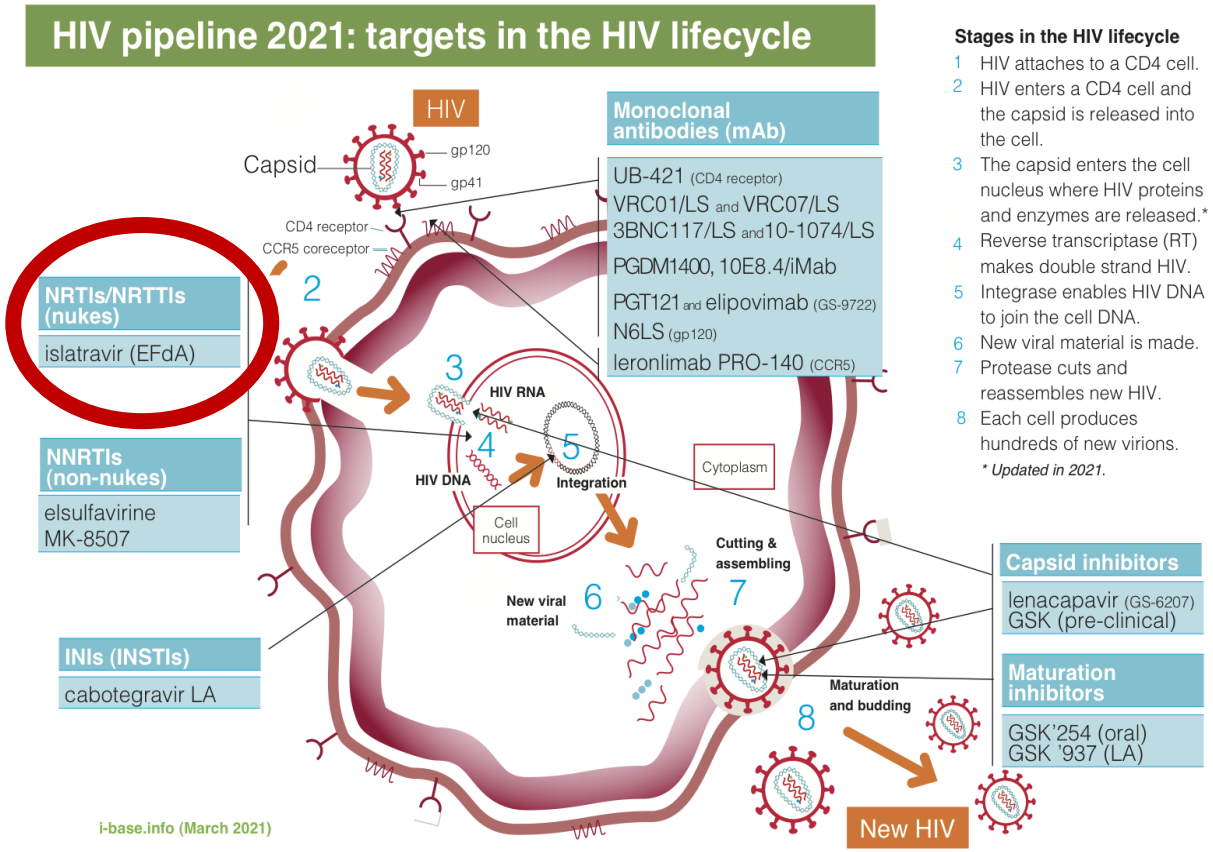
The future of antiretrovirals in Africa: Long-acting agents and beyond Conference

ISLATRAVIR: Mechanism of Action



- **Nucleoside reverse transcriptase translocation inhibitor (NRTTI)**
  - Intermediate chain terminator
  - Delayed chain terminator
  - Misincorporated by RT = mismatched primers that cannot be extended or excised

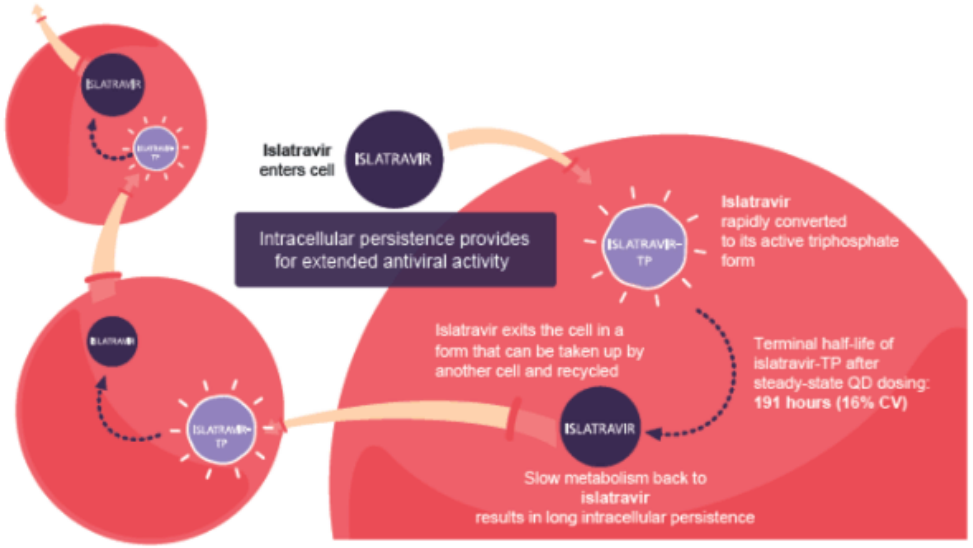
- **Potent activity against HIV-1**
  - Additional activity against HIV-2 and multi-drug resistant HIV strains
  - Developed for both treatment and prevention

ISLATRAVIR: Pharmacology

- **Suited to long-acting formulation**
  - Long elimination half life = extended dosing
  - Highly potent
  - High genetic barrier to resistance

- **Delivery methods under investigation**
  - Oral tablet (daily, weekly)
  - Injectables
  - Implants

Figure 2. Islatravir Properties Contribute to Differentiated Pharmacokinetic (PK) and Long Half-life



Rudd D, Islatravir Metabolic Outcomes in a Phase 2b Trial of Treatment_Naive Adults with HIV-1, CROI 2020

ISLATRAVIR: Safety Signal

In Dec 2021 FDA raised a safety signal for decreases in CD4+ T-cells and total lymphocyte counts

- No associated correlation with increase in clinical AEs related to infection
- Mechanism behind the decrease still unclear

PROTOCOL	ISL arm	Control / placebo
013 (Treatment) *24 weeks*	Mean decr in total lymphocyte counts: • ISL+MK-8507 100mg = **17%** • ISL+MK-8507 200mg = **26%** • ISL+MK-8507 400mg = **30%**	Mean incr in total lymphocyte counts: • Control group = **0.11%**
	Mean decr in CD4 cell counts: • ISL+MK-8507 100mg = **11%** • ISL+MK-8507 200mg = **23%** • ISL+MK-8507 400mg = **30%**	Mean incr in CD4 cell counts: • Control group = **0.25%**
016 (PrEP) *24 weeks*	Mean decr in total lymphocyte counts: • 60mg = **21%** • 120mg = **36%**	Mean incr in total lymphocyte counts: • Placebo = **4%**
017 (Treatment) *48 weeks*	Mean decr in CD4 cell counts: • DOR/ISL = **0.7%**	Mean incr in CD4 cell counts: • Control group = **8.7%**
018 (Treatment) *48 weeks*	Mean incr in CD4 cell counts: • Control group = **0.9%**	Mean incr in CD4 cell counts: • Control group = **12.8%**

ISLATRAVIR: Key Clinical PrEP Trials

MK-8591A-016 (2a) – FULL CLINICAL HOLD

- Safety of 2 different oral doses of ISL (PK study)
- In patients at low-risk for HIV acquisition

MK-8591A-043 (2a) – FULL CLINICAL HOLD

- Once-yearly ISL implant (safety, tolerability and PK parameters)
- In patients at low-risk for HIV acquisition

MK-8591A-035 (2a) – FULL CLINICAL HOLD

- Once monthly oral ISL
- Trans- and gender diverse participants at low-risk for HIV acquisition

MK-8591A-022 (3) – IMPOWER 22 – FULL CLINICAL HOLD

- Once monthly oral ISL
- Cisgender women at high-risk for HIV acquisition

MK-8591A-024 (3) – IMPOWER 24 – FULL CLINICAL HOLD

- Once monthly oral ISL
- Cisgender men who have sex with men, and transgender women who have sex with men at high-risk for HIV acquisition

ISLATRAVIR: Key Clinical HIV-1 Treatment Trials (1)

MK-8591A-011 (2b) – PARTIAL CLINICAL HOLD

- DOR/3TC/ISL in HIV-1 infected patients who are ART naïve (24 weeks)

MK-8591A-013 (2b) – IMAGINE-DR – PARTIAL CLINICAL HOLD

- Switch study in virologically suppressed patients from BIC/TAF/FTC to once-weekly ISL+NNRTI (MK-8507)

MK-8591A-017 (3) – ILLUMINATE SWITCH A – PARTIAL CLINICAL HOLD

- Switch study in virologically suppressed patients from FDC to once daily oral DOR/ISL

MK-8591A-018 (3) – ILLUMINATE SWITCH B – PARTIAL CLINICAL HOLD

- Switch study in virologically suppressed patients from BIC/TAF/FTC to once daily oral DOR/ISL

MK-8591A-033 (3) – ROLLOVER STUDY – PARTIAL CLINICAL HOLD

- Includes participants from previous clinical trials to continue safety evaluations

ISLATRAVIR: Key Clinical HIV-1 Treatment Trials (2)

MK-8591A-019 (3) – ILLUMINATE HTE – PARTIAL CLINICAL HOLD

- DOR/ISL vs DOR/ISL+FDC in HTE patients with HIVDR

MK-8591A-020 (3) – ILLUMINATE NAÏVE – PARTIAL CLINICAL HOLD

- DOR/ISL vs BIC/TAF/FTC in ART naïve patients

MK-8591A-034 (1) – FULL CLINICAL HOLD

- Evaluation of injectable ISL formulation

NCT05052996 (2) – FULL CLINICAL HOLD

- Weekly oral ISL+LEN vs BIC/FTC/TAF in virologically suppressed PLWH

CONCLUSION

- ISL is a promising agent for various delivery modalities
  - Both PrEP and HIV-1 treatment
  - Owing to long elimination half life (dose dependent)

- Concerns around decreases in CD4 cell counts and total lymphocyte counts remain unclear
  - No evidence to currently suggest increase in AEs of clinical significance
  - PrEP trials all on full clinical hold and treatment trials largely on partial clinical hold