Long Acting Antiretroviral Update

Long Acting Options for PreP

1	2	3	4	5
Dapivirine ring	Cabotegravir Long acting Injectable	Islatravir oral	Islatravir implant	Lenacapavir injectable
Available now 2021 WHO Recommendation for use **Monthly** IPM	HPTN083 and 084 reported FDA submission in progress (Possibly Q1 2022) **2 monthly** ViiV	Trials just recruiting **Monthly** Merk	Update CROI 2021 **Annual**	Gilead **6 monthly**

Efficacy and choice

Dapivirine ring
Monthly

TDF/FTC
daily

Cabotegravir
Every 2 mths

Dapivirine Ring

4.1. Therapeutic indications

Reducing the risk of HIV-1 infection via vaginal intercourse in HIV-uninfected women 18 years and older in combination with safer sex practices when oral PrEP is not/cannot be used or is not available.

Although safety has not been established in pregnancy, the benefits of treatment should be considered for pregnant women at high risk of HIV infection, considering the subsequent risk of HIV transmission to the unborn child.

INTERNATIONAL PARTNERSHIP FOR MICROBICIDES

- 25mg Dapivirine NNRTI (releases 4mg over 1mth)
- Flexible silicone ring
- RING study IPM : Almost 2000 women SSA 4.2% who used ring became infected after two years of treatment compared with 6.4% in placebo group - infection **reduction of 35.1% (modelling in follow on study approx. 63% reduction in transmission)**
- **Used when oral prep is not/cannot be used or is not available**
- **HIV negative women 18 yrs and older (and ongoing study on efficacy 18-25)**
- **28 day use ; next ring must be inserted immediately**
- No data for pregnant – risk benefit for use
- Breastfeeding- is found in breast milk – no formal studies- advised to be stopped

- Most common side effects
  - UTI (15.2%)
  - Vaginal discharge (7.1%)
  - Vaginal Pruritus(6.5%)
  - Vulvovaginitis (6.4%)
  - Pelvic pain (6.2%)
- Interactions – low systemic exposure – OK with
  - Oral contraceptives
  - Vaginal miconazole and clotrimazole – caution
- **Approved EMA 23rd July 2020 ; WHO Pqed**
- **Shelf life 4 years**
- **Price $9 /ring**
- **No special temp storage conditions**
- Jan 2021 New WHO recommendation WHO recommends the dapivirine vaginal ring as a new choice for HIV prevention for women at substantial risk of HIV infection

https://www.ema.europa.eu/en/documents/medicine-outside-eu/dapivirine-vaginal-ring-25-mg-medicine-overview_en.pdf

https://www.ema.europa.eu/en/documents/medicine-outside-eu/dapivirine-vaginal-ring-25-mg-product-information_en.pdf

Table 4: HIV-1 infection rate adjusted for adherence to investigational product use in Phase III clinical trial IPM 027: Primary analysis (Cut-off date 16 October 2015) – Modified intent-to-treat population

Age	**≤21 years**		**>21 years**	
Population	**Number of confirmed endpoints/total person-years of follow-up[a]**	**% Reduction in HIV-1 Infection Adherent versus Placebo (95%CI)[b]**	**Number of confirmed endpoints/total person-years of follow-up[a]**	**% Reduction in HIV-1 Infection Adherent versus Placebo (95%CI)[b]**
Trial IPM 027 m-ITT	46/645	28.76 (-37.11 to 62.99)	93/2150	41.60 (8.26 to 62.82)

Adherence was defined by ≤ 23.5 mg of residual dapivirine levels in a used ring and a plasma concentration of ≥ 95 pg/mL.

m-ITT: The m-ITT population consisted of all trial participants who were randomised and were HIV-negative at enrollment.

[a] Follow-up time over all participants during adherent and non-adherent time intervals respectively. A participant can switch between the adherent and non-adherent risk set over time and thus contribute data to both the adherence and non-adherence time. Follow-up time is based on the double-blind on-treatment period.

[b] *P*-value for Adherence effect (vs placebo) = 0.0196, based on Cox proportional hazards model stratified for research centre and including age at baseline as a covariate, adherence as a time-varying covariate and adherence*age at baseline as time-varying interaction.

The Ring Study: 41.6% reduction in > 21yrs versus 28.7% in < 21 yrs

Ongoing studies dapivirine ring

- REACH now recruiting **16-24 yr olds** oral 6 mths followed by ring or vice versa
- B-PROTECTED, or MTN-043 will enroll women who are **breastfeeding**, as well as their babies, at trial sites in Malawi, South Africa, Uganda and Zimbabwe.
- A similar study involving **pregnant women,** called DELIVER (MTN-042), involving pregnant women is also ongoing at the Malawi and Zimbabwe sites as well.
- **3 mthly dapivirine ring** – DPV concentrations and side effects presented at CROI 2021 – further studies ongoing

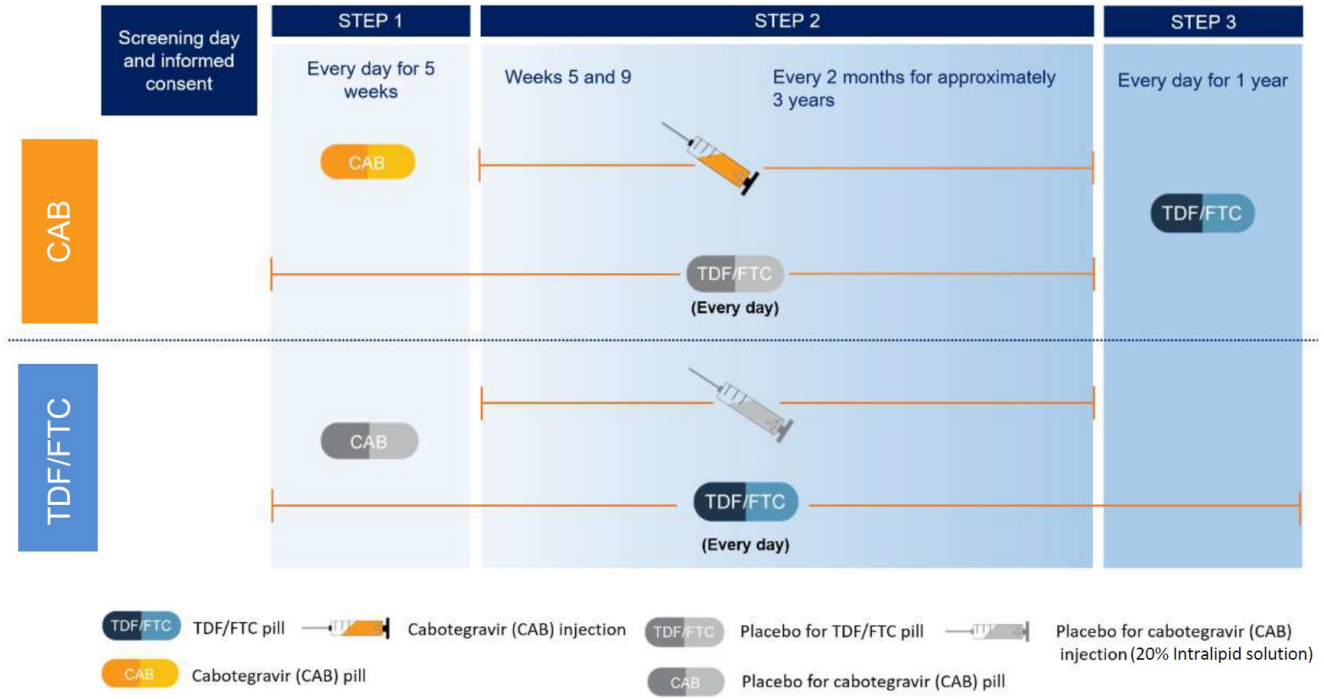
Cabotegravir LA injectable 2 monthly : HPTN 083/084 (ViiV)
FDA: Breakthrough Therapy designation Nov 2020

- HPTN 083, a phase IIb/III randomised, multicentre, double-blind, clinical trial that compared
- **long-acting, injectable cabotegravir (2 mthly) to daily oral emtricitabine/tenofovir disoproxil fumarate 200 mg and 300 mg (FTC/TDF)**
- for HIV prevention among men who have sex with men and transgender women (> 18 yrs) who have sex with men.
- 40 sites 7 countries :Argentina, Brazil, Peru, South Africa, Thailand, the U.S., and Vietnam
- 49% black African american

- Superiority of long-acting cabotegravir,
- **66% more effective at preventing HIV when compared to daily oral FTC/TDF tablets.**
- This translated to an HIV incidence rate of 0.41% in the cabotegravir group (95% confidence interval [CI] 0.22%-0.69%) and 1.22% in the FTC/TDF
- No cold chain needed
- **084 women**
  - **Superior to oral FTC/TDF**
  - **Incidence 0.21 CAB v 1.79 FTC/3TC**
  - **9x the number of infections in TDF/FTC group**

https://www.hptn.org/sites/default/files/inline-files/HPTN083_PrimaryAIDS2020_Landovitz-Final_web.pdf

HPTN 083 Study Design



ındovitz RJ et al. AIDS 2020, #OAXLB01

Outstanding :

- **Awaiting FDA approval ? End 2021 / Q1 2022**
- **CAB LA for adolescents**
  A bridging study (HPTN084/01) has started to enrol adolescent girls. This will assess safety and acceptability in 50 adolescent girls < 18 years at three sites. HPTN083/01 adolescent males
- **Safety during pregnancy and breastfeeding**
  Protocol amendment in HPTN 084 - requiring all women enrolled in HPTN 084 to also take long-acting reversible contraceptives. because of the protocol change very few women in HPTN 084 became pregnant while taking CAB-LA. Monitoring for adverse foetal and pregnancy outcomes will have to be done during OLEs.
- **Real-world implementation issues**
  Where and how CAB LA—which requires an injection every eight weeks—could be delivered, implementation adjustments that may be needed in HIV prevention programmes and health systems, and acceptability issues, will all need to be evaluated and considered. Other implementation assessments are planned or underway.
- **The pharmacokinetic tail—will this be a significant risk for drug resistance?**
  Injectable cabotegravir has a long half-life, which is why it provides long-acting (8 weeks) protection. No INSTI resistance in HPTN 083 in those infected during the tail – more data needed

Oral Islatravir as PREP: Monthly pill (Merk)

- First-in-class **nucleoside reverse transcriptase translocation inhibitor** with multiple mechanisms of action. Besides acting as a defective building block to halt construction of new chains of DNA, it also works at a later step in the viral replication process.
- The enrolment of US participants in **IMPOWER 022** will start now, African participants a few months after that, and **IMPOWER 024** will start enrolling in late summer this year. **Expected to complete 2022**
- The dose tested will be 60mg because it was felt that 120mg was not likely to provide significantly greater efficacy to be worth risking more frequent side effects.

ISL QM oral PrEP – ongoing clinical development program

Impower

	Trial name (protocol number)	Population	Active comparator	ClinicalTrials.gov
Phase 3	IMPOWER-022	Cisgender women at high risk of HIV-1 infection	FTC/TDF	NCT04644029
	IMPOWER-024	Men and transgender women who have sex with men and are at high risk for HIV-1 infection	FTC/TDF or FTC/TAF	NCT04652700

IMPOWER 022 will be done in collaboration with the Bill & Melinda Gates Foundation which intends to provide grant funding to the International Clinical Research Center (ICRC) at the University of Washington Department of Global Health who will be working together with MSD to conduct the trial

FTC, emtricitabine; ISL, islatravir; PrEP, pre-exposure prophylaxis; QM, once monthly; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

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Agent class:
Nucleoside Reverse Transcriptase Translocation Inhibitor (NRTTI)

Novel mechanism of action, being developed as a **monthly pill** and an **implant for prevention**

Islatravir implants- possible to be annual

- Uses Nexplanon applicator
- Initial trial P0007
  - Implants well tolerated
  - Higher dose implant (62mg) projected to have sufficient levels for **at least a year** (Matthews et al IAS 2019)
- Next generation implants radiopaque P008; 56mg implant projected to lead to concentrations above threshold for 52 weeks

Side effects of implant

- 61% reported at least 1 implant site adverse events
- All adverse events were mild or moderate
- No serious AEs and no discontinuations
- No clear relationship between dose and AE severity

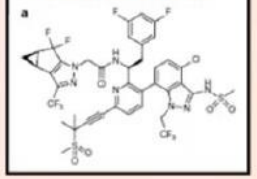
	Number (percent) of individuals reporting AE during study N=8 active/dose, 12 PBO (placebo; mod=moderate)			
	PBO	48 mg	52 mg	56 mg
TOTAL	6 (50)	6 (75)	4 (50)	6 (75)
Erythema	3 (25)	4 (50) 2/4 mod	2 (25)	4 (50) 1/4 mod
Tenderness/pain	4 (33)	2 (25)	4 (50)	4 (50)
Pruritis	3 (25)	5 (63) 1/5 mod	2 (25)	6 (75)
Induration	2 (17)	4 (50)	4 (50)	4 (50)

Lenacapavir (Gilead) : Injectable every 6 mths

Lenacapavir (GS-6207): LA Injectable for HIV Prevention

Agent class:
HIV-1 capsid inhibitor

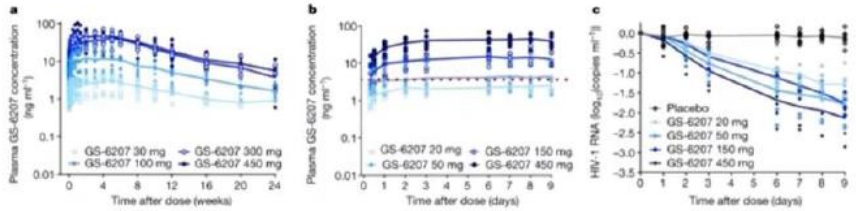
LENACAPAVIR



Dosing Strategy: One injection every 6 months **(ARVs that you only need to take twice a year!)**

Early stages of development

- Single injection shown to reduce HIV-1 viral load in PLHIV with multidrug resistant HIV-1 infection.
- **88%** experienced at least a 0.5 log10 reduction in HIV-1 viral load over 14 days compared to 17% of those in the control arm

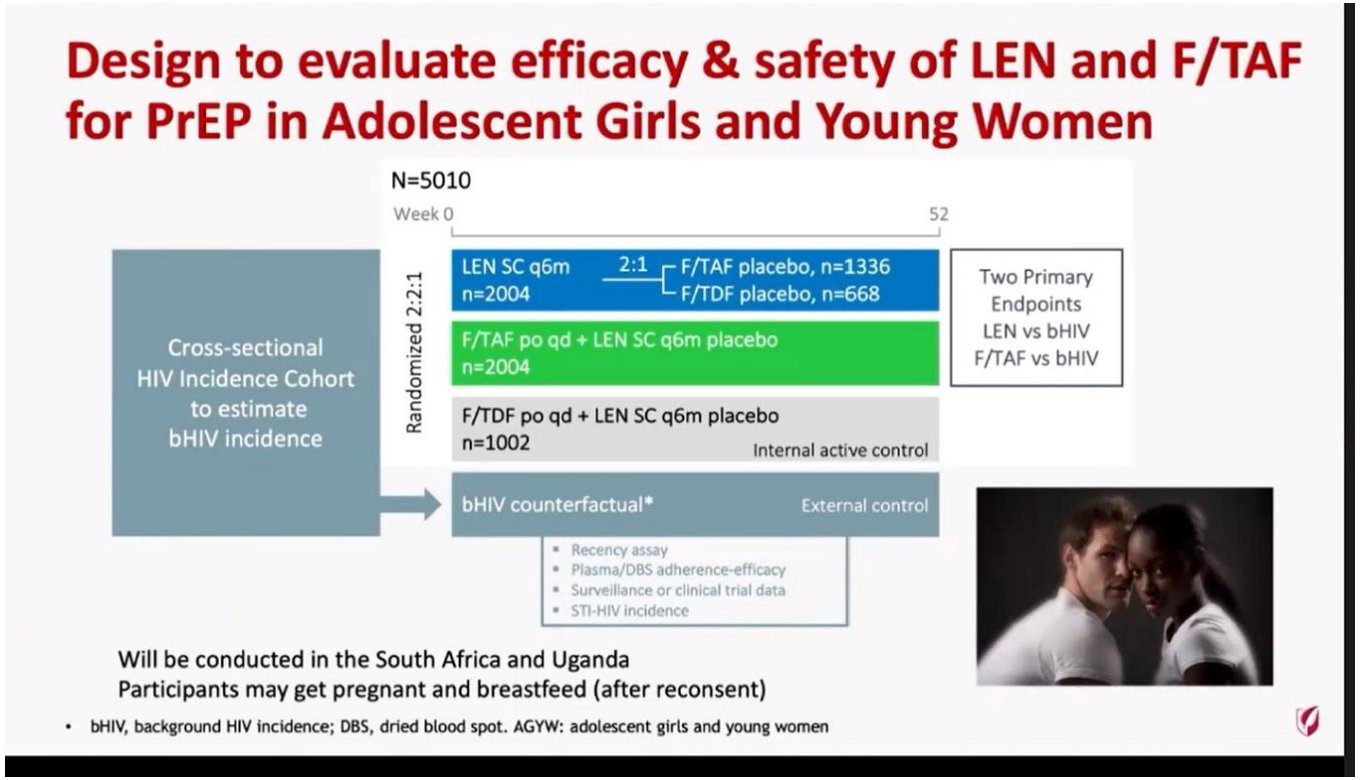


Mean plasma concentration-time profiles of Lenacapavir after a single injection to individuals uninfected with HIV **(Graph A, n=8)** and individuals living with HIV **(Graph B, n=6)**.

Graph C: Mean log10 transformed change in plasma HIV-1 RNA in individuals with untreated HIV-1 infection (drug, n = 6 and placebo, n=2)

Link et al., 2020, Nature

Efficacy and Safety Adolescent Girls and Women



Others in pipeline

TAF implant

Cabotegravir implant

- Successful development of rate controlling membrane
- Successful development of in vitro assay
- Target 1 yr release of CAB to achieve target of plasma 700ng/ml

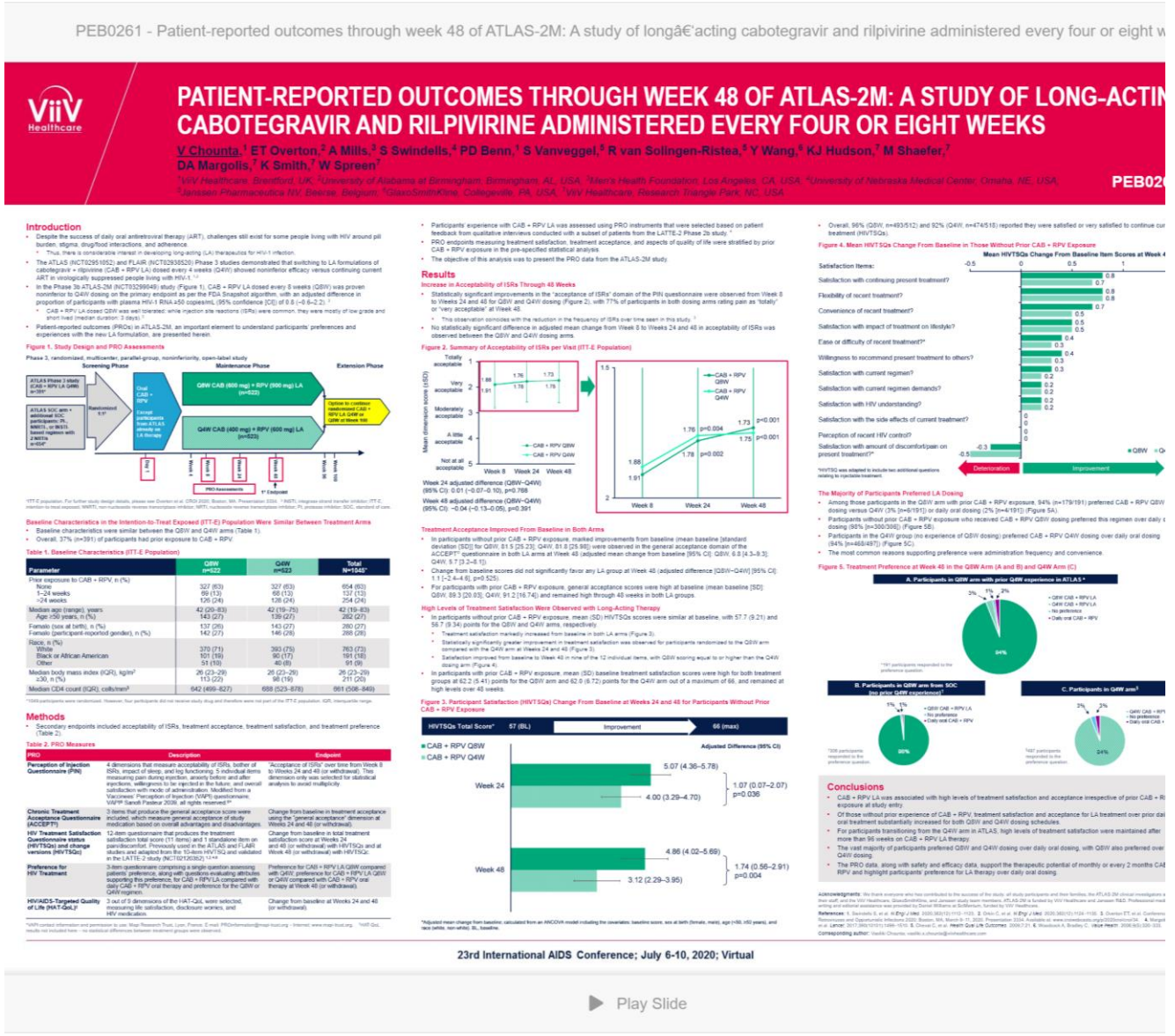
Long acting formulations for Treatment

Cabotegravir (ViiV) and Rilpivirine (Janssen) (Cabenuva) ; FDA approved Jan 2021

- Only used in patients **already virologically suppressed on oral regimen < 50 copies.ml**
- **>18 years**
- **No data pregnant/ breastfeeding**
- No dose adjustment renal impairment
- **Oral lead in** needed for 1 mth (30mg cabotegravir (vocabria) 25mg rilpivirine (edurant)
- Initiate 600mg cab/900mg rilpivirine; continue 400mg cab/600 rilpivirine **every month**
- **Store at 2-6; bring to room temp not exceeding 25; must use within 6 hrs ; once drawn up must be used within 2 hrs**
- **The tail** : residual concentration of cab/ril remain 12 mths or longer ; essential a fully suppressive ART regimen started no later than 1 mth after final injection
- **U.S. sticker price is $5,940 for the one-time initiation dose and $3,960 for the monthly injections after that.**

https://viivhealthcare.com/content/dam/cf-viiv/viiv-healthcare/en_GB/medicines/CABENUVA-VOCABRIA_PM_18-Mar-2020.pdf

- Possible to move to 8 weekly dosing (submitted to FDA Feb 2021)
  - Phase 3b ATLAS-2M- showed 2mthly as effective
  - Both dosing schedules better accepted than daily oral therapy
  - Switched from virologically suppressed
  - Acceptability of injection site reactions- improved over time no diff between the 2 groups
  - improved in both groups
  - 8 weeks favoured at weeks 24 and 48
  - Vast majority satisfied to continue on a long acting
  - 3% selecting monthly
  - Conc: both long acting options provided high levels Rx satisfaction
  - Most selected 4 weeks or 8 weeks over oral daily dosing



Which clinical trials are studying islatravir? Islatravir for HIV treatment

- **Study Names**: MK-8591-011; NCT03272347
  Phase: 2b
  Status: This study is ongoing, but not recruiting participants.
  Locations: Chile, France, United Kingdom, United States
  Purpose: The purpose of this trial is to evaluate the safety and effectiveness of three different doses of islatravir in adults with HIV who have never taken HIV medicines before.[8]

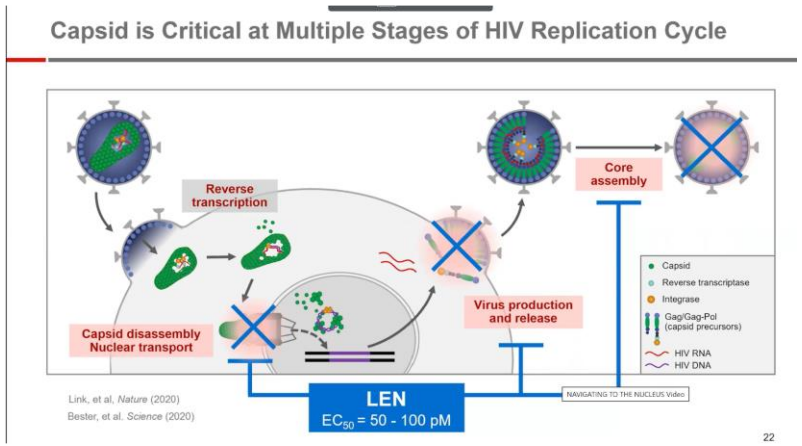
- **Study Names**: MK-8591A-017; NCT04223778
  Phase: 3
  Status: This study is currently recruiting participants.
  Locations: Multiple countries, including United States
  Purpose: The purpose of this trial is to evaluate the safety and effectiveness of a switch from a current ART regimen to a fixed-dose combination (FDC) containing doravirine/islatravir.[9]

- **Study Names**: MK-8591A-018; NCT04223791
  Phase: 3
  Status: This study is currently recruiting participants.
  Locations: Multiple countries, including United States
  Purpose: The purpose of this trial is to evaluate the safety and effectiveness of a switch from bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) to an FDC containing doravirine/islatravir.[10]

- **Study Names**: MK-8591A-019; NCT04233216
  Phase: 3
  Status: This study is currently recruiting participants.
  Locations: Multiple countries, including United States
  Purpose: The purpose of this trial is to evaluate the safety and efficacy of islatravir, doravirine, and an FDC containing doravirine/islatravir, each compared to placebo.[4]

- **Study Names**: MK-8591A-020; NCT04233879
  Phase: 3
  Status: This study is currently recruiting participants.
  Locations: Multiple countries, including United States
  Purpose: The purpose of this trial is to evaluate the safety and efficacy of an FDC containing doravirine/islatravir versus Biktarvy in adults with HIV who have never taken HIV medicines before.[11]

Lenacapavir: capsid inhibitor : Gilead



Once every six months

Treatment

CAPELLA (NCT04150068)

- Ph 2/3 study in highly treatment-experienced PWH
- Subcutaneous LEN Q6M added to an OBR

Segal-Maurer et al. (Oral Abstr. 2228, Tue 3/9/21)
Potent Antiviral Activity of Lenacapavir in Phase 2/3 in Heavily ART-Experienced PWH

CALIBRATE (NCT04143594)

- Ph 2 study in treatment-naïve PWH
- Combination of oral or subcutaneous LEN with oral daily TAF/FTC, TAF, or bictegravir

Once weekly dosing feasible

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Gilead and Merck Announce Agreement to Jointly Develop and Commercialize Long-Acting, Investigational Treatment Combinations of Lenacapavir and Islatravir in HIV

– Collaboration to Focus on Oral and Injectable Formulations of Lenacapavir and Islatravir –

– Agreement Brings Together Potentially Complementary Medicines in Late-Stage Development with the Goal to Provide Innovative, Long-Acting Treatments in HIV –

GILEAD SCIENCES, INC.
NASDAQ:GILD

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Lenacapavir and Islatravir combination

- The first clinical studies of the oral combinations are expected to begin in the second half of 2021
- Across the oral and injectable formulation programs, Gilead and Merck will share global development and commercialization costs 60%/40%, respectively
- For long-acting oral products, Gilead will lead commercialization in the U.S. and Merck will lead commercialization in the EU and rest of the world
- For long-acting injectable products, Merck will lead commercialization in the U.S. and Gilead will lead commercialization in the EU and rest of the world.
- Beyond the potential combinations of lenacapavir and islatravir, Gilead will have the option to license certain of Merck's investigational oral integrase inhibitors to develop in combination with lenacapavir. Reciprocally, Merck will have the option to license certain of Gilead's investigational oral integrase inhibitors to develop in combination with islatravir.

University of Washington –TLC – ART https://depts.washington.edu/tlcart/

- TDF / 3TC/ DTG
- Sub cut – diff platform
- Currently mthly – aim would be every 2-3 mths
- Covers Hep B
- Use in primates – TDF can be 3 mthly
- Accelerated programme with UNITAID
- Ready to use suspension
- No cold chain
- Plastic vial – single or multiple doses
- Pros/ cons mthly injection v 6mthly ART refills
- Pushed to include adolescents and BF

In summary

- Exciting mix of products to expand “ choice” in PreP
- Treatment combinations more questions
  - Challenge of cold chain with Cabenuva
  - Frequency of injection versus our current 6-12 mth visits
  - What populations will more likely benefit – children / adolescents/ those failing