Preexposure Prophylaxis for HIV Infection: PrEParing for the Next Decade



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IAS–USA

1

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

Dr Landovitz reported serving as a consultant for Gilead Sciences, Inc, Merck & Co, Inc, RedQueen Therapeutics, and ViiV Healthcare. (Updated May 5, 2025)

Slide 2

2

Learning Objectives

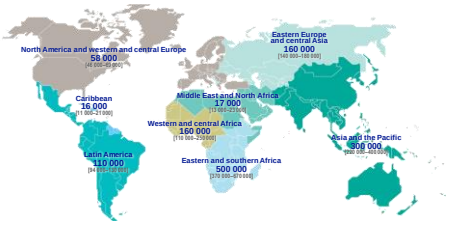
After attending this presentation, learners will be able to:

- Describe the efficacy and safety data for current and advanced PrEP agents
- Describe HIV testing and monitoring in the context of specific PrEP formulations
- List emerging and future HIV prevention strategies

Slide 3

3

40 YEARS INTO THE HIV EPIDEMIC, DESPITE REMARKABLE SCIENTIFIC DISCOVERIES



Total: 1.3 million [1.0 million–1.7 million]

UNAIDS Global AIDS Update 2023

Slide 4

4

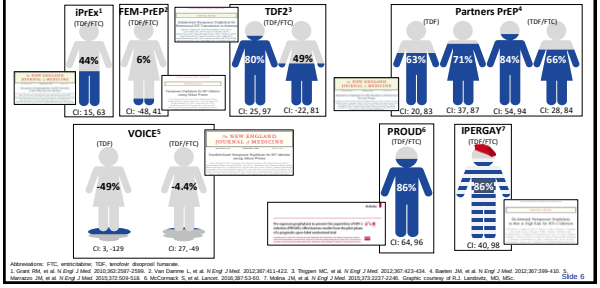


TDF/FTC

Slide 5

5

EFFECTIVENESS OF ORAL PREP IN RANDOMIZED CLINICAL TRIALS



Abbreviations: FTC, emtricitabine; TDF, tenofovir disoproxil fumarate.

1. Grant RM, et al. *N Engl J Med*. 2010;363:2587-2599. 2. Van Damme L, et al. *N Engl J Med*. 2012;367:411-422. 3. Thigpen MC, et al. *N Engl J Med*. 2012;367:423-434. 4. Baeten JM, et al. *N Engl J Med*. 2012;367:399-410. 5. Marrazzo JM, et al. *N Engl J Med*. 2015;372:509-518. 6. McCormack S, et al. *Lancet*. 2016;387:53-60. 7. Molina JM, et al. *N Engl J Med*. 2015;373:2237-2246. Graphic courtesy of B.J. Landovitz, MD, MSc.

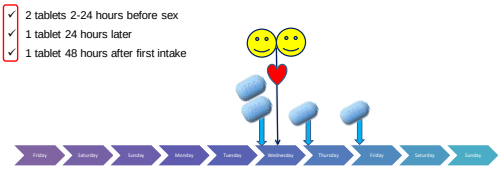
Slide 6

6

IPERGAY

Sex-Driven PrEP

- ✓ 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 contact

Molina JM et al. NEJM. 2015.

Slide 7

7



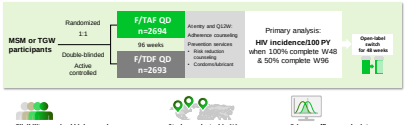
TAF/FTC

Slide 8

8

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 1.46/100 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

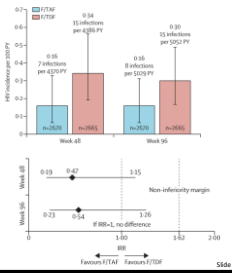
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9

DISCOVER TRIAL

HIV Incidence

- Ongoing, multicenter, phase III, noninferiority trial in Europe and North America
- High-risk MSM randomized to receive TAF/FTC (n = 2694) or TDF/FTC (n = 2693)
- Primary outcome – incident HIV infection at week 96
- TAF/FTC was statistically noninferior to TDF/FTC, with an IRR of 0.54 (95% CI, 0.23-1.26)
  - TAF/FTC 0.16 infections/100 PY
  - TDF FTC 0.30 infections/100 PY

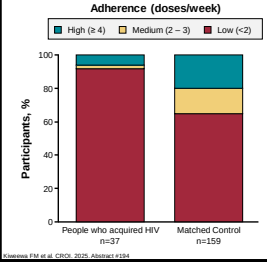


Ogbuagu O, et al. Lancet HIV. 2021

Slide 10

10

RESULTS: Abstract #194, Adherence to F/TAF in Cisgender Women Prevents HIV With Low Risk of Resistance or Diagnostic Delay



89% reduction in odds of HIV acquisition with >=2 doses per week on average

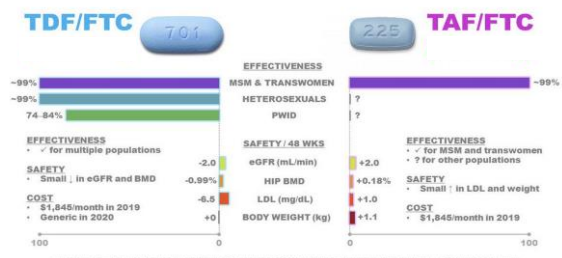
OR (95% CI): 0.11 0.012 – 0.49; p=0.0006

Kiweewa FM et al. CROI. 2025. Abstract #194

Slide 11

11

WHICH MEDICATION SHOULD I PRESCRIBE FOR ORAL PREP?



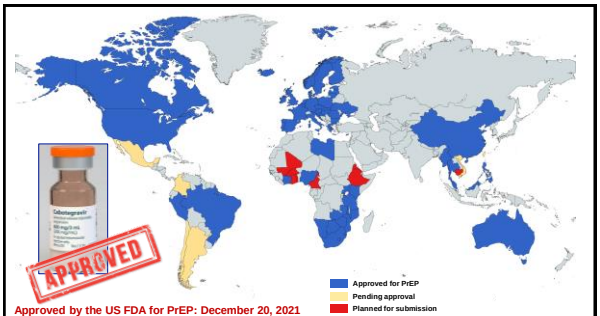
Slide 12

12

LONG-ACTING CABOTEGRAVIR

Slide 13

13



Approved by the US FDA for PrEP: December 20, 2021

AVAC Country Planning for Product Introduction Matrix:
https://app.powerbi.com/view?r=eyJrIjoiMzc4ZWQwZGMtZTk4Yi00MTY4LWJlNGItNjRlNTZiMzUzIiwidCI6IjIwIFiHNjQ0ZDZjLWFlYmUtNDRkMi1hNDc2LTczOTdlZmJlNWEzZiIsImMiOjN9

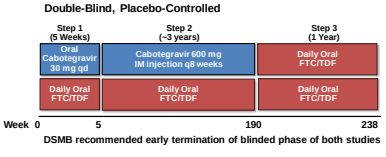
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14

HPTN 083 and 084

Long-acting injectable cabotegravir for PrEP

- Phase 3 studies
- Double-blind, placebo-controlled persons at high-risk for HIV infection in general good health
- No IDU, HCV, HBV, seizure disorder, CVD, abnormal liver function
- HPTN 083: MSM/transgender women
- HPTN 084: cisgender women



Matching oral and IM placebos included in the oral and injection phase double-blind arms.
HPTN 083 was conducted in US, Brazil, Peru, Argentina, South Africa, Vietnam, and Thailand.
HPTN 084 was conducted in Botswana, Kenya, Malawi, South Africa, Swaziland, Uganda, and Zimbabwe.

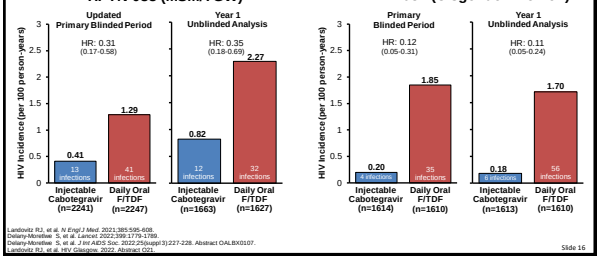
Landovitz RJ, et al. *N Engl J Med*. 2021;385:595-608.
Delany-Moretlwe S, et al. *Lancet*. 2022;399:1779-1789.
Delany-Moretlwe S, et al. *J Int AIDS Soc*. 2022;25(suppl 3):227-228. Abstract OALBX0107.

Slide 15

15

HPTN 083 and 084

HIV incidence

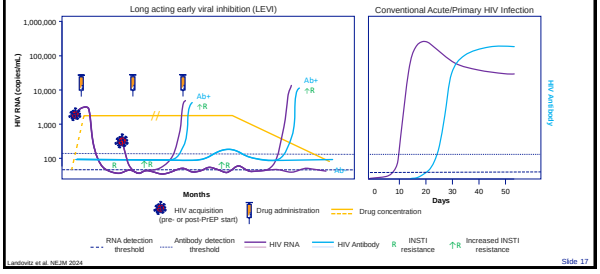


Landovitz RJ, et al. *N Engl J Med.* 2021;385:595-608.
Delany-Moretlwe S, et al. *Lancet.* 2022;399:1779-1789.
Delany-Moretlwe S, et al. *J Int AIDS Soc.* 2022;25(suppl 3):227-228. Abstract OALBX0107.
Landovitz RJ, et al. *HIV Glasgow.* 2022. Abstract O21.

Slide 16

16

EARLY HIV INFECTION WITH LEVI COMPARED TO CONVENTIONAL AHI/PHI



Landovitz et al. NEJM 2024

Slide 17

17

COMPARISON OF AHI TO INFECTIONS THAT OCCUR IN THE SETTING OF LEVI

	AHI	LEVI
Cause	Phase of natural HIV infection	Long-acting anti-viral PrEP agent (prototype: CAB-LA)
Onset	New infection	Infection during PrEP Initiation of PrEP agent during acute/early infection
Viral replication	Explosive	Smoldering
Symptoms	Fever, chills, rash, night sweats, muscle aches, sore throat, fatigue, swollen glands	Protean, often no symptoms reported
Detection	Ag/Ab assay, RNA assays (including less sensitive POC and pooled tests), DNA assays, total nucleic acid assays	Ultrasensitive RNA assay (often low or undetectable RNA, low/undetectable DNA, diminished/delayed Ab production)
Duration	1-2 weeks (until Ab detection)	Months (until viral breakthrough, cessation of anti-viral exposure or ART start)
Persistence	Rare*	Weeks-months after anti-viral agent is discontinued
Transmission	Very likely	Unlikely (except possibly through blood transfusion)
Drug resistance	No (unless transmitted)	Yes (can emerge early when viral load is low)

Slide 18

18

SO WHAT IS THE BEST HIV TESTING ALGORITHM FOR CAB PREP FAILURE?

Slide 19

19

PPV OF HIV TESTING ALGORITHMS WITH CAB-LA

	HPTN 083 (MSM/TGW)		HPTN 084 (Cisgender Women)	
	TDF/FTC	CAB	TDF/FTC	CAB
Rapid Test	91%	84%	86%	40%
Rapid Test + Ag/Ab Test	95%	83%	100%	Insufficient Data
Rapid Test + Ag/Ab Test and RNA Test	100%	100%	100%	100%
Rapid Test + Ag/Ab Test or RNA Test	80%	61%	62%	15%
Ag/Ab Test	86%	66%	70%	17%
CAB-LA < 6 months	N/A	9.1%	N/A	25%

Rapid Test | Ag/Ab Test | RNA Test

1. Landovitz, CROI 2024, Abstract 123
2. Voltal, IAS 2023, Abstract 5769
3. Delany-Moretlwe, CROI 2025, Abstract 101

Slide 20

20



Clinical Review & Education

JAMA | Special Communication

Antiretroviral Drugs for Treatment and Prevention of HIV in Adults: 2024 Recommendations of the International Antiviral Society–USA Panel

Rajesh T. Gandhi, MD; Raphael J. Landovitz, MD; Paul E. Sax, MD; Davey M. Smith, MD; Sandra A. Springer, MD; Huldrych F. Günthard, MD; Melanie A. Thompson, MD; Roger J. Bedimo, MD; Constance A. Benson, MD; Susan P. Buchbinder, MD; Brenda E. Crabtree-Ramirez, MD; Carlos del Rio, MD; Ellen F. Eaton, MD; Joseph J. Eron Jr, MD; Jennifer F. Hoy, MBBS; Clara Lehmann, MD; Jean-Michel Molina, MD; Donna M. Jacobsen, BS; Michael S. Saag, MD

"At initiation or after a long hiatus, HIV screening should include an HIV RNA test and a laboratory-based Ag/Ab test. If RNA testing is unavailable, initiation of PrEP after a rapid HIV antibody test and while awaiting a laboratory-based Ag/Ab test result is recommended. ***For CAB-LA PrEP follow-up, a rapid HIV antibody test and laboratory-based Ag/Ab, not routine RNA testing, is recommended.*** If RNA testing is not available, repeat Ag/Ab testing 1 month after starting or resuming tenofovir-based oral PrEP."

Gandhi et al. JAMA. 2024.

Slide 21

21

WHAT TO START BY TYPE OF EXPOSURE

Exposure	Daily TDF/FTC	On-demand (2-1-1) TDF/FTC	Daily TAF/FTC	Every other month IM CAB
Insertive anal/vaginal sex	✓	✓	✓	✓
Receptive anal sex	✓	✓	✓	✓
Receptive vaginal/neovaginal sex	✓	✗	?	✓
Injection drug use	✓	✗	✗	✗
Pregnant/breastfeeding women	✓	✗	✗	✓
Initiate with double dose	✓	✓	✗	✗
CrCl 30-60	✗	✗	✓	✓
Osteopenia or osteoporosis	✗	✗	✓	✓

Slide 22

22

LENACAPAVIR

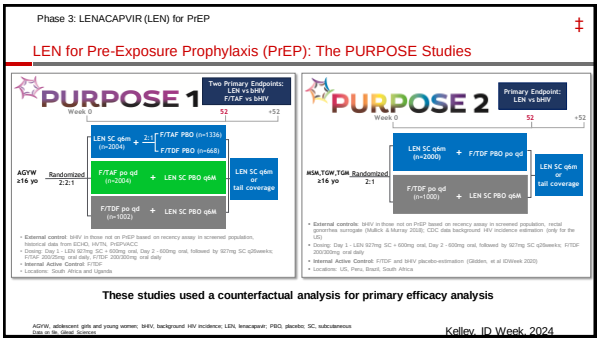
Slide 23

23

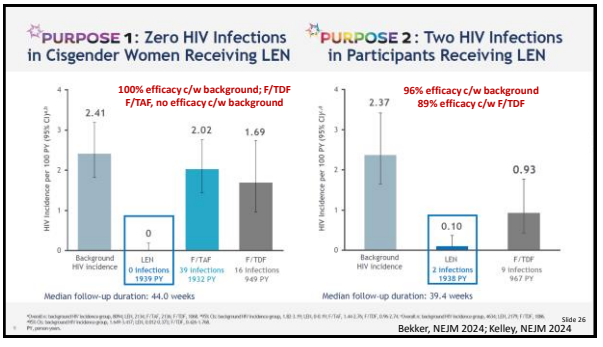


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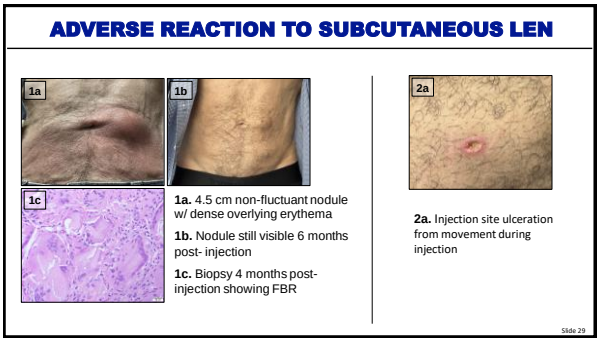
24


Phase 3: LENACAPVIR (LEN) for PrEP
LEN for Pre-Exposure Prophylaxis (PrEP): The PURPOSE Studies
PURPOSE 1
Two Primary Endpoints: LEN vs bHIV F/TAF vs bHIV
Week 0
52
+52
LEN SC q6m (n=2004)
2:1
F/TAF PBO (n=1336)
F/TDF PBO (n=668)
AGYW ≥16 yo
Randomized 2:2:1
F/TAF po qd (n=2004)
+ LEN SC PBO q6M
F/TDF po qd (n=1002)
+ LEN SC PBO q6M
LEN SC q6m or tail coverage
PURPOSE 2
Primary Endpoint: LEN vs bHIV
Week 0
52
+52
LEN SC q6m (n=2000)
+ F/TDF PBO po qd
MSM,TGW,TGM ≥16 yo
Randomized 2:1
F/TDF po qd (n=1000)
+ LEN SC PBO q6M
LEN SC q6m or tail coverage
These studies used a counterfactual analysis for primary efficacy analysis
Kelley, ID Week, 2024

25


PURPOSE 1: Zero HIV Infections in Cisgender Women Receiving LEN
PURPOSE 2: Two HIV Infections in Participants Receiving LEN
100% efficacy c/w background; F/TDF F/TAF, no efficacy c/w background
96% efficacy c/w background 89% efficacy c/w F/TDF
HIV Incidence per 100 PY (95% CI)
2.41
0
2.02
1.69
Background HIV Incidence
LEN 0 Infections 1939 PY
F/TAF 19 Infections 1932 PY
F/TDF 16 Infections 949 PY
Median follow-up duration: 44.0 weeks
2.37
0.10
0.93
Background HIV Incidence
LEN 2 Infections 1938 PY
F/TDF 9 Infections 967 PY
Median follow-up duration: 39.4 weeks
Slide 26
Bekker, NEJM 2024; Kelley, NEJM 2024

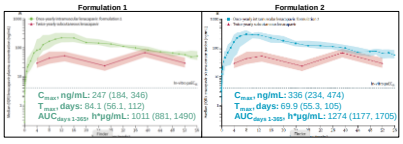
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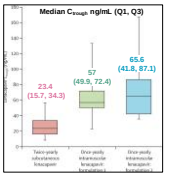

ADVERSE REACTION TO SUBCUTANEOUS LEN
1a
1b
1c
1a. 4.5 cm non-fluctuant nodule w/ dense overlying erythema
1b. Nodule still visible 6 months post- injection
1c. Biopsy 4 months post-injection showing FBR
2a
2a. Injection site ulceration from movement during injection
Slide 29

29

PHARMACOKINETICS: ONCE-YEARLY FORMULATIONS OF LENACAPAVIR

- **Open-label, Phase 1 study evaluating the PK, safety, and tolerability of a single 5000 mg IM dose of two free-acid LEN formulations**
  - Formulation 1: (5% EtOH; n = 20)
  - Formulation 2: (10% EtOH; n = 20)
- **Study drug dosing:** Two 5-mL IM gluteal injections





Singh R et al. CROI. 2025. Abstract #154
Jogiraju, Vamshi et al. The Lancet. 2025.

Slide 30

30

SAFETY: ONCE-YEARLY FORMULATIONS OF LENACAPAVIR

	Lenacapavir formulation 1 (N=20)	Lenacapavir formulation 2 (N=20)
Any TEAE	18 (90%)	16 (80%)
Adverse events occurring in ≥10% of participants in a cohort		
Diarrhoea	2 (10%)	0
Injection-site pain	16 (80%)	15 (75%)
Injection-site bruising	2 (10%)	1 (5%)
Injection-site swelling	4 (20%)	0
Gait disturbance	0	4 (20%)*
Feeling hot	0	2 (10%)
Headache	0	5 (25%)
Dizziness	0	2 (10%)
Study drug-related TEAEs	17 (85%)	16 (80%)
Any grade ≥3 TEAEs	0	2 (10%)
Study drug-related grade ≥3 TEAEs	0	1 (5%)†
Any serious TEAEs	0	1 (5%)
Study drug-related serious TEAEs	0	0
Death	0	0
Grade ≥3 laboratory abnormalities	6 (30%)‡	3 (15%)§



Singh R et al. CROI. 2025. Abstract #154.
Jogiraju, Vamshi et al. The Lancet. 2025.

Slide 31

31

SAFETY: ONCE-YEARLY FORMULATIONS OF LENACAPAVIR


ENDPOINTSNEWS

Gilead plans to skip from Phase 1 to Phase 3 with once-yearly HIV prevention drug

Lei Lei Wu
News Reporter

Gilead said two experimental once-a-year versions of its HIV prevention shot lenacapavir passed muster in an early-stage study with a small group of healthy partici-

Slide 32

32

THE FUTURE OF PREP

Slide 33

33

ISLATRAVIR (MK-8591)

First-in-Class HIV Nucleoside RT Translocation Inhibitor (NRTTI)



In wake of safety scare, Merck scraps monthly PrEP plans for lead HIV drug — while marching ahead with revised clinical plans

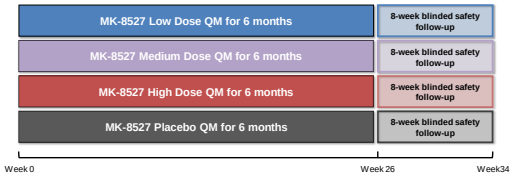
"after careful evaluation and analysis, Merck will discontinue the development of once-monthly oral islatravir for PrEP. A Phase 1b study in adults with HIV-1 infection assessing MK-8527, a novel NRTTI candidate, will commence shortly** (NCT05494736). Merck will continue to engage with key stakeholders as it works to help address the unmet need in HIV prevention."

Slide 34

34

MK-8527: Novel NRTTI

Ongoing Phase 2a, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Oral MK-8527 Once Monthly in Participants at Low-Risk for HIV-1 Infection



To be presented at CROI 2025
Phase 3 to follow

https://clinicaltrials.gov/study/NCT06045507

Slide 35

35

HOW EFFECTIVE DOES A PRODUCT NEED TO BE?



- Flexible silicone vaginal ring
- Woman-initiated
  - Self-inserted
  - Discreet
- Slowly releases ARVs
- Dapivirine (NNRTI) monthly ring reduced women's HIV-1 risk by ~30% in two Phase III trials
- Data from open-label studies show greater use and suggest ~50-60% risk reduction
- **EMA regulatory approval**
- **No US regulatory approval**
- New formulations with a variety of products including MPT in development

Nel A et al. NEJM 2016
Baeten J et al. NEJM 2016
Baeten J et al. Lancet HIV 2021
Nel A et al. Lancet 2021

Slide 36

36

ANTIBODY MEDIATED PREVENTION TRIALS

Broadly Neutralizing Monoclonal Antibodies for HIV Prevention

Phase 2b, proof-of-concept studies in persons at high-risk for HIV infection

- HVTN 704/HPTN 085 (n=2699): MSM/transgender persons
- HVTN 703/HPTN 081 (n=1924): women at high risk for HIV infection

Randomized groups

- VRC01 low/high IV dose (10/30 mg/kg) or placebo q8 weeks

VRC01 did not prevent overall HIV acquisition more effectively than placebo

	HIV Incidence (per 100 person-years)	VRC01 Prevention Efficacy (%)
HVTN 704/HPTN 085		
Pooled VRC01	2.35	27
Placebo	2.98	
HVTN 703/HPTN 081		
Pooled VRC01	2.49	9
Placebo	3.10	
Persons with VRC01-sensitive isolates		
Pooled VRC01	0.20	75
Placebo	0.86	

Corey L, et al. NEJM. 2021.

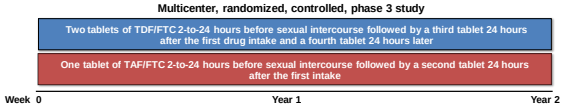
Slide 37

37

ANRS 0029s

Event-Driven TAF/FTC for PrEP

Multicenter, randomized, controlled, phase 3 study



- Evaluate the efficacy, acceptability, and safety of a simplified event-driven pre-exposure prophylaxis of HIV based on oral TAF/FTC
- Up to 524 individuals without HIV-1, aged 18+, MSM
- Enrollment sites in the France and Thailand

Slide 38

38

INSERTS, PATCHES & INJECTABLES

What I am excited about, and why you should be, too

TAF/ELV Insert



Microneedle Array Patches



ULA LEN



ULA CAB



STAY TUNED

Slide 39

39

Thank you!

Questions?
rlandovitz@mednet.ucla.edu

Slide 40

40

Q and A Session



41