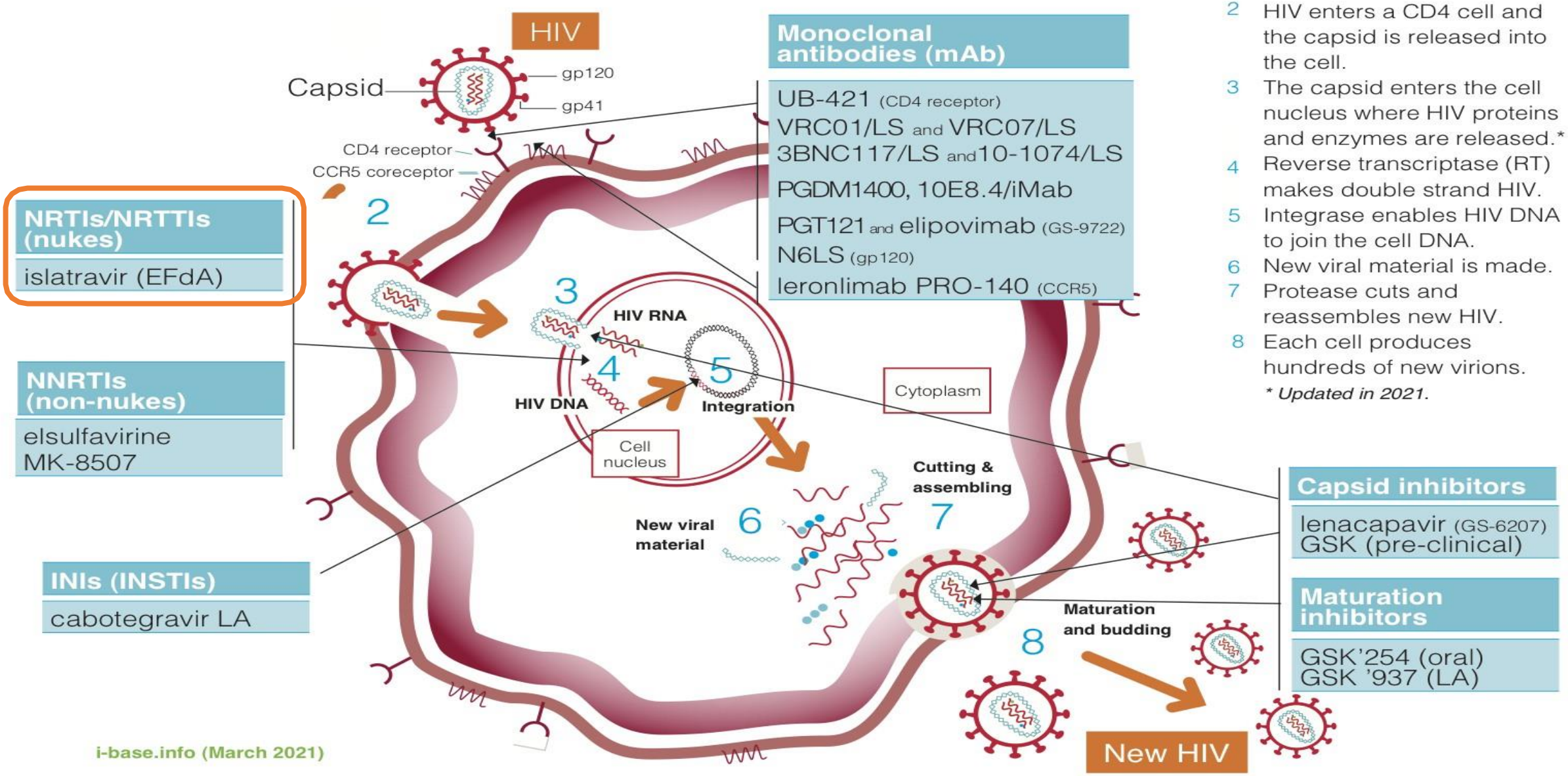
- HCP noted "patient wish" as main reason for switch to LA CAB + RPV (reason given by 92% HCPs)





Scherzer. AIDS 2022. Abstr EPB179.

HIV pipeline 2021: targets in the HIV lifecycle



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5. Integrase enables HIV DNA to join the cell DNA.
6. New viral material is made.
7. Protease cuts and reassembles new HIV.
8. Each cell produces hundreds of new virions.

** Updated in 2021.*

i-base.info (March 2021)

Islatravir

December 13th, 2021

Merck Announces Clinical Holds on Studies Evaluating Islatravir for the Treatment and Prevention of HIV-1 Infection

Dose related immunological concerns:

- Treatment programme: mean drop CD4 cells
- PrEP programme: mean drop in total lymphocyte count

MERCK

NEWS RELEASE

Merck to Initiate New Phase 3 Clinical Program with Lower Dose of Daily Oral Islatravir in Combination with Doravirine for Treatment of People with HIV-1 Infection

9/20/2022

Phase 2 study evaluating an investigational weekly oral combination treatment regimen of islatravir and Gilead Sciences' lenacapavir to resume with lower dose of islatravir

Monthly oral islatravir development for pre-exposure prophylaxis (PrEP) to be discontinued; Merck continues to evaluate other long-acting PrEP candidates

Key Take-home messages for LA therapies

- **LAA clinical trials represent the first systematic evidence of how indispensable patient voice is to the long-term effectiveness of a treatment strategy**

- In CARLOS study of patient and HCP perspectives on switching from daily oral ART to LA CAB + RPV, most common reasons for patients to switch were convenience and daily pill fatigue; for HCPs, most common reason was patient choice

- Extending the evidence to more complex situations such as nonadherent patients, adolescents, pregnant women, elderly patients is a research priority in this area.

Key Take-home messages in HTE

- Incidence of MDR HIV has significantly decreased since 2008-2009, and patients with MDR and VF are increasingly rare
- Many new ART options available with new MoA
- Genotype may predict drug susceptibility with good/high accuracy
- None of the new drugs can be labelled as high genetic barrier drug
- It is pivotal to identify and solve other underlying reasons for VF (adherence, addiction, mental health)
- Every case needs an individualized approach and knowledge in HIV resistance (expert consultation)