New and Investigational Antiretroviral Drugs

Constance A. Benson, MD

Professor of Medicine

Division of Infectious Diseases and Global Public Health

University of California San Diego

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

Dr Benson has served on advisory and data safety monitoring boards for GlaxoSmithKline/ViiV Healthcare, received research grants awarded to her institution from Gilead Sciences, Inc., and serves as a consultant to NDA Partners, LLC. (Updated 09/27/22)

Slide 2

Learning Objectives

After attending this presentation, learners will be able to:

- Evaluate results of recent clinical trials of new or novel antiretroviral drugs in development for treatment of HIV and their potential role(s) in future clinical practice
- Monitor new research findings related to novel long-acting antiretroviral regimens in development

Slide 3

Outline

- The diminishing pipeline - Is there a need for new antiretroviral drugs (ARVs)?
- New ARVs in development
  - Updated data on Long-Acting Cabotegravir/Rilpivirine
  - Islatravir
  - Lenacapravir
  - GSK 3640254
  - Monoclonal and broadly neutralizing antibodies

US DHHS & IAS-USA Guidelines: Recommended Regimens for First-line ART in Patients With HIV Infection

Class	DHHS[1]	IAS-USA[2]
INSTI	▪ BIC/TAF/FTC (AI)* ▪ DTG/ABC/3TC (AI)* ▪ DTG + TAF or TDF + FTC or 3TC ▪ DTG/3TC*	▪ BIC/TAF/FTC* ▪ DTG + TAF or TDF + FTC or 3TC ▪ DTG/3TC*

*Single-tablet regimens.

- Recommendations are adjusted based on baseline HIV-1 RNA, CD4+ cell count, CrCl, eGFR, HLA-B*5701, HBsAg, osteoporosis, and pregnancy status or intent
- No currently recommended first-line regimens contain a pharmacologic-boosting agent
- All options are now available as once daily regimens

1. DHHS ART. Guidelines. January 2022.; 2. Saag. JAMA. 2020;324:1651-69:379.

Available First-Line Single-Tablet Regimens

Agent	Components	Caveats
INSTI regimens		
BIC/TAF/FTC	INSTI + dual NRTI	
DTG/ABC/3TC	INSTI + dual NRTI	Only if HLA-B*5701 neg
EVG/COBI/TDF/FTC EVG/COBI/TAF/FTC	INSTI + booster + dual NRTI	
DTG/3TC	INSTI + NRTI (two drug combination)	Only if HIV-1 RNA < 500,000 copies/mL, no HBV co-infection; only if resistance test results available
NNRTI regimens		
DOR/3TC/TDF	NNRTI + dual NRTI	No restriction on baseline HIV-1 RNA or CD4+ count
EFV/FTC/TDF EFV/TDF/3TC, EFV_{400}mg/TDF/3TC	NNRTI + dual NRTI	
RPV/FTC/TDF RPV/FTC/TAF	NNRTI + dual NRTI	Only if HIV-1 RNA < 100,000 copies/mL and CD4+ count > 200 cells/mm^3
Boosted PI regimens		
DRV/COBI/FTC/TAF	PI + booster + dual NRTI	

Is there a need for new antiretroviral drugs?

- Despite unprecedented progress in treating HIV in the past two decades, there are some opportunities for improvement…
  - Lower pill burden or drug burden
  - The promise of long-acting ARVs
  - Safety?
- Virological failure due to drug resistance or adverse effects
  - Prevalence of transmitted drug resistance in Rhode Island 26% (driven by NNRTIs)
  - Prevalence of transmitted drug resistance in Europe 0.23% for INSTIs, 3.73% for current NRTIs

Novitsky V et al., CROI 2022; Abstr. 517; de Salazar A, et al. CROI 2022; Abstr. 516

CARISEL Phase IIIb Implementation Study: Long-Acting CAB + RPV for ART in Europe

Adults receiving ART ≥6 mo; no prior confirmed VF; HIV-1 RNA <50 copies/mL twice <12 mo before screening and at screening (N = 430) → OLI → **LA CAB + RPV** Doses 1-2 Q1M; doses 3+ Q2M for 10 mo → *Treatment continuation per current clinical practice*

- At 12 mo, **87% had HIV-1 RNA <50 copies/mL** by FDA Snapshot, ITT-E (0.7% with HIV-1 RNA ≥50 copies/mL; 13% with no virologic data)

Characteristics of CVF and SVF Cases

Sex at Birth, BL BMI (kg/m²), country	Type of Failure	BL HIV-1 Subtype	HIV-1 RNA at Failure, c/mL	BL RPV RAMs	BL INI RAMs	RPV RAMs at Failure	INI RAMs at Failure	Phenotypic Resistance (Fold-Change) to RPV/CAB
Female, 29, Germany	CVF	G	214/1861	E138A	None	E138A + M230L	None	22.0/0.9
Male, 30, Spain	SVF*	B	585/NA	None	None	E138K	N155N/S	6.1/1.3

*Participant met SVF criterion at Mo 4 in 2 of 3 tests and withdrew from the trial per PI discretion. ART was changed to DRV/COBI/FTC/TAF.

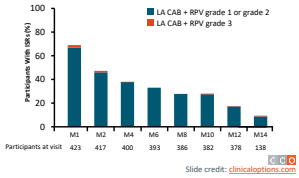
Jonsson-Oldenbüttel. AIDS 2022. Abstr EPLB805.

Slide credit: clinicaloptions.com

CARISEL: Safety Summary and Injection Site Reactions

- 84% reported any AE, 36% drug related, 9% grade ≥3, 6% leading to withdrawal
- ISRs reported in 86% of patients, 98% with mild or moderate severity
- Median ISR duration: 3 days; 82% resolved within 7 days

Injection-Related Parameter	LA CAB + RPV (N = 430)
No. of patients who received ≥1 injection	423
No. of injections ▪ ISR events, n	5844 1867
Pain, n (% of injections)	1540 (26)
Discomfort, n (% of injections)	94 (2)
Induration, n (% of injections)	74 (1)
Grade 3, n (% of ISR events)	32 (2)
Patients withdrawing for injection-related reasons, n (% of participants with injections)	25 (6)



Jonsson-Oldenbüttel. AIDS 2022. Abstr EPLB805.

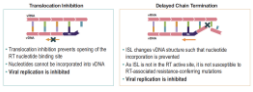
Slide credit: clinicaloptions.com

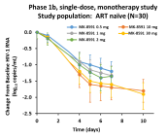
New Antiretroviral Drugs in Development

Entry Inhibitor	NRTI or NRTTI	NNRTI	INSTI	Protease Inhibitor	Capsid Inhibitor	bNAbs	Maturation Inhibitor
Albuvirtide	**Islatravir**	Elsulfavirine	S-365598	GS-1156	**Lenacapavir**	UB-421	**GSK254**
	LA-TAF implant	ACC007				Leronlimab (PRO 140)	GSK937
						VRC 01/LS VRC 07/LS	
						PG121 Elipovimab	
						GS-6423 GS-2872	
						N6LS	

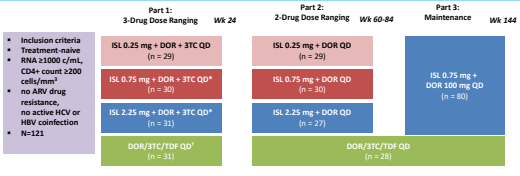
Islatravir (ISL)

- 4'-ethynyl-2-fluoro-2'-deoxyadenosine (MK-8591; EFdA) a nucleoside reverse transcriptase translocation inhibitor (NNRTI) – chain termination
  - Active at sub-nanomolar concentrations; >10x potency compared with current ARVs
  - Plasma half-life 50-60 hrs; active triphosphate intracellular half-life up to 128 hours
  - Being evaluated for prevention and treatment in pill, implant and IV formulations.





Islatravir P011: Phase 2b Study Design

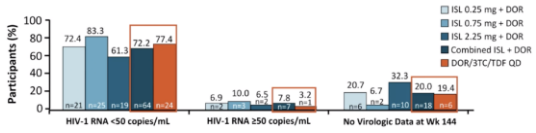


RNA < 50 copies/ml at wk 20

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, et al. IAS 2021; Abstr OAB0304

Islatravir Study P011: Week 144 Efficacy Data



- Protocol-defined virological failure (confirmed HIV RNA ≥ 50 copies/mL) in 7 patients; all discontinued the trial with confirmatory HIV RNA < 80 copies/mL
- No patients had clinically significant confirmed HIV RNA levels ≥ 200 copies/mL or drug resistance analyses

Molina EACS 2021; Abstr OS 1/S

Islatravir (ISL)

Media > News releases > **News release**

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

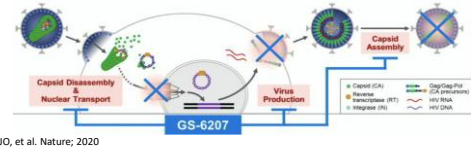
The FDA's clinical hold is based observations of decreases in total lymphocyte and CD4+ T-cell counts in some participants receiving islatravir in clinical studies.

December 13, 2021 5:00 pm ET

Slide courtesy of Dr. Judith Currier

Lenacapavir: A Novel First in Class Capsid Inhibitor

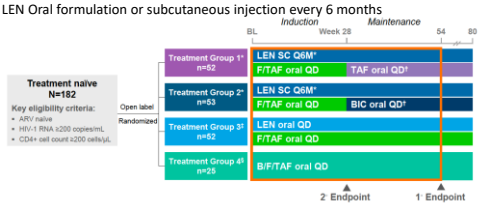
- Active against a broad range of HIV-1 isolates, including those resistant to current NRTIs, NNRTIs, PIs, and INSTIs
  - Modulates stability and/or transport of capsid complexes; inhibits multiple processes necessary for viral replication
  - Picomolar activity; more potent than current ARVs; oral and SC formulations in



Link JO, et al. Nature; 2020

CALIBRATE: LEN in Treatment Naïve PWH

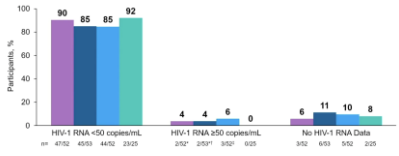
- LEN Oral formulation or subcutaneous injection every 6 months



- Maintenance phase: SC LEN q 6 m + TAF or BIC daily; PO LEN+TAF/FTC daily; or BIC/TAF/FTC

Gupta S, et al. CROI 2022, Abstract 138

CALIBRATE: LEN in Treatment Naïve PWH at Week 54

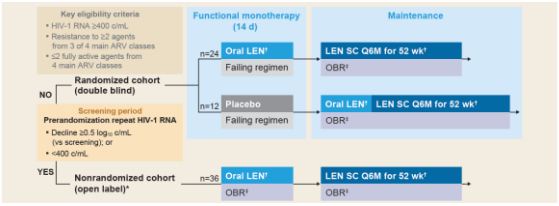


LEN SC Groups 1, 2 (LEN + FTC/TAF then LEN/TAF or LEN/BIC): 88% achieved and maintained virologic suppression at Week 54

- 2 pts (1.5%) developed LEN resistance
  - Q67N +70R in CA preceded by M184M/I
  - Q67H; non-adherence to F/TAF
- Both resuppressed on 2 NRTI + INSTI
- 3 pts with treatment-limiting ISRs

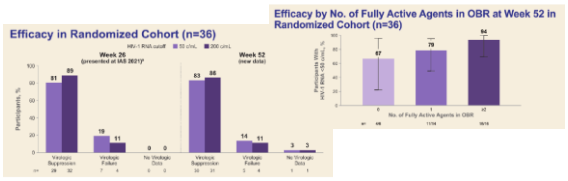
Gupta S, et al. CROI 2022, Abstract 138

CAPELLA: Lenacapavir in People with MDR HIV



Ogbuagu O, et al. CROI 2022, Abstract 491

CAPELLA: Viral Suppression at Week 52



LEN + OBR led to viral suppression at week 52 in 83%

Ogbuagu O, et al. CROI 2022, Abstract 491

Lenacapavir Resistance: CAPELLA and CALIBRATE

- **CAPELLA[1,2]:** LEN in HTE PWH
  - 83% (30/36) achieved HIV-1 RNA <50 copies/mL by 52 wk in randomized cohort
  - LEN RAMs emerged in 8/72 from randomized and nonrandomized cohorts

Participants With CA-R[2]	First Visit With CA-R	CA RAMs	No. of Fully Active Agents	Reason for LEN Monotherapy
1	Wk 26	M66I	3	Lack of adherence to OBR based on plasma concentrations
2	Wk 4	M66M/I, K70K/S	2	
3	Wk 10	K70H, A105A/S/T, T107T/N	2	
4	Wk 4	Q67H, K70R	3	
5	Wk 10	M66I, N74D, A105T	0	No fully active ARVs in OBR
6	Wk 4	M66M/I	0	
7	Wk 4	M66M/I, Q67Q/H/N, K70K/R	1*	
8	Wk 4	M66I, T107A	0	

*TFV active at BL, inactive at Wk 10

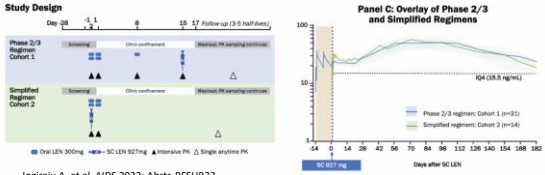
- **CALIBRATE[3,4]:** LEN in treatment-naive PWH
  - 90% (47/52) and 85% (45/53) in LEN SC + FTC/TAF groups achieved HIV-1 RNA <50 copies/mL by 54 wk
  - LEN RAMs emerged in 2/157

Participant With CA-R[4]	First Visit With CA-R	CA RAMs	Adherence
1 (LEN SC + FTC/TAF)	Wk 10	Q67H, K70R	PK on target for LEN; M184I/V developed first, suggests poor adherence to FTC/TAF
2 (LEN PO + FTC/TAF)	Wk 54	Q67H	Poor adherence by pill counts and low LEN and TFV concentrations

1. Ogbuagu. CROI 2022; Abstr 491 2. Margot. AIDS 2022; Abstr EPB240 3. Gupta. CROI 2022; Abstr 138 4. VanderVeen. AIDS 2022; Abstr EPB239

Simplified Subcutaneous Dosing Regimen of Lenacapavir

- LEN concentrations of the simplified regimen were comparable to those of the Phase 2/3 regimen
- Simplified regimen currently evaluated in PrEP trials



Jogiraju A, et al. AIDS 2022; Abstr. PESUB22

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
- 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.

Press Releases

August 22, 2022

Gilead Announces First Global Regulatory Approval of Sunlenca® (Lenacapavir), the Only Twice-Yearly HIV Treatment Option

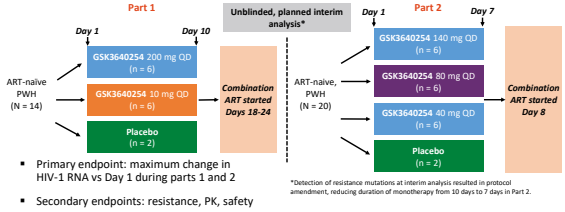
– European Commission Grants Marketing Authorization for Sunlenca, Helping to Address a Critical Unmet Clinical Need for People with Multi-Drug-Resistant HIV Who Have Very Limited Treatment Choices –

Maturation Inhibitors: GSK3640254

- 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 inhibitor (bevirimat).
  - Phase 2a results of the two-part study presented at CROI 2021 and recently published in *Clinical Infectious Diseases.*

Maturation Inhibitors: Phase 2a Study of GSK3640254

- 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.

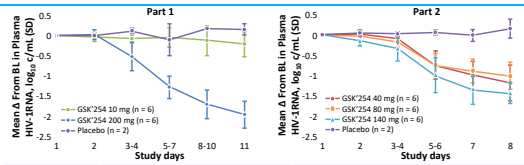


- Primary endpoint: maximum change in HIV-1 RNA vs Day 1 during parts 1 and 2
- Secondary endpoints: resistance, PK, safety

*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 et al., CROI 2021, Abstract 126; Spinner CD et al. *Clin Infect Dis* 2022; 75:786-94

Phase 2a Study of GSK3640254: Antiviral Activity

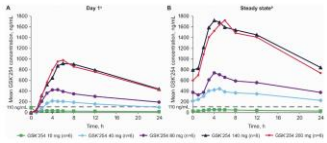


Mean Change in HIV-1 RNA vs BL, log_{10} copies/mL (SD)	Part 1 (Day 11)			Part 2 (Day 8)			
	GSK3640254 10 mg (n = 6)	GSK3640254 200 mg (n = 6)	Placebo (n = 2)	GSK3640254 40 mg (n = 6)	GSK3640254 80 mg (n = 6)	GSK3640254 140 mg (n = 6)	Placebo (n = 2)
Primary endpoint	-0.22 (0.309)	-1.96 (0.337)	0.14 (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 et al., CROI 2021; Abstract 126. Reproduced with permission; Spinner CD, et al. *Clin Infect Dis* 2022

Phase 2a Resistance and PK for GSK3640254

- Resistance mutation A364A/V detected in 4 of 6 patients receiving GSK3640254 200 mg QD at Day 11 in part 1 resulting in full conversion and phenotypic resistance in 1 of 4 patients
  - 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)



PK parameters after single dose (A) and repeat dosing at steady state; dashed line = target threshold for which ≥ 95% of participants in Phase 2b expected to exceed target trough concentration of 110 ng/ml.

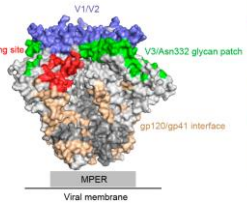
Spinner CD, et al. *Clin Infect Dis* 2022

GSK3640254 Conclusions

- In ART-naive persons with HIV, GSK3640254 demonstrated dose-response antiviral activity
  - HIV-1 RNA decreased 1.5 log_{10} copies/mL with the 140mg QD dose and 2.0 log_{10} copies/mL with the 200mg QD dose
- GSK3640254 was well-tolerated
  - No grade 3/4 AEs and no AEs leading to d/c
- DYNAMIC: Phase 2b study of GSK3640254 (100, 150 or 200 mg QD) + dolutegravir vs DTG + 3TC control arm in ART-naïve pts is in progress (NTC04900038)
- DOMINO: Phase 2b study to evaluate the safety and efficacy of GSK3640254 (100, 150 or 200 mg QD) vs DTG/3TC/ABC vs DTG/FTC/TAF in ART-naive adults (NTC04493216)

Broadly Neutralizing Antibodies against HIV

- Generally safe
- Long half lives
- Antiviral activity suppresses viremia
- Might boost existing immune responses
- Potential to directly eliminate infected cells (reduce reservoirs?)
- Selection of resistance with monotherapy common



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

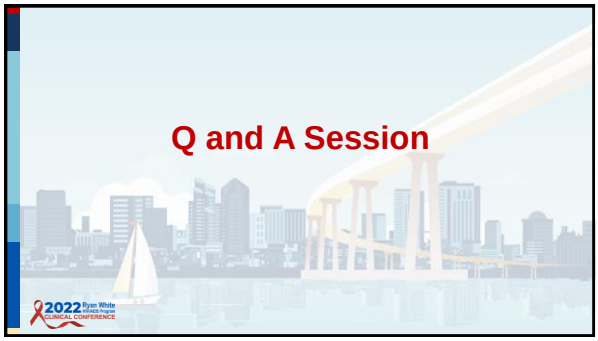
Figure courtesy of Pablo Tebas, MD

bNAb Approaches and Combinations in Clinical Trials

- LS variants (prolonged half-life) of 3BNC117 and 10-1074 in combination [Caskey M, et al. CROI 2022, Abstr. 140]
  - 1.9 log10 copies/mL reduction in plasma viremia
  - Faster decay in viremic pts vs those suppressed on ART; greater and more durable antiviral response in those with pre-Rx sensitivity by Phenosense assay
- Triple bNAb cocktail (PGDM1400, PGT121, VRC07-523LS) [Joelg B, et al. CROI 2022, Abstr. 139]
  - Mean decline in HIV RNA -2.04 log10 after 10d; all pts had viral rebound within 13-70 days due to resistance (PGDM1400 and/or PGT121) or low plasma levels (VRC07-523LS)
- Combinations in clinical trials
  - A5357: A single arm trial of long-acting CAB + VRC07LS as maintenance ART
  - A5377, a first-in-human Phase 1 clinical trial of a tri-specific monoclonal antibody (SAR441236)
  - Lenacapavir + GS-5423 + GS-2872

Conclusions

- There is an ongoing need for new antiretroviral drug development
  - Less urgent than in the past
  - The pipeline is not robust
- Greatest efforts are in the area of long-acting injectable drugs
  - Hiccups along the way
  - Complexities of implementation need to be addressed
- Uncertain clinical path for non-traditional agents, e.g., bNAbs
  - Especially for treatment


Q and A Session
2022 Ryan White HIV/AIDS Program CLINICAL CONFERENCE