3rd Long-Acting HIV Treatment and Prevention Conference

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What the trials are telling us: LA treatment data in review

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Why LA treatment?

South Africa at forefront of HIV:

- Basic Sciences
- Clinical and programmatic research
- Policy, guidelines, models of care
- Advocacy & Activism

Advance LA treatment agenda

Why LA ART?

- LA CAB/RPV available in Europe/USA routine care since 2023. Equity issue.
- Clinical research in Uganda – advanced HIV disease – 2/3rd ART experienced, 1/3rd die from OI
- LA ART can be life-saving and life-enhancing
- In whom, when & how to use LA ART in Africa?
- CARES & IMPALA trials, with colleagues at Ezinthsha, DTHF and CAPRISA
- LA CAB/RPV preferred by ~95% of people

Background & Outline

- What does the future hold?
- Communities and clinicians are frustrated at lack of access and the pace of progress in SSA
- LA ART is the direction of travel – both in terms of community / clinician demand and drug development

Outline today

RCT evidence only – phase 2 / 3 (AIDS 2026)

Pipeline of LA agents / regimens

Injectables

- Q8W CAB/RPV
  - LATA / IMPALA / special populations
- LEN/TAB/ZAB

Oral

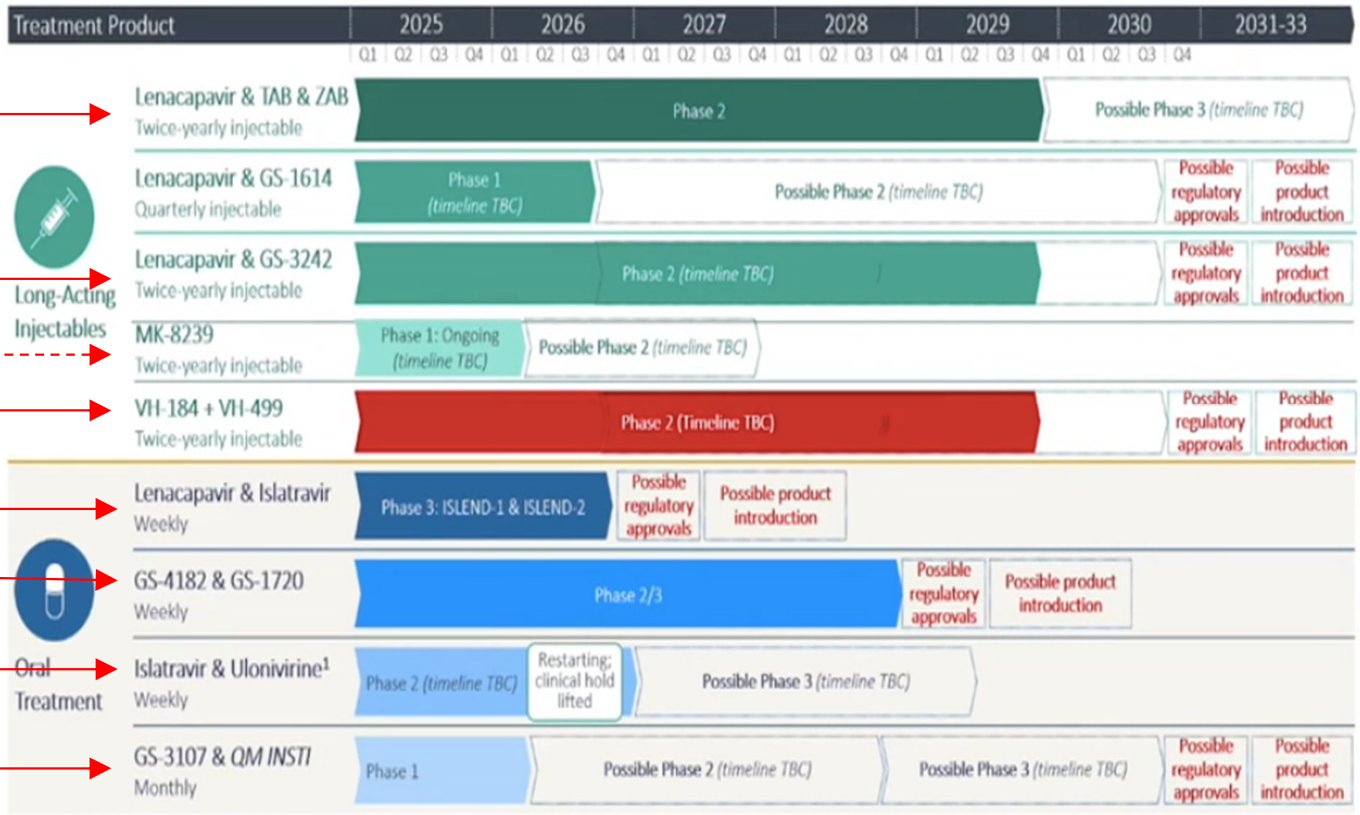
- ISL/LEN
- ISL/ULO

LA Treatment Pipeline

TWICE YEARLY INJECTABLE (phase 2)

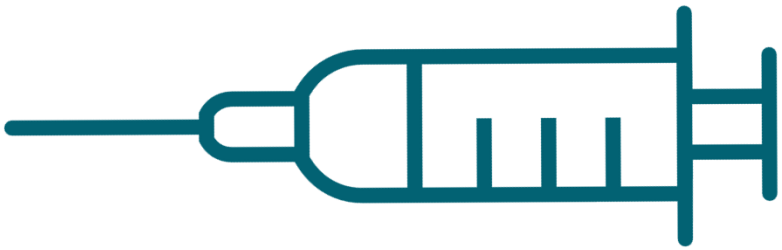
WEEKLY ORAL (phase 2/3)

MONTHLY ORAL! (phase 1/2)



Compound
VH310 proCAB
INSTI LAI PrEP / Tx

Injectable LA options



CAB/RPV – 8-weekly injectable

J Antimicrob Chemother
https://doi.org/10.1093/jac/dkae480

Journal of Antimicrobial Chemotherapy

Safety and efficacy of long-acting cabotegravir/rilpivirine versus standard oral antiretroviral therapy: a systematic review and meta-analysis

Samuel Bungaran Partahi Saud Manalu [1]*, Andrea Perez Navarro[2], Cassandra Fairhead [3] and Andrew Hill [4]

[1]School of Public Health, Imperial College London, London, UK; [2]School of Medicine, Imperial College London, London, UK; [3]Charite Universitatsmedizin Berlin, Institute of Tropical Medicine and International Health, Sudring 2-3, Berlin, Germany; [4]Department of

- Six trials (FLAIR, LATTE-2, SOLAR, ATLAS, **CARES**, LATITUDE)
- LA CAB/RPV was non-inferior to standard oral therapy in suppressing HIV RNA <50 copies/mL [91.5% vs 91.5%, RD −0.00; 95% CI, −0.03–0.02; P = 0.83]
- LA CAB/RPV was associated with higher drug resistance

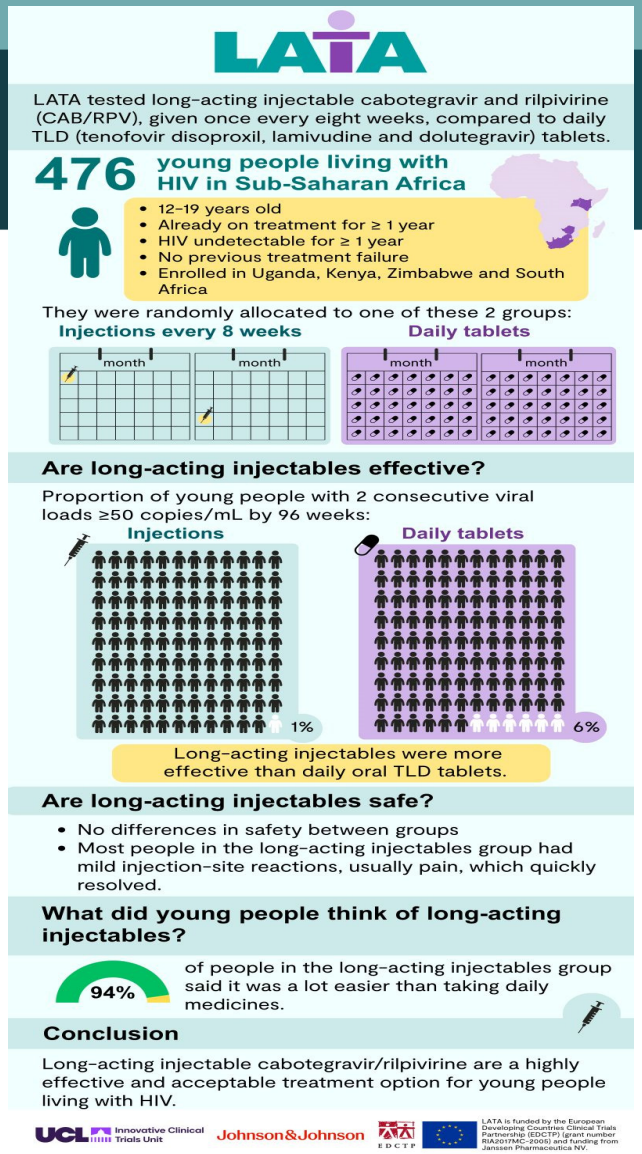
Long-acting injectable cabotegravir + rilpivirine can be used as an **alternative switching option for adults and adolescents with undetectable HIV viral load on oral ART and without active hepatitis B infection**.
Conditional recommendation, moderate-certainty evidence.

Since then:

- LATA W96
- IMPALA W96
- 4 monthly CAB/RPV regimen in trials

1. Manalu SBPS, Journal Antimicrobial Chemotherapy. 2025.
2. WHO. WHO recommendations on HIV and sexually transmitted infection testing, prevention, treatment, care and service delivery. 2025

LATA - adolescents



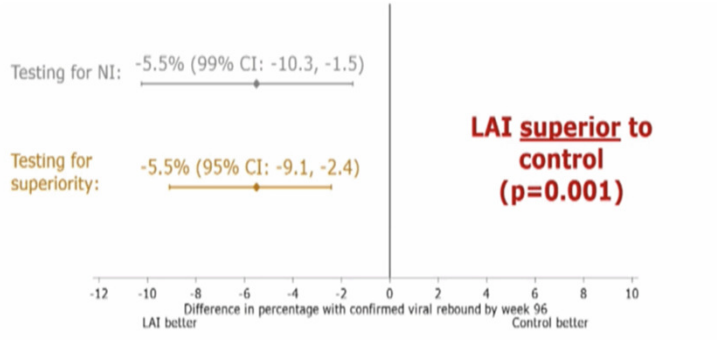
- First randomized trial of LA Q8W CAB/RPV in adolescents
- Adolescents have poorer treatment outcomes
- Inclusion as shown on left, plus HBsAg negative
- No baseline DRT and 6-monthly VL testing

- 476 randomised in Uganda, Kenya, Zimbabwe, S. Africa
- Median age 16 yrs. 54% female
- 98% vertically acquired HIV
- **Primary endpoint:** Confirmed viral rebound (2 x VL ≥50 c/ml) anytime through week 96), ITT population.

- **0.9% on LA compared to 6.4% on oral ART**

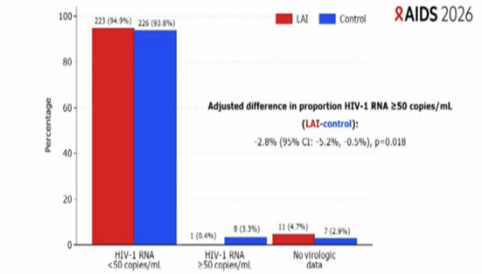
LATA W96 results

- **2 (0.9%) LAI versus 15 (6.4%) control had confirmed viral rebound (>50 copies/ml)**



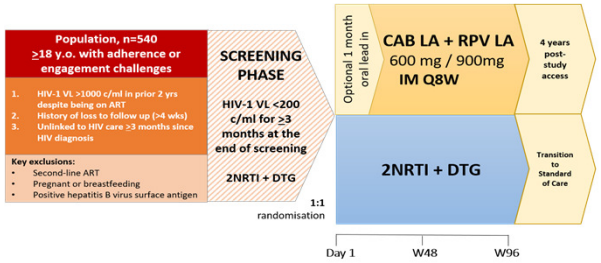
- Treatment failure:
  - **1**: LAI failure at week 24, INSTI – G140GA/Q148R (high-level CAB-R, int-level DTG-R), NNRTI – K101E, Y181C (high-level RPV-R). Switched to DRVr/TDF/3TC.
  - 2: Switched off LAI (AE) prior to rebound. No RAMs.

- **VL <50 c/ml 95% vs 93%**



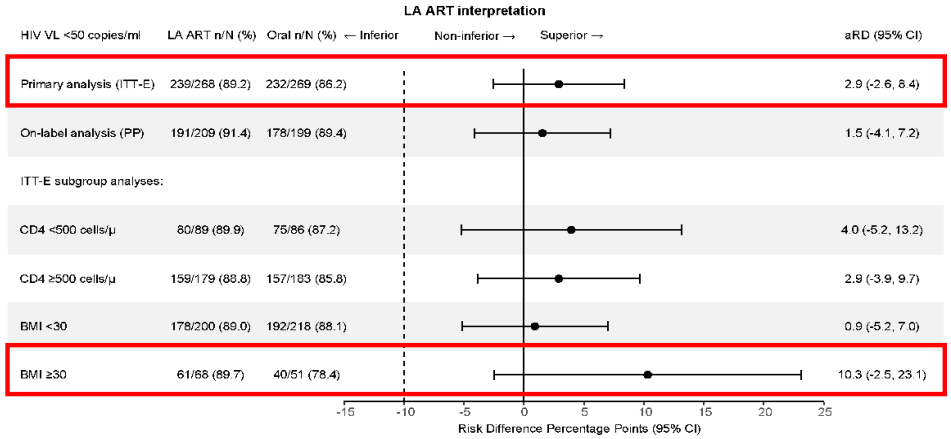
- Safe, well tolerated
- No ISR-related discontinuations
- 94% reported LAI making taking medicine a lot **easier**

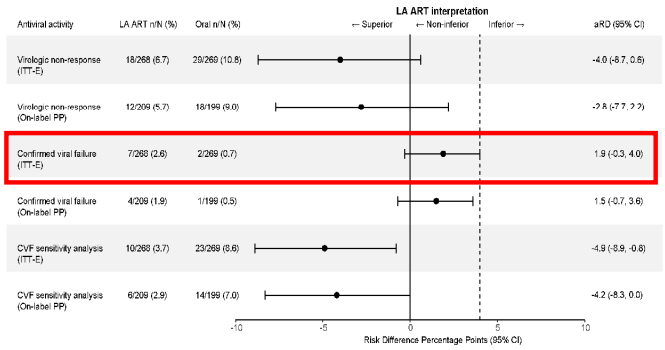
IMPALA W96 – adults with adherence / engagement challenges



Baseline Characteristics	Total (n=540)
Age, median years (IQR)	40 (33–48)
Cis-female, n (%)	324 (60)
Black African, n (%)	538 (99.6)
Hepatitis B core antibody positive, n (%)	168 (31.1)
Formal employment, n (%)	96 (17.8)
BMI ≥30, n (%)	120 (22.2)
CD4, median cells/µl (IQR)	629 (453–873)
ART duration, median yrs (IQR)	7.5 (4.6–10.8)
Prior AIDS-defining illness, n (%)	142 (26.3)
Prior exposure to NNRTI, n (%)	411 (78.3)
HIV subtype A1[&], n (%)	173 (50.4)
Major RPV RAM[&] n (%)	18 (5.7)
Major CAB RAM[&] n (%)	1 (0.3)

- In the IIT-e popln, **89.2% (239/268) of participants in the LA arm and 86.2% (232/269) in the oral arm had VL <50 c/ml at 96 weeks.** Risk difference = 2.9% [95% CI -2.6 to 8.4]. Non-inferior.





Up to week 96, in the IIT-E population, CVF since baseline occurred in:

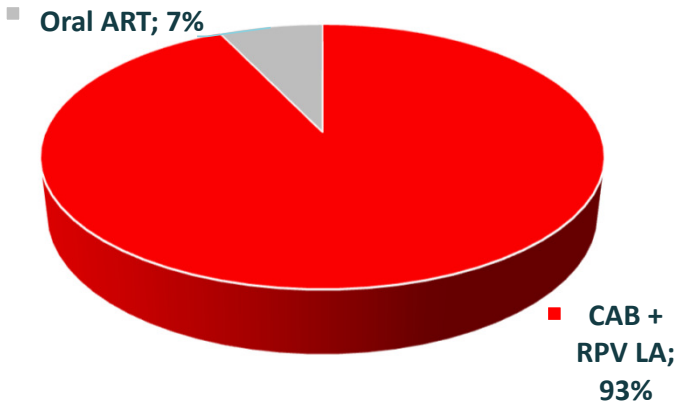
- 2.6% (7/268) in the LA arm
- 0.7% (2/269) in the oral arm
- Two new cases each arm after W48
- RD 1.9% (-0.3 to 4.0)

IMPALA W96

Metabolic outcomes

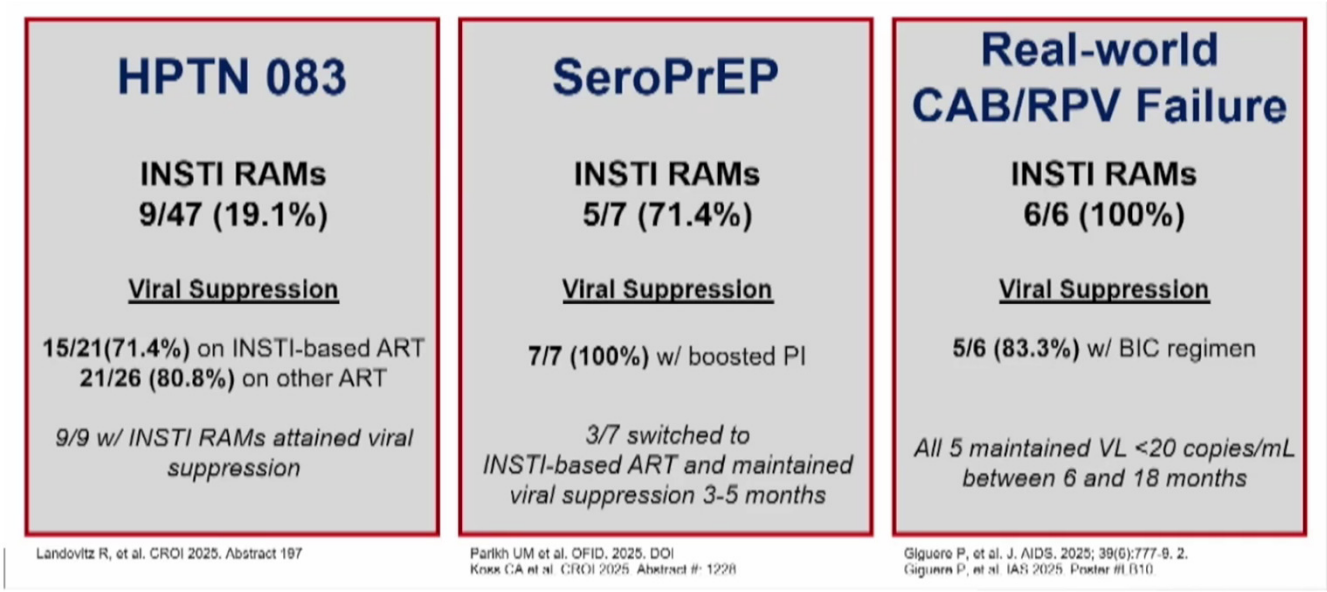
- Greater mean weight gain in the CAB+RPV LA arm compared to the oral ART arm: adjusted mean difference over 96 weeks: +0.57 kg; p=0.133
- Overall, females had a 2-fold higher risk of ≥10% weight gain than males: aRR 2.12; 95% CI 1.19, 3.77
- Lipid (TC:HDL ratio) and glycaemic control (HbA1c) were similar between arms
- CAB/RPV is renal friendly - greater increase in eGFR vs oral ART group observed: adjusted mean difference +7.80 mL/min; p<0.001

Treatment preference in CAB + RPV LA arm at week 96



Kitonsa J. AIDS2026. Posters LB24 and TUPEB102

Accumulating evidnece on INSTI use to salvage CAB-LA failure



IMPALA 7 CVF at 2 yrs

- INSTI resistance (Q148R +/- E138K) in 5 of 7
- Low or intermediate DTG-R
- 5/7 (71%) remain suppressed (<200 c/ml) on DTG at 1 yr of F/U

Raphael Landowitz, AIDS 2026

LAI – viraemia and at-risk populations

PERSISTENT / RECALCITRANT VIRAEMIA

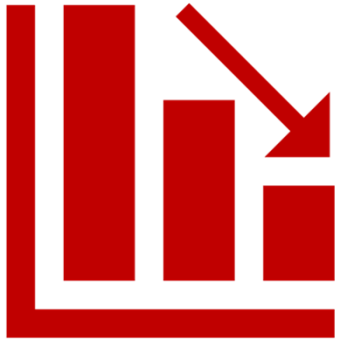
- CROWN – Q8W initiated with viraemia, view to change label
- LANCET – ACTG, CAB/LEN (based on encouraging observational data)

ADVANCED HIV DISEASE

- Viral suppression at 6 months post OI is unacceptability low
- Post-hospital d/c mortality remains high (20-30%)
- Regimen? DDIs with rifampicin.

PREGNANT AND BREASTFEEDING WOMEN

- DOLPHIN-3, CAB/RPV in breastfeeding mothers
- SUPPRESS-LA – ACRN, S. Africa, Zimbabwe, Uganda. CAB/LEN?

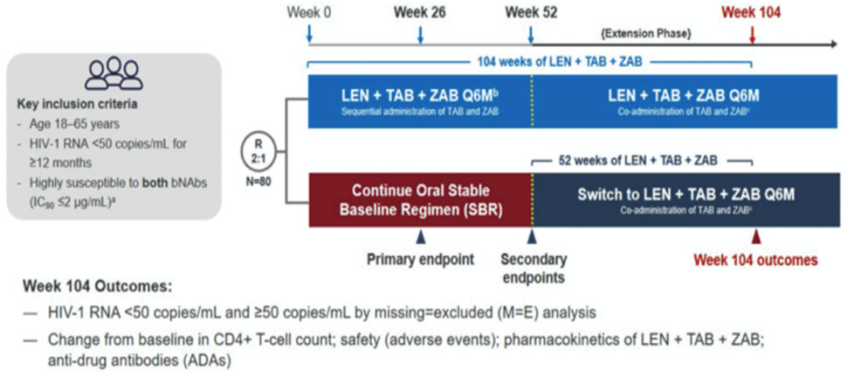


HIV-related deaths & Transmissions

LEN/TAB/ZAB – 6-monthly - hope or hype?

- Lenacapavir – 6-monthly subcutaneous capsid inhibitor
- Teropavimab and Zinlirvimab – 6-monthly bNAbs by intravenous infusion
- TAB targets CD4 binding site of gp120 and ZAB targets V3 glycan on HIV1 envelope

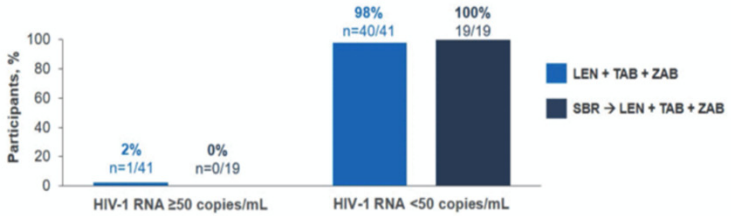
- Phase 2, AIDS 2026, n=80 randomised



- Week 104 analysis compared those who switched at week 0 (light blue) to week 52 (dark blue)

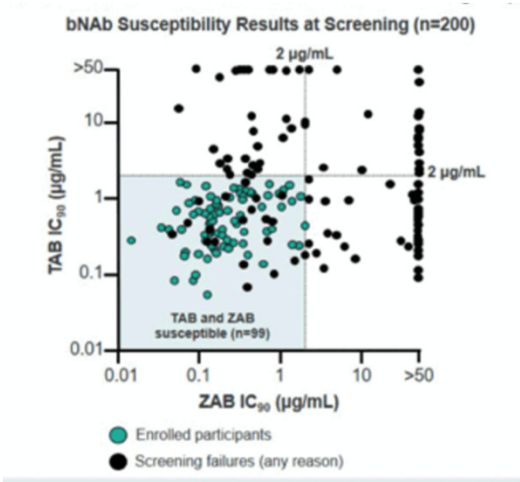
LEN/TAB/ZAB - results

- Week 104 results:



- 2 participants experienced virological rebound (one per arm)
- Both resistant to TAB/ZAB and LEN RAMs (?barrier)
- Despite all drugs being within PK range

- High rates of viral suppression up to 2 years -> phase 3 trial
- Only **99 of 241 screened were susceptible to TAB and ZAB**
- Science advancing in an encouraging direction
- bNAbs - favourable toxicity profile

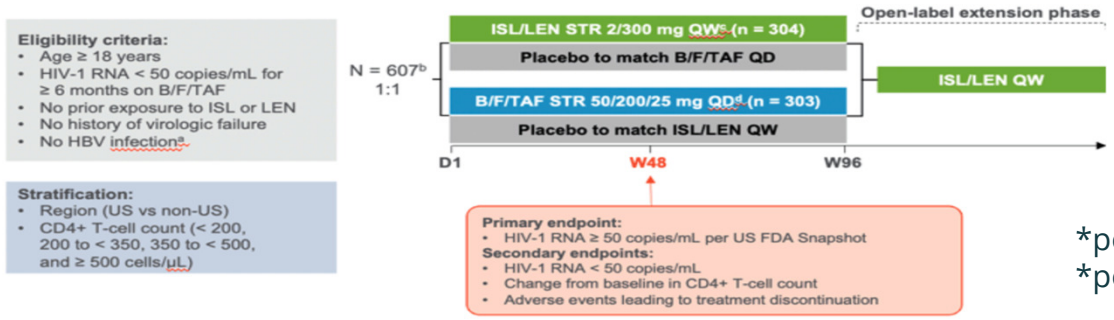


Oral LA options

ISL/LEN – ISLEND 1 – weekly oral

- Islatravir 2mg – NRTTI (higher dose related to CD4 lymphocyte depletion)
- Lenacapavir 300mg – Capsid inhibitor
- Once weekly (QW) - reduce pill fatigue

- ISLEND-1: phase 3, double-blind, noninferiority trial, virally suppressed adults, comparator B/F/TAF
- Primary endpoint: HIV VL ≥50 c/ml per FDA snapshot algorithm

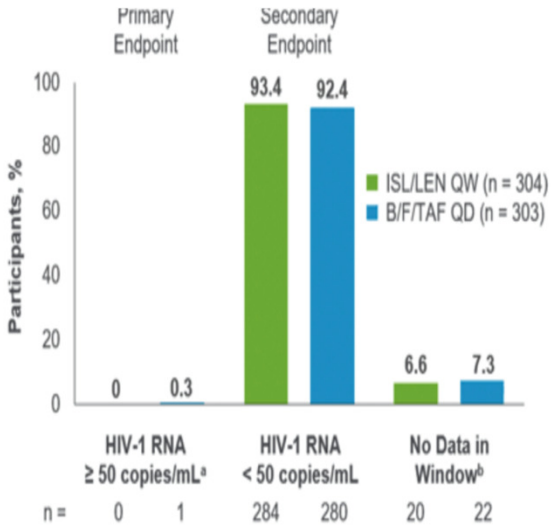


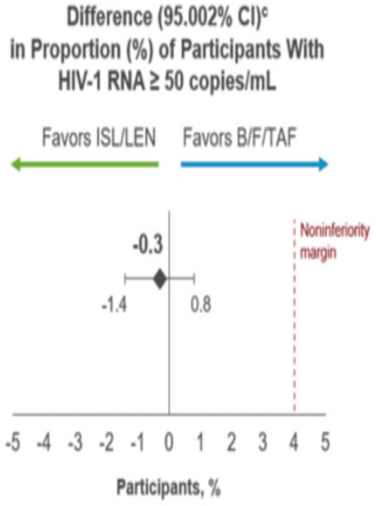
*positive HBsAg excluded
*positive HBcAb with negative HBsAb excluded

- Enrolled 607 adults, 80% male

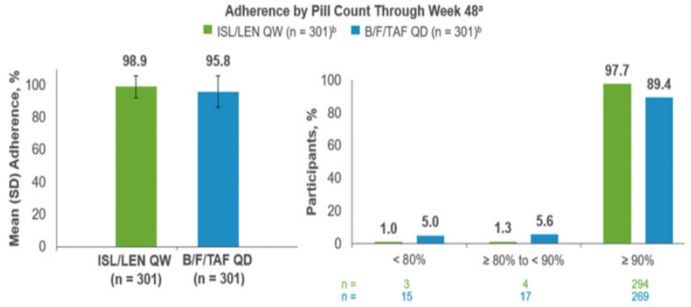
ISL/LEN – ISLEND 1 – weekly oral

- Efficacy of weekly oral ISL/LEN was non-inferior to daily B/F/TAF
- No emergent resistance to ISL or LEN

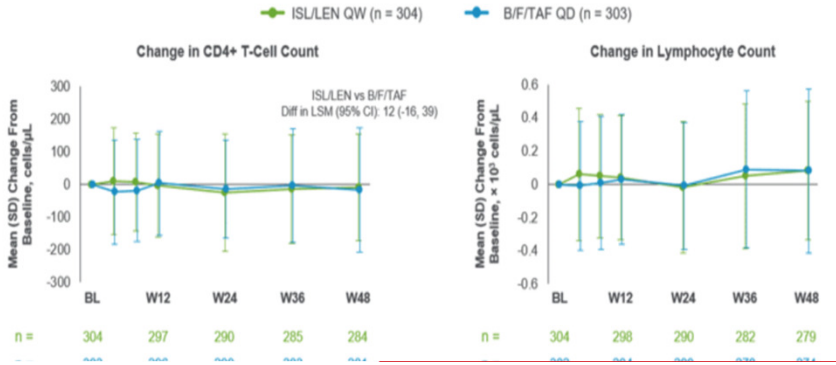




- Adherence better with weekly than daily



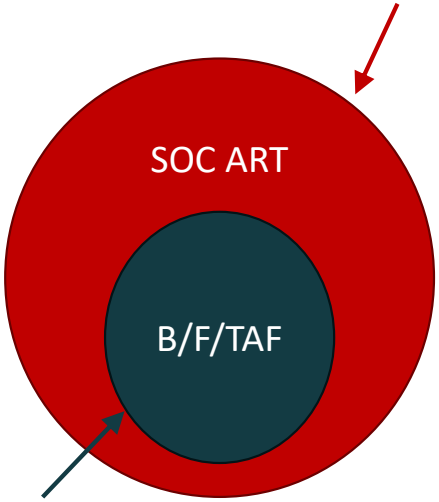
- CD4 count and lymphocytes stable to W48



ISL/LEN – ISLEND 2, phase 3

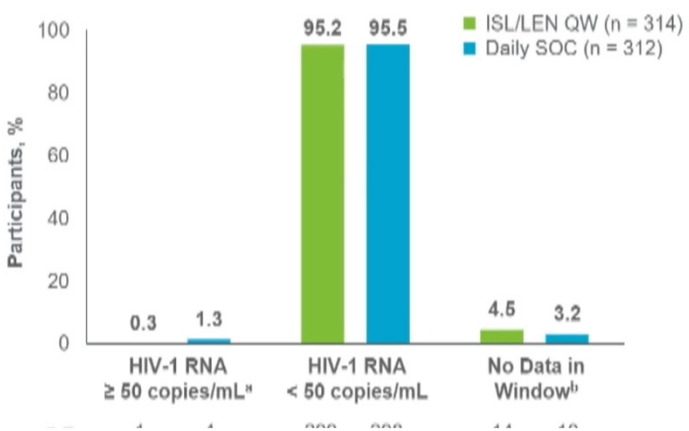
- Same as ISLEND –1 but SOC daily ART rather than B/F/TAF as comparator

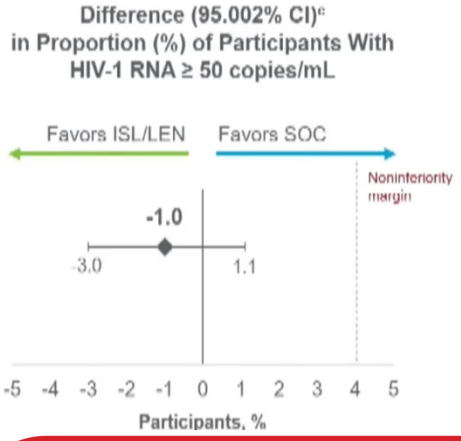
ISLEND-2 - Once weekly ISL/LEN STR compared to **standard of care ART**



ISLEND-1 - Once weekly ISL/LEN STR compared to **B/F/TAF**

- ISL/LEN was non-inferior to SOC ART
- No emergent resistance – very potent!
- Registration underway – which territories?

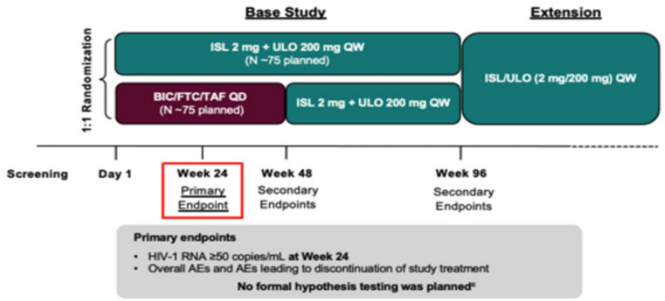


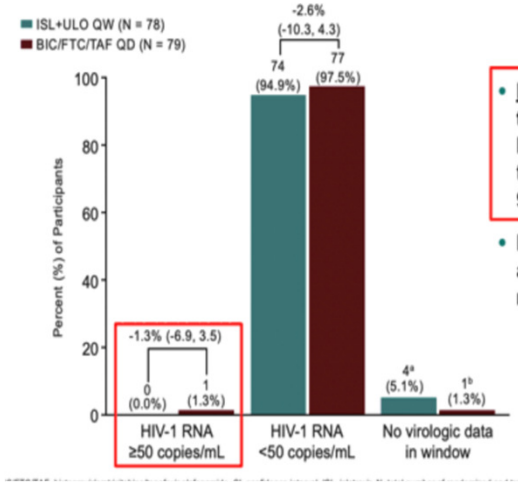


ISL/ULO – phase 2b – weekly oral

- Islatravir 2mg – NRTTI
- Ulonivirine 200mg – old class, novel **NNRTI**, activity despite common RAMS (Y181C/G190A/K103N)
- Weekly dosing, oral
- Phase 2b open-label, in virally suppressed adults on B/F/TAF for >6 months
- Primary endpoint VL ≥50 copies/ml at week 24

Eligibility:
- No treatment failure
- K103N, Y181C, G190A not exclusionary (no ULO RAMs)
- HBV (HBsAg+ or HBcAb+ without sAb
- CD4 >=200





- **Primary endpoint**: at Week 24, **0.0% (0/78) of the participants who switched to ISL+ULO had HIV-1 RNA ≥50 copies/mL** vs 1.3% (1/79) of those continuing BIC/FTC/TAF (difference: -1.3%; 95% CI: -6.9, 3.5)
- No participants had HIV-1 RNA ≥200 copies/mL, and thus none met criteria for post-baseline resistance analysis

Phase 3

3rd LA ART Conference

Do we need two weekly oral options?

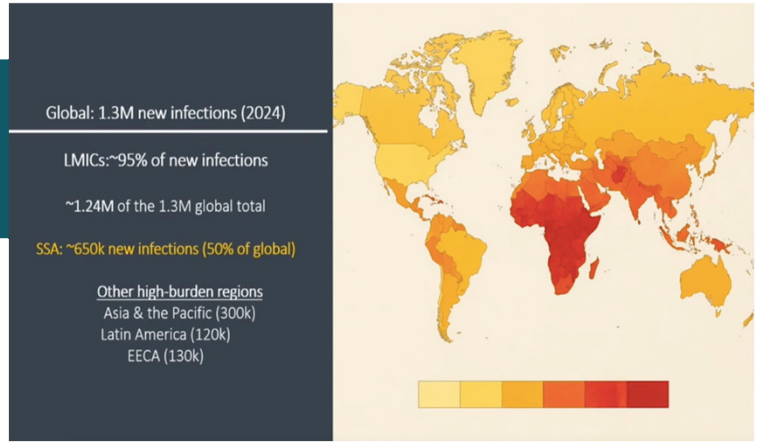
- **Different classes**
  - ULO - NNRTI
  - ISL – NRTTI
  - LEN - Capsid
- **Different resistance profiles**
- **Different drug-drug interactions**
- **Further R&D**
  - Extend dosing interval
  - ISL/ULO treatment naïve study ongoing (could be weekly DOT)
- **CHOICE**
- **COMPETITION**
- **ISL/ULO – one originator company (Merck/MSD)**

Emerging Strategic Vision for LMICs | LAI/LAO anticipated to reduce pill burden & increase cost effectiveness

1. LAI PrEP is expected to be an alternative in LMICs due to higher anticipated cost
2. Achieving technical success with a monthly single 2DR FDC is challenging; however, even a TMP of two pills per month still offers a significant

Latailla

Results to roll out…



- **The clinical need for LA treatment is greatest in SSA**

- **Hep B risk with 2DR in SSA**, context matters
  - HBsAg+ ~5%, POCT availability (*INELIGIBLE FOR 2DR*)
  - 1in 3 has prior infection (HBcAb+), small risk of HBVr when TDF removed
  - Routine childhood HBV vaccine introduced ~2001. Most PWH >25y.o. are unvaccinated! Risk of incident HBV [IMPALA (1/269, 0.4%), French cohort of 5/1247 (0.4%)]
  - **Let's vaccinate our cohorts in anticipation, it is national policy!**

- **Special populations** – pregnancy/BF, AHD, extremes of age, comorbidities, CNS

- Work on the **delivery systems** now and make them person-centred (Sheetal Kassim)

LA is an opportunity....

...all actors need to come together to maximise that opportunity

Innovative & efficient programming

Adequate resources

Political will

Licensing, Pricing, Access

Autonomy, agency

Collaboration

Implement, measure and learn

Co-development of services

Moral standards (Pharma & implementers)

Digital tools e.g. EmERGE

Science creates the possibilities, collaboration creates the impact, communities create the future