Terapia long-acting

Giuliano Rizzardini
Dipartimento Malattie Infettive ASST Fatebenefratelli Sacco, Milano
School of Clinical Medicine, Faculty of Health Science,
University of the Witwatersrand, Johannesburg

Sistema Socio Sanitario
Regione Lombardia
ASST Fatebenefratelli Sacco

Disclosure

Advisory committees, speaking and teaching:

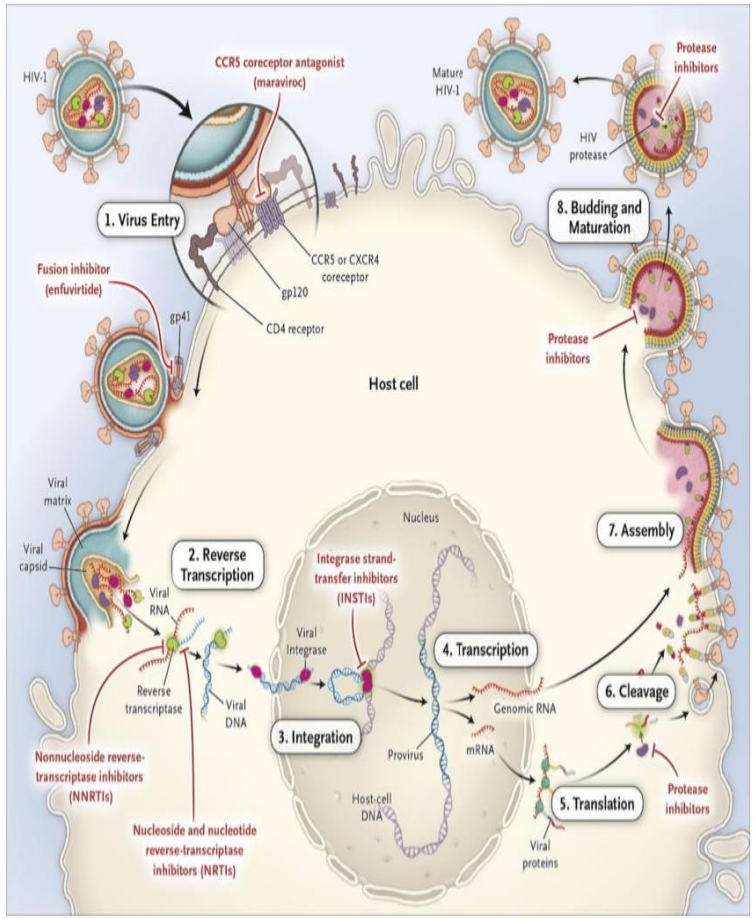
AbbVie, Angelini, Gilead, Janssen, GSK, Merck, ViiV

Grant and research support:

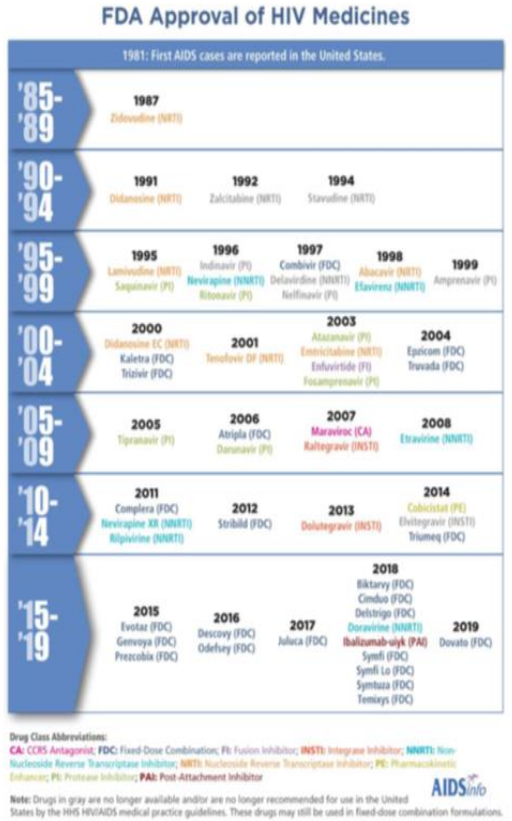
Abbvie, Gilead, Merck, GSK

Antiretroviral therapy: a success story

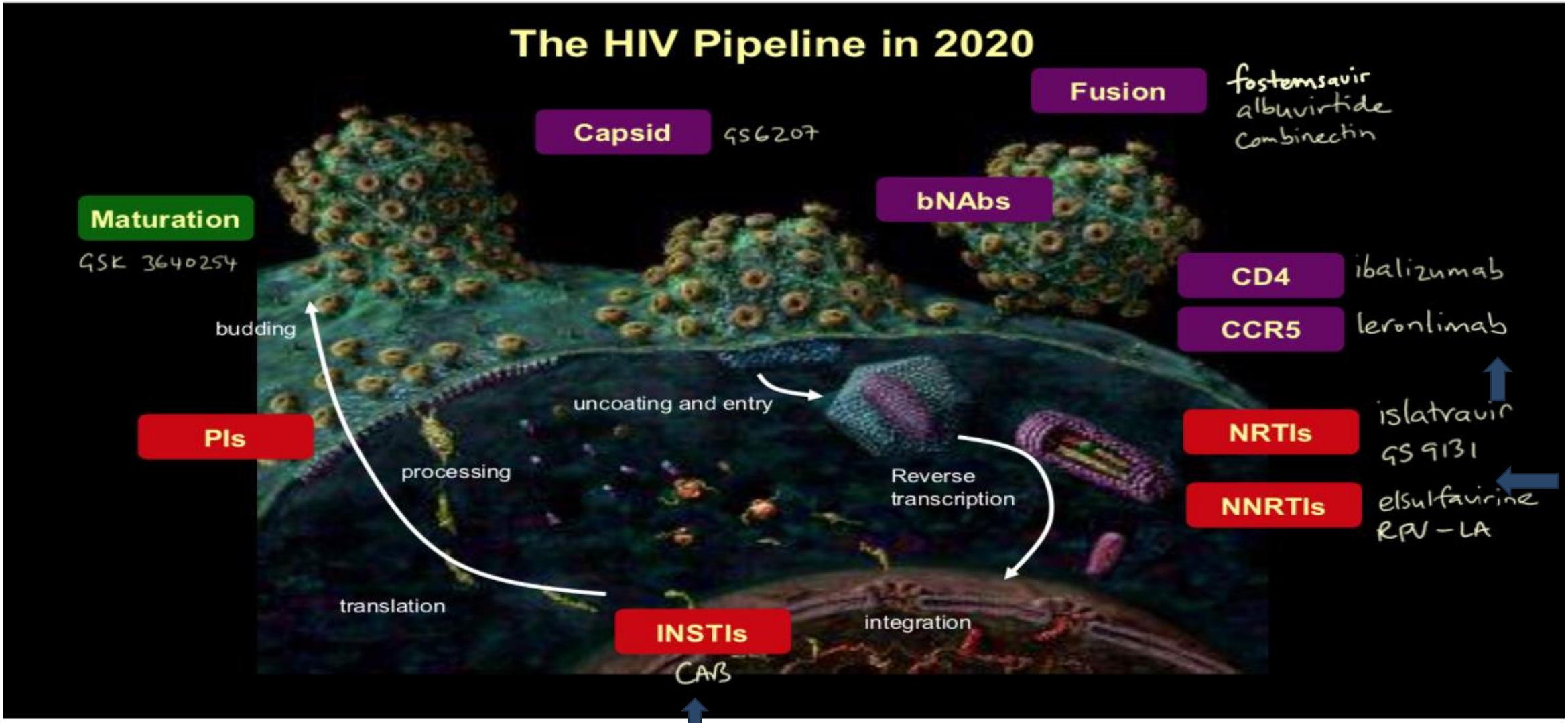
HIV Life Cycle



https://www.hiv.uw.edu/go/antiretroviral-therapy/general-information/core-concept/all#antiretroviral-regimens-initial-therapy

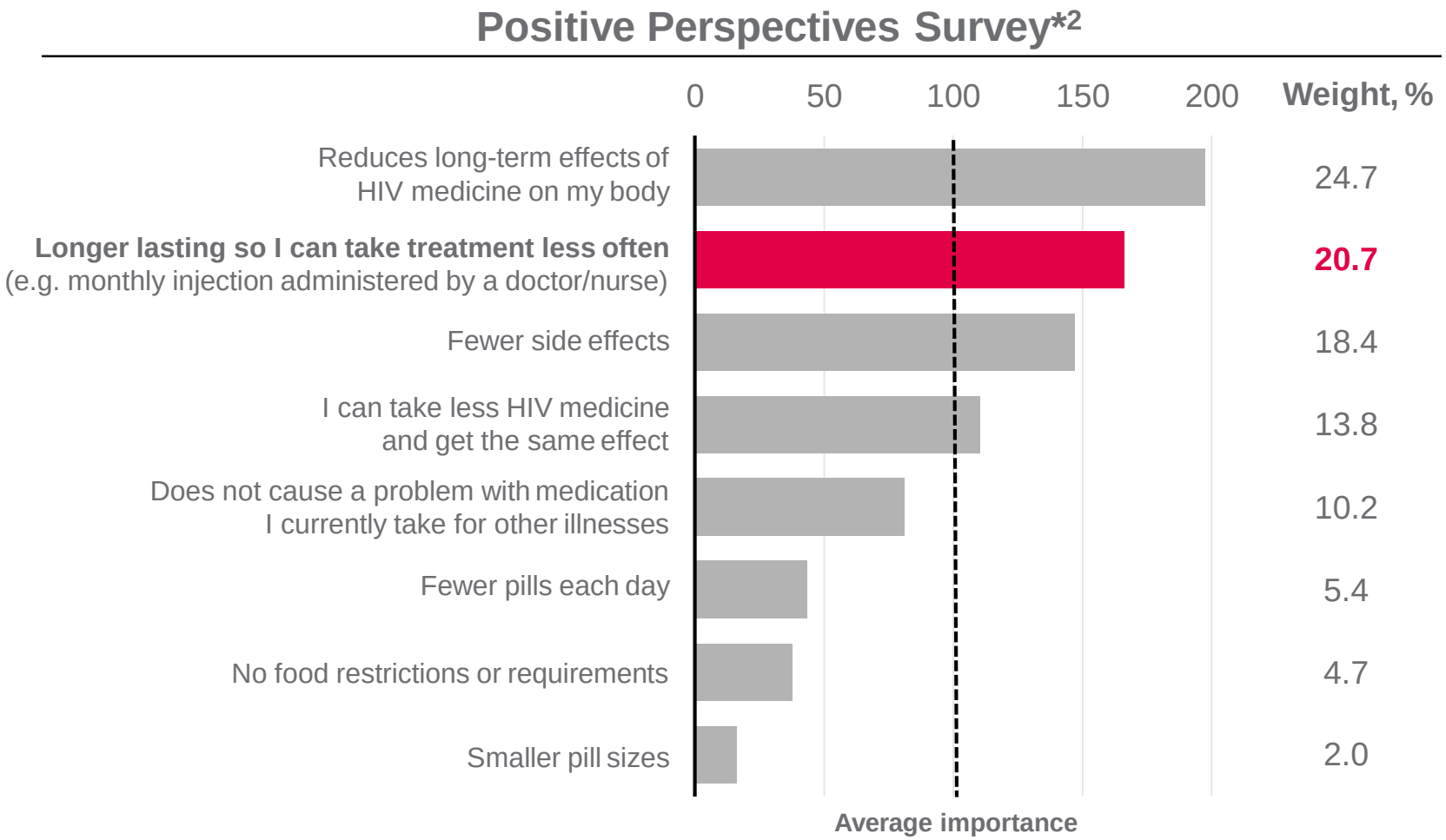


Do we need new antiretorvirals?



Unmeet NEEDS (PLHW): issues still left unsolved in HAART era

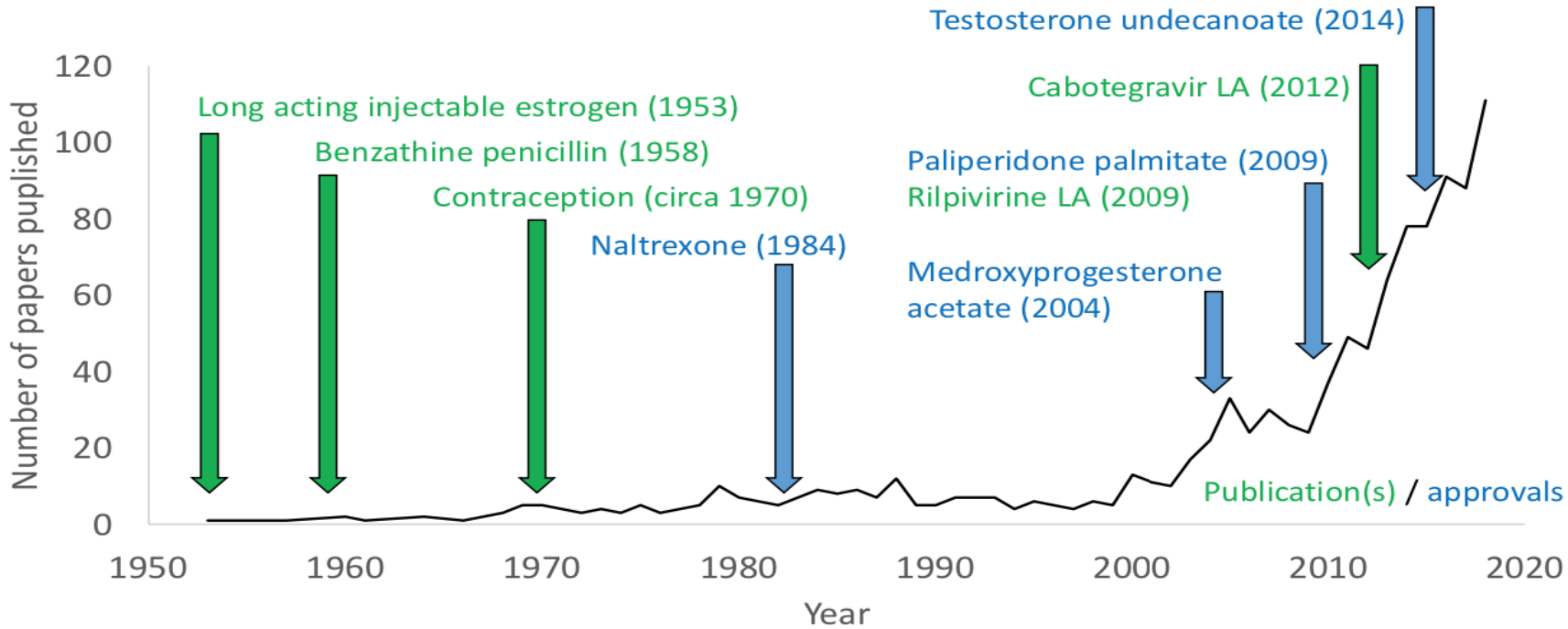
- Treatments need to fit in with an individual patient's routine, expectations, and preferences[1]
- Long-lasting treatment, requiring less frequent dosing, is one of the most important unmet needs for PLHIV – more so than reduction of side effects and pill burden[2]



*The Positive Perspectives Survey was conducted between 2016 and 2017 in nine countries. Participants were enrolled from North America, Europe, and Australia (N=1,111)

1. DHHS. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Dec 2019
2. Young B, et al. IDWeek 2017. Poster 1393

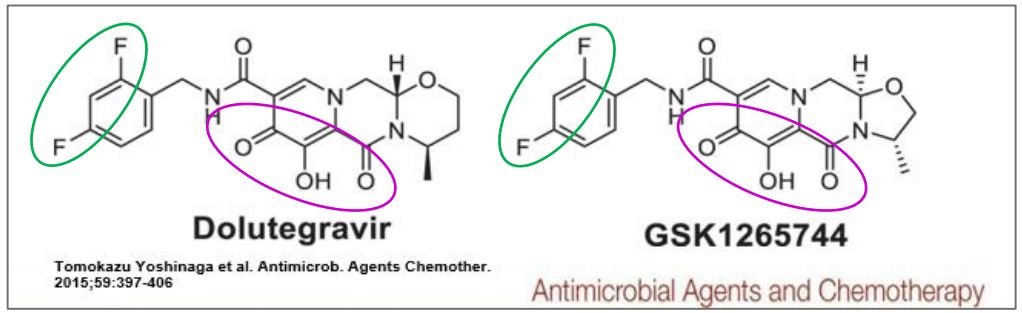
Long-acting injectables / parenterals: brief history



Using Pubmed search term: *"long acting injectable" OR "long acting parenteral" OR "long acting depot"*

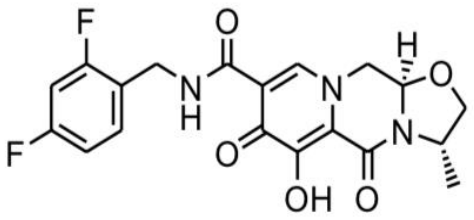
Commitment to Next Generation INIs (2009)[1]

1. Engineered to deliver improvements to patients
   - Superior resistance profile
   - Dosing convenience
2. S/GSK1265744 has similar attributes to S/GSK1349572
   - Unboosted, once daily dosing
   - Low PK variability
   - Potent antiretroviral activity in a phase 1-2a study
3. S/GSK1265744 is the backup compound to S/GSK1349572

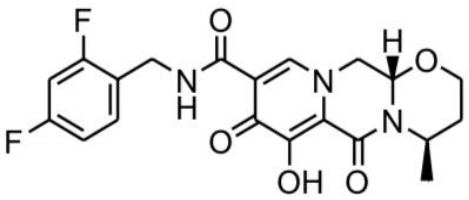


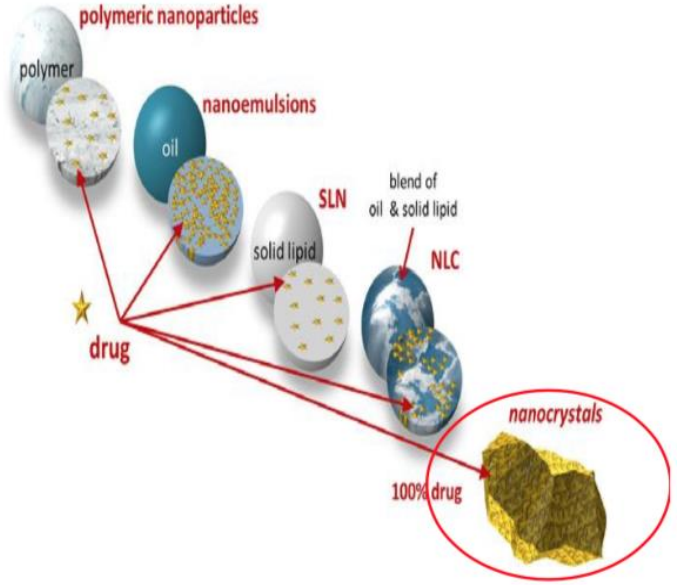
GSK744 LA is Formulated as a 200 mg/mL Nanosuspension

GSK1265744
(GSK744)



Dolutegravir





R H. Müller, et al. European Journal of Pharmaceutics and Biopharmaceutics 78 (2011) 1-9
W. Spreen,7th IAS, Jun 2013.
S. Min, et al, 49th ICAAC, Sept 2009. Abstract H-1228
Y. Taoda, et al, 11th International Congress on Drug Therapy in HIV Infection, Nov 2012. Abstract P206

1. Min, et al. 49th ICAAC, 12–15 September 2009, San Francisco, CA, USA. Abstract #H1228.

Background

- Cabotegravir (CAB) is an HIV-1 integrase inhibitor
  - Oral 30 mg tablet, $t_{½}$ ~40 hours
  - IM LA injection 200 mg/mL, $t_{½}$ ~40 days
- Rilpivirine (RPV) is an HIV-1 NNRTI
  - Oral 25 mg tablet, $t_{½}$ ~50 hours
  - IM LA injection 300 mg/mL, $t_{½}$ ~90 days

- LATTE-2: CAB LA + RPV LA given IM every 4 or 8 weeks maintained high rates of HIV-1 RNA <50 copies/mL through 3 years[1]

ART, antiretroviral therapy; CAB, cabotegravir; IM, intramuscular; LA, long acting; RPV, rilpivirine; $t_{½}$, half-life.

1. Margolis D, et al. *HIV Glasgow*, UK. Poster 118.

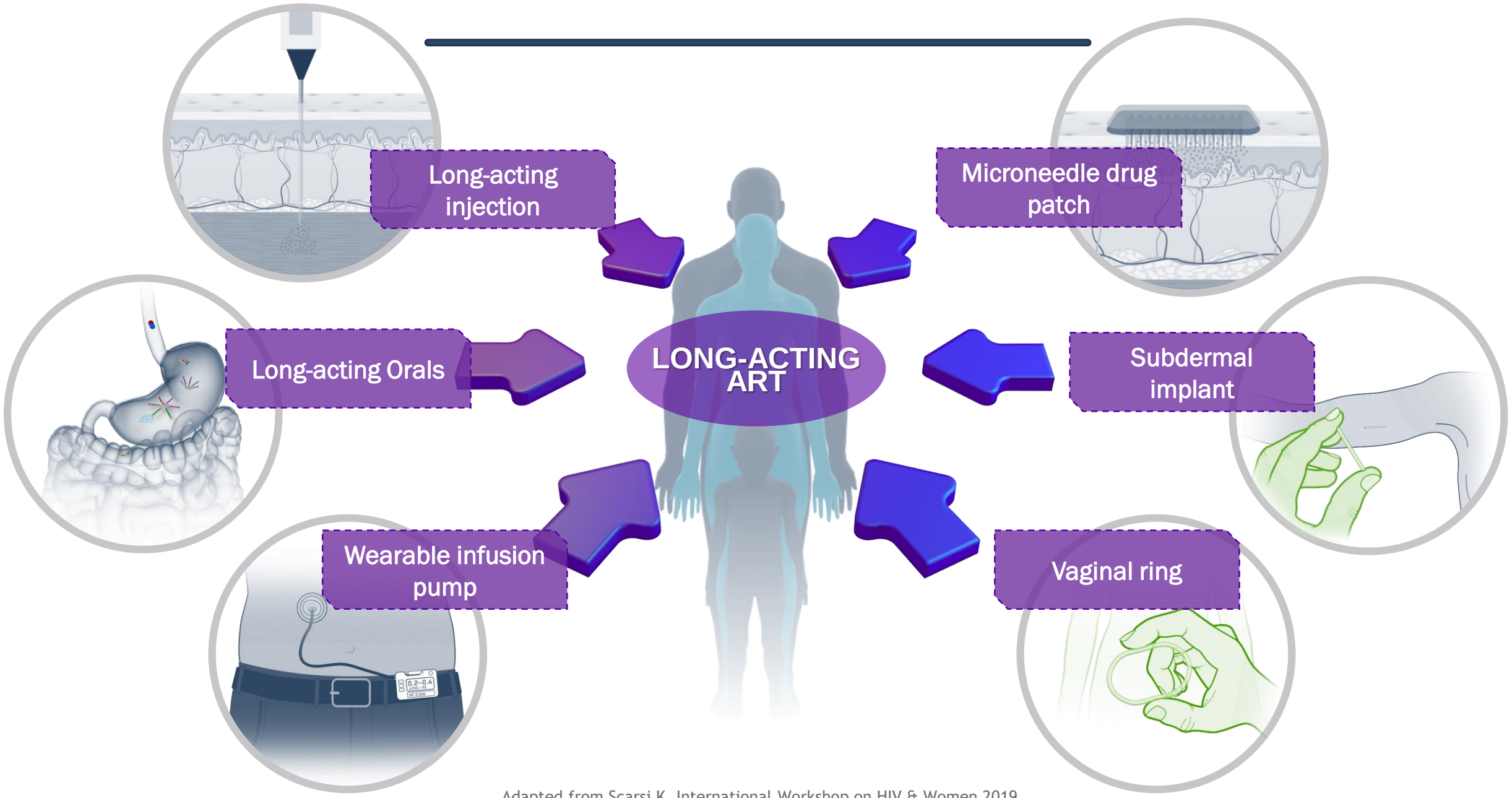
Update on long-acting ART

Mechanistic drug class	Agents	Formulation	Stage of development
Nucleoside reverse transcriptase inhibitors	EFdA (MK-8591)	Implant	Preclinical
	Tenofovir alafenamide	Implant	Preclinical
	GS-9131	Implant	Preclinical
Nonnucleoside reverse transcriptase inhibitors	Rilpivirine	Injectable	Phase III
	Elsulfavirine	Injectable	Preclinical
Protease inhibitors	Atazanavir	Injectable	Preclinical
	Ritonavir	Injectable	Preclinical
Integrase inhibitors	Cabotegravir	Injectable	Phase III
	Raltegravir	Injectable	Preclinical
Entry inhibitors	Ibalizumab	Intravenous	US FDA approved
	PRO 140	Intravenous	Phase II
	Albuvirtide	Intravenous and subcutaneous	Approved in China
	Broadly neutralizing antibodies	Intravenous	Phase II/III
	Combinectin	Intravenous	Preclinical
Capsid inhibitors	GS-CA1	Injectable	Preclinical

Abbreviation: EFdA, 4′-ethynyl-2-fluoro-2′-deoxyadenosine.

Ann. Rev. Med. 2019;70:137-50.

We have a lot of modalities for drug delivery



Adapted from Scarsi K, International Workshop on HIV & Women 2019.

Update on long-acting ART -outline

- **Treatment**

Cabotegravir & Rilpivirine

- **Prevention**

Cabotegravir

- **Novel agents in development**

Lenacapavir

Islatravir

Update on long-acting ART -outline

- **Treatment**

  Cabotegravir & Rilpivirine

- **Prevention**

  Cabotegravir

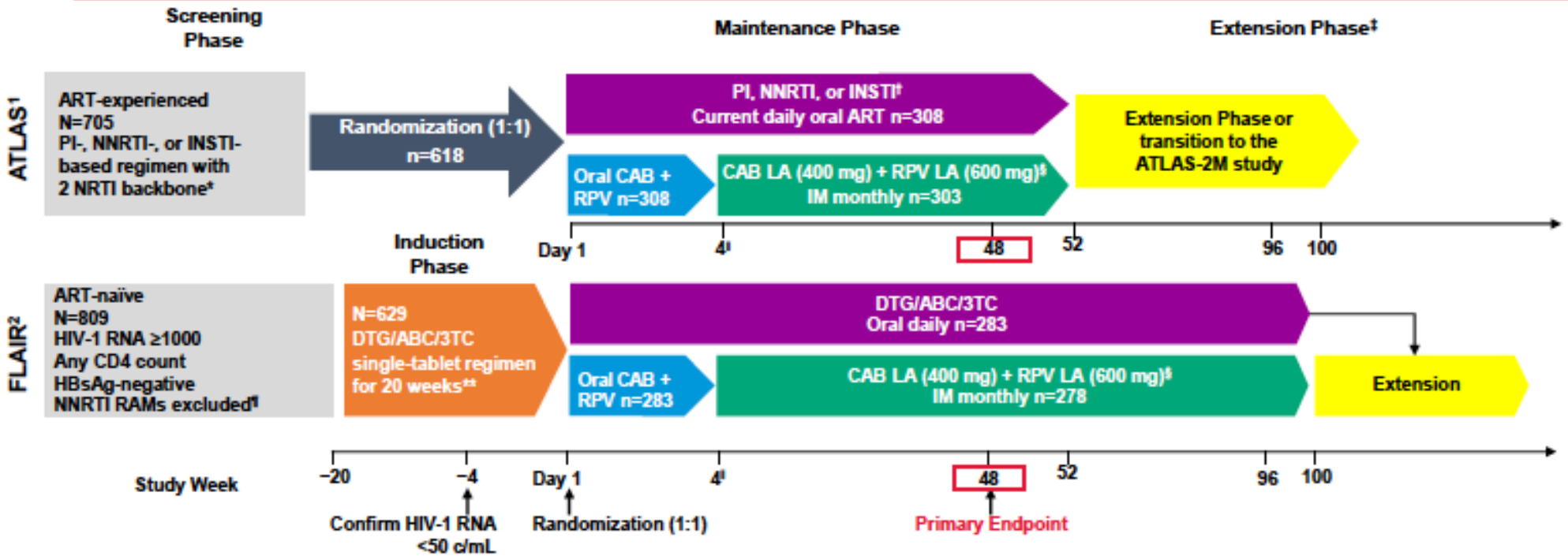
- **Novel agents in development**

  Lenacapavir

  Islatravir

ATLAS and FLAIR

Randomised, multicentre, international, open-label, non-inferiority studies



*Uninterrupted ART 6 months and VL <50 c/mL at Screening; 2× VL <50 c/mL ≤12 months; †INSTI-based regimen capped at 40% of enrollment; Triumeq excluded from study; ‡Optional switch to CAB LA + RPV LA at Week 52 for those on CAR; §Participants who withdraw/complete IM CAB LA + RPV LA must complete 52 weeks of follow-up; ||Participants received an initial loading dose of CAB LA (600 mg) and RPV LA (900 mg) at Week 4b. From Week 8 onwards, participants received CAB LA (400 mg) + RPV LA (600 mg) injections every 4 weeks; ¶NNRTI RAMs but not K103N were exclusionary; **DTG plus two alternative non-ABC NRTIs was permitted if participant was intolerant or HLA-B*5701-positive.

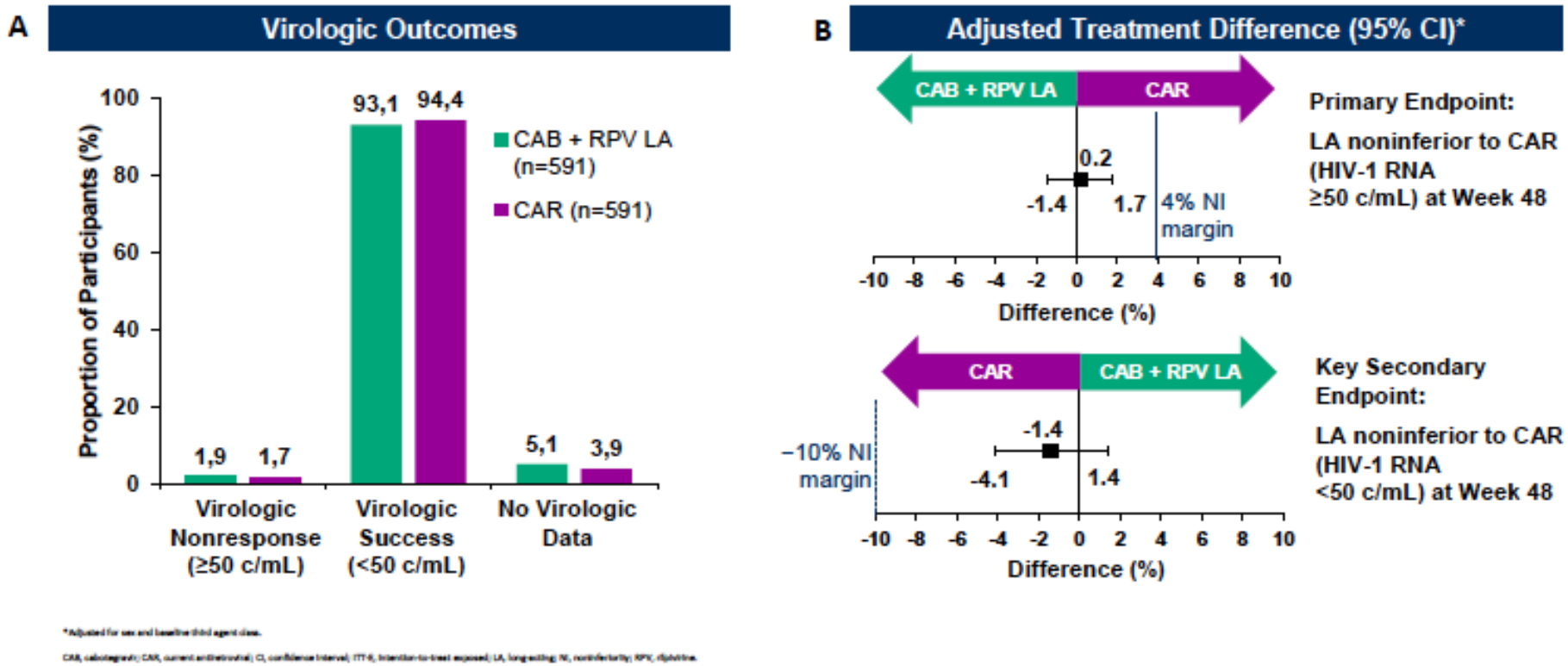
3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; CAB, cabotegravir; CAR, current antiretroviral; DTG, dolutegravir; IM, intramuscular; INSTI, integrase strand transfer inhibitor; HBsAg, hepatitis B surface antigen; HLA, human leukocyte antigen;

LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RAM, resistance-associated mutation;

RPV, rilpivirine; VL, viral load.

1. Swindells S, et al. CROI 2019; Seattle, WA. Abstract 1475;
2. Orkin C, et al. CROI 2019; Seattle, WA. Abstract 3947.

ATLAS and FLAIR
Virologic snapshot outcomes at Week 48 for ITT-E

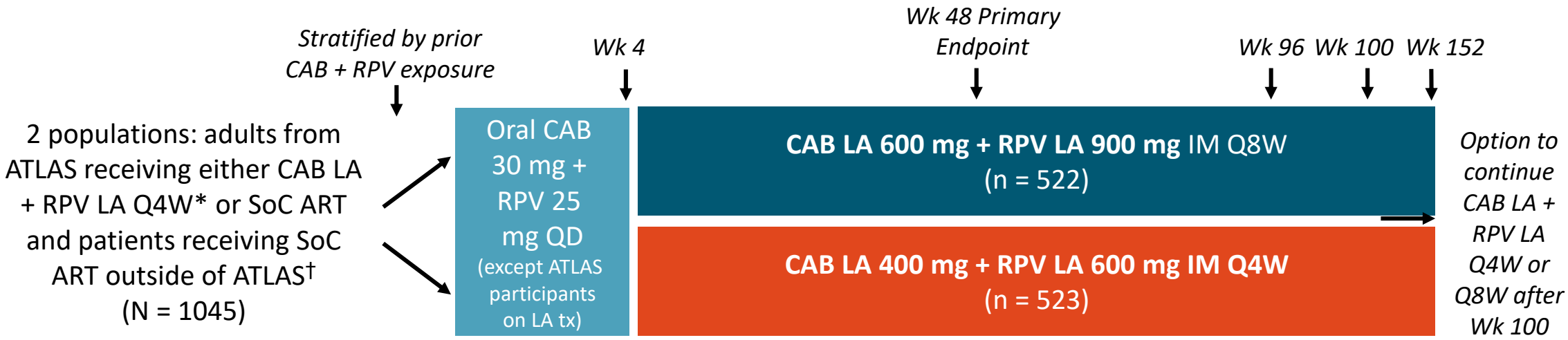


*Adjusted for sex and baseline third agent class.

CAB, cabotegravir; CAR, current antiretroviral; CI, confidence interval; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; RPV, rilpivirine.

ATLAS-2M: Study Design

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



*Participants transitioning from ATLAS must have been on CAB LA + RPV LA Q4W or a current ART regimen through at least Wk 52 and had HIV-1 RNA < 50 c/mL at screening. †SoC participants not transitioning from ATLAS study on uninterrupted current regimen (initial or second combined ART) for ≥ 6 mos prior to screening and documented evidence of ≥ 2 plasma HIV-1 RNA < 50 c/mL in 12 mos prior to screening (one 6-12 mos and one within 6 mos prior to screening). Participants excluded if history of VF or if prior genotype results show any major INSTI or NNRTI mutations (except K103N).

- Primary endpoint: HIV-1 RNA ≥ 50 copies/mL at Wk 48 by FDA snapshot in ITT-E
- Secondary/other endpoints: plasma HIV-1 RNA ≥ 50 or < 50 copies/mL at Wk 152 by FDA snapshot in ITT-E, safety and tolerability, VF in patients with CVF

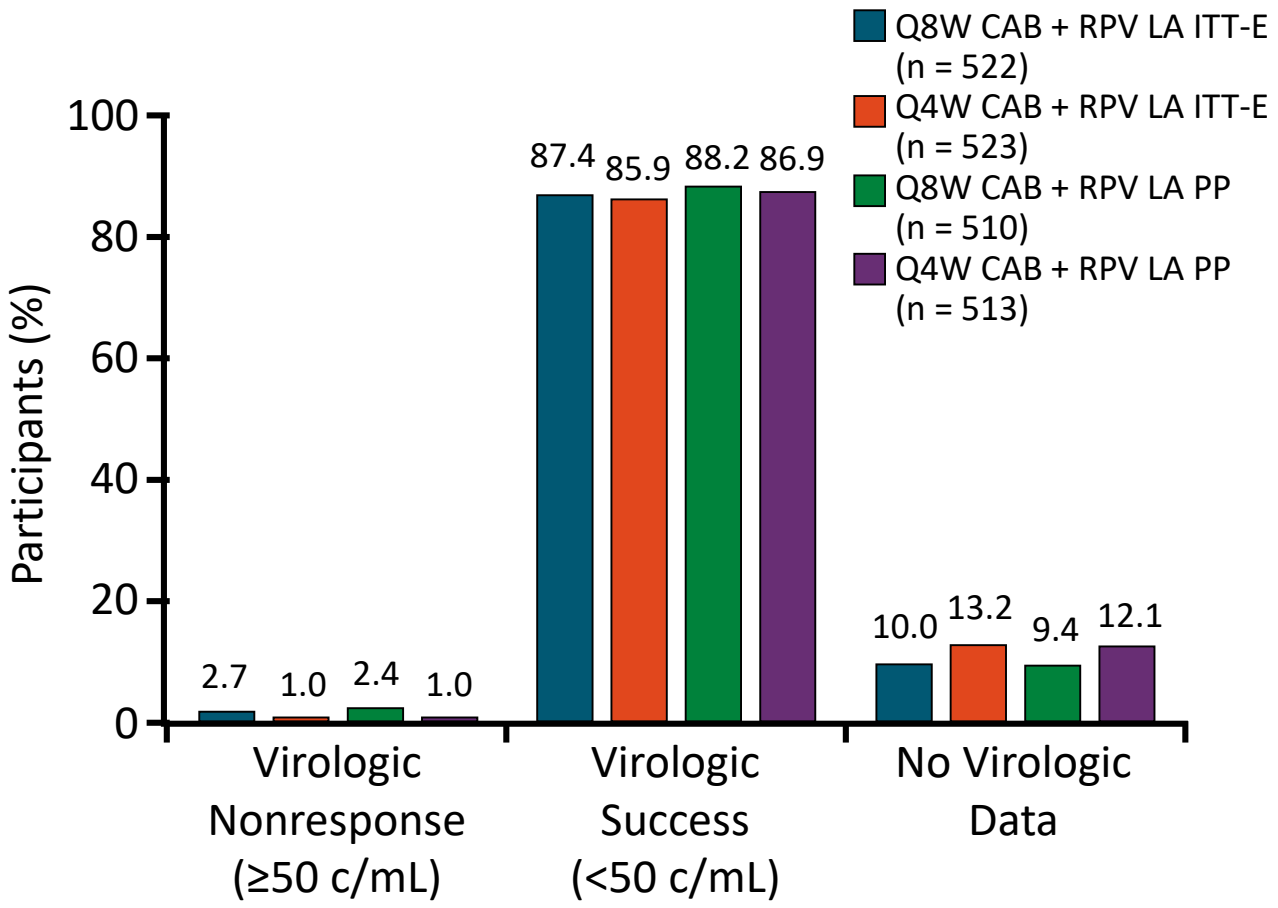
Overton. CROI 2022. Abstr 479.

LONG-ACTING CABOTEGRAVIR+RILPIVIRINE EVERY 2 MONTHS: ATLAS-2M WEEK 152 RESULTS

Edgar T. Overton[1], Gary Richmond[2], Giuliano Rizzardini[3], Anders Thalme[4], Pierre-Marie Girard[5], Alexander Wong[6], Norma Porteiro[7], Carlos Martín Español[8], Carolina Acuipil[9], Asma Aksar[10], Yuanyuan Wang[11], Ronald D'Amico[12], Christine Talarico[12], Kati Vandermeulen[13], William R. Spreen[12]

[1]University of Alabama at Birmingham, Birmingham, AL, United States; [2]Nova Southeastern University, FL, United States; [3]Department of Infectious Diseases, Fatebenefratelli Sacco Hospital, Milan, Italy & School of Clinical Medicine, Faculty of Health Science University of the Witwatersrand, Johannesburg, South Africa; [4]Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden; [5]Department of Infectious and Tropical Diseases & Inserm, University of Paris, St Antoine Hospital, Paris, France; [6]University of Saskatchewan, Regina, Canada; [7]Fundacion IDEAA, Buenos Aires, Argentina; [8]GlaxoSmithKline, Brentford, United Kingdom; [9]GlaxoSmithKline, Buenos Aires, Argentina; [10]GlaxoSmithKline, Manchester, United Kingdom; [11]GlaxoSmithKline, Collegeville, PA, United States; [12]ViiV Healthcare, Research Triangle Park, NC, United States; [13]Janssen Research & Development, Beerse, Belgium

ATLAS-2M: Wk 152 Virologic Outcomes



- 2 additional participants (both male at birth, BMI <30 kg/m^2) in Q8W arm met CVF criteria between Wk 96 and 152 (Wk 112, 120)
  - At BL, neither had RAMs; participant with A6 subtype had L74I integrase polymorphism

Country	Baseline	At Failure		
	HIV-1 Subtype	HIV-1 RNA (c/mL)	RPV RAMs	INI RAMs
Germany	B	24,221	E138A+ M230M/L	Q148R
Russia	A6*	59,467	E138A+ Y181Y/C	Q148R

*Originally classified as A1; later reclassified as A6 upon reanalysis

- Through Wk 152, 13 participants had CVF: Q8W, n = 11 (2%); Q4W, n = 2 (<1%)
  - None with injection >7 days late

Overton. CROI 2022. Abstr 479.

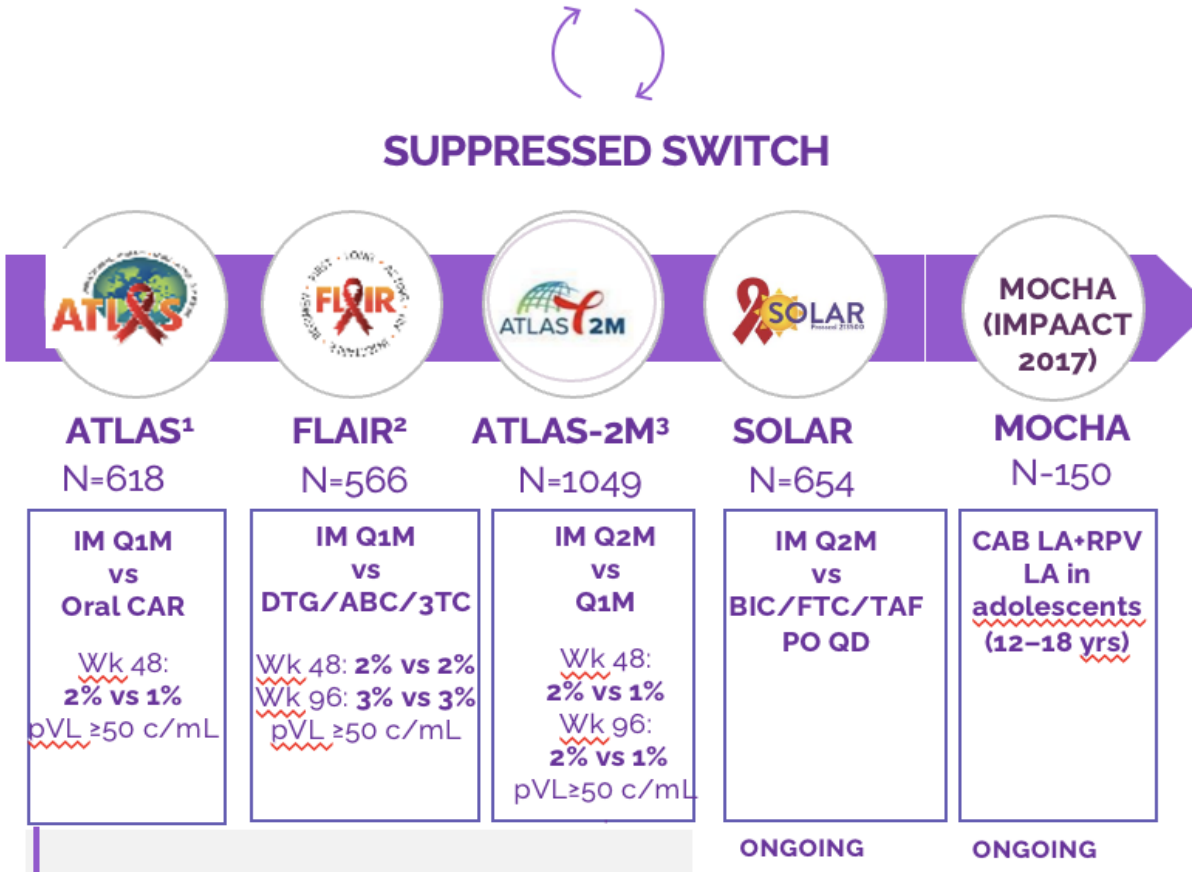
ATLAS-2M: ISRs and Treatment Satisfaction Through Wk 152

injection-site reactions	Q8W (n = 522)	Q4W (n = 523)
Participants who received ≥1 injection, n (%)	516 (99)	517 (99)
Number of injections	20,563	39,478
ISR events, n ▪ Injection site pain, n (% of injections) ▪ Injection site nodule, n (% of injections)	4168 3189 (16) 259 (1)	5494 4180 (11) 457 (1)
Grade 3, n (% of ISR events)	54 (1)	50 (1)
Median duration, days (IQR)	3 (2-5)	3 (2-5)
Participants withdrawing for injection-related reasons, n (%)	8 (2)	13 (3)

- HIV treatment satisfaction questionnaire scores from participants without prior CAB
  - Total mean scores significantly improved from BL to Wk 152 for both groups
  - Adjusted mean change from BL significantly favored Q8W dosing at Wk 24, 48, and 152

Overton. CROI 2022. Abstr 479.

Treatment : LA CAB+ RPV



Efficacy:
Non inferior to oral therapy at 48, 96, 124 and 152 weeks

Adverse events (AE's):
2% AE-related withdrawal rate
Mild/moderate in severity
Injection Site Reactions (ISR's) reduced over time

Confirmed virological failure rate:
N=23/ 1431
1-1.6% overall. (2.7% Q8 vs 1% Q4 ATLAS 2M)

Resistance:
Usually to two classes and mostly in first year **(4/23 beyond Wk 48)**

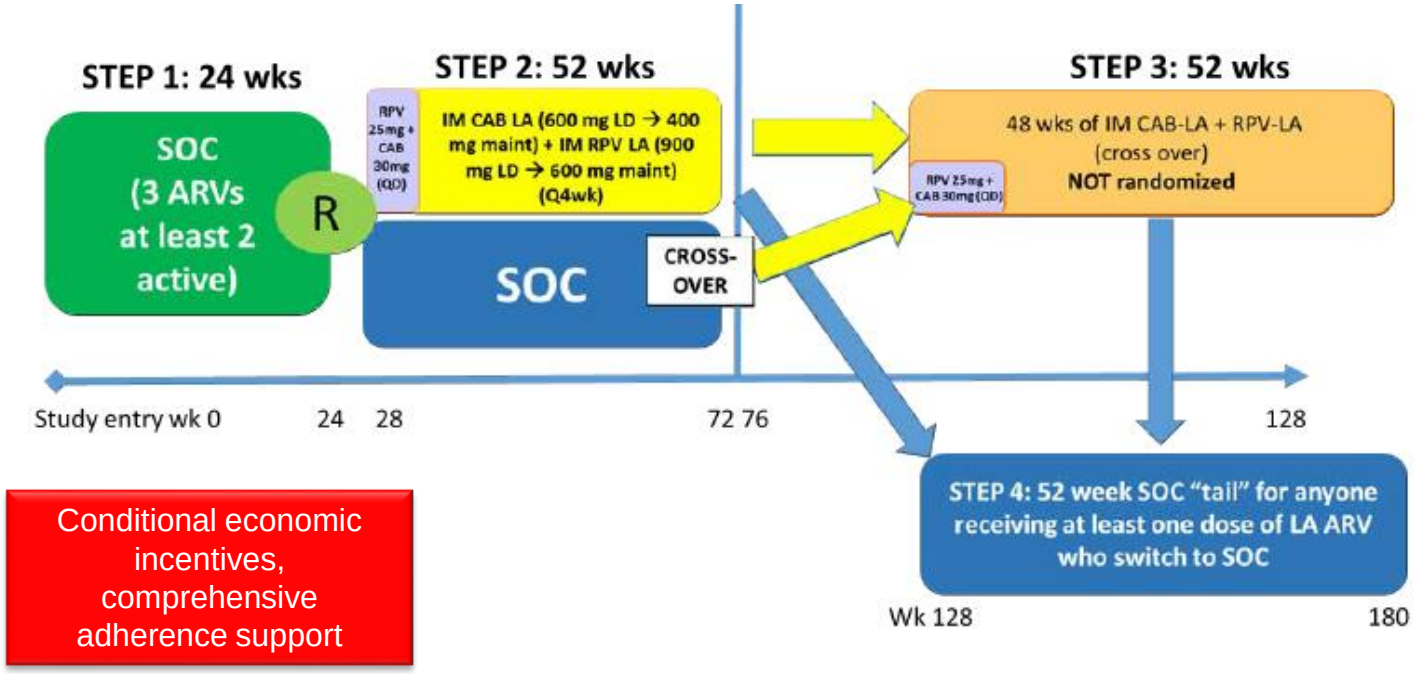
Oral Lead in:
Can be used with or without without oral lead in

Preference :
9 out of 10 patients preferred it to oral therapy

Swindells S, et al. N Eng J Med 2020;382:1112–232.
Orkin C, et al. N Eng J Med 2020;382:1124–353.
Overton ET, et al. CROI 2020. Oral 3334,
Overton et al abstract 479 CROI 2022

Long Acting Cabotegravir and Rilpivirine for people who are NOT suppressed: Research in Progress

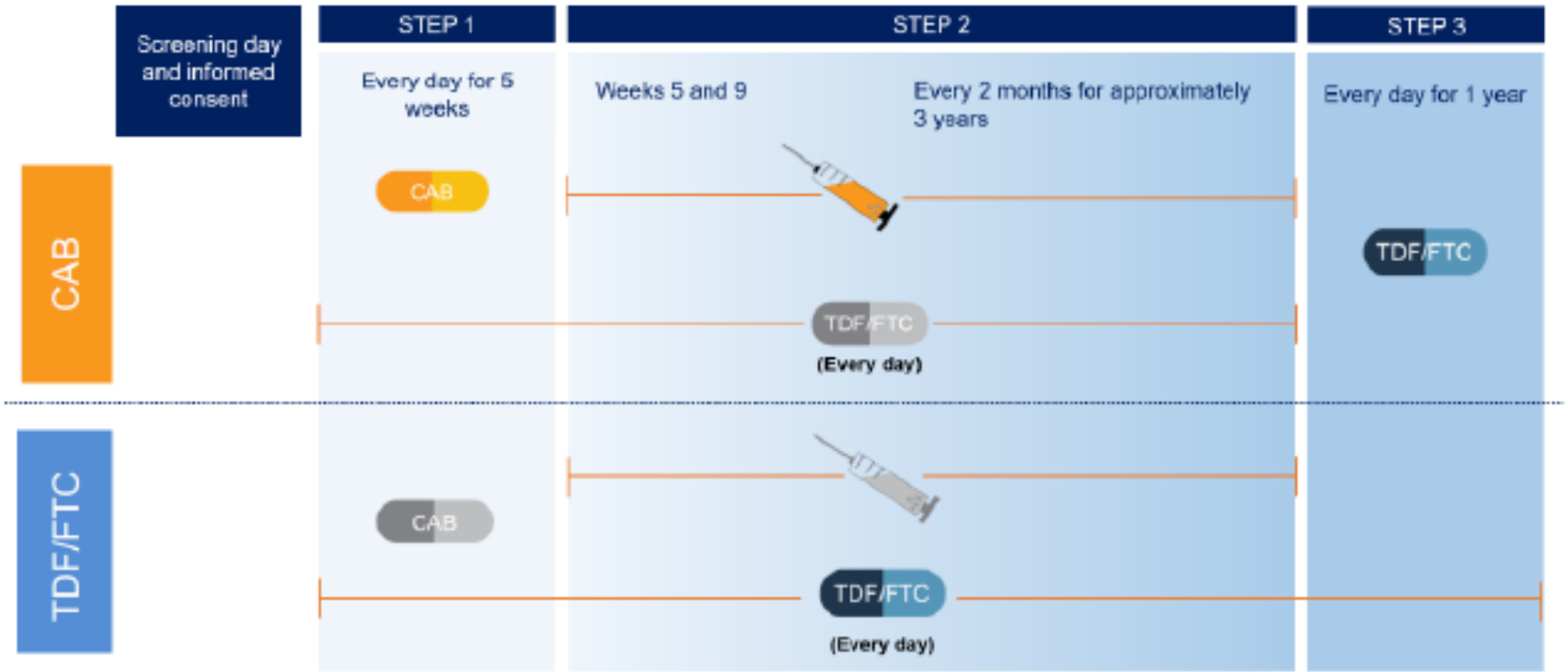
- **LATTITUDE: a randomized controlled trial of LA-cabotegravir and rilpivirine in participants who are unable to be suppressed on oral ART (Trial leadership Castillo-Mancilla, Rana, Tashima, Landovitz)**



Update on long-acting ART -outline

- Treatment
  - *Cabotegravir & Rilpivirine*
- **Prevention**
  - *Cabotegravir*
- Novel agents in development
  - *Lenacapavir*
  - *Islatravir*

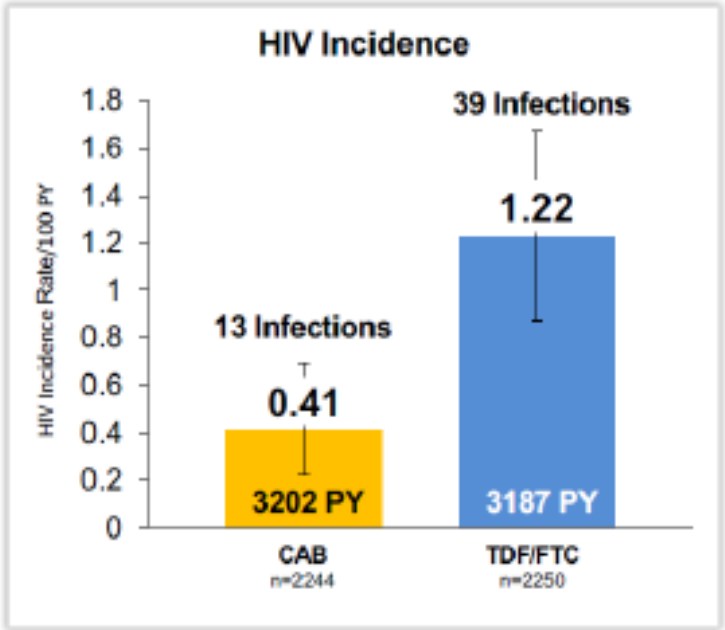
HPTN 083 Study Design

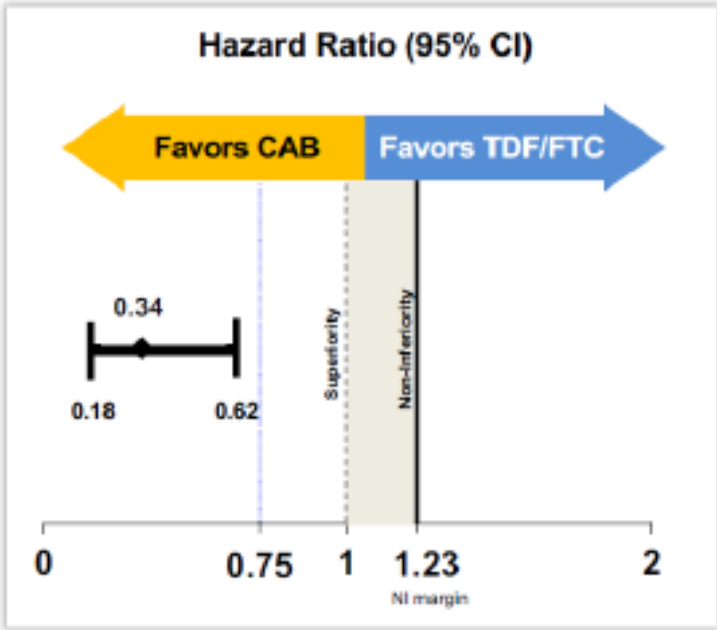


Landovitz RJ et al. AIDS 2020, #OAXLB01

HIV Incidence
CAB vs. TDF/FTC

52 HIV infections in 6389 PY of follow-up
1.4 (IQR 0.8-1.9) years median per-participant follow-up
Pooled incidence 0.81 (95%CI 0.61-1.07) per 100 PY





CI, confidence interval

Landovitz RJ et al. AIDS 2020, #OAXLB01

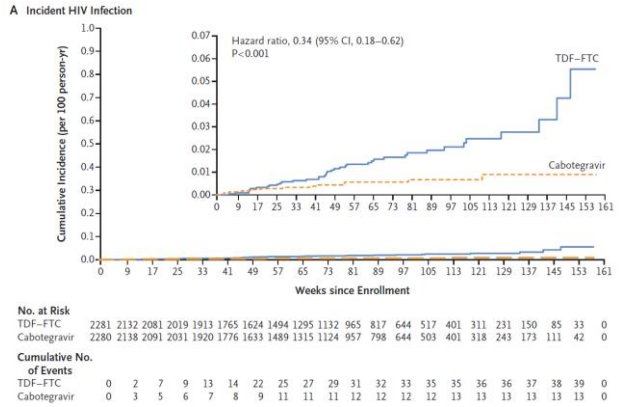
Injectable Cabotegravir for HIV pre-exposure prophylaxis

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

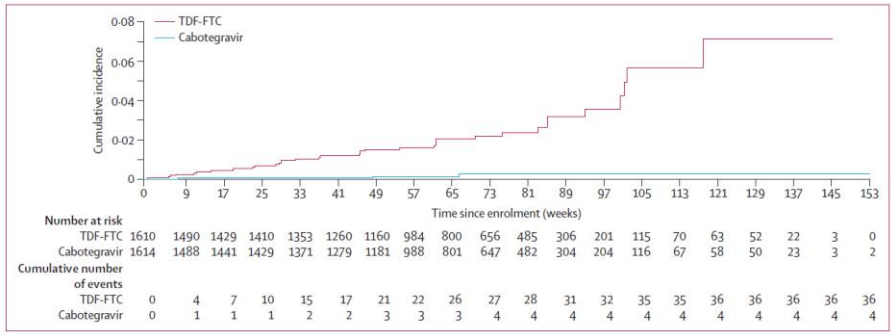
N Engl J Med 2021;385:595-608.
DOI: 10.1056/NEJMoa2101016

Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women



Lancet 2022; 399: 1779–89

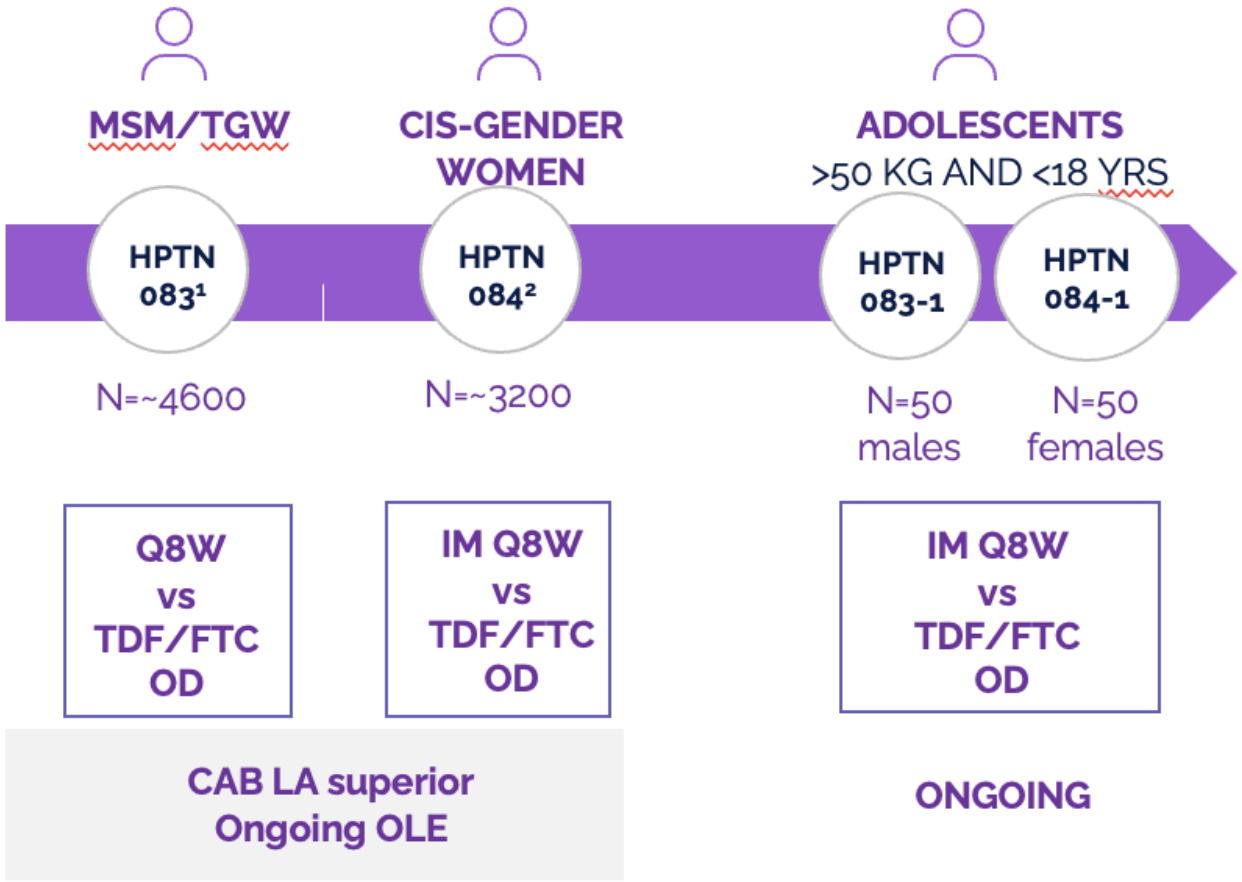
Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial



April 1, 2022
https://doi.org/10.1016/
S0140-6736(22)00538-4

- HPTN 084: IM CAB-LA superior to TDF-FTC in preventing HIV infection among MSM & transgender women: HR 0.34; 95%CI 0.18 to 0.62
- HPTN 083: IM CAB-LA superior to TDF-FTC in preventing HIV infection among women: HR 0.12 95% CI 0.05-0.31
- FDA approval and inclusion in CDC recommendations for PrEP regimens

PrEP : LA CAB



CAB LA superior to TDF/FTC in preventing HIV acquisition in a broad and diverse population.

In MSM and TGW who have sex with men:
- 68% fewer HIV infections on CAB LA

In cis-gender women:
- 89% fewer HIV infections on CAB LA

ISRs mostly Grade 1-2 few discontinuations
NO discontinuations in women's study

Adverse events other than ISR:
similar to daily oral PrEP

Consistent **preference** for Q2M dosing

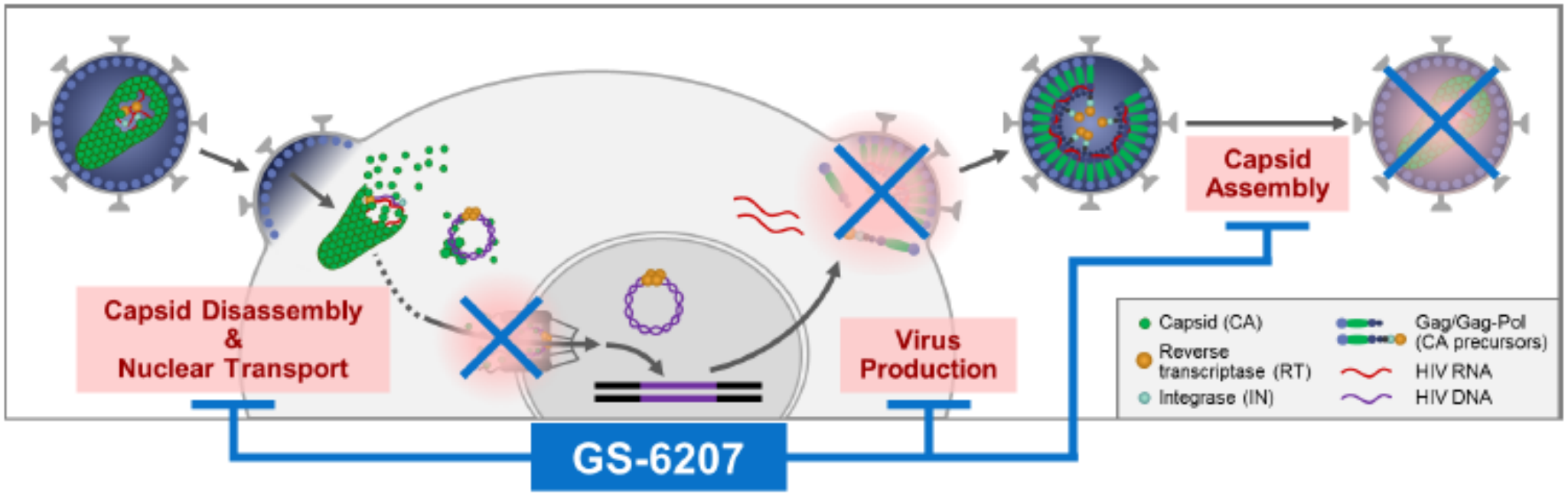
1. Landowitz RJ, N Engl J Med 2021;385:595-608 . 2 Delaney-Moretlwe S, LB1479 R4P virtual conference, 27 January 2021

Update on long-acting ART -outline

- **Treatment**
  - *Cabotegravir & Rilpivirine*
- **Prevention**
  - *Cabotegravir*
- **Novel agents in development**
  - *Lenacapavir*
  - *Islatravir*

Lenacapavir SC (first-in-class HIV capsid inhibitor)

Mechanism of Action

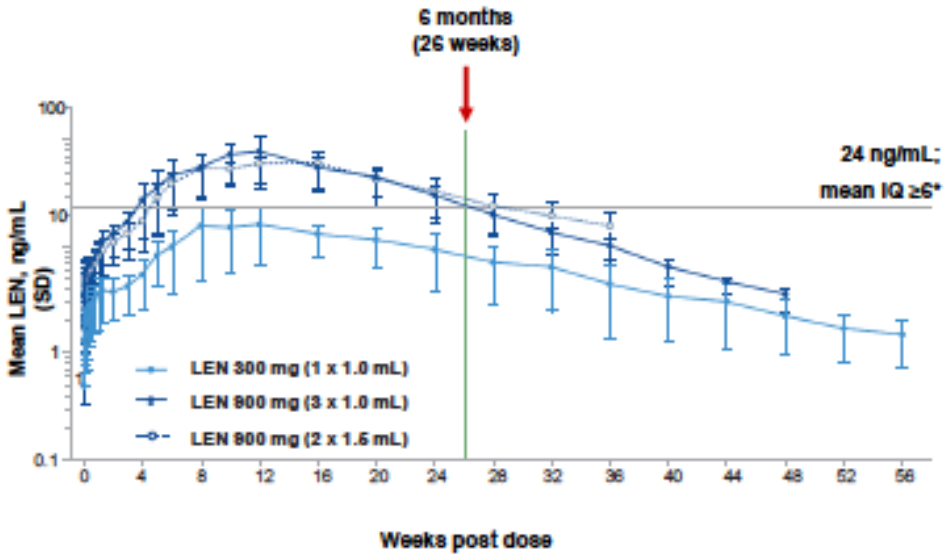


- GS-6207 inhibits multiple processes essential for viral replication
- GS-6207 modulates the stability and/or transport of capsid complexes

Yant SR, et al. CROI 2019. Seattle, WA. Poster 480
Sager JE, et al. CROI 2019. Seattle, WA. Oral 141

Lenacapavir SC
Pharmacokinetics and Safety in HVs

Mean (SD) LEN Single Dose Plasma Concentration-Time Profiles



- Single SC doses of up to 900 mg LEN were generally safe and well tolerated
  - No serious or Grade 2, 3, or 4 AEs related to study drug†
  - No AEs leading to discontinuation
  - ISRs were common (80%) and all mild
- Target concentrations sustained for ≥6 months after single 900 mg dose
  - Slow release necessitates oral PK loading dose prior to first injection

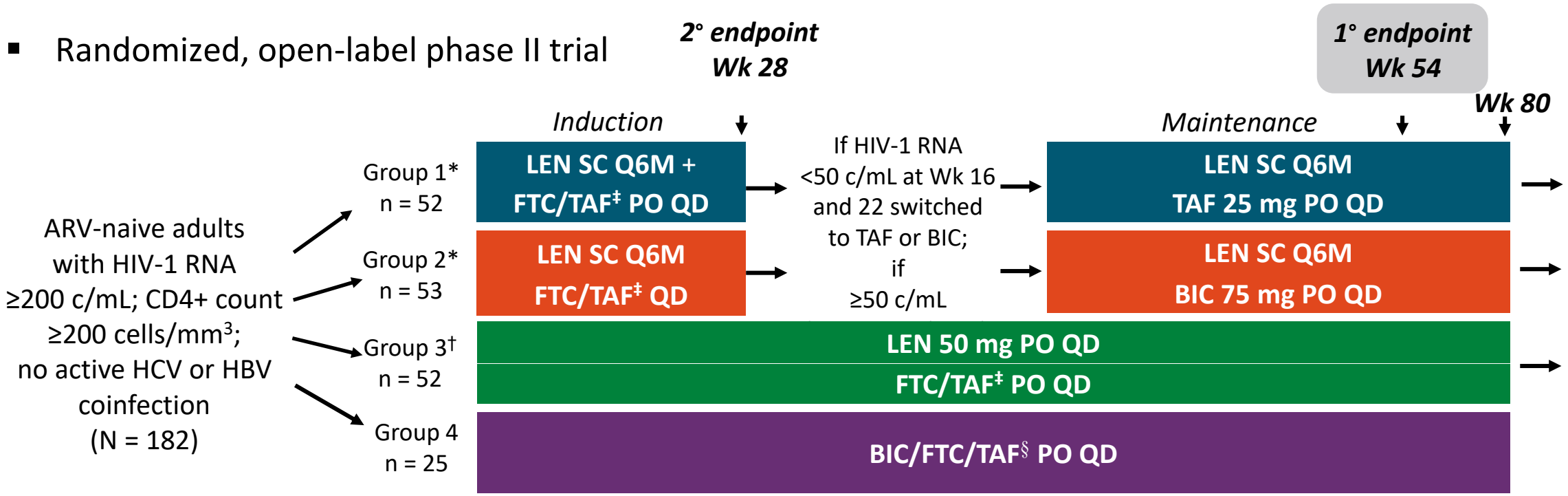
Preliminary PK and safety data support continued clinical development of long-acting SC LEN in conjunction with an oral LEN loading dose

ISRs, injection site reactions
IQ: Ratio of LEN plasma concentration/EC_{95} *$paEC_{95}$ = 1.16 ng/mL (macrophages), 2.32 ng/mL (CD4+ T cells), and 3.87 ng/mL (MT-4 cells)
†One participant had Grade 3 AEs of abscess (also serious AE), cellulitis, and MRSA infection, none of which were related to LEN

Begley R, et al. AIDS 2020. PEB0265

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**
- 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. CROI 2022. Abstr 138.

CALIBRATE Primary Analysis: Wk 54 Virologic Outcomes

Virologic Outcome, %	LEN SC + FTC/TAF → TAF (n = 52)	LEN SC + FTC/TAF → BIC (n = 53)	LEN PO + FTC/TAF (n = 52)	BIC/FTC/TAF (n = 25)
FDA Snapshot analysis (ITT)				
▪ HIV-1 RNA <50 c/mL	90	85	85	92
▪ HIV-1 RNA ≥50 c/mL	4*	4*†	6‡	0
▪ No data	6	11	10	8
FDA Snapshot analysis among patients virologically suppressed at Wk 28				
▪ HIV-1 RNA <50 c/mL	94	92	90	92
▪ HIV-1 RNA ≥50 c/mL	4	0	6	0
▪ No data	2	8	4	8

*3 participants (2 in Group 1 and 1 in Group 2) discontinued due to not having HIV-1 RNA <50 c/mL prior to Wk 28. †1 participant discontinued on Day 2.
‡2 of 3 participants with HIV-1 RNA ≥50 c/mL at Wk 54 were suppressed at a subsequent visit.

- In pooled LEN SC cohort (Groups 1 and 2):
  - 88% achieved and maintained virologic suppression at Wk 54
  - 93% of those virologically suppressed at Wk 28 maintained virologic suppression at Wk 54

Gupta. CROI 2022. Abstr 138.

CALIBRATE: Resistance and Safety

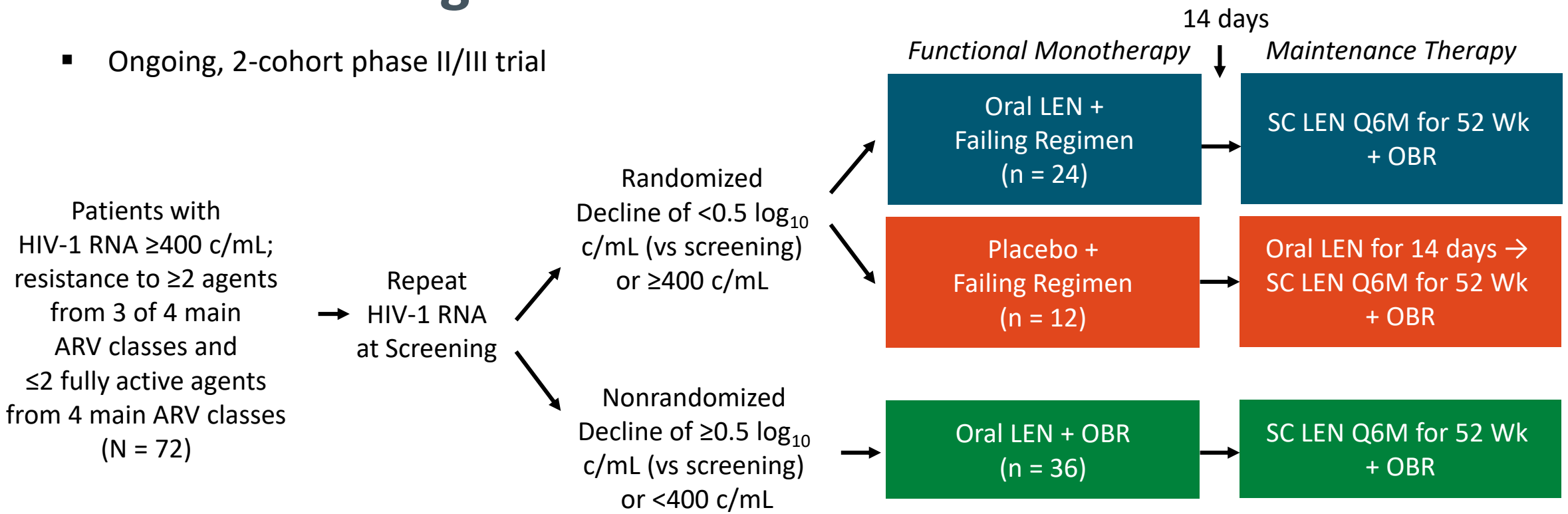
- Emergent LEN resistance observed in 2/157 (1.5%) patients
  - 1 patient receiving **LEN SC + FTC/TAF → BIC** at Wk 10
    - CA: Q67H + K70R (LEN fold change = 20) in CA + M184M/I in RT
    - Pattern suggests incomplete adherence to FTC/TAF
  - 1 patient receiving **LEN PO + FTC/TAF** at Wk 54
    - Q67H (LEN fold change = 7) in CA
    - Nonadherent to FTC/TAF based on pill count, drug levels
- Both later resuppressed on regimen of INSTI + 2 NRTI

- LEN well tolerated with favorable safety profile
  - No SAEs or grade 3/4 AEs related to study drug
  - Most common AEs: headache and nausea (13% each)
  - GI AEs in SC vs PO LEN
    - Nausea: 14% vs 12%
    - Diarrhea: 7% vs 10%
    - Vomiting: 4% vs 8%
- ISRs (15% after first injection) mostly grade 1/2; only 1 grade 3 ISR
- 3 discontinuations due to ISRs (due to grade 1 induration or erythema and swelling)

Gupta. CROI 2022. Abstr 138.

CAPELLA: Lenacapavir in People With Multidrug-Resistant HIV

- Ongoing, 2-cohort phase II/III trial

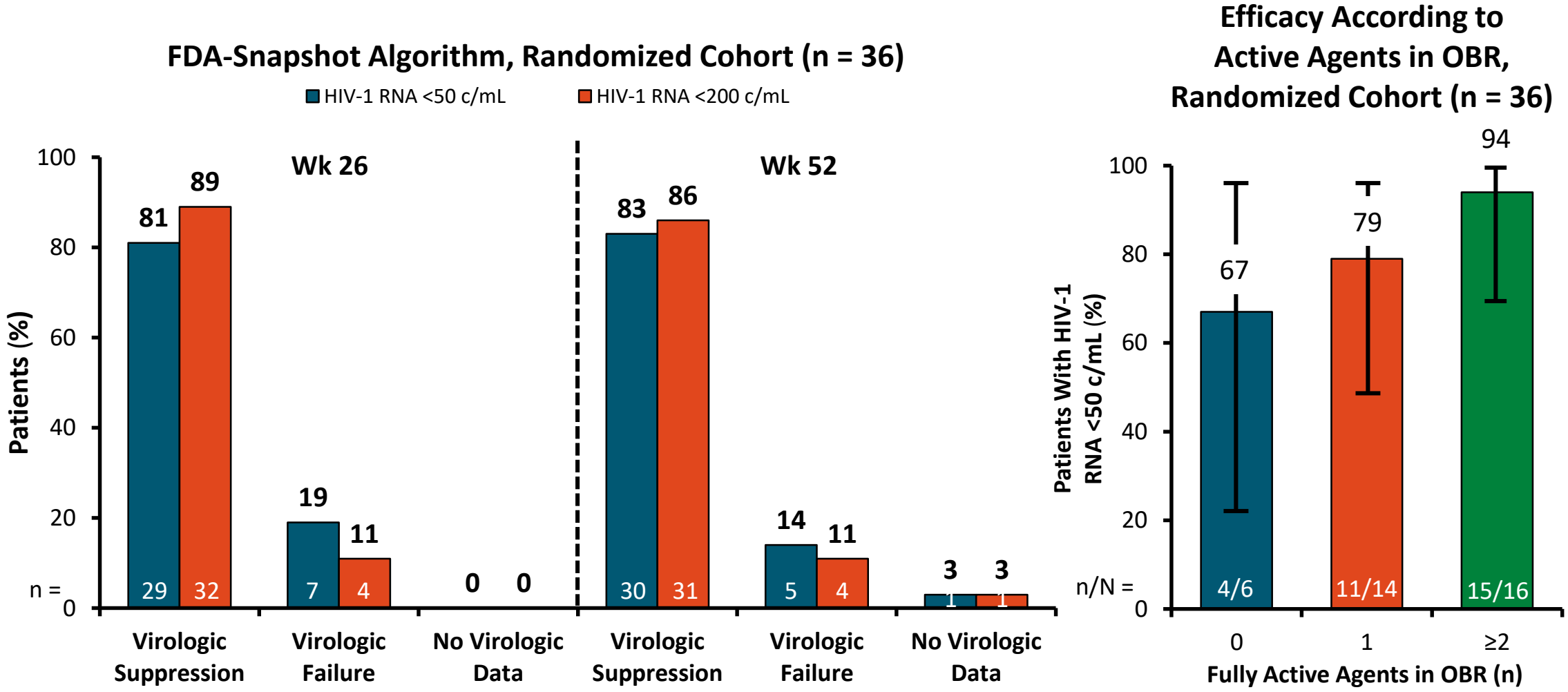


Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8; SC LEN administered as 927 mg (2 x 1.5 mL) in the abdomen on Day 15 and Q6M thereafter.

- Primary endpoint achieved in prior analysis: ≥0.5 $\log_{10}$ c/mL decline in HIV-1 RNA at Day 14 in randomized cohort
- Secondary endpoints: HIV-1 RNA <50 c/mL, <200 c/mL at Wk 26 and 52 in randomized cohort

Ogbuagu. CROI 2022. Abstr 491.

CAPELLA Secondary Endpoints: Lenacapavir Efficacy at Wk 52 in Randomized Cohort



Ogbuagu. CROI 2022. Abstr 491.

CAPELLA: Other Lenacapavir Efficacy and Safety Outcomes in Randomized Cohort

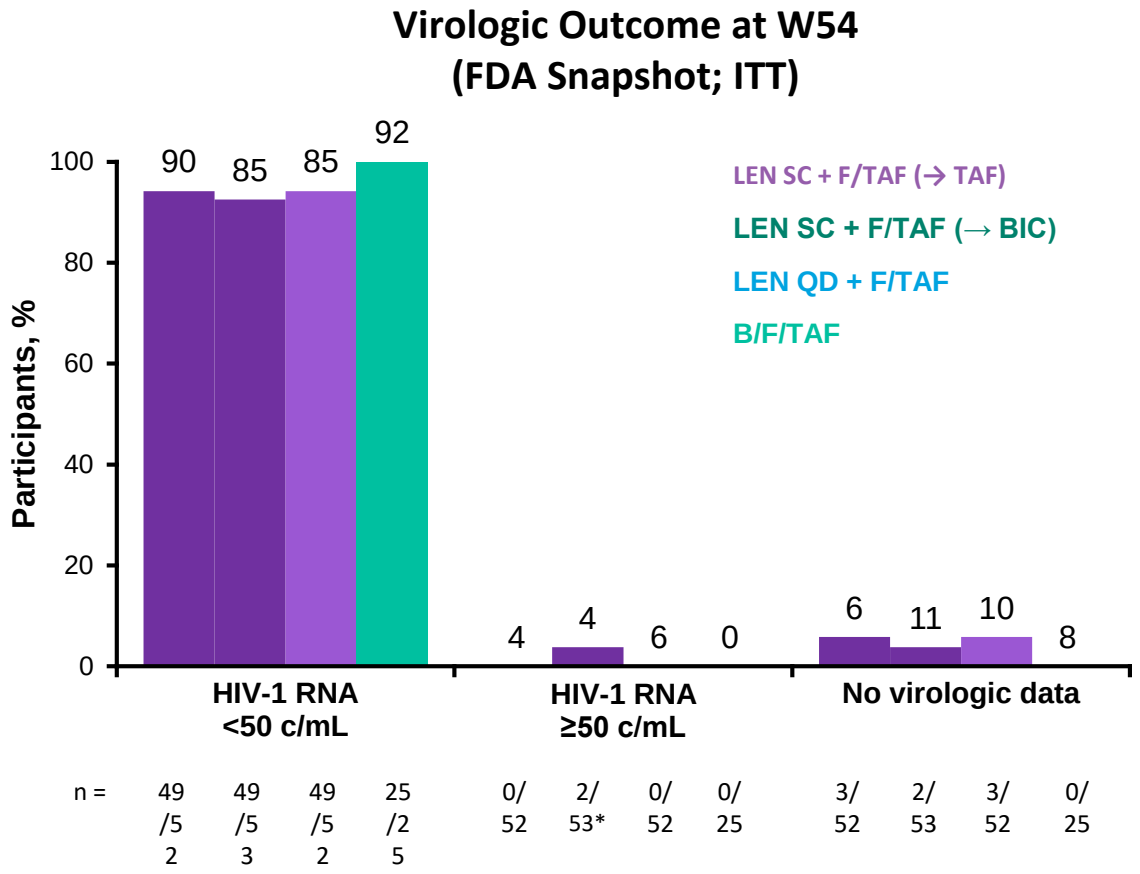
- LEN resistance occurred in 4 patients through Wk 26, but not thereafter
  - All had no fully active drugs in OBR or inadequate adherence to OBR
- Mean change in CD4+ cell count at Wk 52: +83 cells/mm^3
- Incidence of very low CD4+ cell count (<50 cells/mm^3) decreased from 22% (8/36) at baseline to 3% (1/36) at Wk 52
- Incidence of CD4+ cell count ≥200 cells/mm^3 increased from 25% (9/36) at baseline to 60% (21/36) at Wk 52
- ISRs most common AE with SC LEN
  - Most ISRs were grade 1 or 2
  - 2 patients had grade 3 ISRs
  - All nodules were grade 1, except 1 patient with 2 AEs of grade 2 nodules after second and third injections (both resolved in 3 days)
- 1 patient discontinued LEN at Wk 52 due to ISR (nodule; grade 1)

Ogbuagu. CROI 2022. Abstr 491.

Lenacapavir: Current status

- Clinical hold in December 2021- due to potential concern for an issue of compatibility between the drug and the vials made of borosilicate
- Gilead has provided update to FDA for a path forward, hold released May 22, 2022
- NDA for lenacapavir for heavily-treatment experienced people with MDR HIV in June 2021
- Lenacapavir was approved for use in heavily pre-treated in EU.

LEN (SC & oral) + F/TAF rapidly achieved high rates of suppression



Mean CD4 increase ~ 200 cells

LEN resistance:

- Two cases of resistance on LEN arms
- CA: Q67H + K70R; RT: M184M/I (wk10)
- CA: 67H (week54)
- Both poor adherence.
- Plasma concentrations of LEN in target range
- Both re-suppressed on 2 NRTI+ INSTI

Injection site reactions:

- Most were grade 1/2 and resolved within days
- 3 discontinuations due to ISRs

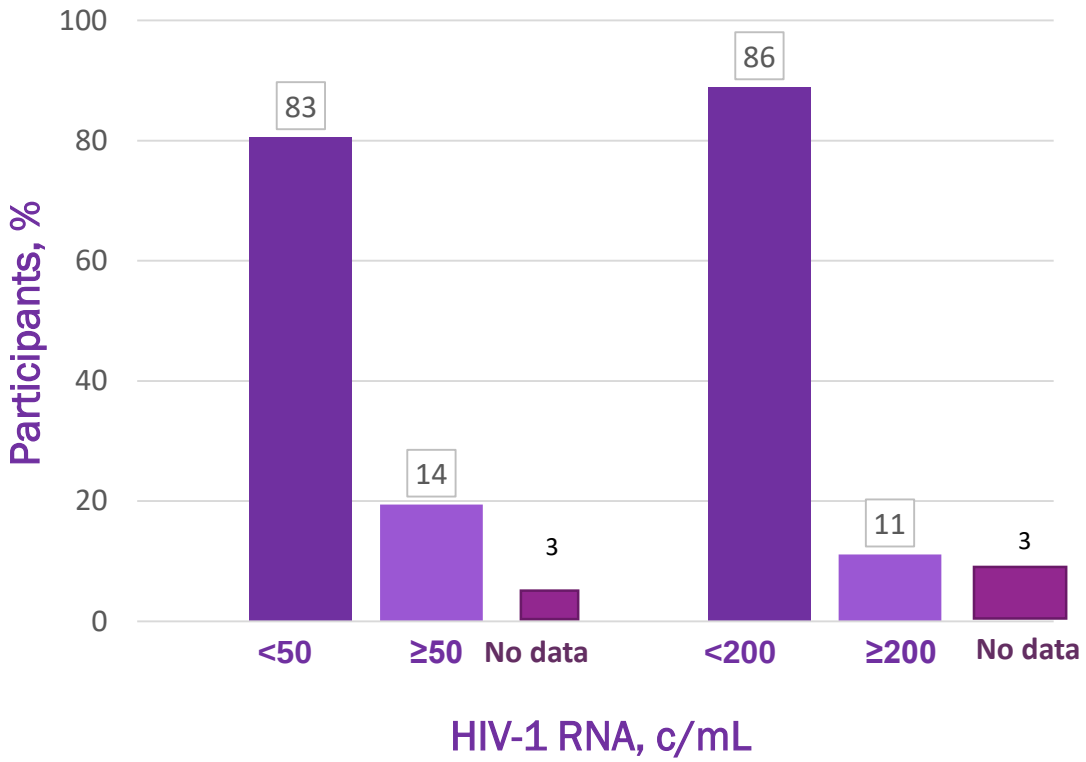
LEN was well tolerated:

- No SAEs or grade 4 AEs related to LEN
- Most common AEs: headache and nausea

CROI 2022 Gupta S, Abstract 138 CROI 2022

Efficacy at W52 in the LEN Arm

FDA Snapshot Algorithm randomized cohort (n=36)



LEN + OBR led to high rates of virologic suppression in THE
Mean CD4 rise ~83 cells

HTE, heavily treatment-experienced; OBR, optimized background regimen

1. Segal-Maurer. N Engl J Med 2022; 386:1793-1803.

LEN resistance:

- No new resistance beyond week 26
- 4 participants developed resistance: M66I
- 2 on functional monotherapy; 2 non adherent
- 3 resuppressed without resistance to OBR

Injection site reactions:

- Mostly grade 1 and resolved within days
- 1 discontinuation due to ISRs

LEN was well tolerated:

- No AEs that led to discontinuation
- No SAEs related to LEN

PrEP LENACAPAVIR 6 monthly subcutaneous injection

	Trial name (protocol number)	Population	Active comparator	Study design	Primary Endpoint
Phase 3	PURPOSE 1	Adolescent girls and young women at high risk	FTC/TDF or FTC/TAF	Randomized, double blind, placebo-controlled	LEN vs bHIV F/TAF vs bHIV
	PURPOSE 2	Men, TGM and non-binary people who have sex with men; transgender women at high risk	FTC/TDF	Randomized, double blind, placebo-controlled	LEN vs bHIV

Study design: counterfactual analysis

Use of recency assays to identify incident infections in screening population as a comparator

PURPOSE 1:

- **External control**: bHIV in those not on PrEP based on recency assay in screened population, historical data from ECHO, HVTN, PrEPVACC
- Dosing: Day 1 - LEN 927mg SC + 600mg oral, Day 2 - 600mg oral, followed by 927mg SC q26weeks; F/TAF 200/25mg oral daily, F/TDF 200/300mg oral daily
- **Internal Active Control**: F/TDF
- Locations: South Africa and Uganda

PURPOSE 2

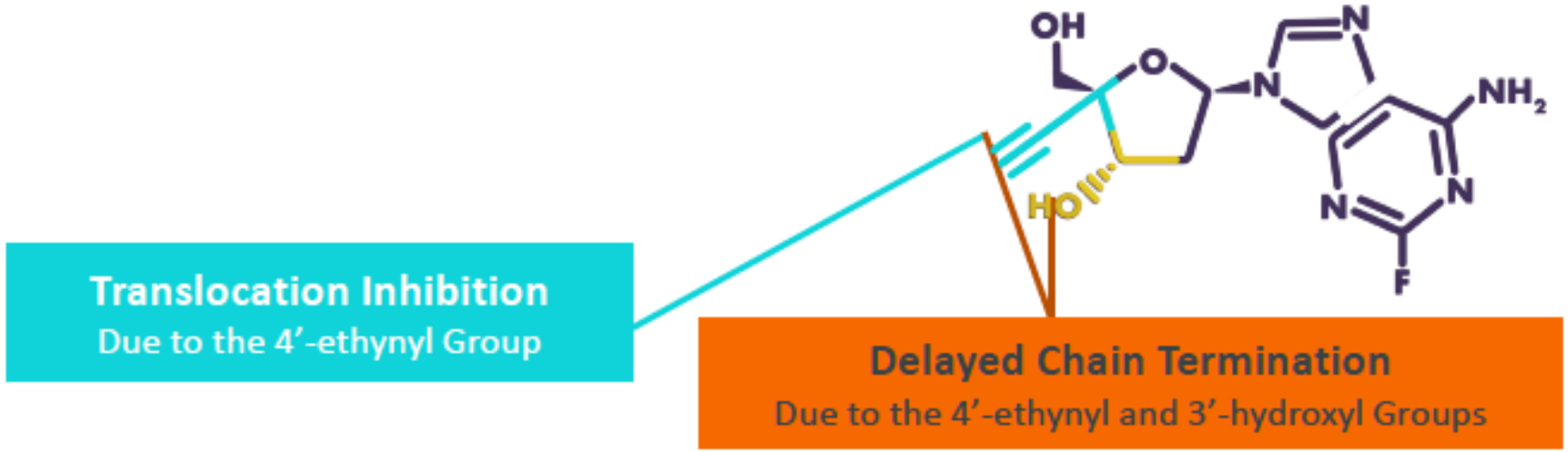
- **External controls**: bHIV in those not on PrEP based on recency assay in screened population, rectal gonorrhea surrogate (Mullick & Murray 2018); CDC data background HIV incidence estimation (only for the US)
- Dosing: Day 1 - LEN 927mg SC + 600mg oral, Day 2 - 600mg oral, followed by 927mg SC q26weeks; F/TDF 200/300mg oral daily
- **Internal Active Control:** F/TDF and bHIV placebo-estimation (Glidden, et al IDWeek 2020)
- Locations: US, Peru, Brazil, South Africa

PURPOSE 1 NCT04994509; PURPOSE 2 NCT04925752

Islatravir (MK-8591)

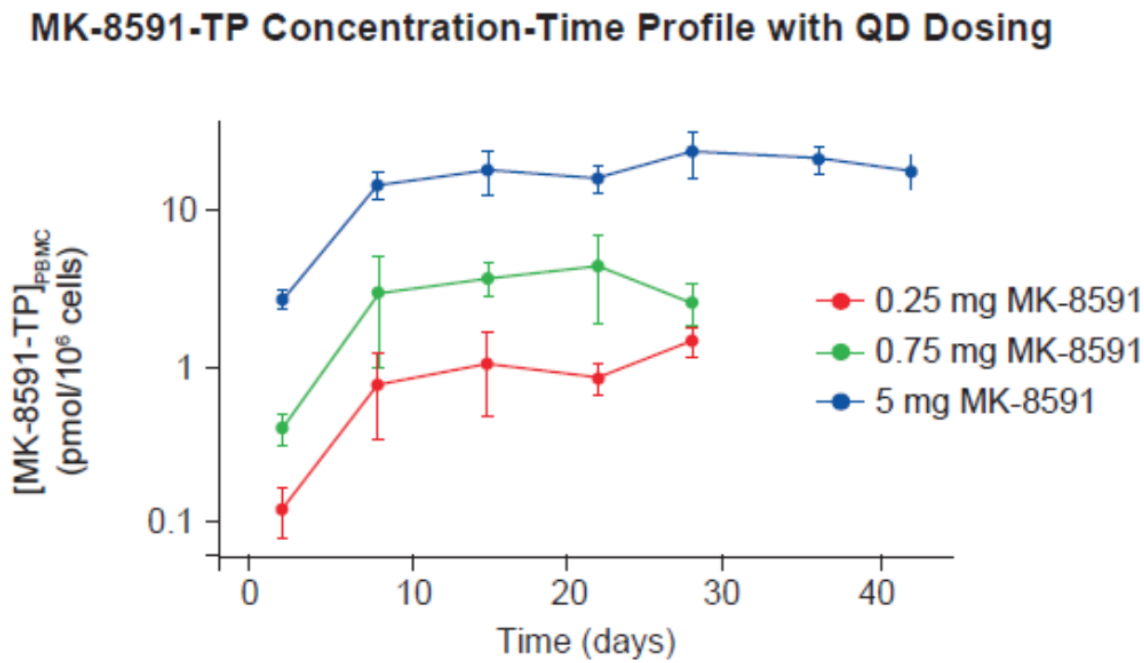
‡

First-in-class nucleoside reverse transcriptase translocation inhibitor

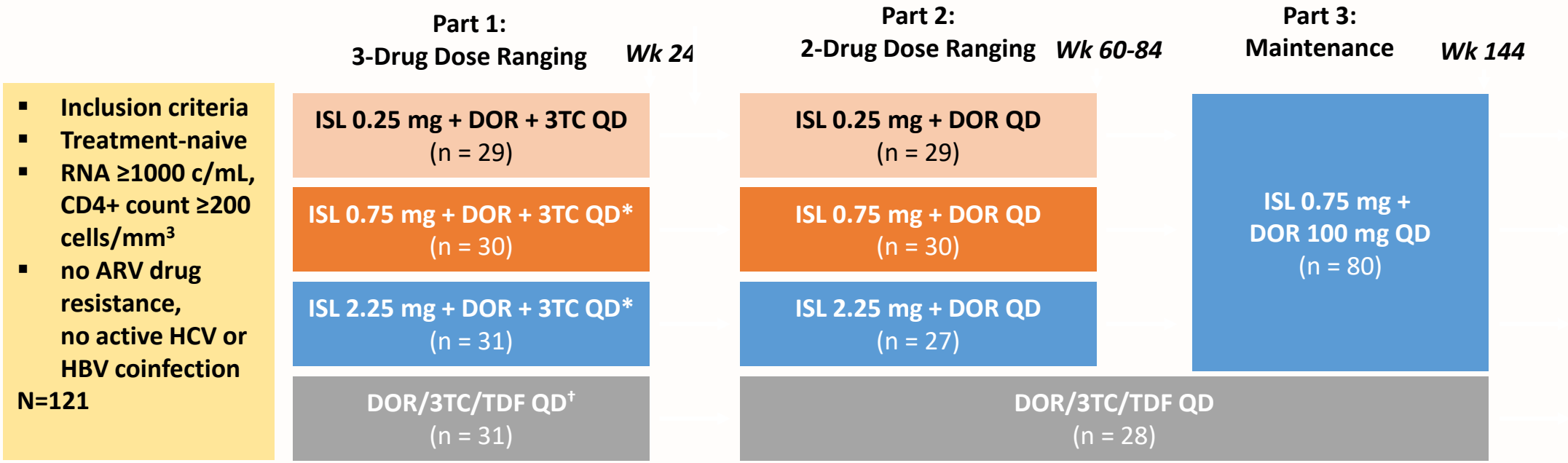


Multiple mechanisms contribute to islatravir high potency against HIV-1, drug-resistant variants and high barrier to resistance.

MK-8591-TP Accumulates to High Levels at Low Doses in Humans and Exhibits a Long Intracellular $t_{1/2}$



Islatravir: Phase 2 trial
P011 Study Design: from 3 to 2 drugs, 3 doses



RNA < 50 copies/ml at wk 20

Key findings: 1 Serious drug related AE in the ISL +DOR part 3 arm, No discontinuations for safety events after week 48

Most common AE in ISL + DOR groups: **headache** (6.5%) ; most common AE in DOR/3TC/TDF group: **diarrhea** (19%)
Similar Incidence of both at Weeks 48 and 96

Molina et al, JAIDS Vol 91, Number 1, September 1, 2022

Islatravir: Safety Data Laboratory (P011 Study)

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** • **Grade 4: ≥20.0 x ULN**	 4/29 (13.8) 1/29 (3.4)	 0/30 (0) 2/30 (6.7)	 0/31 (0) 3/31 (9.7)	 1/31 (3.2) 1/31 (3.2)
• **Mean change from baseline in total lymphocytes (x 10^9 cells/L****	0.24	-0.13	-0.13	0.32

No apparent dose related changes in grade 3 and 4 AE's
** post hoc analysis

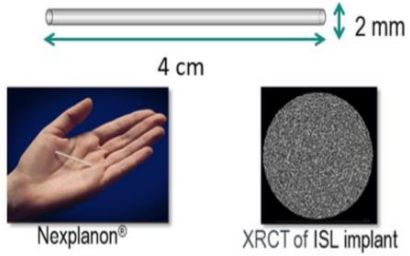
Molina et al, JAIDS Vol 91, Number 1, September 1, 2022

ISLATRAVIR Implant design similar to Nexplanon®

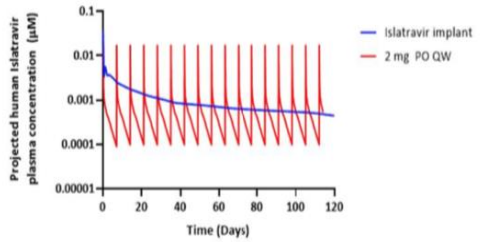
- ISL implant based on Implanon®/Nexplanon®
  - Uses same polymer
  - Removable (not bioerodible)
- Able to use Nexplanon® applicator

- Initial trial uses prototype implant

Polymer + **ISL**

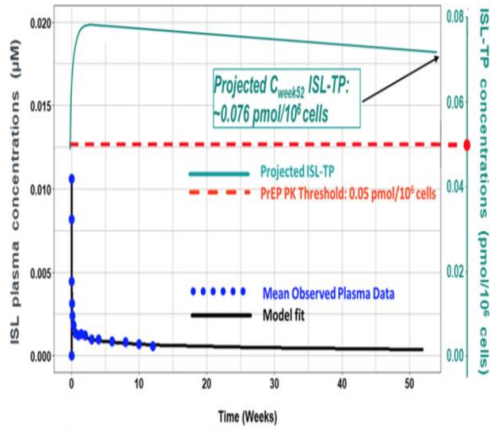


Simulated Human PK Profiles



R. Matthews IAS 2019.

62mg Implant projected lead to concentrations above threshold for at least 12 months



- 62 mg implant will continue to release through 52 weeks
- ISL-TP should be above threshold (0.05 pmol/10^6 cells) for >12 months
  - Projected concentration at 12 months: **0.076 pmol/10^6 cells**
  - Projected time at which concentration falls below 0.05 pmol/10^6 cells: 68-70 weeks (**~16 months**)

- ISL protype implants were generally well-tolerated, with no discontinuations due to an AE and no severe implant-related AEs
- No laboratory or other signs of systemic reactions
- Local tolerability (erythema, induration) generally mild and possibly dose dependent
- Both implants (54 and 62 mg) had concentrations above PK threshold at 12 weeks
- 62 mg implant projected to be well above threshold at 12 months and likely for several months beyond

Supports potential of the ISL implant as a once yearly PrEP option

R. Matthews IAS 2019.

Islatravir: Efficacy at 96 weeks

	ISL (0.25 mg) + DOR QD	ISL (0.75 mg) + DOR QD	ISL (2.25 mg) + DOR QD	ISL Combined	DOR/ 3TC/ TDF QD
	N=29	N=30	N=31	N=90	N=31
Outcome (FDA Snapshot Approach)					
HIV-1 RNA < 50 copies/ mL, n (%)	**25 (86.2)**	**27(90.0)**	**21(67.7)**	**73(81.1)**	**25(80.6)**
HIV-1 RNA ≥ 50 copies/ mL, n (%)	2 (6.9)	2 (6.7)	5 (16.1)	9 (10.0)	2 (6.5)
No virologic data at Week 96 window , n (%)	2 (6.9)	1 (3.3)	5 (16.1)	8 (8.9)	4 (12.9)

Molina et al, JAIDS Vol 91, Number 1, September 1, 2022

Islatravir programme still on FDA hold or partial hold

- Dose-related immunological concerns:
  - Treatment programme - mean drop CD4 cells
  - PrEP Programme - mean drop in total lymphocyte count

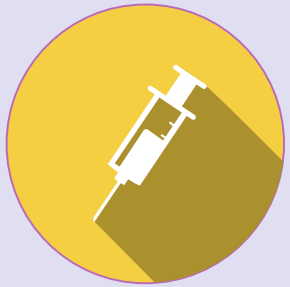
- Clinically:
- No lymphopaenia or leukopaenia
- No differences infection events or COVID episodes vs comparator
- Review of all safety data across whole programme – no findings of concern

Compounds by modality and indication

Treatment

- Islatravir
- Lenacapavir

ORAL



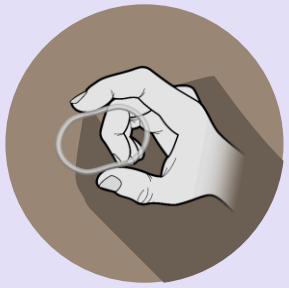
INJECTABLE
IM, SC, IV

- Albuvirtide
- bNabs
- Lenacapavir
- Elsulfavirine
- Islatravir

Prevention

IVR/TOPICAL/ MPT

- Dapivirine IVR
- MIV 150 PC1005
- TAF/EVG insert
- Tenofovir IVR
- EVO-100 gel
- Dapivirine + C
- MB66 film
- Dual prevention pill



IMPLANTS PATCHES/IM

- Lenacapavir
- Islatravir implant
- INSTI MAP
- TAF implant
- RPV IM

Grazie per l’attenzione