Update From vCROI 2021

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Financial Relationships With Commercial Entities

Dr Lennox has received research support from ViiV Healthcare. (Updated 04/24/21)

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Learning Objectives

After attending this presentation, learners will be able to:

- Explain the results of treatment with a maturation and with a capsid inhibitor
- Advise their patients regarding weight gain and bone loss on ART
- Use SARS-CoV-2 mAbs for treatment and prevention

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CROI 2021 - Statistics

- Abstracts accepted: 698
- Oral abstracts: 109
  - 17 Late breaker
- Posters: 589
- SARS-COV-2 161 (23%)

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New ARVs

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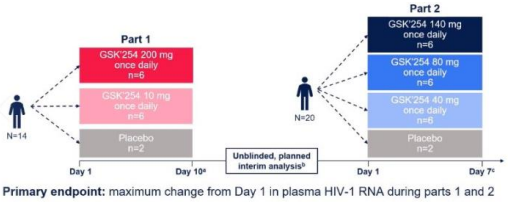
GSK 3640254 – Maturation Inhibitor

- Small Phase IIA dose-ranging study in 6 patients per dose



Primary endpoint: maximum change from Day 1 in plasma HIV-1 RNA during parts 1 and 2

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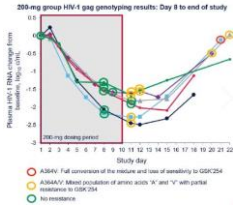
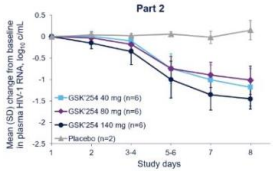
Spinner CROI 2021

GSK 3640254 – Maturation Inhibitor

- Phase 1: resistance emerged in the high dose, 10-day arm
- Phase 2: No resistance in 7-day arm, good antiviral activity





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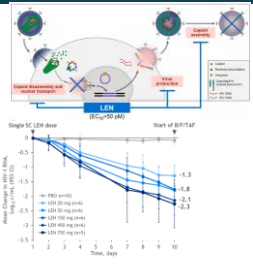
Spinner CROI 2021

Lenacapavir – Capsid Inhibitor

- Potent antiviral at the picomolar level against all HIV-1 subtypes
- Active against clinical isolates with resistance to other ART
- Half-life compatible with once <u>weekly</u> dosing
- Single Sub-Q dose produced HIV RNA reduction of ~2 log



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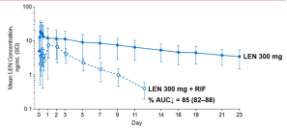
Cihlar & Lutz CROI 2021

Lenacapavir – Drug interaction Study

- Administered with DRV/r (3A4 inhibitor), ATV/r (UGT1A1 + PgP inhibition), Rifampin (3A4/PgP/UGT inducer), Famotidine
- Minimal effect with PI, acid reducer
- Do not use Rifampin with Lenacapavir

85% Decrease in LEN AUC by Strong CYP3A/P-gp/UGT Induction



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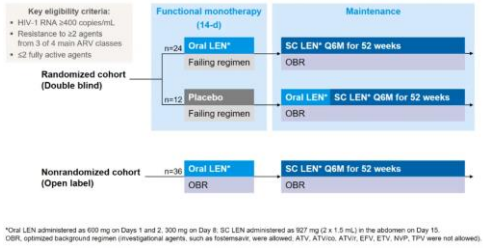
Lutz CROI 2021

Lenacapavir in Treatment Experienced

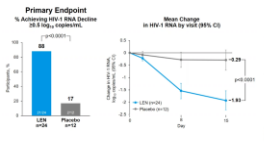


*Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8; SC LEN administered as 927 mg (2 x 1.5 mL) in the abdomen on Day 15.
OBR, optimized background regimen (investigational agents, such as fostemsavir, were allowed; ATV, ATV/co, ATV/r, EFV, ETV, NVP, TPV were not allowed).

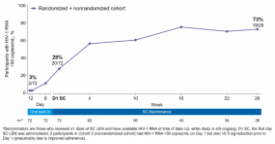
Segal-Maurer CROI 2021

Lenacapavir- Results

Functional Monotherapy



With OBR



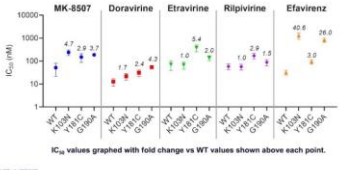
- Injection Site Reactions in 33/72, mostly mild
- 2/72 participants developed LEN resistance

Segal-Maurer CROI 2021

MK8507 – NNRTI

- Resistance profile similar to Doravirine
- Plasma t1/2~70 hours suitable for once weekly dosing

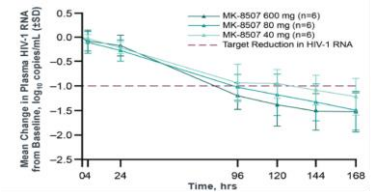
MK-8507 has potency changes <5-fold against common NNRTI resistance-associated variants (K103N, Y181C, G190A)



IC_{90} values graphed with fold change vs WT values shown above each point.

Diamond CROI 2021

MK8507 – Single Dose Antiviral Potency

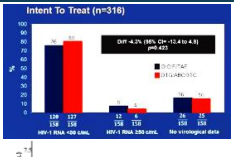


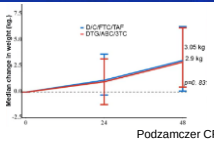
- Plan – Once weekly Islatravir + MK8507 for HIV treatment

ARV Strategies & Complications

DRV/c/FTC/TAF v. DTG/3TC/ABC – SYMTRI

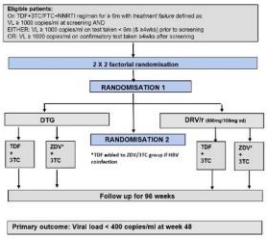
- Randomized, open label, non-Inferiority, **Rx naïve**, 316 patients, >90% men
- Primary endpoint HIVRNA <50c/ml @ 48 wk, **10%** NI
- DRV/c/FTC/TAF not <u>non</u>-inferior to DTG/3TC/ABC
- No difference in weight gain (~3kg)





DRV/r vs DTG for second line- NADIA

- Compared DRVr v DTG, and TDF/3TC v AZT/3TC
- Failing NNRTI based therapy, no resistance testing- Similar to WHO TLD plan



Paton CROI 2021

DRV/r vs DTG for second line- NADIA

- 58% TDF resistant and 92% 3TC resistant at switch
- TLD switch for NNRTI failure may result in DTG resistance

Efficacy outcomes: DTG vs DRV/r

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

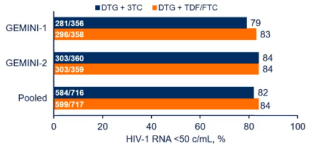
* ≥1 major DTG mutation: 4
≥1 major DRV mutation: 0

(1) T66TA, G118R, E138K, G149GA, G163GR (high-level); (2) E138K, G140A, Q148R (high-level); (3) T66I, G118R, E138K, G149GA (high-level); (4) R263K, M50R (intermediate level).

Paton CROI 2021

Continued Follow up of DTG/3TC – Week 144

- Naïve trials of DTG/3TC vs DTG+3TC/TDF
- After week 96 open label
- Week 144 data on ~1250
- During 48 weeks extension DTG/3TC gained 1.3kg more weight than 3 drug arm, no differences by race or sex

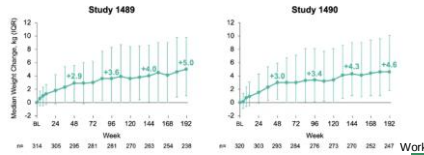


Orkin CROI 2021

Naïve BIC/FTC/TAF– Metabolic Outcomes

- Week 192 open label extension of trials #1489, #1490
- BMD changes maximal at 16 weeks (-0.9% spine, -1.4% hip), no change thereafter

Weight Changes From Baseline Through Week 192 on B/F/TAF



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Workowski CROI 2021

Efficacy BIC/FTC/TAF – Baseline ARV Resistance

- In naïve trials (1489/1490) subjects excluded if baseline RT resistant, not NNRTI resistant
- Retrospective deep sequencing for resistance to INI, RT, NNRTI, PI

	HIV RNA <50c @ wk 48	
Baseline Resistance	**BIC/FTC/TAF**	**DTG+ ABC/3TC or FTC/TAF**
NRTI	21/21 (100)	14/14 (100)
NNRTI	81/82 (99)	96/98 (98)
PI	18/18 (100)	24/25 (96)
INSTI	7/7 (100)	9/10 (90)

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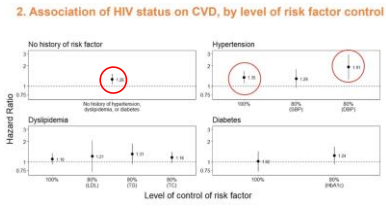
Acosta CROI 2021

Effect of HIV status on CVD Risk

- Population: Kaiser N. California
- 8285 HIV+, 179,517 HIV-
- CVD events and treated risk factors analyzed 2013-17



Treated HIV increased CVD risk, as did well controlled HTN

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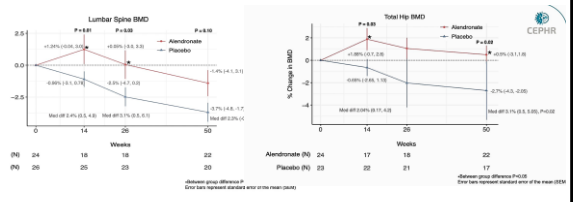
Silverberg CROI 2021

Preventing Bone Loss Due to ARV-

- Ofotokun showed that bone loss was prevented with one-time long-acting injectable bisphosphonate given at ART initiation
- APART study compared oral Alendronate 70mg weekly for 14 weeks vs placebo in ART naïve
- Analysis stratified by gender and ART type. ART was primarily TDF and INSTI based

Alendronate to Prevent Bone Loss



COVID-19

Convalescent Plasma for Severe COVID-19

- 14 sites Netherlands performed a Randomized trial of CP
- SARS-COV-2+ within 96 hours, not on Mechanical Ventilation > 96 hrs
- Plasma selected to have high titer antibody
- Trial Stopped for Futility
  - No difference in mortality
  - No difference in time to discharge

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Jordens CROI 2021

BLAZE 2 – Bamlanivimab Prophylaxis

- Nursing homes with COVID + residents
- Bam 4200mg IV vs. placebo, 1:1 as prevention
- 1 Outcome: Prevention of symptomatic COVID-19 + no disease progression
- 2 Outcome: Prevention of all COVID-19
- 1175 persons enrolled (residents and employees). 29% > 65 years (78% of residents).

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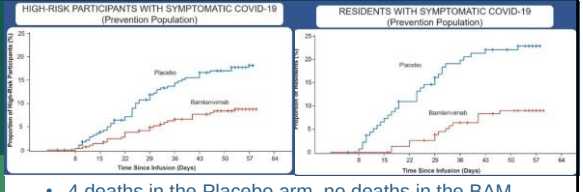
Cohen CROI 2021

BLAZE 2 – Bamlanivimab Prophylaxis



- 4 deaths in the Placebo arm, no deaths in the BAM arm
- NP Viral load was lower in those in the BAM arm who became infected

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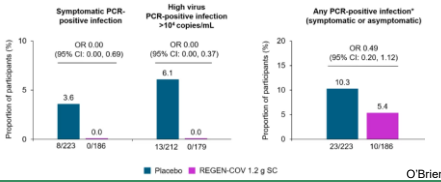
Cohen CROI 2021

Casirivimab + Imdevimab – Prophylaxis

- Interim analysis in household contacts of COVID-19 randomized SubQ injection 1.2g Combo mAb v. PLA
- Mean age 45, 78% White, 53% female



O'Brien CROI 2021

Bamlanivimab + Etesevimab Treatment

- Phase 3 follow up to Phase 2 study (JAMA)
- Mild–Moderate COVID diagnosed within 72 hours and ≥1 risk factor for progression to severe disease
- Randomized to BAM + ETS (both 2800mg) IV v. PLA
- 1035 enrolled, >90 White, 52% female, 31% ≥ age 65, Mean BMI 32

Dougan CROI 2021

Bamlanivimab + Etesevimab Results

COVID-19 RELATED HOSPITALIZATION OR ANY-CAUSE DEATH BY DAY 29

Treatment	N	Events	Rate	p
Placebo	517	36	7.0%	-
Bamlanivimab 2800 mg + Etesevimab 2800 mg	518	11	2.1%	0.0004

MEAN VIRAL LOAD

	Placebo	Bamlanivimab + Etesevimab	p
Day 1	6.52	6.51	-
Day 3	5.74	5.04	<0.001
Day 5	4.68	3.85	<0.001
Day 7	4.05	2.87	<0.001
Day 11	2.69	2.21	<0.001

- All 10 Deaths occurred in the placebo arm

Dougan CROI 2021


Question-and-Answer Session