

# Strategies to Optimize PrEP: Schedules, Formulations, and Innovative Approaches

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

Dr Molina has received grant support paid to his institution from Gilead Sciences, Inc., and served as a consultant to Merck & Co, Inc., Gilead Sciences, Inc., ViiV Healthcare, Bristol-Myers Squibb, Janssen Therapeutics, and Teva. (Updated 11/16/21)

Slide 2

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## Ideal PrEP Regimens

- **Effectiveness**
  - 100% effectiveness when taken as recommended
  - Work for all populations (MSM, heterosexual men and women, IDU, adolescents, pregnancy)
- **Adherence**
  - Simple with high forgiveness: long-acting formulations, clear guidance on how to start/stop PrEP
  - Simple assessment of adherence (DBS for TFV-DP)
- **Breakthrough HIV-infection**
  - Rapid and simple diagnosis of breakthrough HIV-infections
  - Low risk for resistance and cross-resistance within class to avoid compromising treatment options
- **Safety and Tolerability:** Almost perfect without need for safety monitoring
- **Implementation**
  - Easy to use and self-administered
  - Affordable cost
  - Multipurpose tools (HIV, contraception, STIs) and multiple options for PrEP

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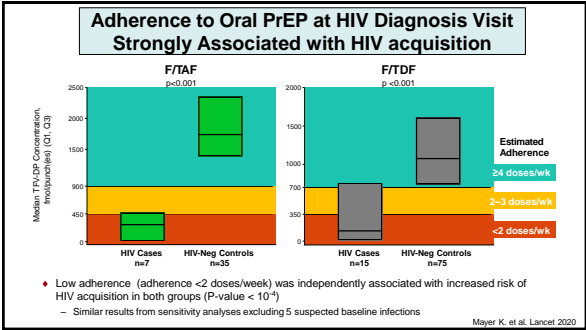
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**Potential Benefits of On Demand Oral PrEP**

- Convenient dosing regimen could improve adherence
- Clear guidance on how to start and stop PrEP
- Better safety due to lower drug exposure (kidneys, bones)
- Improved cost-effectiveness

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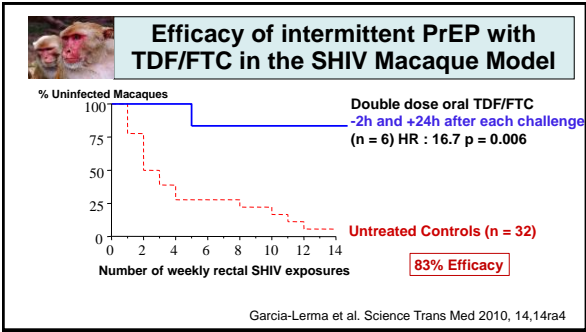
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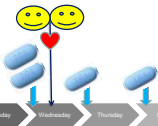
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## IPERGAY: Sex-Driven iPrEP

- ✓ 2 tablets 2-24 hours before sex
- ✓ 1 tablet 24 hours later
- ✓ 1 tablet 48 hours after first intake



4 pills of TDF/FTC taken over 3 days to cover one sexual intercourse

On demand PrEP tells you How to Start and How to Stop PrEP

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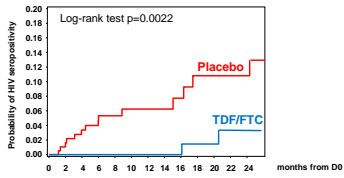
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## Effectiveness of On Demand PrEP with TDF/FTC in MSM in France and Canada





Mean follow-up of 12 months: 16 subjects infected (14 placebo, 2 in TDF/FTC)

Incidence : 6.6/100 PY (9.17 in Paris) placebo and 0.9/100 PY with TDF/FTC

**Effectiveness = 86%** in relative reduction in the incidence of HIV-1 (95% CI : 40-98, p=0.002)

Molina JM et al NEJM 2015

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## PrEP with Daily or On Demand TDF/FTC among MSM

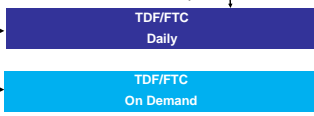


Open-Label Prospective Cohort Study in the Paris Region

n ≥ 3,000

May 3<sup>rd</sup> 2017

September 30, 2020



- HIV-negative high risk adults
- Inconsistent Condom use
- eGFR ≥ 50 mL/min
- HbS Ag negative if On Demand

- Participants opted for either Daily or On Demand PrEP and could switch regimen
- Follow-up every 3 months with 4th Gen ELISA HIV test and plasma creatinine
- Condoms, gels, risk reduction and adherence counseling, Q on sexual behavior

Molina JM et al CROI 2021

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PrEP with Daily or On Demand  
TDF/FTC among MSM

Global HIV Incidence: 0.11/100 PY (95% CI: 0.04-0.23) (6 cases)

Mean Follow-up of 22.1 months and 5633 Person-Years

Treatment	Follow-Up Pts-years	HIV Incidence per 100 Pts-years (95% CI)	IRR (95%CI)
TDF/FTC Daily	2583.25	0.12 ( 0.02 – 0.34 )	0.99
TDF/FTC On Demand	2553.68	0.12 ( 0.02 – 0.34 )	(0.13-7.38)

Molina JM et al CROI 2021




TECHNICAL BRIEF

WHAT'S THE 2+1+1?

EVENT-DRIVEN ORAL PRE-EXPOSURE  
PROPHYLAXIS TO PREVENT HIV FOR MEN  
WHO HAVE SEX WITH MEN: UPDATE TO WHO'S  
RECOMMENDATION ON ORAL PREP

JULY 2019

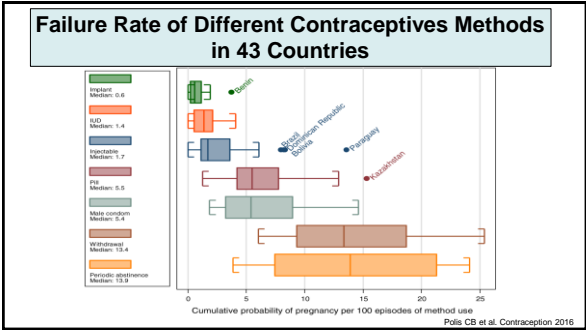


Limitations of Event-Driven with  
TDF/FTC for the Prevention of HIV

- More frequent drug-related Gastro-Intestinal AEs
- No data in women
- No data with TAF/FTC
- Can we simplify the 2-1-1 dosing regimen ?

PrEParing for PrEP: From Policy to Implementation -- November 19, 2021

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**Approved and Investigational Long Acting PrEP Regimens**

- Topical
  - Dapivirine ring
- Oral
  - Islatravir
- Parenteral
  - Cabotegravir LA IM
  - Lenacapavir SC
  - Implants (Islatravir, cabotegravir, TAF)
  - Broadly Neutralizing Antibodies (bNabs)

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**Dapivirine Vaginal Rings**

- EMA approval in July 2020 and WHO recommendation in January 2021 for DPV-VR as a new choice for HIV prevention for women
- Flexible, silicone, vaginal ring with 25 mg of DPV, self-inserted every 4 weeks:
  - 27-30% reduction in HIV-incidence in placebo-controlled trials; 39 to 62% in open-label trials
- More studies ongoing in Africa:
  - Adolescent girls and young women: REACH study; Pregnant women: DELIVER study
  - Breast-feeding women: B-PROTECTED in Africa
  - Extended duration vaginal rings: 3-monthly dapivirine vaginal rings
  - Multipurpose technologies: rings with dapivirine and levonorgestrel
- Limitations
  - Low effectiveness due to topical PrEP
  - Transmitted NNRTI resistance
  - Long-term acceptability

Nei et al. NEJM 2016; Lancet HIV 2021 Baeten et al. NEJM 2016; Lancet HIV 2021

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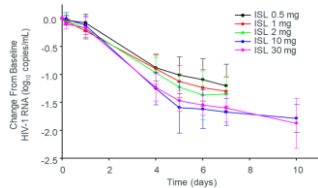
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## Islatravir: A New Potent and Long-Acting Antiretroviral Agent

- Nucleoside reverse transcriptase translocation inhibitor.
- Potent antiviral activity with low in vitro  $IC_{50}$  and activity against NRTI-resistant HIV-1 strains.
- Single-dose oral ISL associated with reduction in plasma HIV-RNA without emergence of viral resistance.
- Robust viral load decline associated with ISL-TP concentrations as low as **0.05 pmol/10<sup>6</sup> cells**.
- Long ISL-TP half-life ~120 hr in healthy adults.



Schurmann D. et al. Lancet HIV 2020;7:e164-72

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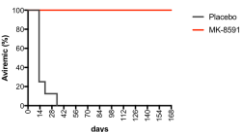
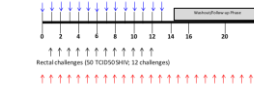
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## Weekly Islatravir Protects Against SHIV Infection in a Low Dose Rectal Challenge Rhesus Macaque Model

10% Tween 5mL/kg with or without MK-8591 3.9mg/kg by oral gavage (14 time points)

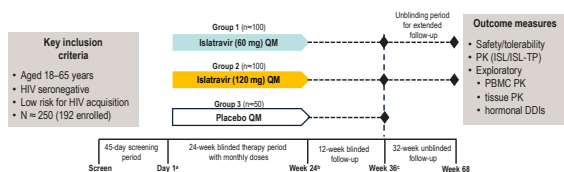


- ISL was completely protective at dose levels  $\geq 0.43$  mg/kg and highly protective at doses as low as 0.1 mg/kg in the rhesus macaque/IR SHIV109CP3 challenge model.
- ISL-TP in PBMC was  $> 0.1$  pmol/ $10^6$  PBMCs with 0.43 (---) to 1.3 (---) mg/week of ISL in animals
- ISL-TP levels that are protective in this model are achievable in humans suggesting ISL utility in extended duration prophylaxis against HIV infection.

Markowitz M. et al. JID 2020;221:1398

[illegible]

## Randomized Placebo Controlled Study of Monthly Oral Islatravir for PrEP



Hillier S. et al HIV R4P 2021 virtual

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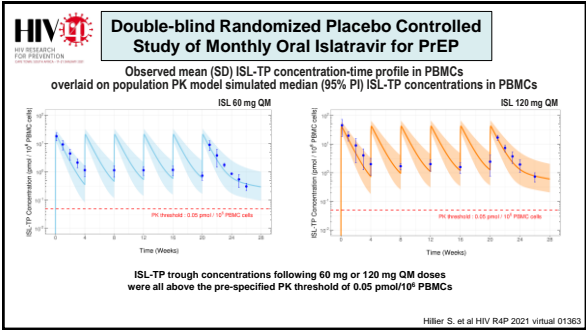
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### ISL 60 mg QM Oral PrEP Clinical Development Program

**Impower**

	Trial name (protocol number)	Population	Active comparator	ClinicalTrials.gov
Phase 3	IMPOWER-022	4,500 Cisgender women and adolescent girls at high risk of HIV-1 infection in Sub-Saharan Africa	FTC/TDF	NCT04644029
	IMPOWER-024	1,500 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

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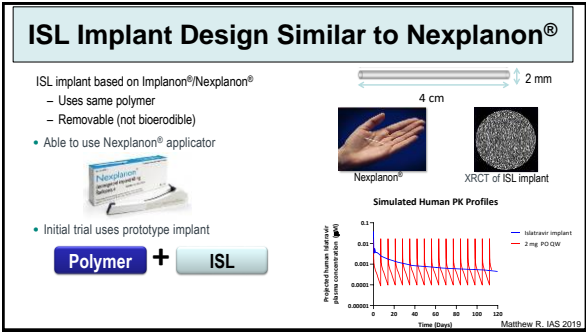
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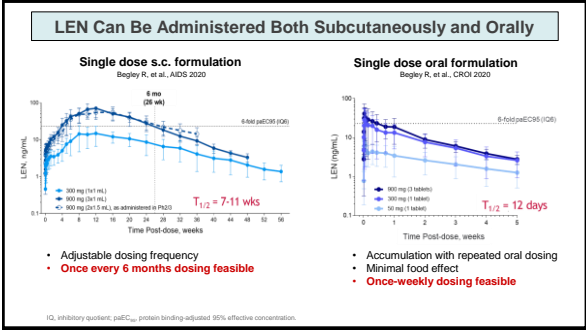
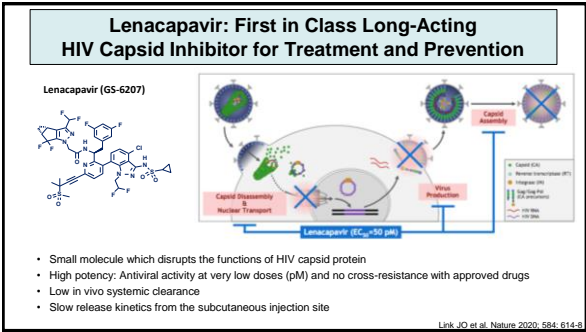
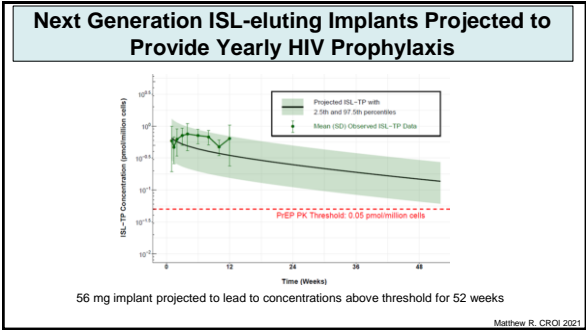
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### The AMP Studies: Phase 2b Proof of Concept Trials to Test the Efficacy of VRC01 Antibody to Prevent HIV Acquisition

Two harmonized protocols:

- HVTN 704/HPTN 085 (~2,700 MSM and TG in the Americas & Europe)
- HVTN 703/HPTN 081 (~1,900 Women in sub-Saharan Africa)
- Placebo controlled trial of VRC01 mAb (IV), given on q2 month schedule
- Both trials opened in April/May 2016



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### Prevention Efficacy of bNabs





- Pooled analysis of 2 AMP trials in 4623 MSM and young Women
- Overall non significant reduction in HIV-1 incidence with VRCO1:  
Reduction in HIV incidence of 8.8% in Women, 26.6% in MSM (P> 0.10)

HIV IC <sub>80</sub> (µg/ml)	Regimen	Nb HIV-infections	Incidence /100 PY	Efficacy (95% CI)
< 1	Placebo	19	0.86	75.4
	VRCO1 pooled	9	0.26	(45;89)
1-3	Placebo	10	0.45	4.2
	VRCO1 pooled	19	0.43	(-108;56)
> 3	Placebo	35	1.59	3.3
	VRCO1 pooled	70	1.58	(-48;37)

Corey L. et al. N Engl J Med. 2021 Mar 18;384(11):1003-1014

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### AMP Studies Summary



- Proof of concept that long-term bNabs can prevent HIV-acquisition
- In vitro HIV-1 susceptibility to VRCO1 influences preventive efficacy (only 30% of the circulating HIV-1 strains exhibited IC<sub>80</sub> < 1 µg/ml)
- A neutralization titer or Ab concentration in serum established as a biomarker of protection
- Multiple bNabs will be needed for optimal prevention

Corey L. et al. N Engl J Med. 2021 Mar 18;384(11):1003-1014

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