2nd Long-Acting Treatment and Prevention Conference

29 October 2024 | Johannesburg

SOUTHERN AFRICAN HIV CLINICIANS SOCIETY

Lenacapavir: a summary

Francois Venter, Wits Ezintsha, University of the Witwatersrand

* Note: Not a Gilead Sciences representative

Disclosures: Francois Venter

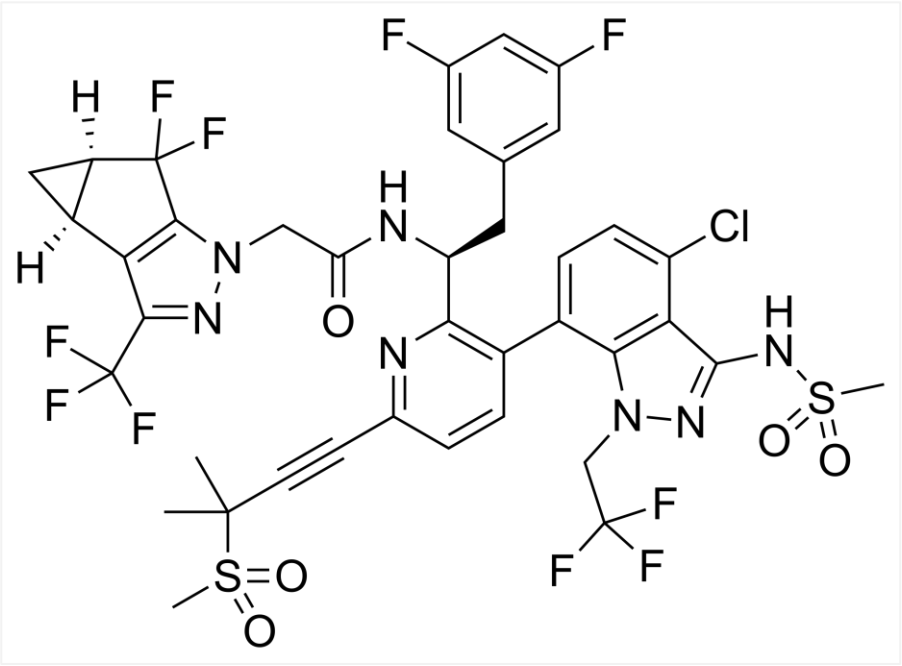
- Research Support: USAID; Unitaid; South African Medical Research Council; Bill and Melinda Gates Foundation; study drug donations from ViiV Healthcare, Merck and Gilead Sciences; study support Merck, ViiV, J&J
- Speaker's Bureau/Board Member/Advisory Panel: Gilead, ViiV, Mylan/Viatris, Merck, Adcock-Ingram, Aspen, Abbott, Roche, J&J, Sanofi, Boehringer Ingelheim, Thermo-Fischer and Virology Education
- The unit does investigator-led studies with Merck, J&J and ViiV providing financial support and is doing commercial drug studies for Merck, Gilead and Novo. The unit performs evaluations of diagnostic devices for multiple biotech companies.

Wits

Ezintsha

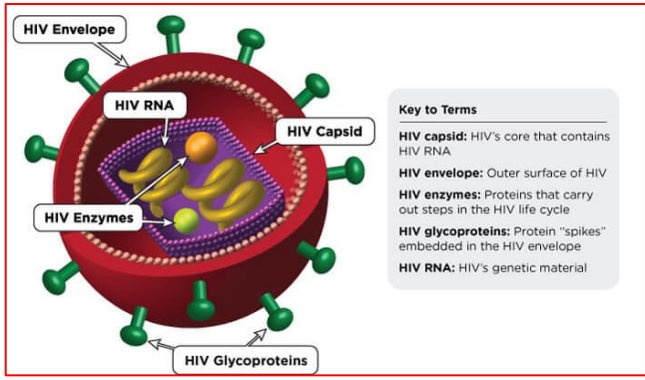
INVESTIGATE INNOVATE ADVANCE

Lenacapavir



- Approved for heavily pretreated ARV patients in small study, on optimised backbone – registered FDA/EMA 2022
- Huge excitement – prevention results, but also potentially for treatment
- 6-monthly dosing opened up previously unimagined ideas – “as close to a vaccine as we’ve seen”
- Immediate data on possible low cost of production further excited everyone
- This talk focuses on drug properties and PREVENTION, treatment will be discussed later

- Capsid inhibitor – 1st in its class, developed by Gilead Sciences



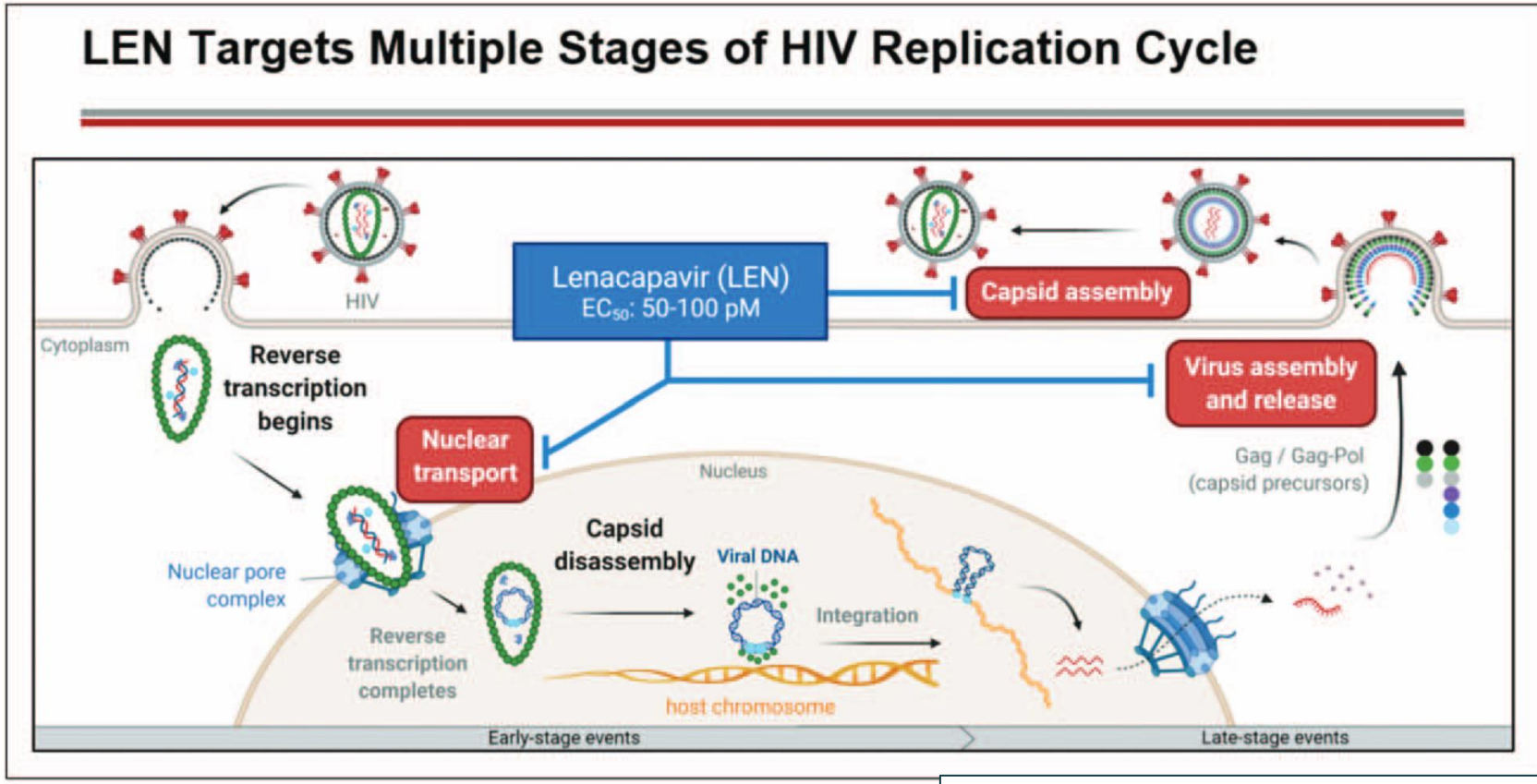


FIGURE 1. Lenacapavir targets multiple stages of the HIV replication cycle.

CURRENT OPINION **Lenacapavir: a first-in-class HIV-1 capsid inhibitor**

Hadas Dvory-Sobol, Naveed Shaik, Christian Callebaut, and Martin S. Rhee

For those who want to nerd out:

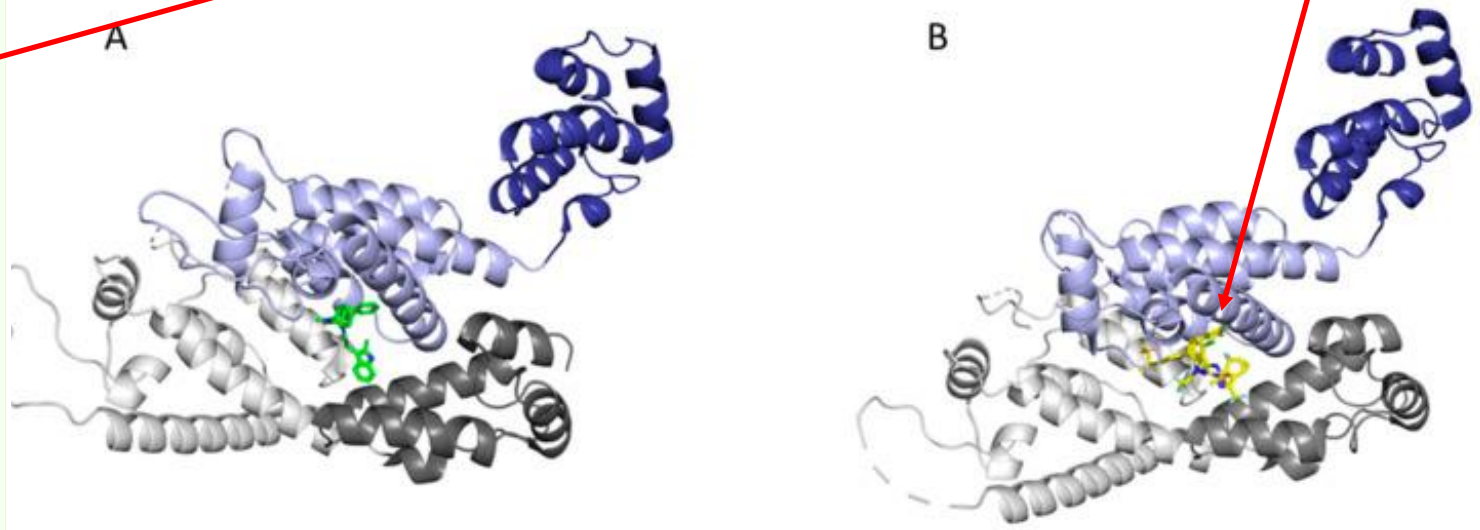
Table 1.

Summary of capsid-binding host cell factors.

Abbreviation	Name	Binding Site on CA	Related Process	Complex PDB ID
ATP	Adenosine triphosphate	R18 pore	Reverse Transcription	-
BICD2	Bicaudal D2	-	Trafficking	-
CLASP2	Cytoplasmic linker-associated protein 2	-	Trafficking	-
CLIP170	Cytoplasmic linker protein 170	EB1-like domain at pentamer interface	Trafficking	-
CPSF6	Cleavage and polyadenylation specificity factor 6	Interprotomer Pocket	Nuclear Import and Localization	4WYM
CypA	Cyclophilin A/ Peptidylprolyl isomerase A	CypA loop (residues 85 to 93)/Inter-hexamer interface	Uncoating	5FJB 6Y9W 6Y9V
Daxx	Death domain-associated protein	CA-CypA complex	Uncoating Inhibition	-
dNTP	Deoxynucleoside triphosphate	R18 pore	Reverse Transcription	-
DRFs	Diaphanous-related formins	-	Uncoating/ Trafficking	-
ERK2	Extracellular signal-regulated kinase 2	Phosphorylates Ser-16 of CA	Uncoating	-
FEZ1	Fasciculation and elongation protein zeta-1	R18 pore	Trafficking	-
IP6	Inositol Hexaphosphate	R18 pore	Reverse Transcription	6ES8 6BHT
MAP1A/ MAP1S	Microtubule-associated proteins 1A and 1S	Monomeric CA interface	Trafficking	-
MELK	maternal embryonic leucine zipper kinase	Phosphorylates Ser-149 of CA	Uncoating	-
MxB	Myxovirus resistance protein B	Inter-hexamer interface	Uncoating Inhibition/Nuclear Import Inhibitor	-
NONO	Non-POU domain-containing octamer-binding protein	CA NTD	cGAS Response	-
NUP153	Nucleoporin 153	Interprotomer Pocket	Nuclear Import	4U0C 6AYA
NUP358	Nucleoporin 358	CA NTD	Nuclear Import	4LQW
PDZD8	PDZ domain-containing protein 8	Gag	Uncoating	-
Pin1	Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1	Phosphorylated Ser-16 of CA	Uncoating	-
REAF	RNA-associated early-stage antiviral factor	-	Uncoating Inhibitor/ Reverse Transcription Inhibitor	-
TNPO3/ TRN-SR2	Transportin 3	CA-CPSF6 complex	Uncoating, Nuclear Import and Integration	-
TRIM11	Tripartite motif-containing protein 11	-	Uncoating	-
TRIM34	Tripartite motif-containing protein 34	-	Reverse Transcription Inhibition	-
TRIM5α	Tripartite motif-containing protein 5	Capsid lattice near CypA binding loop	Uncoating Inhibition	-
TRN1	Transportin 1	CypA binding loop (G89 crucial)	Nuclear Import	-

Daxx	Death domain-associated protein	CA-CypA complex	Uncoating Inhibition	-

Len!



Rossi E, Meuser ME, Cunanan CJ, Cocklin S. Structure, Function, and Interactions of the HIV-1 Capsid Protein. Life (Basel). 2021 Jan 29;11(2):100

Development?

- Phase 1: 1a – healthy volunteers, 1b - PLWH, no adverse events, viral load reductions
- Phase 2/3 – CALIBRATE and CAPELLA studies (more later)
- PURPOSE prevention studies

How is it available?

- Orally and subcutaneously
- Oral – 300mg tablet
- Subcutaneously – 3 and 6 monthly (?can be dosed other intervals), 1.5ml 463mg in each syringe, given as TWO injections
- NB: Subcut takes time to reach peak value, so needs a loading dose – has significant implications for programmes

Lenacapavir Dosing Schedule

Slide acknowledgement: National HIV Curriculum, www.hiv.uw.edu

Lenacapavir Dosing Schedule	
Initiation Option 1	
Day 1	927 mg by subcutaneous injection (2 x 1.5 mL injections) + 600 mg orally (2 x 300 mg tablets)
Day 2	600 mg orally (2 x 300 mg tablets)
Initiation Option 2	
Day 1	600 mg orally (2 x 300 mg tablets)
Day 2	600 mg orally (2 x 300 mg tablets)
Day 8	300 mg orally (1 x 300 mg tablets)
Day 15	927 mg by subcutaneous injection (2 x 1.5 mL injections)
Maintenance	
927 mg by subcutaneous injection (2 x 1.5 mL injections) every 6 months (26 weeks) from date of the last injection +/-2 weeks	
Missed dose: If more than 28 weeks since last injection and clinically appropriate to continue lenacapavir, restart initiation from Day 1, using either Option 1 or Option 2	

Source: Lenacapavir Prescribing Information

Major problems?

- Important – tiny treatment studies, huge prevention studies
- Well tolerated
  - Nausea, headache, almost always mild
  - Injection site reactions – generally mild, nodules annoying in some patients, case reports of necrosis – but large prevention studies seem to show this is unusual
- Drug-drug interactions?
  - Actually pretty OK – can give with antacids (oral), oral contracepives, sex-affirming hormones, all modern ART (not efavirenz, nevirapine, atazanavir)
  - Strong inducers of CYP3A/P-gp/UGT1A – eg: rifampicin – reduce LEN concentration, hence contraindicated
  - LEN a moderate inhibitor of CYP3A, so care with those
- What about resistance?

Lenacapavir in Multidrug Resistant HIV
CAPELLA Study: Capsid Inhibitor

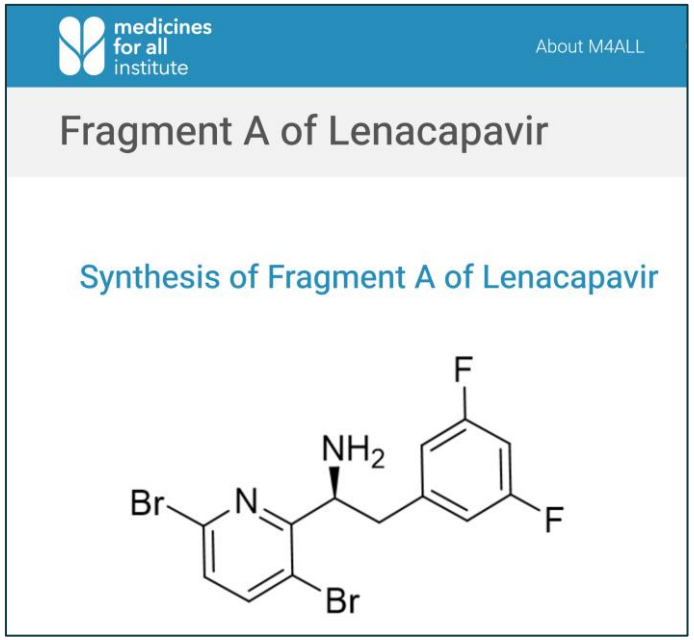
Mutations and median change in lenacapavir susceptibility

- M66I: 234-fold decrease
- 1 with Q67H + K70R: 15-fold decrease
- 1 with K70H: 265-fold decrease

Source: Segal-Maurer S, et al. N Engl J Med. 2022;386:1793-1803.

Manufacturing and costs

- Current cost >$42 000/year in USA ($21 000, R370 000/2 injections)
- Relatively simple to make (apparently) BUT…
- Active pharmaceutical ingredient is complicated and expensive to make – multiple steps being “optimised”



“Sunlenca” x 2 injections

PURPOSE 1 and 2 registration studies

- Very complex, very thoughtfully designed, women actively recruited from the get-go, pregnancy factored in
- Data for women published July 2024, men released Sept 2024 (not yet published)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Twice-Yearly Lenacapavir or Daily F/TAF for H Prevention in Cisgender Women

Authors: Linda-Gail Bekker, M.B., Ch.B., Ph.D., Moupali Das, M.D., M.P.H., Quarraisha Abdool Karim, Khatija Ahmed, M.B., B.Ch., Joanne Batting, M.B., Ch.B., D.F.S.R.H., D.R.C.O.G., Dip. HIV Man., William M.B., Ch.B., Dip. HIV Man., Katherine Gill, M.B., Ch.B., M.P.H., +33, for the PURPOSE 1 Study Team*
Affiliations

RESULTS

Among 5338 participants who were initially HIV-negative, 55 incident HIV infections were observed: 0 infections among 2134 participants in the lenacapavir group (0 per 100 person-years; 95% confidence interval [CI], 0.00 to 0.19), 39 infections among 2136 participants in the F/TAF group (2.02 per 100 person-years; 95% CI, 1.44 to 2.76), and 16 infections among 1068 participants in the F/TDF group (1.69 per 100 person-years; 95% CI, 0.96 to 2.74). Background HIV incidence in the screened population (8094 participants) was 2.41 per 100 person-years (95% CI, 1.82 to 3.19). HIV incidence with

Participants who received a diagnosis of HIV infection were referred for local HIV care, and we randomly assigned HIV-negative participants in a 2:2:1 ratio to receive subcutaneous lenacapavir (927 mg, in two 1.5-ml injections) every 26 weeks (within a window of ±7 days), daily oral TAF (200 mg of emtricitabine and 25 mg of F), or daily oral F/TDF (200 mg of emtricbine and 300 mg of TDF). Participants in the nacapavir group received placebo tablets tching either F/TAF or F/TDF (in a 2:1 ratio); rticipants in the F/TAF and F/TDF groups reived placebo injections matching lenacapavir. Participants receiving lenacapavir received loading doses of two 300-mg tablets of lenacapavir on each of days 1 and 2; participants receiving F/TAF or F/TDF received two tablets of matched lenacapavir placebo on each of days 1 and 2.

Cis-gendered men in PURPOSE 2?

- Await publication, ‘96% risk reduction vs background’ and ‘statistical superiority over TDF/FTC - only two out of the 2,180 participants on LEN got HIV!

PHARMA

With another phase 3 win, Gilead races toward 2025 launch for long-acting PrEP drug

By **Zoey Becker** · Sep 12, 2024 11:45am

Gilead Sciences | Sunleca | PrEP | Apretude

- Opaque access plan from Gilead after prevention results – several generics licenced in internal arrangement Sept 2024
  - NOT for treatment beyond highly experienced patients!
  - Prevention volumes envisaged late 2027
  - ??? cost
  - Gilead says ‘will make enough drug for everyone’ till generics make it

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JOURNAL ARTICLE

Lenacapavir to prevent HIV infection: current prices versus estimated costs of production

Get access >

Andrew Hill, Jacob Levi, Cassandra Fairhead ✉, Victoria Pilkington, Junzheng Wang, Madison Johnson, Jevon Layne, David Roberts, Joseph Fortunak

Journal of Antimicrobial Chemotherapy, dkae305, https://doi.org/10.1093/jac/dkae305

Published: 03 September 2024 **Article history** ▾

Results

The lenacapavir API is currently exported from India for $64 480/kg on 1 kg scale. Based on the ROS and KSMs, API COGs of $25 000/kg and $10 000/kg are achievable for a committed demand of 1 million (2 million tonnes/annum of API) and 10 million treatment-years, respectively. Including formulation steps, injectable lenacapavir could be mass produced for approximately $94 pppy for 1 million and $41 for 10 million treatment-years, if voluntary licences are in place and competition between generic suppliers substantially improves. Greater scale-up with improvements in manufacturers' ROS could reduce prices further. Currently lenacapavir costs $25 395–44 819 pppy.

Conclusions

Lenacapavir could be mass produced for <$100 pppy at launch. Voluntary licensing and multiple suppliers are required to achieve these low prices. This mechanism is already in place for other antiretrovirals. To date, Gilead has not agreed lenacapavir voluntary licences with the Medicines Patent Pool.

STAT Reporting from the frontiers of health and medicine

Biotech Pharma Public Health Health Tech Policy Science First Opinion | STAT Summit

OPINION FIRST OPINION

Tested in Africa, used in America

How can we end the practice of HIV wonder drug experimentation in Africa?

A lab technician working with vials of lenacapavir, the new HIV prevention injectable drug, at the Desmond Tutu Health Foundation's Masiphumelele Research Site, in Cape Town, South Africa. Nardus Engelbrecht/AP

By Mark Siedner and Rochelle Walensky Sept. 18, 2024

Siedner is an infectious disease clinician and associate professor of medicine at Harvard Medical

https://www.statnews.com/2024/09/18/lenacapavir-cabotegravir-hiv-aids-clinical-trials-africa/

Where are we?

- Groundbreaking prevention drug – IF we can get it
- Lead-in dose and operational issues are significant barriers
- More on treatment in a moment

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Lenacapavir: Can we use it for treatment?

Francois Venter, Wits Ezintsha, University of the Witwatersrand

Disclosures: Francois Venter

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Wits

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Table 2 Summary of the phase II/III clinical trials for lenacapavir

Study	Phase	Population	Treatment arms	Outcomes	Results
CALIBRATE[30,31]	II	Treatment-naïve PWH with HIV-1 RNA levels ≥200 copies/mL and CD4 cell count ≥200 cells/μL (n=182)	Group 1: PO LEN 600 mg on days 1 and 2, PO LEN 300 mg on day 8, SC LEN 927 mg on day 15 + PO FTC 200 mg and PO TAF 25 mg daily until week 28, then SC LEN 927 mg Q6 months + PO TAF 25 mg daily (n=52) Group 2: PO LEN 600 mg on days 1 and 2, PO LEN 300 mg on day 8, SC LEN 927 mg on day 15 + PO FTC 200 mg and PO TAF 25 mg daily until week 28, then SC LEN 927 mg Q6 months + PO BIC 75 mg daily (n=53) Group 3: PO LEN 600 mg on days 1 and 2, then PO LEN 50 mg daily + PO FTC 200 mg and PO TAF 25 mg daily (n=52) Group 4: PO BIC 50 mg + PO FTC 200 mg + PO TAF 25 mg daily (n=25)	Percent of participants with VL <50 copies/mL at week 28	Group 1: 94% Group 2: 92% Group 3: 94% Group 4: 100%
				Percent of participants with VL <50 copies/mL at week 54	Group 1: 90% Group 2: 85% Group 3: 85% Group 4: 92%
				Percent of participants with VL <50 copies/mL at week 80	Group 1: 87% Group 2: 75% Group 3: 87% Group 4: 92%
				Mean change in CD4 cell count from baseline to week 80	Group 1: +272 cells/μL Group 2: +251 cells/μL Group 3: +245 cells/μL Group 4: +260 cells/μL
CAPELLA[33–36]	III	Cohort 1: PWH with HIV RNA ≥400 copies/mL Cohort 2: PWH with HIV RNA <400 copies/mL, a decrease of at least 0.5 log_{10} copies/mL between screening and cohort selection visits, or cohort 1 eligible patients who joined the study after cohort 1 selection	Cohort 1: Group 1: PO LEN 600 mg + previous ART regimen on days 1 and 2, PO LEN 300 mg + previous ART regimen on day 8, SC LEN 927 mg Q6 months + OBT starting on day 15 (n=24) Group 2: Previous ART regimen + placebo on days 1–14, PO LEN 600 mg + OBT on days 15 and 16, PO LEN 300 mg + OBT on day 22, SC LEN 927 mg Q6 months + OBT thereafter (n=12) Cohort 2: Group 3: PO LEN 600 mg + OBT on Days 1 and 2, PO LEN 300 mg + OBT on Day 8, SC LEN 927 mg Q6 months + OBT starting on Day 15 (n=36)	Percent of participants with ≥0.5 log_{10} reduction in HIV-1 RNA copies/mL at day 15	Group 1: 88% Group 2: 17%
				Percent of participant with VL <50 copies/mL at week 26	Cohort 1: 81% Cohort 2: 83%
				Percent of participants with VL <50 copies/mL at week 52	Cohort 1: 83% Cohort 2: 72%
				Percent of participants with VL <50 copies/mL at week 104	81.5% (of those that continued into follow-up)
				Mean change in CD4 cell count from baseline to week 104	+122 cells/μL

ART, antiretroviral therapy; BIC, bictegravir; FTC, emtricitabine; LEN, lenacapavir; OBT, optimized background therapy; PWH, people with HIV; Q6 months, every 6 months; TAF, tenofovir alafenamide; VL, viral load.

Treatment studies (registration):

- Works for highly treated cases - ?role here
- Small numbers
- Resistance seen in isolated cases

Is lenacapavir useful for treatment?

Instinctively, hell yes! 6 monthly!

- And we have pregnancy data from prevention studies!
- Potentially low cost
- But pause for some (major) issues
- No partner drug 6-monthly – ‘asynchronous dosing’ (?) – closest we have is cabotegravir
- Originator relationship with other drug companies varies – hence no commercial studies with IMI cabotegravir, but there are with oral islatravir
- Also, can’t use in TB or for hep B (?an issue)
- Cost, availability for independent studies, only study in ACTG tiny study after 2 years
- Resistance
- Operational issues – loading doses, tails

Do we need a lenacapavir/cabotegravir study for LMICs?

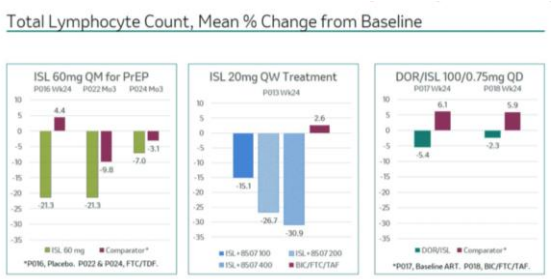
- Most obvious combination
  - Pregnancy data
  - Plenty safety, acceptability data
  - TB less of an issue, hep B will need resolution with any LAI without TDF/3TC
- CAB may be amenable to 3, 4, 6 monthly dosing, more ‘synchronous’
- Cost likely to approach TLD if administration devices kept simple, volumes high, HCW approach kept simple

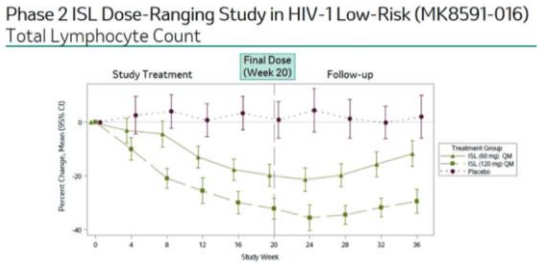
What would persuade guidelines/ policy ma s to move to LEN/CAB?

- ? A traditional non-inferiority study
  - 500-600 naïve, 96-week study vs TLD? With costing.
  - ?use TLD instead of the lenacapavir oral dosing
  - ?use CAB 3 monthly ?use with LEN 3 monthly
  - ?dose 'new' CAB 4 monthly with LEN 4 monthly
- A switch study in parallel?

Alternative addition: Islatravir (MSD/Merck)

- Nucleoside reverse transcriptase translocation inhibitor (NRTTI)
- Derived from soy sauce flavouring
- Developed by Merck/MSD when bought in 2012
- Oral – daily, weekly; monthly (PrEP/implant paused due to side effects)
- High resistance barrier, very well tolerated, very low dose





Islatravir continued

- Current plan is oral weekly combo with LEN – preliminary data phase 2 promising, also plans for oral daily with doravirine
- No access discussions, minimal pregnancy data
- Combination is potentially very cheap to make, and package
- Provisional safety and resistance data very encouraging
- Same number of tablets for 6 months as usually provided monthly
- Concerns:
  - Adherence for weekly dosing unfamiliar in HIV world
  - Pregnancy data, TB and hep B issue
  - How big a step forward is this really for LMICs? Why not wait for injectables?

Current situation for treatment access

- No access to promising agents like LEN for necessary studies – for changing guidelines or demonstration projects
- Even if all drug companies allowed instant access today, we need:
  - Studies of different drugs in different combinations
  - Switch studies, naïve studies, unsuppressed studies, pk studies, special population studies
- And THEN we need to start working how to scale in LMIC health systems