PrEP State of the Science Overview

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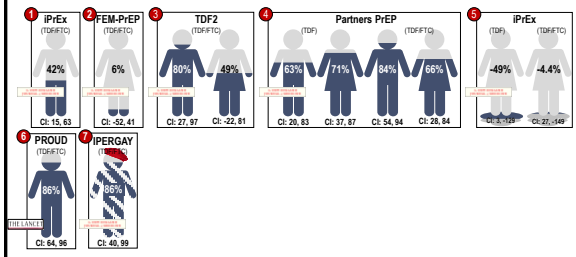
Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years:

Dr Landovitz has served on scientific advisory boards for Gilead Sciences, Inc., and Merck & Co, Inc. (Updated 11/15/21)

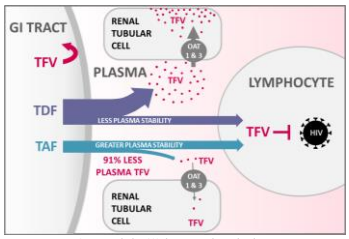
Slide 2

Effectiveness of PrEP in Placebo-Controlled Clinical Trials



1. Grant et al. NEJM. 2010.
2. Van Damme et al. NEJM. 2012.
3. Thigpen et al. NEJM. 2012.
4. Baeten et al. NEJM. 2012.
5. Marrazzo et al. NEJM. 2015.
6. McCormack et al. Lancet. 2016.
7. Molina et al. NEJM. 2015.

TAF/FTC: Works for Treatment—How about PrEP?

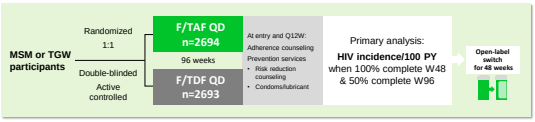


TAF 25 mg results in >90% lower TFV plasma levels

OAT, organic anion transporter; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir.

Sax P, et al. Lancet 2015
Wohl D, et al. CROI 2016. Boston, MA. #681

DISCOVER: A Randomized, Noninferiority Trial of F/TAF for PrEP



Eligibility required high sexual risk of HIV
- 2+ episodes condomless anal sex in past 12W or rectal gonorrhea/ chlamydia, syphilis in past 24W
- HIV & HBV negative, eGFR ≥60 mL/min
- Prior use of PrEP allowed

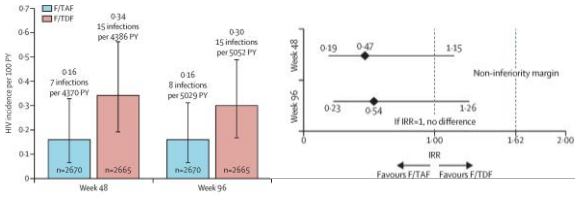
Study conducted in NA, EU in cities/sites with high HIV incidence
- 94 sites in 11 countries
- Participants: US, 60%; EU, 34%; Canada, 7%

Primary efficacy endpoint: HIV incidence
- Evaluated by rate ratio with noninferiority (NI) margin <1.62
- Expected incidence of 1.44/100 PY based on pooled studies: iPrEx, PROUD, IPERGAY

F/TAF dose: 200/25 mg; F/TDF dose: 200/300 mg; eGFR, estimated glomerular filtration rate.

Slide courtesy of Gilead Sciences

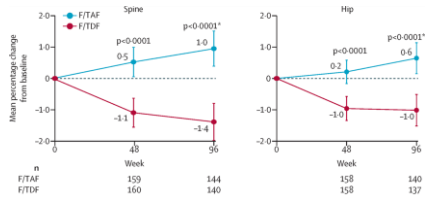
DISCOVER: HIV Incidence



Incidence of HIV per 100 PY in the F/TAF and F/TDF groups and IRR (F/TAF divided by F/TDF). Error bars represent 95% CIs.
F/TAF=emtricitabine and tenofovir alafenamide. F/TDF=emtricitabine and tenofovir disoproxil fumarate. IRR=incidence rate ratio. PY=person-year.

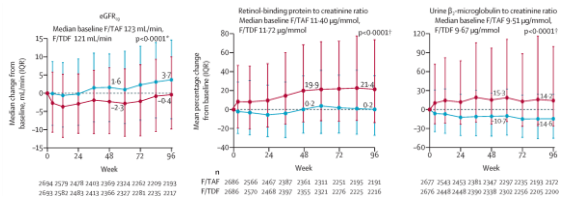
Ogbuagu O et al. Lancet HIV. 2021

DISCOVER: Bone Safety



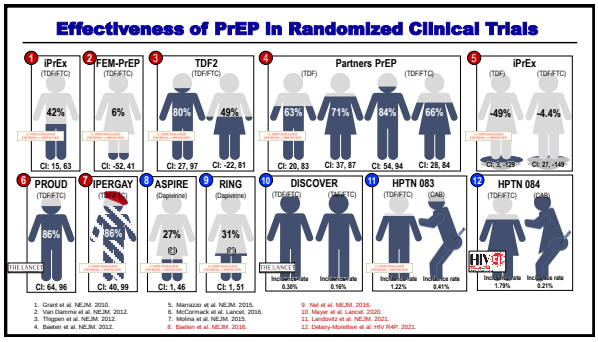
Ogbuagu O et al. Lancet HIV. 2021

DISCOVER: Renal Safety



Ogbuagu O et al. Lancet HIV. 2021

Which medication should I prescribe for daily PrEP?

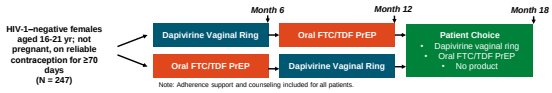


Monthly Dapivirine Ring

- Flexible silicone vaginal ring developed by IPM
- Woman-initiated
  - Self-inserted monthly
  - Discreet
- Slowly releases ARV dapivirine
- Reduced women's HIV-1 risk by ~30% in two Phase III trials
- Interim data from open-label studies show greater use and suggest ~50% risk reduction
  - New interim data presented at R4P
- EMA regulatory approval!
- Under US regulatory review

Nel A et al. NEJM 2016
Baeten J et al. NEJM 2016
Baeten J et al. CROI 2018, #143LB
Nel A et al. CROI 2018, #144LB

REACH: Adherence and Key Outcomes Through Month 12



Note: Adherence support and counseling included for all patients.

Outcome, %	Dapivirine Vaginal Ring	Oral PrEP
Adherence		
• High	50.2	58.6
• Medium	45.4	39.9
• Low/none	4.4	1.5
Compliance*		
• Full compliance	50.2	22.4
• Below full compliance	49.8	77.6
Acceptable		
• Yes	88.5	63.9
• No	11.5	36.1

- High Adherence
  - DPV: ≥0.1071 mg/day
  - TDF/FTC: ≥4 doses/wk (>500 fmol/punch at Wk 4, >700 fmol/punch at Wk 8)
- Medium Adherence
  - DPV: 0.0321 - <0.1071 mg/day
  - TDF/FTC: ~1-3 doses/wk (16.6-499 fmol/punch at Wk 4, 16.6-699 fmol/punch at Wk 8)
- Low Adherence
  - DPV: ≤0.0321 mg/day
  - TDF/FTC: No drug detected (<16.6 fmol/punch)

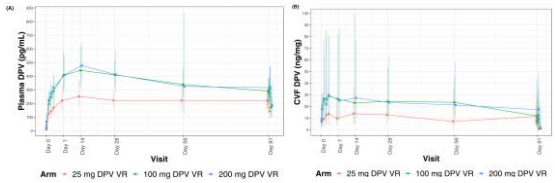
- **HIV-1 incidence: 0.5/100 woman-yr (1/247)**
- **Pregnancy incidence: 1.8/100 woman-yr (4/247)**

* Full compliance to ring defined as leaving the ring in place a full month; full compliance to oral PrEP defined as 6+ doses per week.

Slide credit: clinicaloptions.com

Nair. IAS 2021. Abstr OALC01LB01.

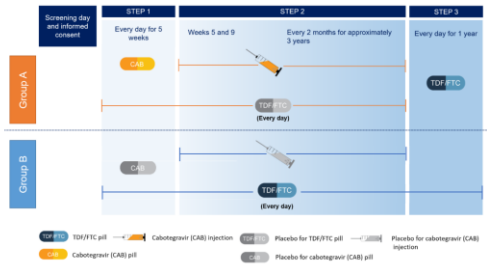
MTN-036/IPM 047: Phase 1 PK of Study of Extended Duration Dapivirine Vaginal Rings in the United States



Geometric means of DPV concentration in (A) blood plasma (pg/mL) and (B) CVF (ng/mg). Vertical bars indicate the back transformation of [Mean ± 1 SD] intervals of log-transformed concentrations.

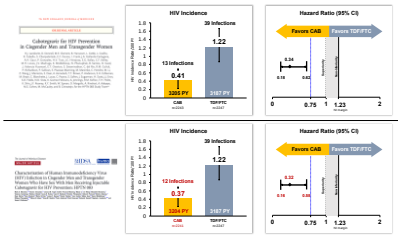
Lui A et al. JIAS 2021.

HPTN 083 Study Design



Landovitz RJ et al. AIDS 2020, #OAXLB0101

HIV Incidence: CAB vs. TDF/FTC

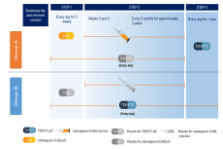


CI, confidence interval

HPTN 084 Study Design

- **Primary Objective: Reduce HIV Incidence** (superiority, double blind, double dummy design)
- Endpoint-driven trial (HIV infection) – monitored by NIAID DSMB every 6 months
- Est. study duration: enrollment 24 months; follow-up up to 4.5 years
- N=3200 at 20 sites in Kenya, Malawi, South Africa, Swaziland, Uganda, Zimbabwe

Sinead Delaney-Moretlwe and Mina Hosseinipour, *Protocol Chairs*



Start Nov 2017
Blinded Study halted by DSMB November 2020

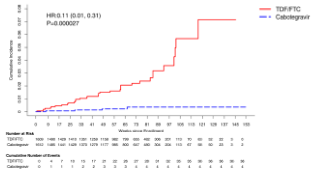
Delany-Moretlwe S, et al. R4P 2021, Abstract LB1479

HIV Incidence: CAB vs. TDF/FTC

40 infections over 3892 person-years
Pooled HIV incidence 1.03 (0.73, 1.4) per 100 person-years

	CAB	TDF/FTC
HIV infections	4	36
Person-years	1,953	1,939
HIV incidence (95% CI)	0.2 (0.06, 0.52)	1.86 (1.3, 2.57)

Wald test z statistic - 4.20, efficacy stopping bound (z scale) - 3.61

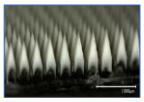


*Women in the CAB group had an **89% lower risk of HIV infection,** compared to TDF/FTC group*

Delany-Moretlwe S, et al. R4P 2021, Abstract LB1479

What's Next for CAB?

- Microarray Patch (MAP) for Long-Acting HIV PrEP



Light microscopic image (x25) of MAP

Rein-Weston, ID Week Oct 2019
https://doi.org/10.1093/ofid/ofz415.2491

- CAB LA Reformulation: double-strength concentration (400mg/mL)

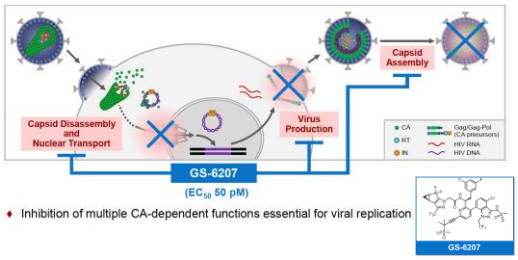
- ViiV/GSK internal program
- ClinicalTrials.gov NCT04484337

- CAB Implant: non-biodegradable, retrievable

- ViiV/GSK internal & external collaboration (Northwestern Univ. SLAP-HIV UM1 NIH grant)

Hope, et al. HIV R4P Jan 2021 Virtual

Lenacapavir (GS-6207): First-in-Class HIV Capsid Inhibitor

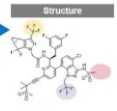


- Inhibition of multiple CA-dependent functions essential for viral replication

Lenacapavir (GS-6207) and LEN Analog (GS-CA1)

Gilead Long-acting Capsid Inhibitors

- Multi-stage capsid-specific MOA
- High metabolic stability, low clearance & low solubility

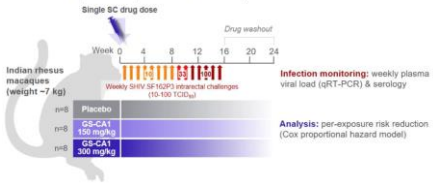
	Structure	Status	PBMC EC_{50} (nM)
LEN[1] (GS-6207)		• Favorable safety & tolerability profile in clinical trials* • 2.3-log_{10} HIV-1 RNA decline after 9 days of monotherapy* • Q6M formulation in Phase 2/3 trials in PLWH	HIV† 0.050 SHIV‡ 0.569
GS-CA1[2] (LEN analog)		• Preclinical efficacy in hu-mice • Tool compound for preclinical research studies	HIV† 0.130 SHIV‡ 0.748

*GS-US-200-4538; GS-US-200-4071; GS-US-200-4072, †Tested in human PBMC, ‡Tested in rhesus macaque PBMC

Bekerman E, et al. CROI 2021, Abstract #717

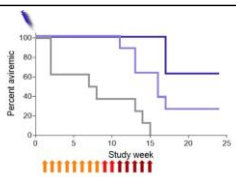
GS-CA1: Repeat Mucosal Challenge Macaque Model

Study objective: To determine the efficacy of GS-CA1 long-acting formulation at preventing infection after repeat SHIV exposure in rhesus macaques



Bekerman E, et al. CROI 2021, Abstract #717

GS-CA1: Repeat Rectal Challenge Macaque Model



	No. Protected	Median Weeks to Infection (95% CIs)	Hazard Ratio	p-value
GS-CA1 300 mg/kg	5 / 8	Not reached (17, –)	0.038	**0.0002**
GS-CA1 150 mg/kg	2 / 8	16 (11, –)	0.141	**0.0061**
Placebo	0 / 8	7.5 (2,14)	1	

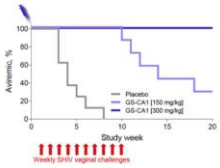
Hazard ratios, p-values calculated using Cox regression model.

- 100% infection of placebo controls within 15 challenges
- Significant infection risk reduction with GS-CA1 vs placebo (86% and 96% for low- and high-dose groups, respectively)
- Infections in GS-CA1-dosed groups occurred only after marked compound washout (9+ weeks post dose*)

*Assumes 2-week infection-detection window

Bekerman E, et al. CROI 2021, Abstract #717

GS-CA1: Repeat Vaginal Challenge Macaque Model



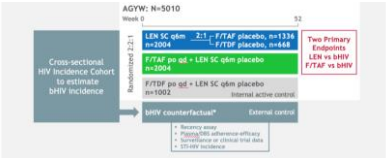
Study group	No. Protected	Median wks to viremia (95% CIs)	p-value vs placebo
Placebo	0 / 8	4 (3,6)	n/a
GS-CA1 150 mg/kg	2 / 8	14 (10, –)	<0.0001
GS-CA1 300 mg/kg	8 / 8	Not reached	<0.0001

- 100% infection of placebo controls within 8 weeks
- Significant delay in time to viremia and protection against vaginal SHIV acquisition with 1050mg/kg GS-CA1 vs placebo
- Complete protection against 10 vaginal SHIV challenges in the high-dose group

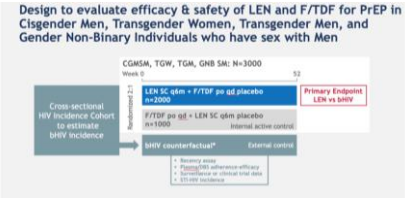
*Assumes 2-week infection-detection window

Bekerman E, et al. IAS 2021, Abstract #2474

PURPOSE 1: Safety and Efficacy of Lenacapavir and Emtricitabine/Tenofovir Alafenamide for Pre-Exposure Prophylaxis in Adolescent Girls and Young Women at Risk of HIV Infection



PURPOSE 2: Study to Assess the Effectiveness and Safety of Lenacapavir for Human Immunodeficiency Virus (HIV) Pre-Exposure Prophylaxis

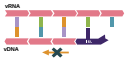


Islatravir (MK-8591): First-in-Class HIV Nucleoside RT Translocation Inhibitor (NRTTI)

- ISL is the first nucleoside reverse transcriptase translocation inhibitor (NRTTI) in development for the treatment and prevention of HIV-1 infection[1]
- ISL is rapidly converted to its active TP form within target cells,[1] which inhibits reverse transcriptase by multiple mechanisms of action to suppress HIV-1 replication

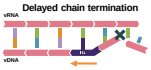
ISL-TP has high antiviral potency against HIV-1 and drug-resistant variants,[1,2] and a half-life in PBMCs of approximately 190 hours after oral administration in adults without HIV[3]

Translocation inhibition



- Translocation inhibition prevents opening of the RT nucleotide binding site
- Nucleotides cannot be incorporated into vDNA
- **Viral replication is inhibited**

Delayed chain termination



- Islatravir changes vDNA structure such that nucleotide incorporation is prevented
- Islatravir is not in the RT active site and is not susceptible to RT-associated resistance mutations
- **Viral replication is inhibited**

ISL, islatravir; PBMCs, peripheral blood mononuclear cell; RT, reverse transcriptase; TP, triphosphate; vDNA, viral DNA; vRNA, viral RNA.
1. Markowitz M, Grobler JA. *Curr Opin HIV AIDS* 2020;15:27–32; 2. Grobler JA et al. *HIV Glasgow* 2018 poster #O343; 3. Ankrom W Islatravir Intracellular Triphosphate T1/2 Supports Extended Dose Intervals. CROI 2021. #2101.

Hillier S, et al. HIV R4P Abstract: OA04.05

IMPOWER-022, IMPOWER-024, and Beyond

A Phase 3, Randomized, Active-Controlled, Double-blind Clinical Study to Evaluate the Efficacy and Safety of Oral Islatravir (MK-8591) Once-Monthly as Preexposure

Enrollment goal: 4,500
Age range: 16 – 45 years
Population: Cisgender women
Site locations: US & South Africa
Status: Enrolling

A Phase 3, Randomized, Active-Controlled, Double-Blind Clinical Study to Evaluate the Efficacy and Safety of Oral Islatravir Once-Monthly as Preexposure Prophylaxis in Cisgender Men and Transgender Women Who Have Sex With Men, and Are at High Risk for HIV-1 Infection

Enrollment goal: 1,500
Age range: 16+
Population: MSM, Transgender women
Site locations: US, France, Japan, Peru
Status: Enrolling

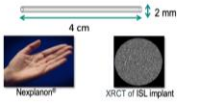
- Trans-specific protocol under discussion
- Adolescent-specific protocol under discussion

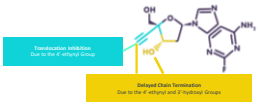
Next-generation islatravir implants

- ISL implant based on Implanon®/Nexplanon®
  - Uses same polymer
  - Removable (not bioerodible)
- Able to use Nexplanon® applicator

- Initial trial uses prototype implant

Polymer + ISL





Matthews R, et al. IAS2019, Abstract: TUAC0401LB

The Menu: Appetizers

- Counterfactual-comparison TAF PrEP studies in cisgender women
  - Still need onset/offset of protection/forgiveness data
  - Long term safety advantage?
- Topical preparations (vaginal)
  - Longer interval rings (TFV or DPV 3 month)
  - MPT rings
  - Inserts/films/threats/gels – TAF/EVG
- Cabotegravir
  - Implementation?
  - Implants?
  - MAPs?

The Menu: Entrees

- Islatravir
  - Oral – monthly (Phase 3); MSM/TGW; Cisgender women (Counterfactual)
  - Implant – Phase 2?
- Lenacapavir
  - Phase 3 MSM/TGW, Cisgender women
  - Barrier to resistance?
- Diagnostics
  - Do we need more sensitive diagnostics?
  - Does earlier detection have advantages?
  - Scalability/Cost/Implementation

The Menu: Dessert

Thank you!

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