New and Investigational ART Drugs and Strategies

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2021 Ryan White HIV/AIDS Program CLINICAL CONFERENCE

Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years

Dr Currier has no relevant financial relationships with ineligible companies to disclose. (Updated 9/20/21)

Learning Objectives

At the end of this presentations, learners will be able to:

- List 2 investigational drugs currently in phase III trials
- Describe how these investigational agents might be used in treatment in the future

New Drugs on the Horizon

Islatravir

Lenacapravir

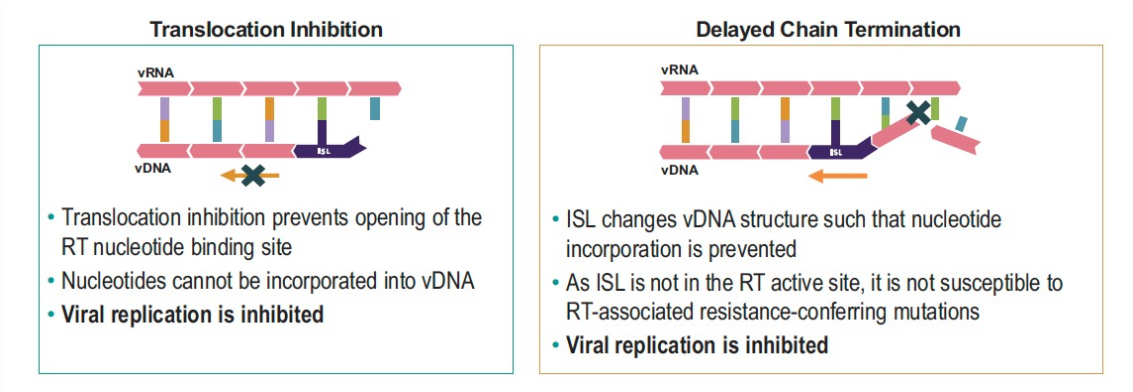
GSK 3640254 (aka GSK “254)

Investigational Aspects of Recently approved Agents

Long acting Cabotegravir and Rilpivirine

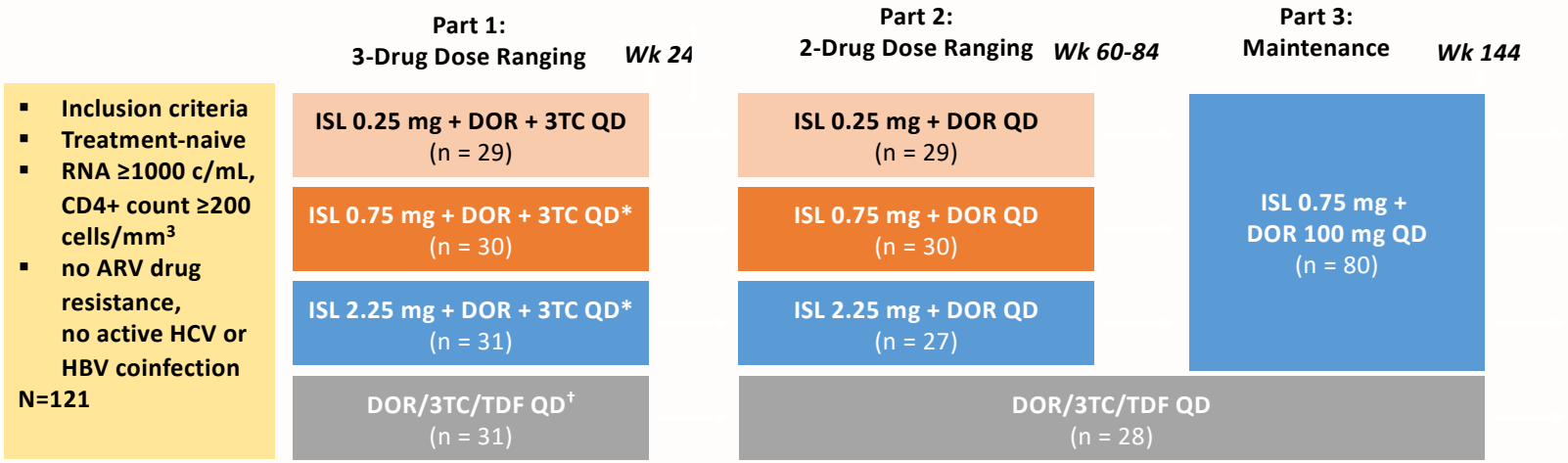
Islatravir

- **Other Names:** EFdA, ISL, MK-8591
- **Drug Class:** Nucleoside Reverse Transcriptase Translocation Inhibitors



- Currently under evaluation for both prevention and treatment, including both a pill formulation and an implant.
- For treatment: Phase 3 trials combined as a single tablet with Doravirine.

Islatravir:
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

Cunningham. IAS 2021. Abstr OAB0304.

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)

No apparent dose related changes in grade 3 and 4 AE's

Cunningham. IAS 2021. Abstr OAB0304.

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)
Reasons for no virologic data in window					
Discontinued due to death or Ae[a] , n (%)	0	0	2 (6.5)	2 (2.2)	1 (3.2)
Discontinued for other reasons, n (%)	1 (3.4)	1 (3.3)	3 (9.7)	5 (5.6)	3 (9.7)
On treatment but missing data, n (%)	1 (3.4)	0	0	1 (1.1)	0

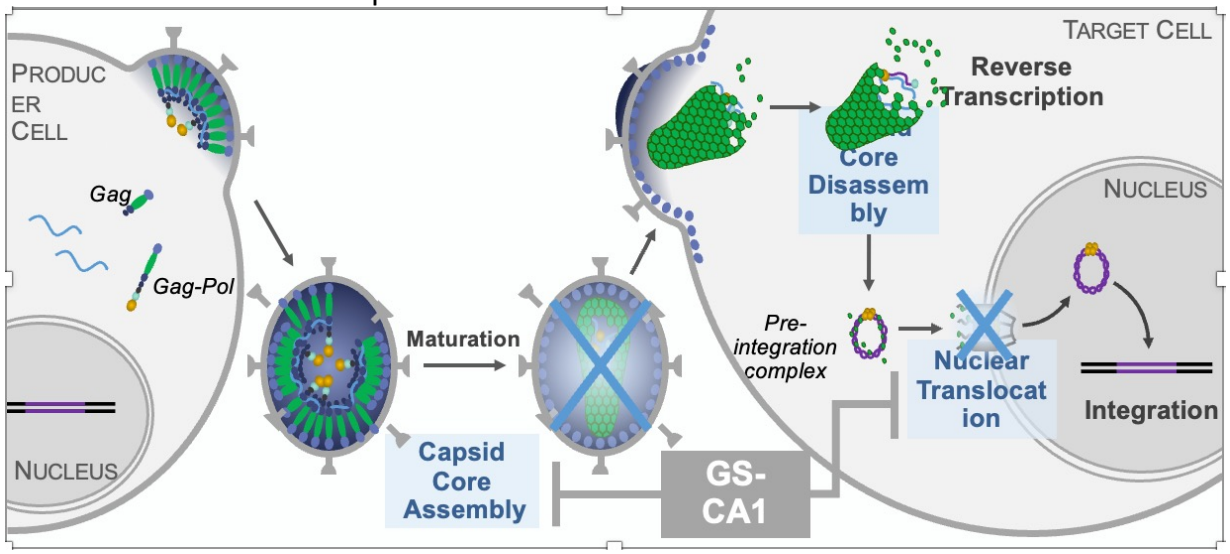
Molina JM et al. HIV Glasgow 2020, abstract O415.
Orkin C et al. HIV Glasgow 2020, abstract P047.

Islatravir: Ongoing trials

- Phase III studies of treatment-naive people (NCT04233879),
- Heavily treatment-experienced people (NCT04233216)
- People with viral suppression who are switching from other regimens (NCT04223778 and NCT04223791).
- A phase II study of children and adolescents is also planned (NCT04295772).

Lenacapravir: Background

- Lenacapavir: HIV capsid inhibitor that prevents nuclear assembly, virus assembly and release, and capsid assembly. EC_{50} 50 picomolar
  - Retains full activity against NRTI-, NNTRI-, PI-, and INSTI-resistant HIV-1 in vitro[3-5]
  - Oral and SC formulations in development

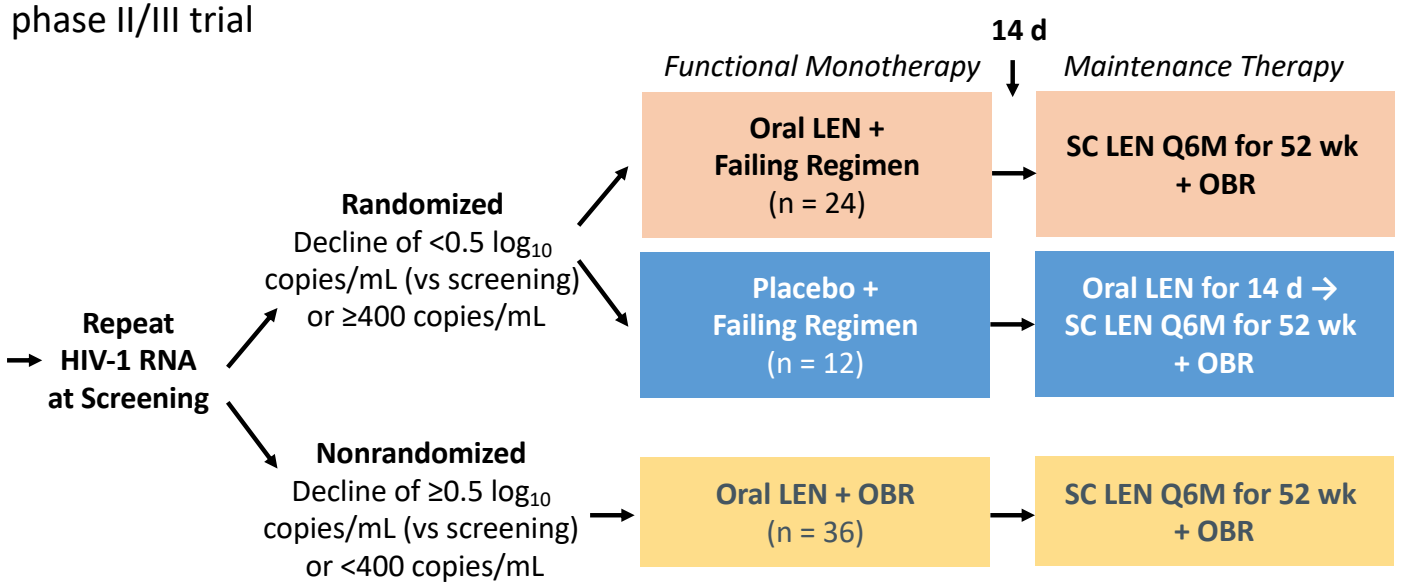


1. Link. Nature. 2020;584:614. 2. Bester. Science. 2020;370:360. 3. Yant. CROI 2019. Abstr 480. 4. Margot. CROI 2020. Abstr 529. 5. VanderVeen. CROI 2021. Abstr 128. 6. Segal-Maurer. CROI 2021. Abstr 127. 7. Molina. IAS 2021. Abstr OALX01LB02.

Slide adapted from : clinicaloptions.com

CAPELLA: Study Design with Lenacapravir

- Ongoing, 2-cohort, phase II/III trial



- Primary endpoint achieved in prior analysis: ≥0.5 $\log_{10}$ copies/mL decline in HIV-1 RNA at Day 14 in randomized cohort (90% of LEN vs 17% placebo)
  - 1.93 log 10 reduction in viremia in LEN group in first 14 days
- Secondary endpoints: HIV-1 RNA <50 copies/mL, <200 copies/mL at Week 26 in randomized cohort

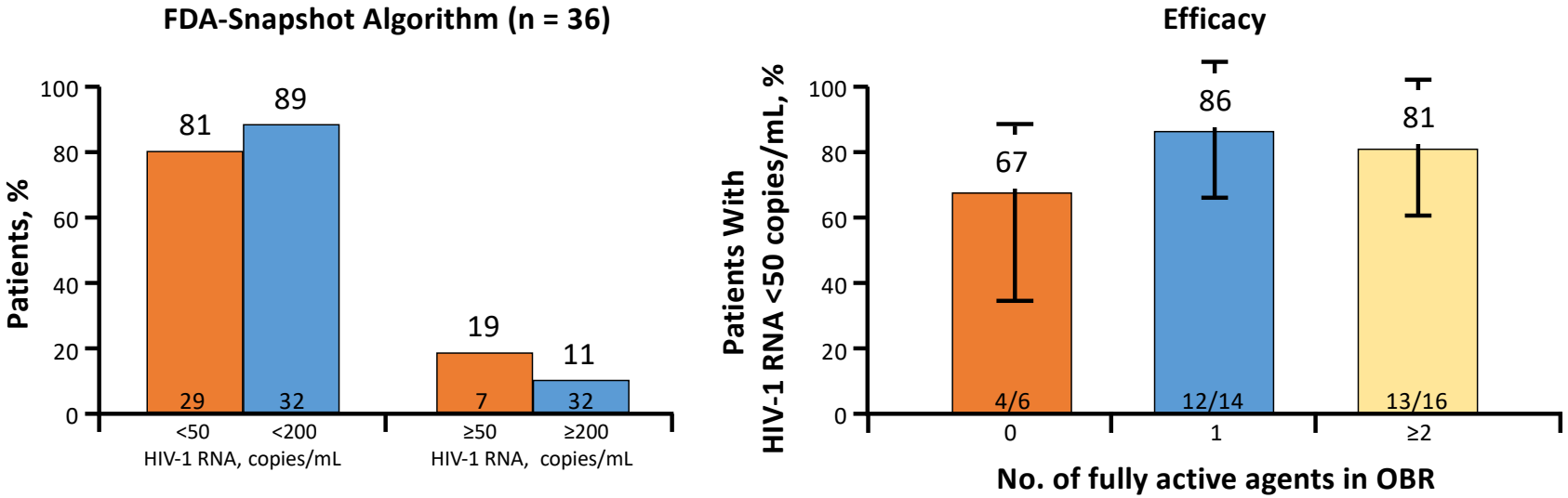
Molina. IAS 2021. Abstr OALX01LB02.

CAPELLA: Baseline Characteristics

Characteristic	Randomized		Nonrandomized	Total (N = 72)
	LEN (n = 24)	Placebo (n = 12)	LEN (n = 36)	
Median age, yr (range)	55 (24-71)	54 (27-59)	49 (23-78)	52 (23-78)
Female at birth, %	29	25	22	25
Black, %	42	55	31	38
Hispanic/Latinx, %	25	36	14	21
Median HIV-1 RNA, log_{10} copies/ml (range)	4.2 (2.3-5.4)	4.9 (4.3-5.3)	4.5 (1.3-5.7)	4.5 (1.3-5.7)
▪ >75,000 copies/mL, %	17	50	28	28
Median CD4+ cell count, cells/mm^3 (range)	172 (16-827)	85 (6-237)	195 (3-1296)	150 (3-1296)
▪ ≤200 cells/mm^3, %	67	92	53	64
Median time since HIV diagnoses, yr (range)	27 (13-39)	26 (14-35)	23 (9-44)	24 (9-44)
Median prior ARVs, No. (range)	9 (2-24)	9 (3-22)	13 (3-25)	11 (2-25)
Median ARVs in failing regimen, No. (range)	3 (1-7)	3 (2-6)	4 (2-7)	3 (1-7)
Resistance to ≥2 drugs in class, %				
▪ NRTI	96	100	100	99
▪ NNRT	92	100	100	97
▪ PI	83	67	83	81
▪ INSTI	83	58	64	69

Molina. IAS 2021. Abstr OALX01LB02.

CAPELLA Secondary Endpoints: LEN Efficacy at Week 26 in Randomized Cohort



- Mean change in CD4+ cell count: +81 cells/mm^3
- Incidence of very low CD4+ cell count (<50 cells/mm^3) decreased from 22% (8/36) at baseline to 0% (0/34) at Week 26

CAPELLA: Emergence of LEN Resistance

Outcome, n (%)	Randomized Cohort (n = 36)
Patients meeting criteria for resistance testing*	11 (31)
No emergent LEN resistance	7 (19)
Emergent LEN resistance	4 (11)
▪ M66I	4
▪ Q67H	1
▪ K70N/R/S	1
▪ N74D	1

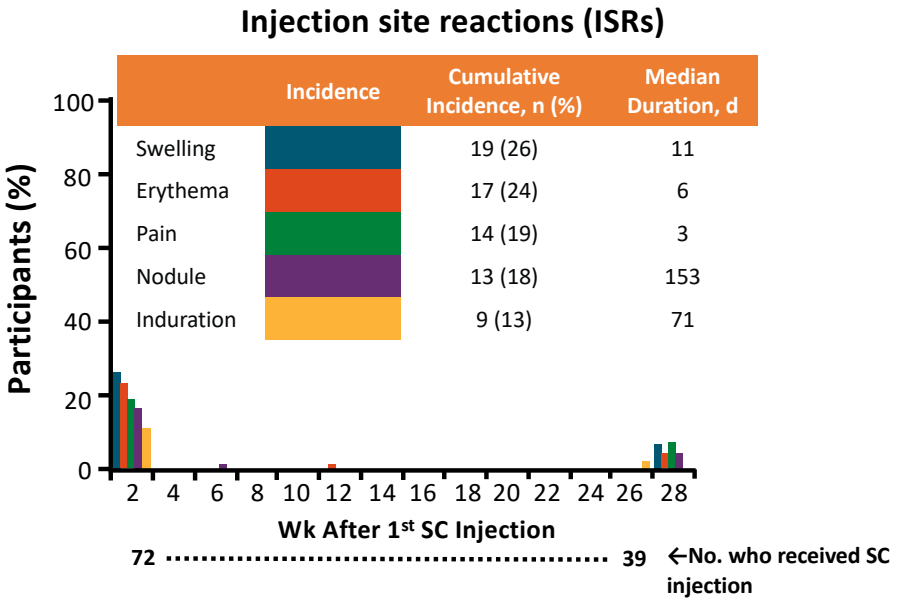
* Capsid genotypic and phenotypic resistance testing performed in any patients with HIV-1 RNA ≥50 copies/mL and <1 $\log_{10}$ HIV-1 RNA decrease from Day 1 at Week 4 appt, at any appt after attaining HIV-1 RNA <50 copies/mL and rebound to ≥50 copies/mL, and at any appt with >1 $\log_{10}$ increase from nadir. If suboptimal virologic response or rebound were confirmed: HIV-1, reverse transcriptase, protease, and integrase genotypic and phenotypic testing were done.

- All 4 patients with emergent LEN resistance remained on LEN
  - 3 patients achieved HIV-1 RNA resuppression at a later visit, 2 without and 1 with OBR change
  - 1 patient with no fully active agents never achieved suppression (max decline in HIV-1 RNA: 1.7 $\log_{10}$ copies/mL)
- No patients developed additional resistance to OBR agents

Molina. IAS 2021. Abstr OALX01LB02.

CAPELLA: Wk 26 Safety, Injection Site Reactions in Randomized and Nonrandomized Cohorts

Outcome with incidence ≥5%, n (%)	Total (N = 72)
Adverse event	
▪ Diarrhea	6 (8)
▪ Nausea	6 (8)
▪ Cough	5 (7)
▪ Headache	5 (7)
▪ Pyrexia	5 (7)
▪ Urinary tract infection	5 (7)
▪ Abdominal distension	4 (6)
▪ Arthralgia	4 (6)
▪ Back pain	4 (6)
▪ Constipation	4 (6)
▪ Oral candidiasis	4 (6)
▪ Rash	4 (6)
Any grade 3/4 lab abnormality	19 (26)
▪ Low creatinine clearance/high creatinine	8 (11)
▪ Glycosuria	4 (6)
▪ Nonfasting/fasting hyperglycemia	4 (6)



- 56% (40 of 72) had ≥1 ISR related to LEN; 28 grade 1, 2 grade 3, no grade 4
- All 36 patients in randomized cohort received second LEN injection

Molina. IAS 2021. Abstr OALX01LB02.

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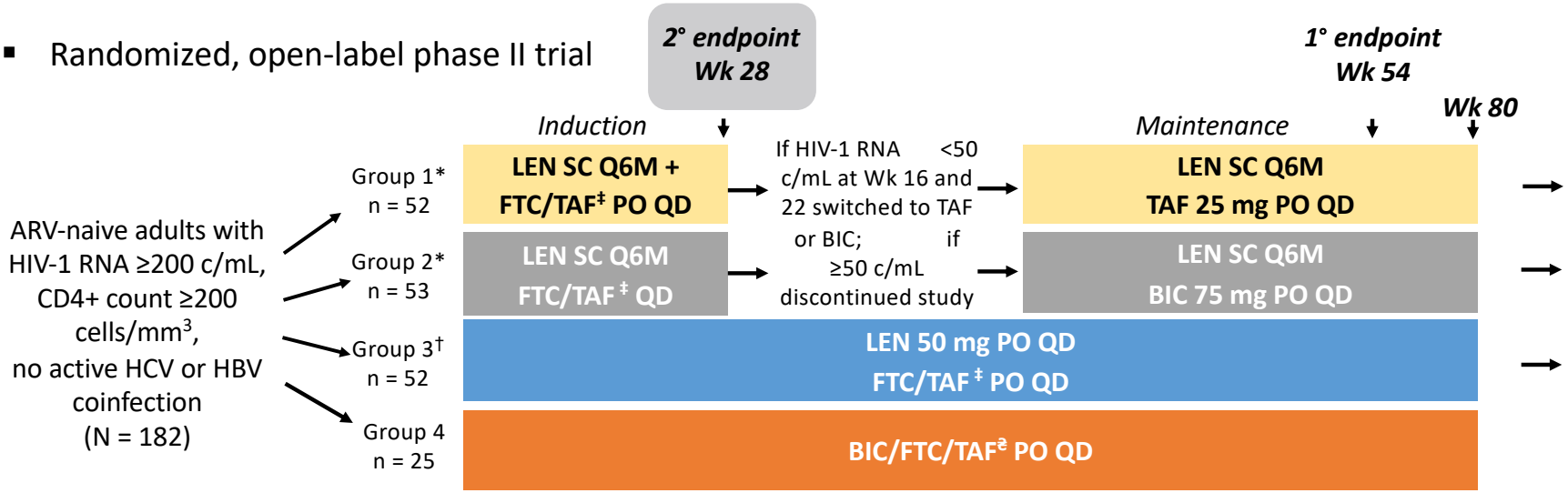
CAPELLA: Lenacapravir in MDR HIV

- Lenacapavir, in combination with OBR, demonstrated favorable efficacy and safety at Week 26 in heavily treatment-experienced patients with MDR HIV-1 infection
  - High rate of virologic suppression (81%)
  - Increase in CD4+ cell count (+81 cells/mm^3)
    - No patients had CD4+ cell count <50 cells/mm^3 at Week 26 vs 22% at baseline
  - Treatment well tolerated with no AEs leading to discontinuation
  - All randomized patients received second SC lenacapavir injection
- Data support ongoing evaluation of lenacapavir for HIV-1 treatment and prevention in heavily treatment-experienced patients with MDR HIV-1 infection
- More information on resistance needed

Molina. IAS 2a021. Abstr OALX01LB02.

CALIBRATE: Lenacapavir in Treatment-Naive

- Randomized, open-label phase II trial

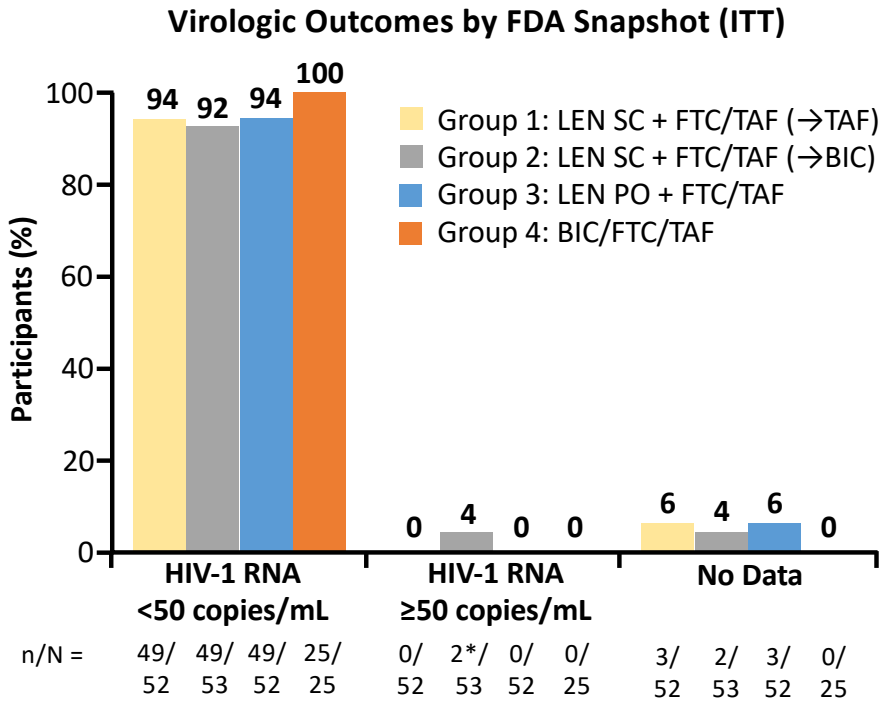


*LEN oral lead-in 600 mg Days 1 and 2, 300 mg Day 8; LEN 927 mg SC Day 15 and then Q6M.
†LEN 600 mg Days 1 and 2, then 50 mg from Day 3. ‡FTC/TAF 200/25 mg. ‡BIC/FTC/TAF 50/200/25 mg.

- 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.

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.

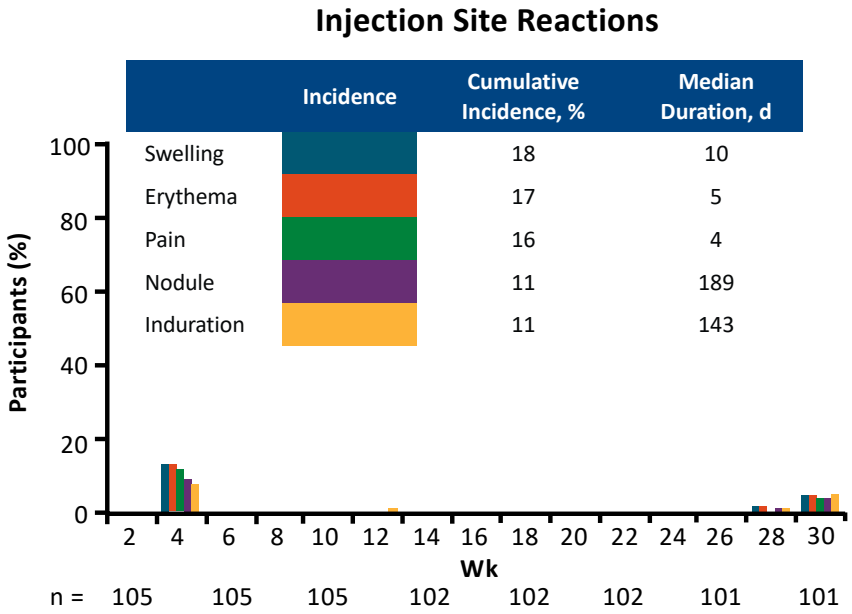
- One participant in **LEN SC + FTC/TAF → BIC** arm had emergent resistance mutations at Wk 10
  - CA: Q67H + K70R (LEN fold change = 20)
  - RT: M184M/I
- Plasma LEN concentrations consistently in target range

Gupta. IAS 2021. Abstr OALB0302.

Slide credit: clinicaloptions.com

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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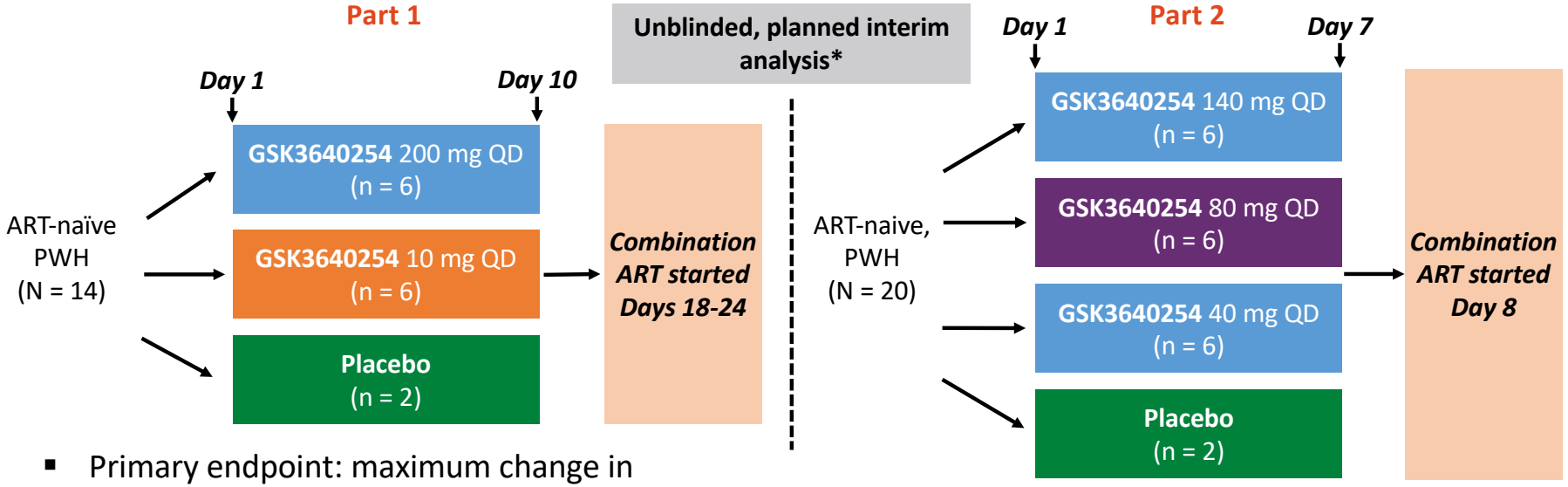
Next Generation Maturation Inhibitor: GSK3640254

- GSK'254
  - Prevents the proteolytic cleavage of specific portions of the Gag protein which prevents processing of the Gag-Pol polyprotein in late stage of HIV replication.
  - Pre-existing mutations at the cleavage site led to termination of development of an earlier maturation inhibibitor (bevirimat).

-Phase 2 A results of a two part study of GSK '254 presented at CROI 2021.

Phase IIa Study of GSK3640254: Study Design

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



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

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

Spinner. CROI 2021. Abstr 126.

Phase IIa Study of GSK3640254: Baseline Characteristics

Characteristic	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)		
Mean age, yrs (SD)	32.7 (8.3)	27.7 (6.9)	32.8 (6.2)	33.2 (8.2)	29.3 (3.9)	36.5 (9.3)	31.8 (7.2)
Male, n (%)	6 (100)	5 (83)	6 (100)	5 (83)	6 (100)	4 (100)	32 (94)
Mean BMI (SD)	25.3 (3.7)	23.9 (4.3)	24.8 (3.7)	23.4 (1.6)	22.6 (2.2)	23.0 (1.3)	23.9 (3.0)
Race, n (%)							
▪ White	2 (33)	5 (83)	4 (67)	5 (83)	5 (83)	3 (75)	24 (71)
▪ Black	0	1 (17)	2 (33)	1 (17)	0	0	4 (12)
▪ Other	4 (67)	0	0	0	1 (17)	1 (25)	6 (18)
Mean HIV-1 RNA, $\log_{10}$ copies/mL (SD)	4.19 (0.311)	4.67 (0.233)	4.43 (0.510)	4.53 (0.577)	4.82 (0.476)	4.25 (0.417)* 4.25 (0.417)†	4.47 (0.489)* 4.57 (0.592)†

*Part 1. †Part 2.

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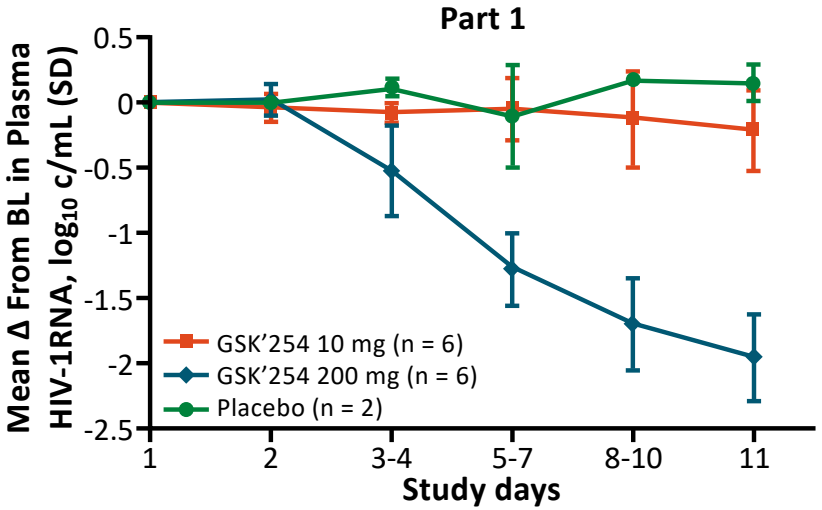
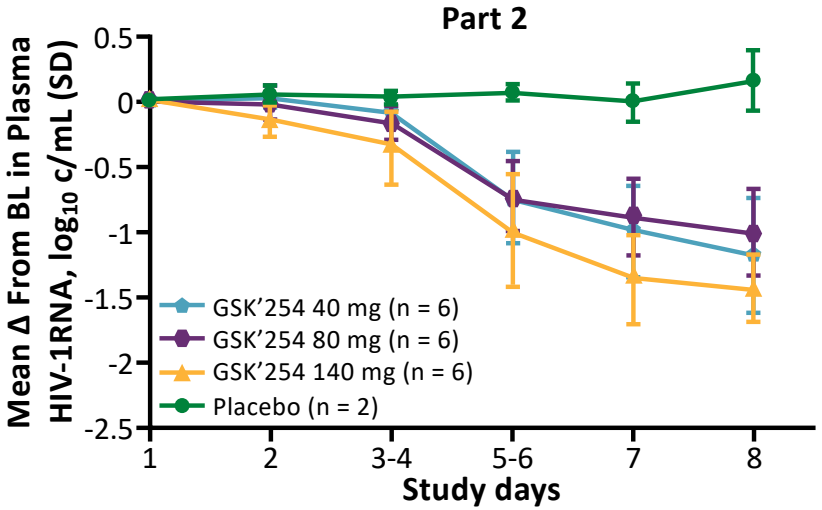
Phase IIa Study of GSK3640254: Antiviral Activity





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)

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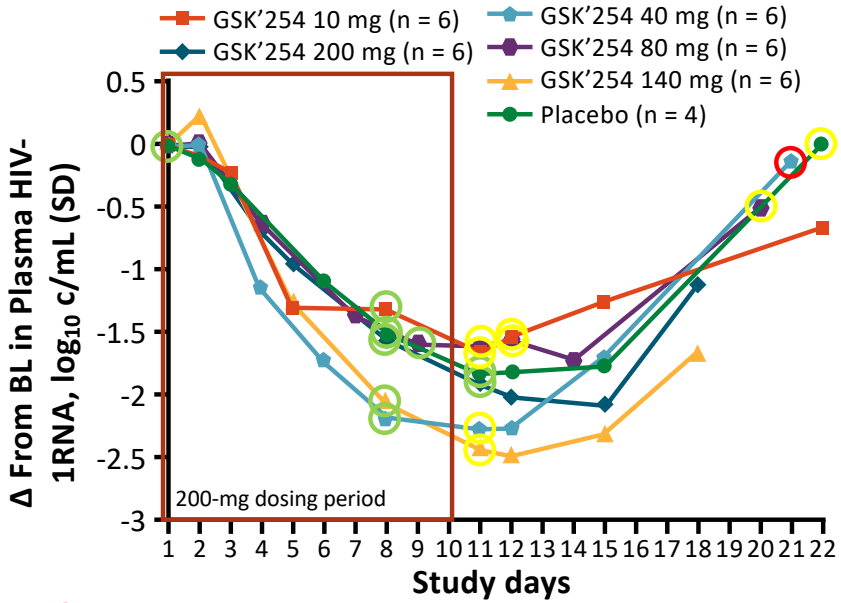
Phase IIa Study of GSK3640254: Resistance

- Resistance mutation A364A/V detected in 4 of 6 patients receiving GSK3640254 200 mg QD at Day 11 in part 1
  - Full conversion and phenotypic resistance in 1 of 4
- No resistance in 10 mg QD group
- Protocol amendment reduced duration of monotherapy from 10 days to 7 days in Part 2
- No resistance detected at any dose in part 2 (140 mg, 80 mg, or 40 mg)

HIV-1 *Gag* Genotyping Results in GSK3640254 200 mg Group



A364V: Full conversion of the mixture and loss of sensitivity to GSK'254

A364A/V: Mixed population of amino acids "A" and "V" with partial resistance to GSK'254

No resistance

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GSK'254 Summary

- In ART-naive persons with HIV, novel HIV-1 maturation inhibitor, GSK3640254, demonstrated dose-response activity
  - HIV-1 RNA decreased 1.5 $\log_{10}$ copies/mL with 140-mg QD dose and 2.0 $\log_{10}$ copies/mL with 200-mg QD dose
- GSK3640254 was well-tolerated
  - No grade 3/4 AEs and no AEs leading to d/c
- Investigators conclude these findings support evaluation of GSK3640254 (100 mg QD, 150 mg QD, and 200 mg QD) in combination with 2 NRTIs in phase IIb study

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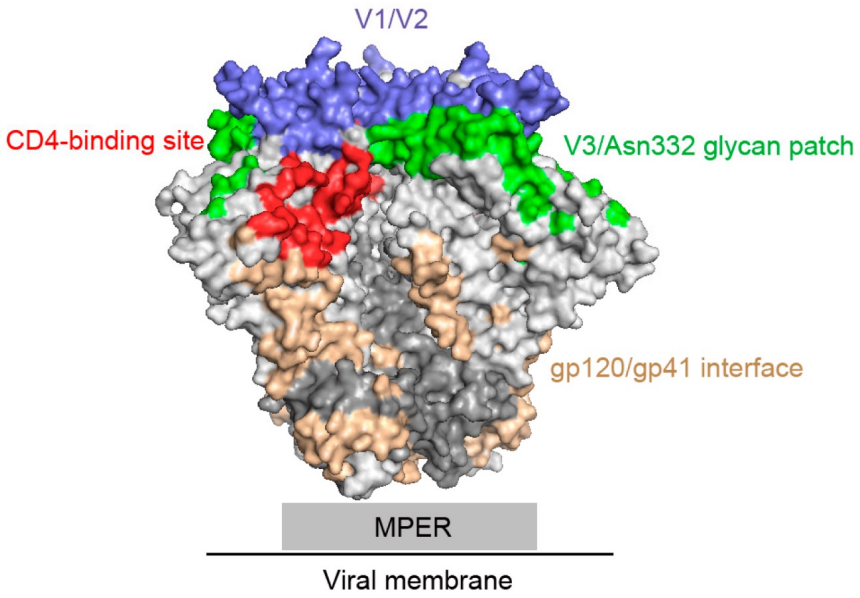
Broadly Neutralizing Antibodies against HIV



CD4-binding site
b12, VRC01, VRC07, NIH45-46, 3BNC117, VRC-PG04

V1/V2
PG9, PG16, CH01-04, PGT141-145, PGDM1400

V3/Asn332 glycan patch
PGT121-123, PGT125-131, PGT135, 10-1074, 2G12

gp120/gp41-interface
PGT151, 35O22, 8ANC195

MPER
2F5, 4E10, 10E8

Future Combinations and Approaches in the works

- Long acting cabotegravir and a broadly neutralizing antibodies
  - A5357: A single arm trial of long-acting cabotegravir and VRC07LS (a broadly neutralizing antibody; bNAb) as maintenance ART
  - A5364: A single arm trial of two bNAbs (3BNC117-LS & 10-1074-LS) to prevent relapse of viremia of discontinuation of oral ART
  - A5377, a first-in-human Phase 1 clinical trial of a tri-specific monoclonal antibody (SAR441236) to establish safety, pharmacokinetics, and preliminary antiviral activity
- Ongoing Phase 1 study combined with GS-5423 (AKA 3BNC117-LS) in people with virologic suppression

Investigational Approaches with recently approved agents: Long Acting Cabotegravir and Rilpivirine

- Long acting cabotegravir and rilpivirine approved for use in patients with viral suppression and no prior resistance in an every 4 week dosing schedule in US and Canada. January 21, 2021. (approved for q8 in EU)
- Approved in both an oral formulation cabotegravir 30 mg and rilpivirine and in the sustained release injection to be initiated after an oral lead in.
- ATLAS 2M compared 4 week with 8 week dosing in people who were suppressed on 4 week dosing or suppressed on ART outside the trial
  - Week 96 follow-up (CROI 2021) HIV RNA during q 8 week (91% < 50 copies) non-inferior to q 4 week dosing (90% < 50 copies/ml)
  - Very few grade 3 ISR- rates decreased over time

ACTG 5359
A Phase III Randomized-Control Trial to Evaluate Long-Acting Antiretroviral Therapy in Non-adherent HIV-Infected Individuals

Co- Chairs: Aadia Rana, Jose Castillo-Mancilla Co- Vice Chairs: Raphael J. Landovitz, Karen Tashima

Utilizes cash incentives to help obtain viral suppression followed by use of long acting Cabotegravir

Study Population:

- ART-experienced, HIV-infected males and non-pregnant females ≥18 years of age with:
    - HIV-1 RNA >200 copies/mL
    - Evidence of non-adherence according to at least one of the following criteria:
        - Poor virologic response within 18 months prior to entry in individuals who have been prescribed ART for at least 6 consecutive months.
        - Loss to clinical follow-up within 18 months prior to study entry with ART non-adherence for ≥6 consecutive months.
    - No evidence of any clinically relevant RPV or INSTI resistance-associated mutations (historically or upon screening).
    - Ability of site clinician, in conjunction with participant, to construct a ≥3-drug ART regimen with ≥2 drugs predicted to be fully active, including a boosted PI/cobi and/or an INSTI.

ACTG AIDS CLINICAL TRIALS GROUP

Summary

- New drugs with novel mechanisms of action and less frequent dosing are progressing in development.
  - Islatravir
  - Lenacapravir
  - GSK’254
- Use of approved combination of long acting cabotegravir/rilpivirine slowly being rolled out
  - Investigational approaches with q 8 week dosing, combination with other agents and use in populations that have struggled with adherence in progress.

Question-and-Answer Session

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