One Pill a Day?

Alternative Approaches for Pre-Exposure Prophylaxis

AETC AIDS Education & Training Center Program Southeast

NCHTEC
North Carolina HIV Training & Education Center at the UNC School of Medicine

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The views expressed are not necessarily those of HRSA or NIH.

Objectives

- Name the currently available options for pre-exposure prophylaxis (PrEP) in the United States.
- Outline the pre-clinical and clinical trials data supporting “on demand” PrEP.
- Identify candidates for on-demand PrEP according to current US guidance.
- Describe data behind the long-acting, injectable form of PrEP and when it is likely to be approved.

USPSTF recommends PrEP, June 2019

U.S. Preventive Services TASK FORCE

Final Recommendation Statement

Prevention of Human Immunodeficiency Virus (HIV) Infection: Preexposure Prophylaxis

June 11, 2019

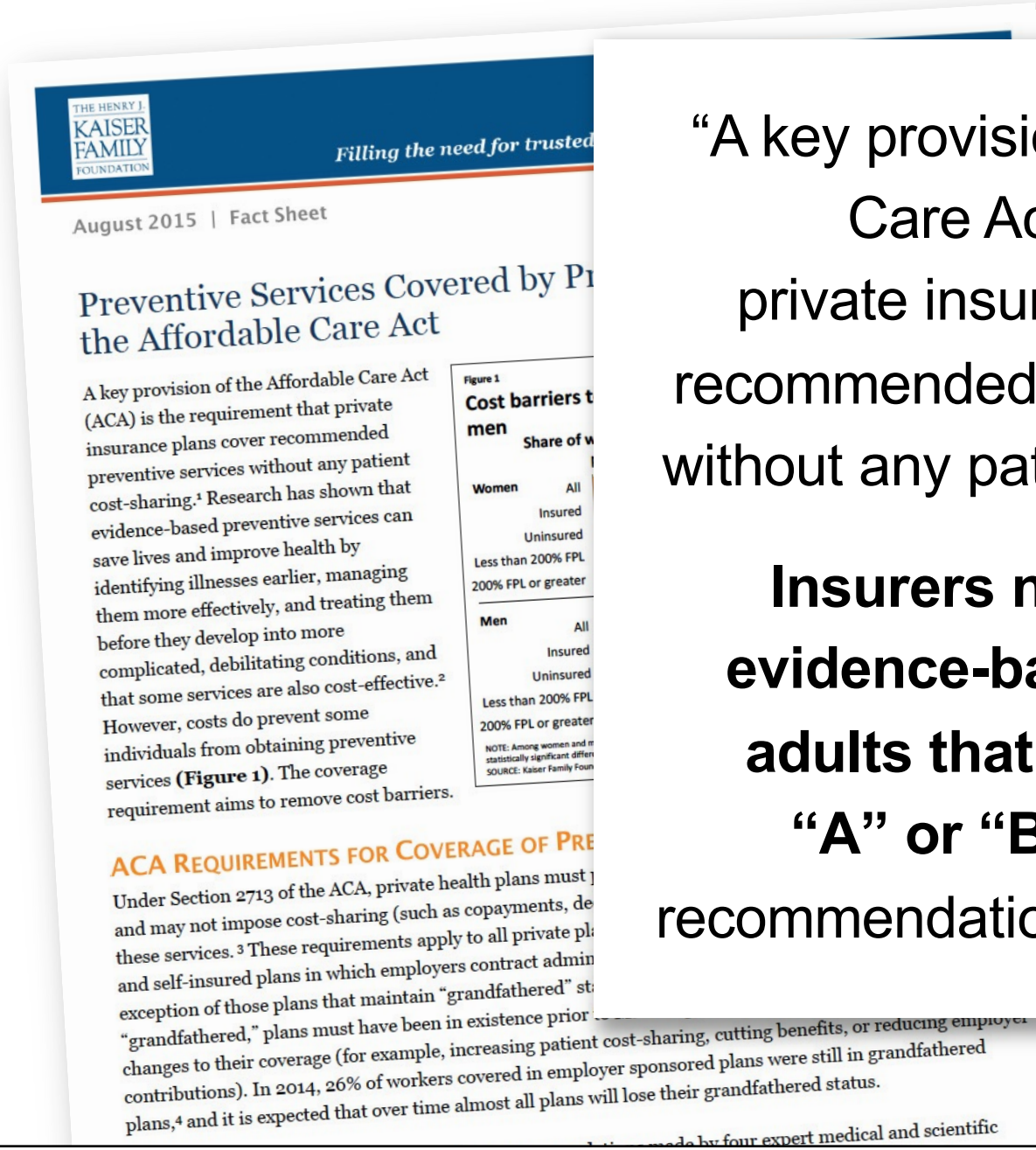
Recommendations made by the USPSTF are independent of the U.S. government. They should not be construed as an official position of the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Recommendation Summary

Population	Recommendation	Grade
Persons at high risk of HIV acquisition	The USPSTF recommends that clinicians offer preexposure prophylaxis (PrEP) with effective antiretroviral therapy to persons who are at high risk of HIV acquisition. See the Clinical Considerations section for information about identification of persons at high risk and selection of effective antiretroviral therapy.	A

https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/prevention-of-human-immunodeficiency-virus-hiv-infection-pre-exposure-prophylaxis

What impact does USPSTF have on costs?


THE HENRY J. KAISER FAMILY FOUNDATION

Filling the need for trusted

August 2015 | Fact Sheet

Preventive Services Covered by Pr… the Affordable Care Act

A key provision of the Affordable Care Act (ACA) is the requirement that private insurance plans cover recommended preventive services without any patient cost-sharing.[1] Research has shown that evidence-based preventive services can save lives and improve health by identifying illnesses earlier, managing them more effectively, and treating them before they develop into more complicated, debilitating conditions, and that some services are also cost-effective.[2] However, costs do prevent some individuals from obtaining preventive services **(Figure 1)**. The coverage requirement aims to remove cost barriers.

Figure 1

Cost barriers t… men

Share of w…

Women	All
	Insured
	Uninsured
Less than 200% FPL	
200% FPL or greater	
Men	All
	Insured
	Uninsured
Less than 200% FPL	
200% FPL or greater	

NOTE: Among women and m… statistically significant differ…
SOURCE: Kaiser Family Foun…

ACA Requirements for Coverage of Pre…

Under Section 2713 of the ACA, private health plans must … and may not impose cost-sharing (such as copayments, de… these services.[3] These requirements apply to all private pl… and self-insured plans in which employers contract admin… exception of those plans that maintain "grandfathered" st… "grandfathered," plans must have been in existence prior … changes to their coverage (for example, increasing patient cost-sharing, cutting benefits, or reducing employer contributions). In 2014, 26% of workers covered in employer sponsored plans were still in grandfathered plans,[4] and it is expected that over time almost all plans will lose their grandfathered status.

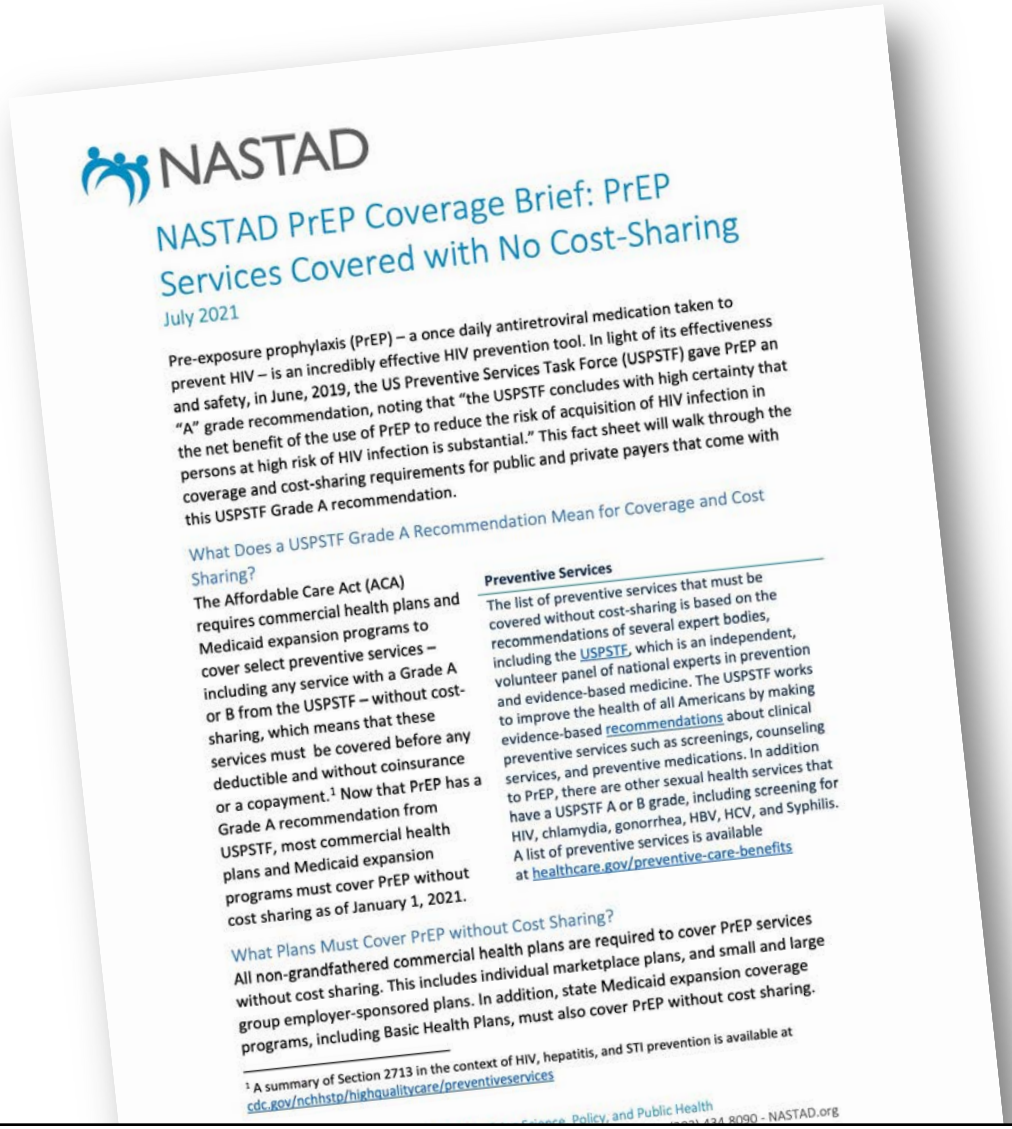
… made by four expert medical and scientific

"A key provision of the Affordable Care Act (ACA) is … private insurance plans cover recommended preventive services without any patient cost-sharing. …

Insurers now must cover evidence-based services for adults that have a rating of "A" or "B" in the current recommendations of the [USPSTF]"

The Biden admin removed ambiguity in July ’21

https://www.nastad.org/resource/nastad-prep-coverage-brief-prep-services-covered-no-cost-sharing



NASTAD

NASTAD PrEP Coverage Brief: PrEP Services Covered with No Cost-Sharing

July 2021

Pre-exposure prophylaxis (PrEP) – a once daily antiretroviral medication taken to prevent HIV – is an incredibly effective HIV prevention tool. In light of its effectiveness and safety, in June, 2019, the US Preventive Services Task Force (USPSTF) gave PrEP an "A" grade recommendation, noting that "the USPSTF concludes with high certainty that the net benefit of the use of PrEP to reduce the risk of acquisition of HIV infection in persons at high risk of HIV infection is substantial." This fact sheet will walk through the coverage and cost-sharing requirements for public and private payers that come with this USPSTF Grade A recommendation.

What Does a USPSTF Grade A Recommendation Mean for Coverage and Cost Sharing?

The Affordable Care Act (ACA) requires commercial health plans and Medicaid expansion programs to cover select preventive services – including any service with a Grade A or B from the USPSTF – without cost-sharing, which means that these services must be covered before any deductible and without coinsurance or a copayment.[1] Now that PrEP has a Grade A recommendation from USPSTF, most commercial health plans and Medicaid expansion programs must cover PrEP without cost sharing as of January 1, 2021.

Preventive Services

The list of preventive services that must be covered without cost-sharing is based on the recommendations of several expert bodies, including the USPSTF, which is an independent, volunteer panel of national experts in prevention and evidence-based medicine. The USPSTF works to improve the health of all Americans by making evidence-based recommendations about clinical preventive services such as screenings, counseling services, and preventive medications. In addition to PrEP, there are other sexual health services that have a USPSTF A or B grade, including screening for HIV, chlamydia, gonorrhea, HBV, HCV, and Syphilis. A list of preventive services is available at healthcare.gov/preventive-care-benefits

What Plans Must Cover PrEP without Cost Sharing?

All non-grandfathered commercial health plans are required to cover PrEP services without cost sharing. This includes individual marketplace plans, and small and large group employer-sponsored plans. In addition, state Medicaid expansion coverage programs, including Basic Health Plans, must also cover PrEP without cost sharing.

[1] A summary of Section 2713 in the context of HIV, hepatitis, and STI prevention is available at cdc.gov/nchhstp/highqualitycare/preventiveservices

Science, Policy, and Public Health

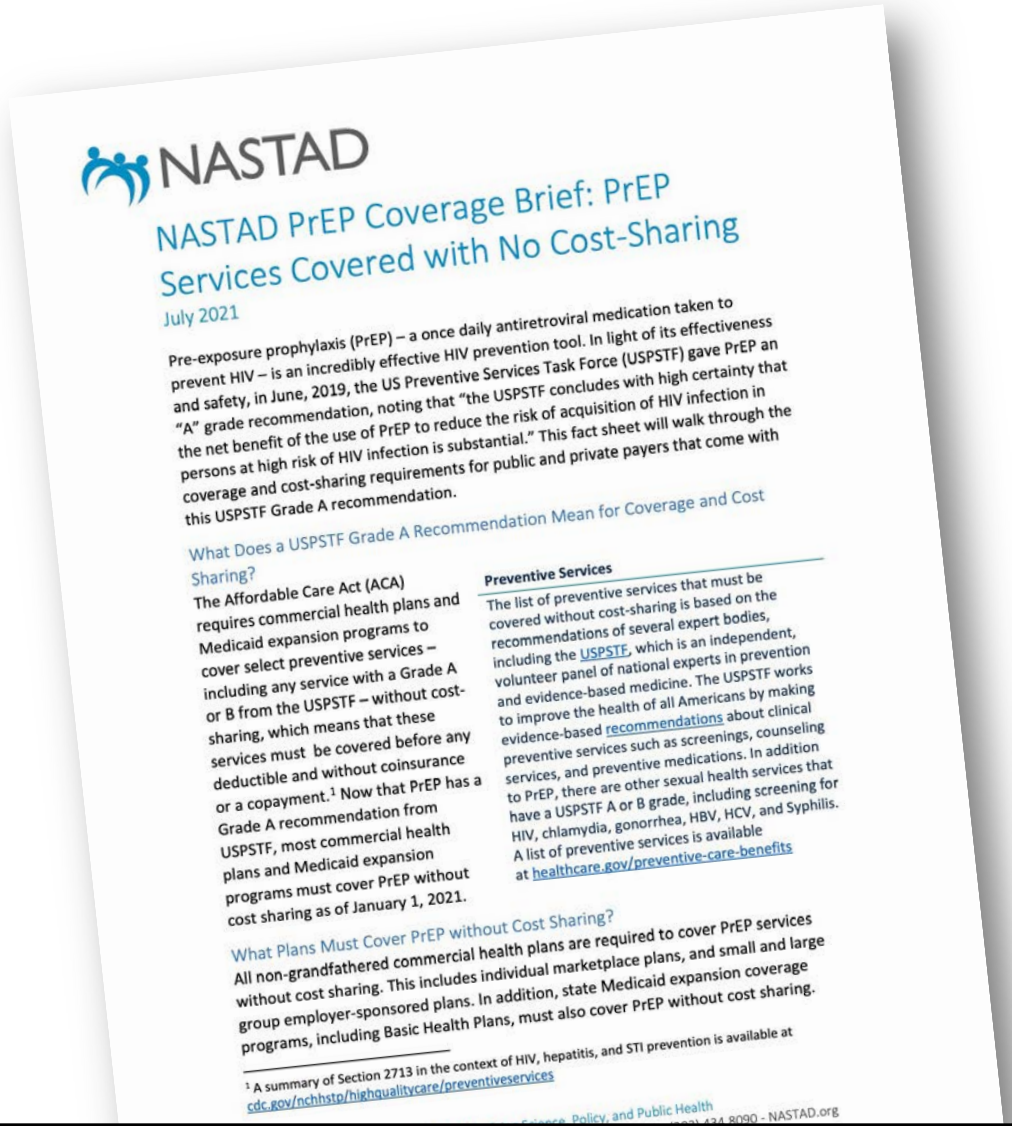
(202) 434-8090 - NASTAD.org

By <u>17 September 2021</u>, non-grandfathered health plans were required to cover PrEP <u>services</u> without cost-sharing (before deductible and without coinsurance or copayment).

- Marketplace plans
- Employer-sponsored plans
- Medicaid
- Medicare provider & lab services

PrEP is defined as the service, not the drug

https://www.nastad.org/resource/nastad-prep-coverage-brief-prep-services-covered-no-cost-sharing



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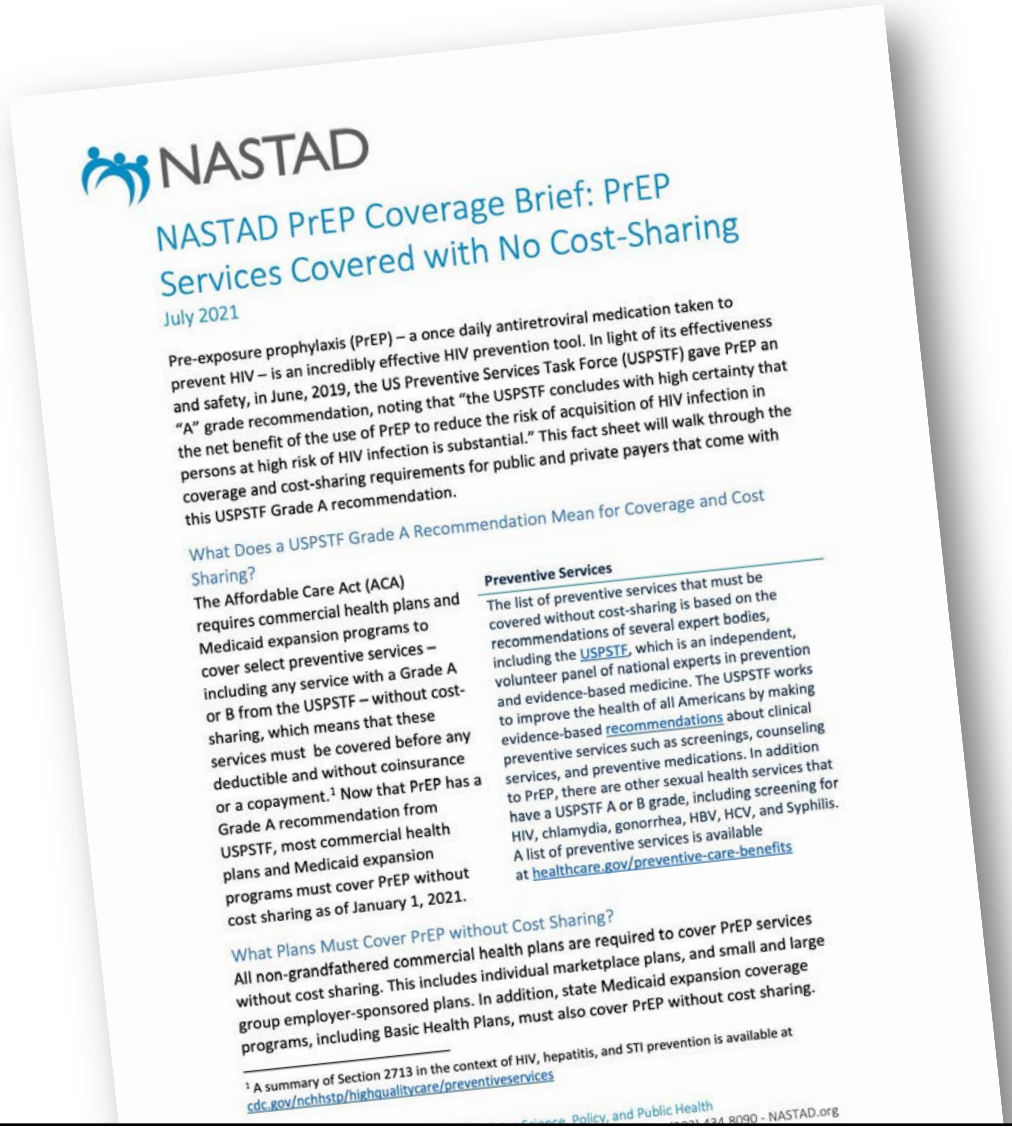
What's covered?

- HIV testing every 3 months
- Baseline hepatitis B screening
- Baseline and periodic hepatitis C screening
- Creatinine assessments
- Pregnancy testing
- STI screening from exposed anatomical sites
- Adherence counseling
- Medications approved for PrEP

One extra step is needed: modifier 33

https://www.nastad.org/resource/nastad-prep-coverage-brief-prep-services-covered-no-cost-sharing



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Just to be on the safe side, append modifier 33 to these encounters!

"When the primary purpose of the service is the delivery of an evidence-based service in accordance with a [USPSTF] A or B rating in effect and other preventive services identified in preventive services mandates … the service may be identified by adding 33 to the procedure."

Two approved options for <u>daily</u> use

Truvada[TDF]

emtricitabine / tenofovir disoproxil fumarate

Approved in 2012

<u>Proven</u> to protect people during:

Injection drug use
Insertive vaginal sex
Insertive anal sex (topping)
Receptive vaginal sex
Receptive anal sex (bottoming)

Descovy[TAF]

emtricitabine / tenofovir alafenamide fumarate

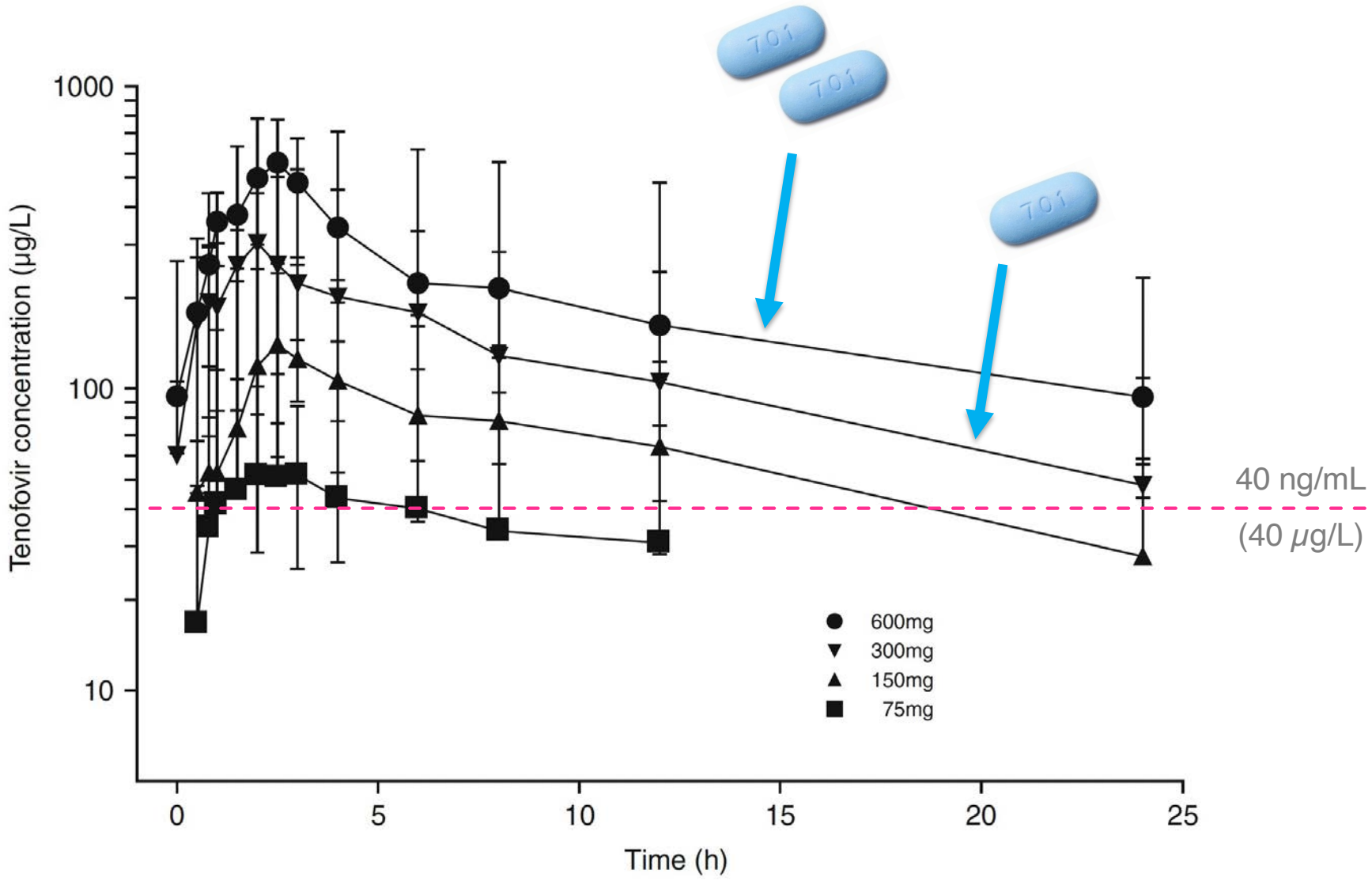
Approved in 2019

<u>Proven</u> to protect people during:

~~Injection drug use~~
~~Insertive vaginal sex~~
Insertive anal sex (topping)
~~Receptive vaginal sex~~
Receptive anal sex (bottoming)

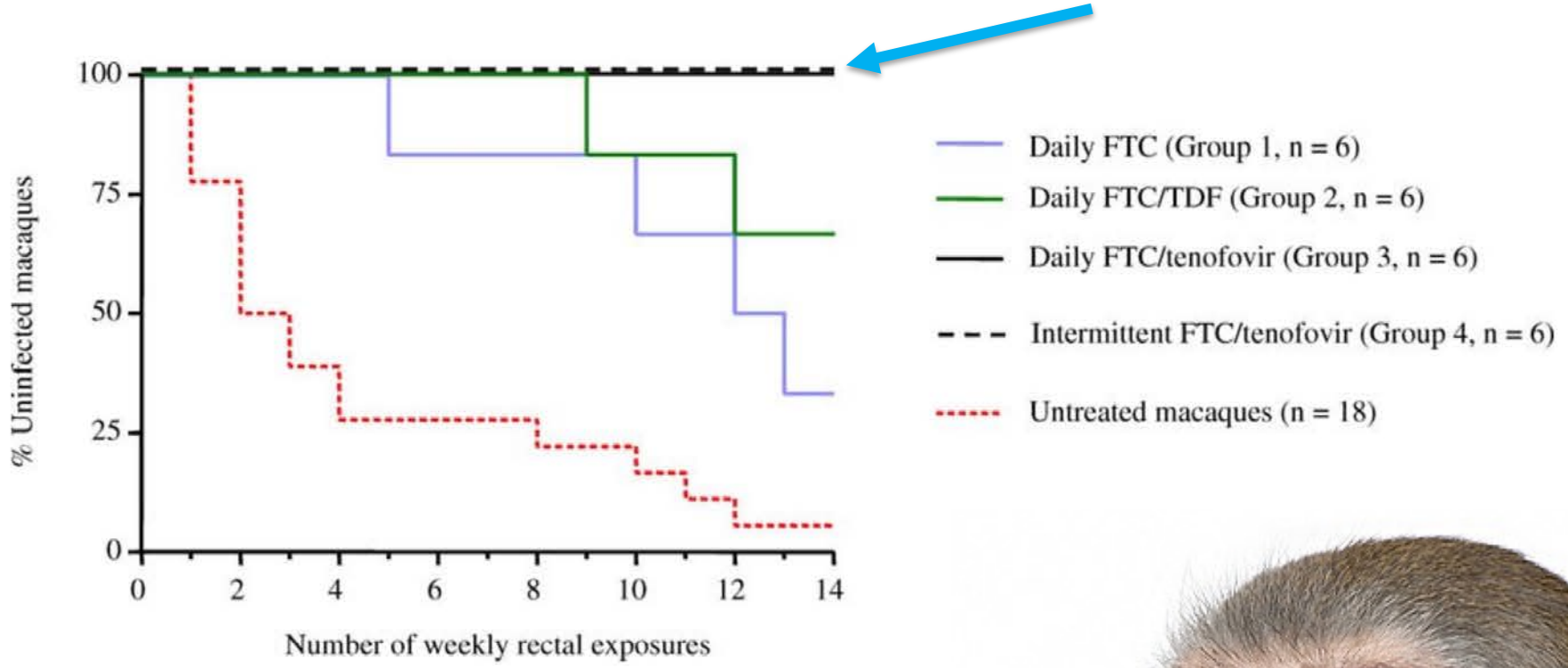
What's the evidence suggesting less frequent dosing could work?

Rapid rise to protective level, sustained over time



Conc'n published in → Barditch-Crovo P, at al. *Antimicrob Agents Chemother*. 2001;45(10):2733-2739
Figure from → Kearney BP, et al. *Clin Pharmacokinet*. 2004;43(9):595-612
40 ng/mL protective threshold from → Donnell D, et al. *JAIDS*. 2014;66(3):340-348

Rectal challenge studies showed promise



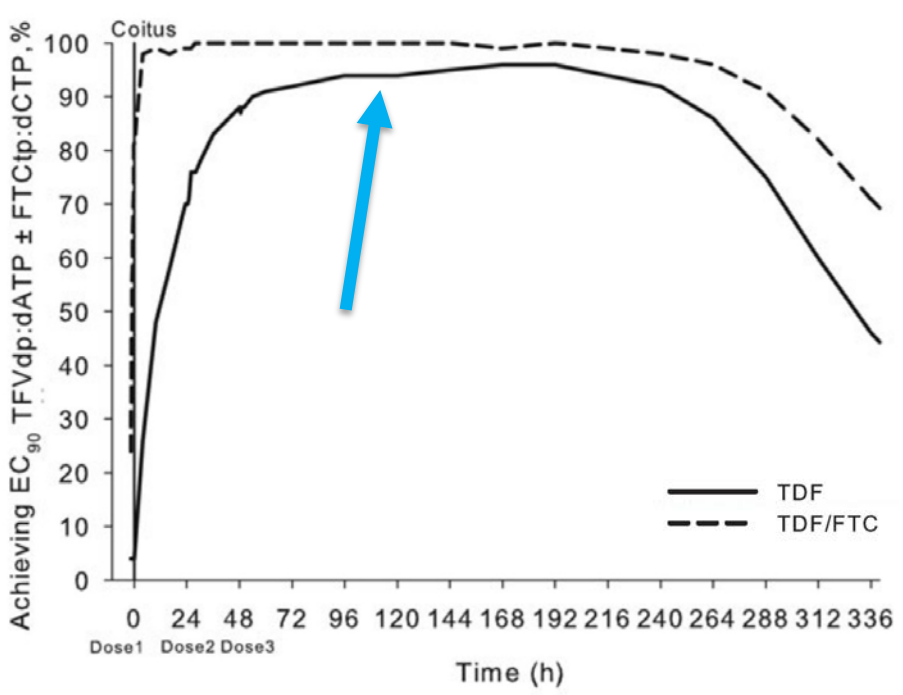
Intermittent = 2h before and 24h after each weekly virus challenge

García-Lerma JG, et al. PLoS Med. 2008;5(2):e28

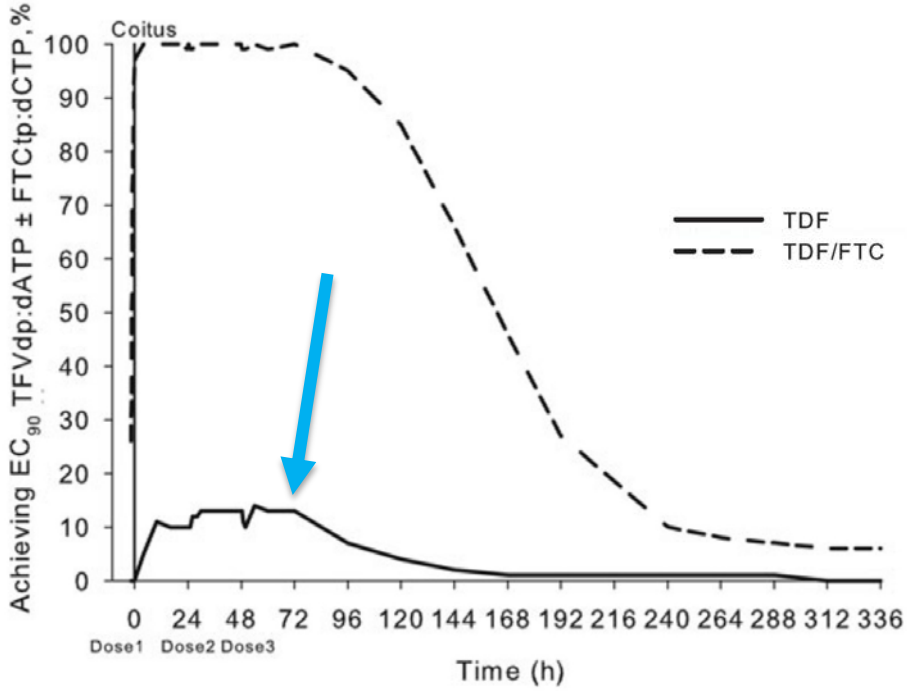
Protection differs markedly by tissue type

Two FTC/TDF tablets 2h before sex (600 mg TDF)
Third tablet 24h after first two
Fourth tablet 24h after third

Rectal tissue



Cervicovaginal tissue



Very promising for protection during anal sex, but not during vaginal sex

Cottrell ML, et al. *J Infect Dis*. 2016;214(1):55-64

ANRS IPERGAY

Montréal & multiple sites in France

ipergay
ANRS
Intervention Préventive
de l'Exposition aux Risques
avec et pour les Gays

Feb 2012 – Jan 2015

400

At-risk men
who have sex
with men

50%

On-Demand
Placebo
(n=201)

50%

On-Demand
FTC/TDF
(n=199)

35

median age at
study entry
(IQR 29-43)

8

median partners
in prior 2 months
(IQR 5-17)

10

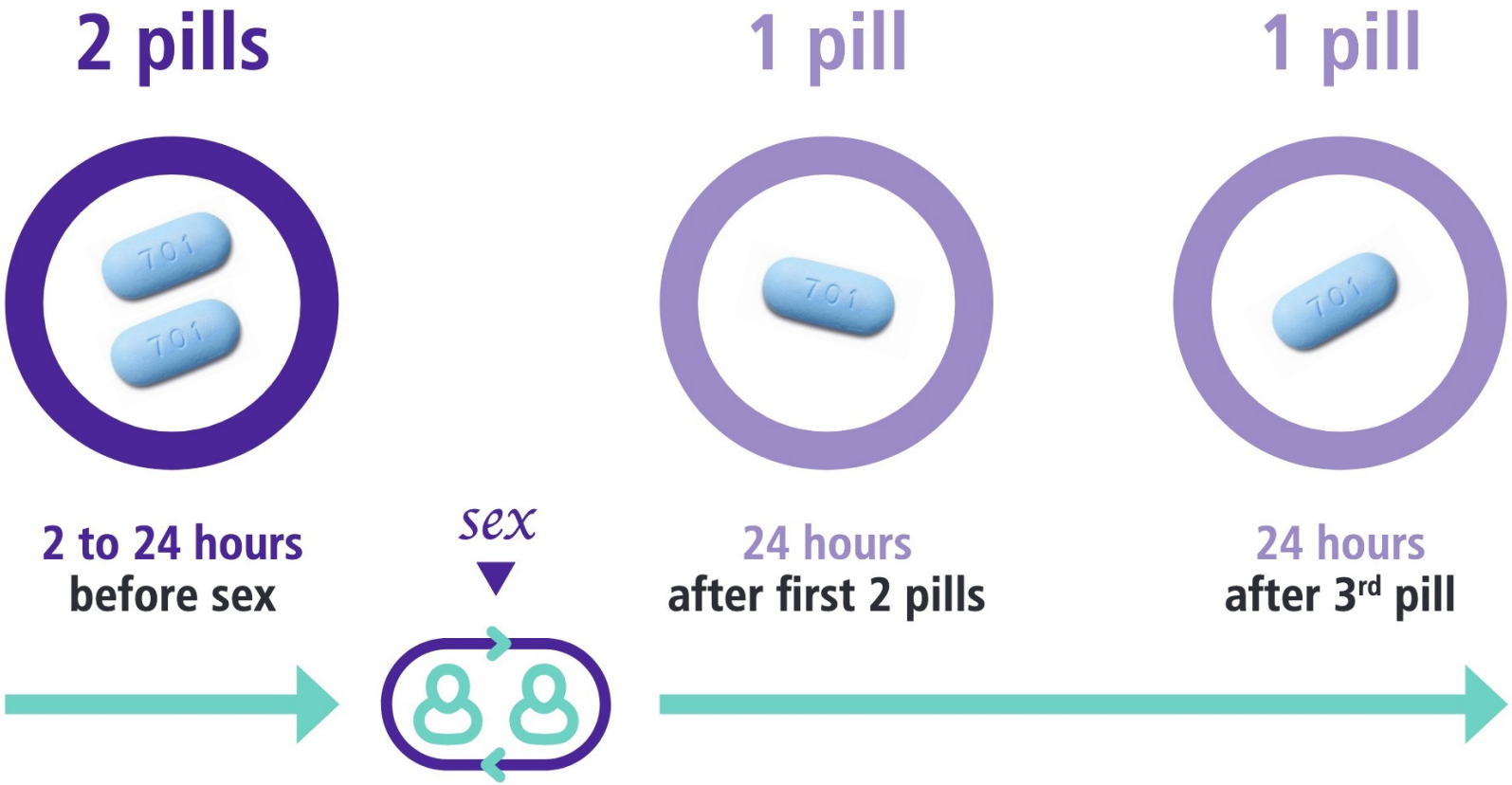
median episodes of
sex in prior 4 weeks
(IQR 6-18)

Molina JM, et al. N Engl J Med. 2015 Dec 3;373(23):2237-46

ANRS IPERGAY

On-demand oral **FTC/TDF versus placebo**

ipergay
ANRS
Intervention Préventive
de l'Exposition aux Risques
avec et pour les Gays



Molina JM, et al. *NEJM*. 2015;373(23):2237-46
Molina JM, et al. AIDS 2016, Durban, South Africa. Abstract WEAC0102
Graphic modified from https://www.who.int/hiv/pub/prep/211/en/

ANRS IPERGAY

Montréal & multiple sites in France

Study Phase	N	Total F/U (PY)	Median Pills/ Month	HIV Incidence / 100 PY		Risk Reduced (%)	*P*
				FTC/TDF	Placebo		
Placebo controlled RCT[1]	400	431.3	15	0.91	6.60	86	.002
Open-label extension[2]	361	518	18	0.19	6.60	97	NR

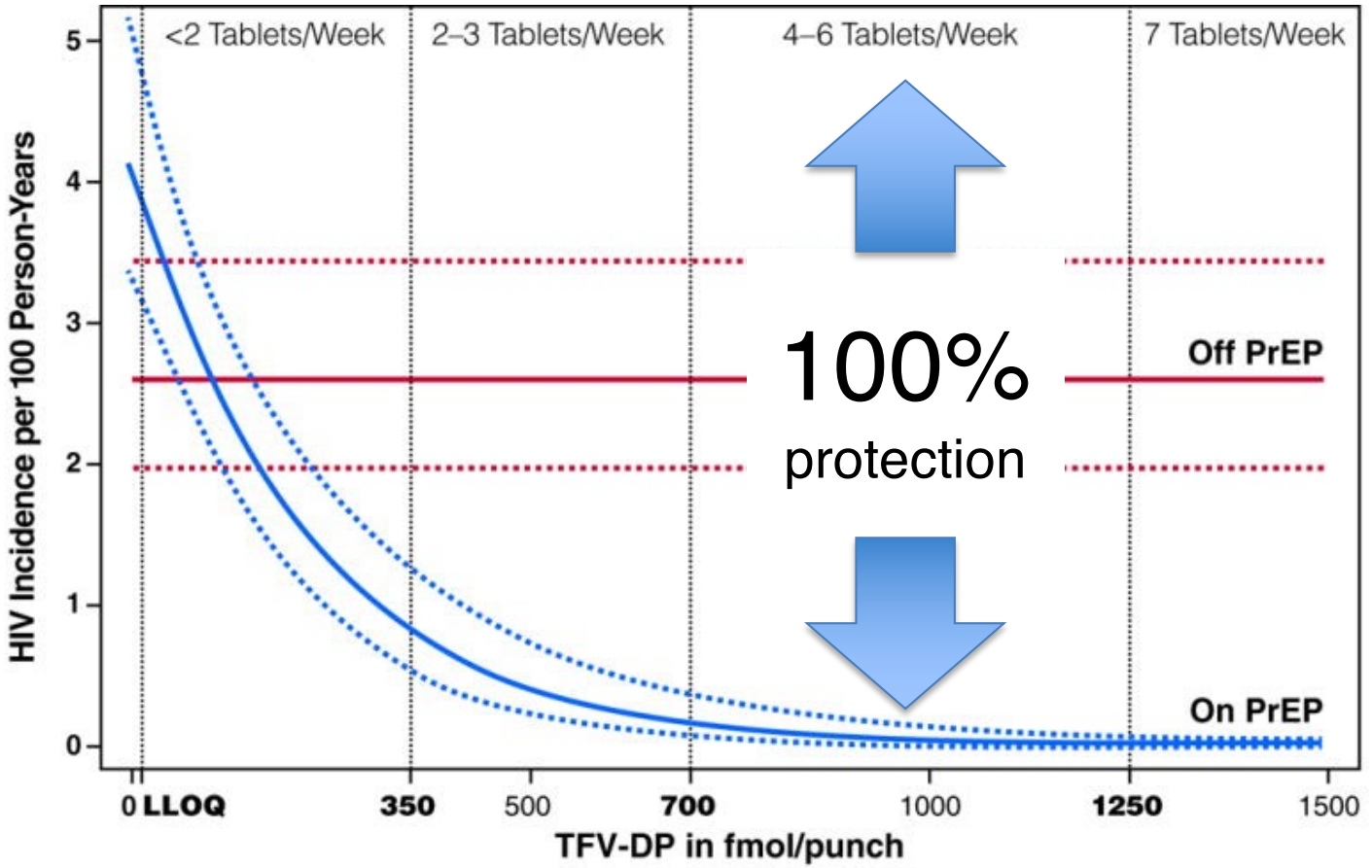
Adapted from slide by clinicaloptions.com

1. Molina JM, et al. N Engl J Med. 2015;373:2237-2246.
2. Molina JM, et al. Lancet HIV. 2017;4:e402-e410.
3. Antoni G, et al. Lancet HIV. 2020 Feb;7(2):e113-e120.

16 pills per month = 4 per week…

Post-hoc analysis from iPrEx OLE

June 2011 - June 2012



TFV-DP in DBS	(fmol/punch)	BLQ	LLOQ to <350	≥350 to <700	≥700 to <1250	≥1250
Estimated Dosing	(Tablets/Week)	None	<2	2–3	4–6	7
Follow-up	(% of Visits)	25%	26%	12%	21%	12%
HIV Infections		18	9	1	0	0
Person Years		384	399	179	316	181
HIV Incidence Rate	(95% CI)	**4.70** (2.99–7.76)	**2.25** (1.19–4.79)	**0.56** (0–2.50)	**0** (0–0.61)	**0** (0–1.06)

Grant RM, et al. *Lancet Inf Dis*. Sep 2014;14(9):820-9

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Montréal & multiple sites in France

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Placebo controlled RCT[1]	400	431.3	15	0.91	6.60	86	.002
Open-label extension[2]	361	518	18	0.19	6.60	97	NR
Substudy (men with less frequent sex)[3]	269	134	9.5	0	9.3	100	NR

Adapted from slide by clinicaloptions.com

1. Molina JM, et al. N Engl J Med. 2015;373:2237-2246.
2. Molina JM, et al. Lancet HIV. 2017;4:e402-e410.
3. Antoni G, et al. Lancet HIV. 2020 Feb;7(2):e113-e120.

ANRS Prévenir

Multicenter, open-label cohort study in Paris

May 2017 – Sept 2020

3067

At-risk persons
(target N = 3000)

98.5% MSM

51%

Daily
FTC/TDF
(n=1544; 8769 acts)

49%

On-Demand
FTC/TDF
(n=1515; 8507 acts)

3 **new HIV infections**
on daily PrEP arm
(all had stopped PrEP)

3 **new HIV infections**
on-demand arm
(all had stopped PrEP)

Molina JM, et al. CROI 2021. Abstract 148. http://www.croiwebcasts.org/p/2021croi/croi/148 https://www.natap.org/2021/CROI/croi_55.htm

2+1+1 with FTC/TDF* works for MSM…

"Event-driven" PrEP is appropriate for MSM who:

- have infrequent sex
- are able to plan for sex at least 2h in advance
- can delay sex for at least 2h [to allow for dosing]

* Truvada, NOT Descovy

There are NO EFFICACY DATA on Descovy for on-demand PrEP

https://www.who.int/hiv/pub/prep/211/en/

…and American HIV experts concur…

Clinical Review & Education

JAMA | Special Communication

Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults
2018 Recommendations of the International Antiviral Society-USA Panel

Michael S. Saag, MD; Constance A. Benson, MD; Rajesh T. Gandhi, MD; Jennifer F. Hoy, MBBS; Raphael J. Landovitz, MD; Michael J. Mugavero, MD, MHSc; Paul E. Sax, MD; Davey M. Smith, MD; Melanie A. Thompson, MD; Susan P. Buchbinder, MD; Carlos del Rio, MD; Joseph J. Eron Jr, MD; Gerd Fätkenheuer, MD; Huldrych F. Günthard, MD; Jean-Michel Molina, MD; Donna M. Jacobsen, BS; Paul A. Volberding, MD

IMPORTANCE Antiretroviral therapy (ART) is the cornerstone of prevention and management of HIV infection.

OBJECTIVE To evaluate new data and treatments and incorporate this information into updated recommendations for initiating therapy, monitoring individuals starting therapy, changing regimens, and preventing HIV infection for individuals at risk.

EVIDENCE REVIEW New evidence collected since the International Antiviral Society-USA 2016 recommendations via monthly PubMed and EMBASE literature searches up to April 2018; data presented at peer-reviewed scientific conferences. A volunteer panel of experts in HIV research and patient care considered these data and updated previous recommendations.

FINDINGS ART is recommended for virtually all HIV-infected individuals, as soon as possible after HIV diagnosis. Immediate initiation (eg, rapid start), if clinically appropriate, requires adequate staffing, specialized services, and careful selection of medical therapy. An integrase strand transfer inhibitor (InSTI) plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) is generally recommended for initial therapy, with unique patient circumstances (eg, concomitant diseases and conditions, potential for pregnancy, cost) guiding the treatment choice. CD4 cell count, HIV RNA level, genotype, and other laboratory tests for general health and co-infections are recommended at specified points before and during ART. If a regimen switch is indicated, treatment history, tolerability, adherence, and drug resistance history should first be assessed; 2 or 3 active drugs are recommended for a new regimen. HIV testing is recommended at least once for anyone who has ever been sexually active and more often for individuals at ongoing risk for infection. Preexposure prophylaxis with tenofovir disoproxil fumarate/emtricitabine and appropriate monitoring is recommended for individuals at risk for HIV.

CONCLUSIONS AND RELEVANCE Advances in HIV prevention and treatment with antiretroviral drugs continue to improve clinical management and outcomes for individuals at risk for and living with HIV.

Editorial page 347
Author Audio Interview
Related article page 327
Supplemental content
CME Quiz at jamanetwork.com/learning

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Michael S. Saag, MD, School of Medicine, University of Alabama at Birmingham, 845 19th St S, BBRB 256, Birmingham, AL 35294 (msaag@uabmc.edu).

"On-demand" PrEP is appropriate for MSM who:

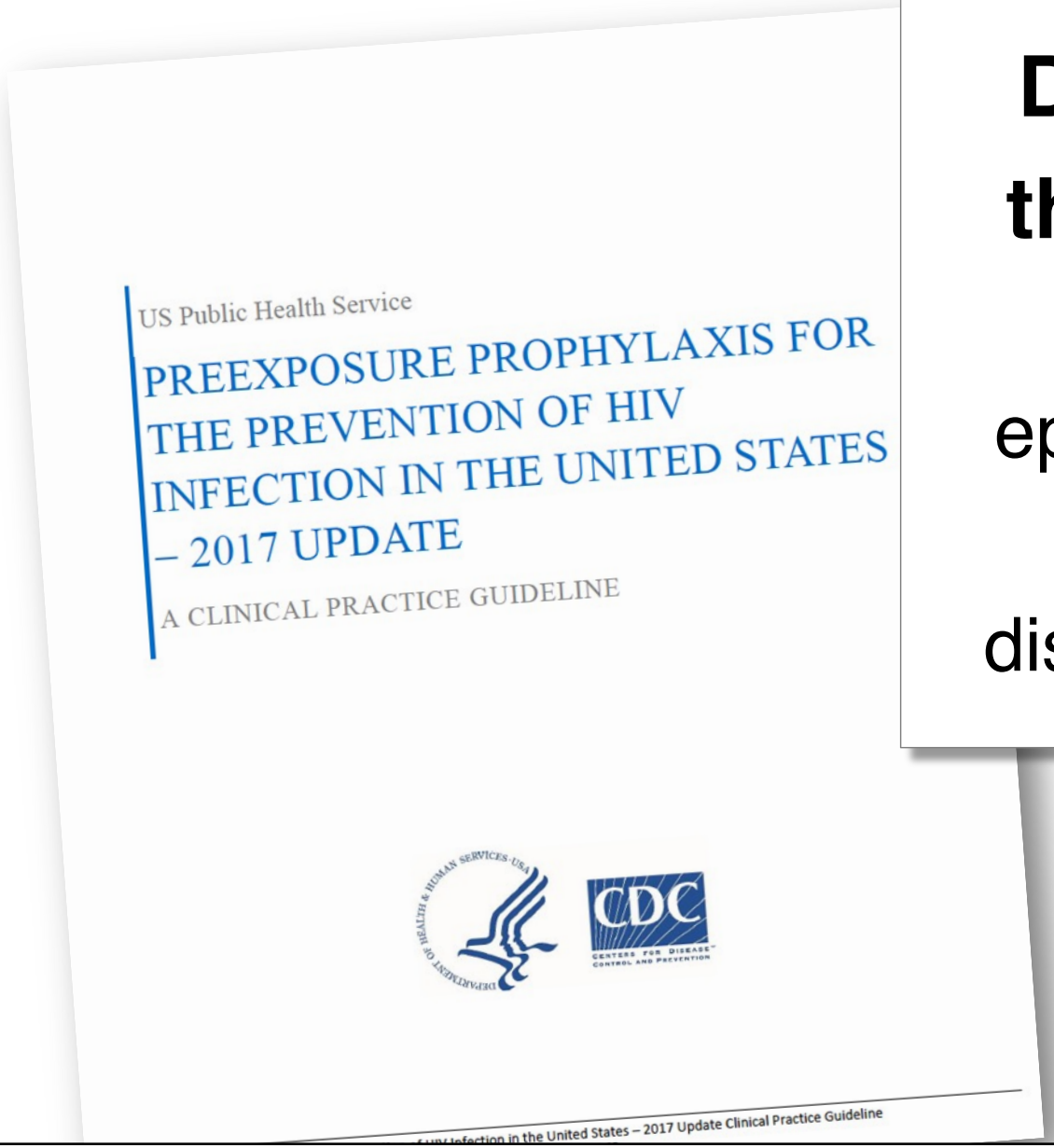
- have infrequent sex
- are able to plan for sex at least 2h in advance
- do NOT have active hepatitis B infection

* Truvada, NOT Descovy

There are NO EFFICACY DATA on Descovy for on-demand PrEP

Saag MS, et al. JAMA. 2018;320(4):379-96

…but it's NOT recommended in the US



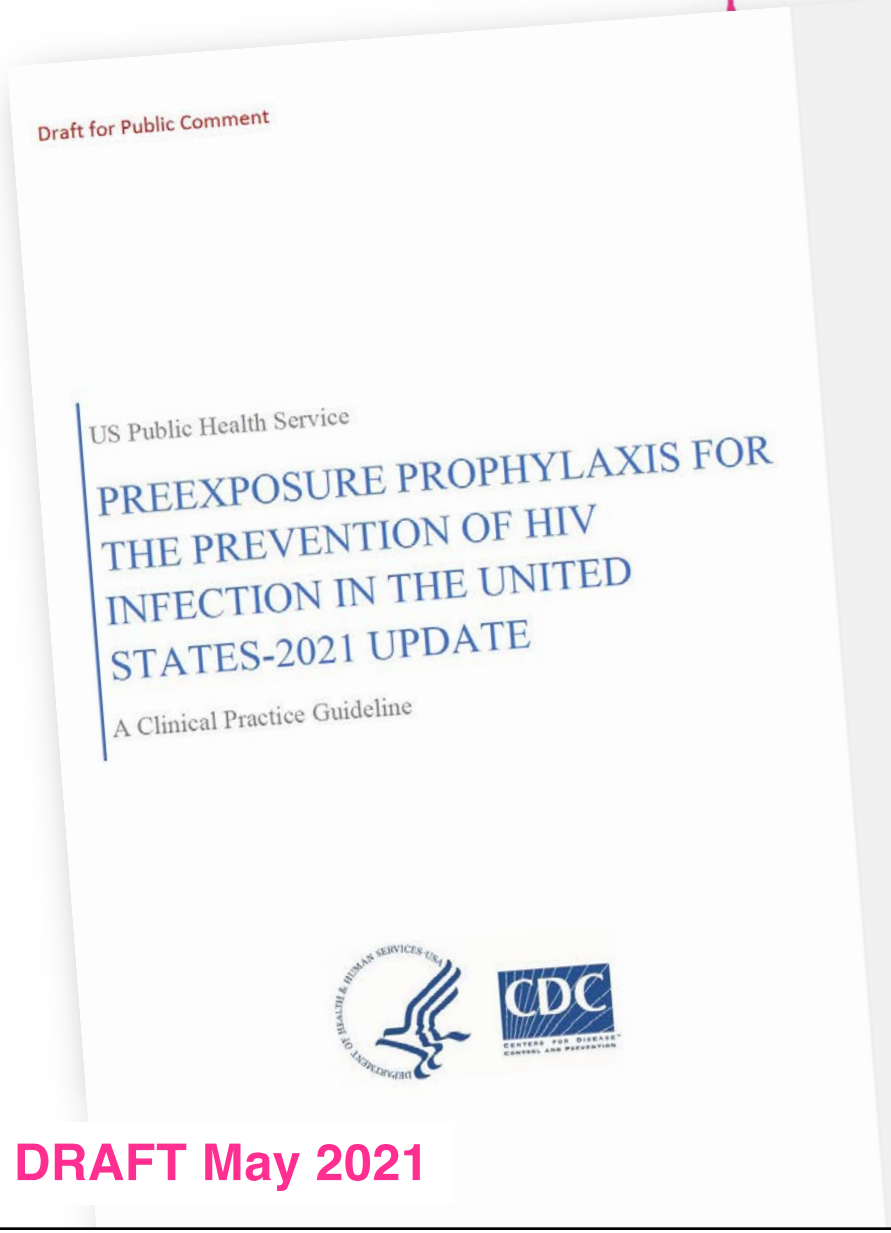
Do not use other than daily dosing

(e.g., intermittent, episodic [pre/post sex only], or other discontinuous dosing)

https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf

…but it's NOT recommended in the US

yet

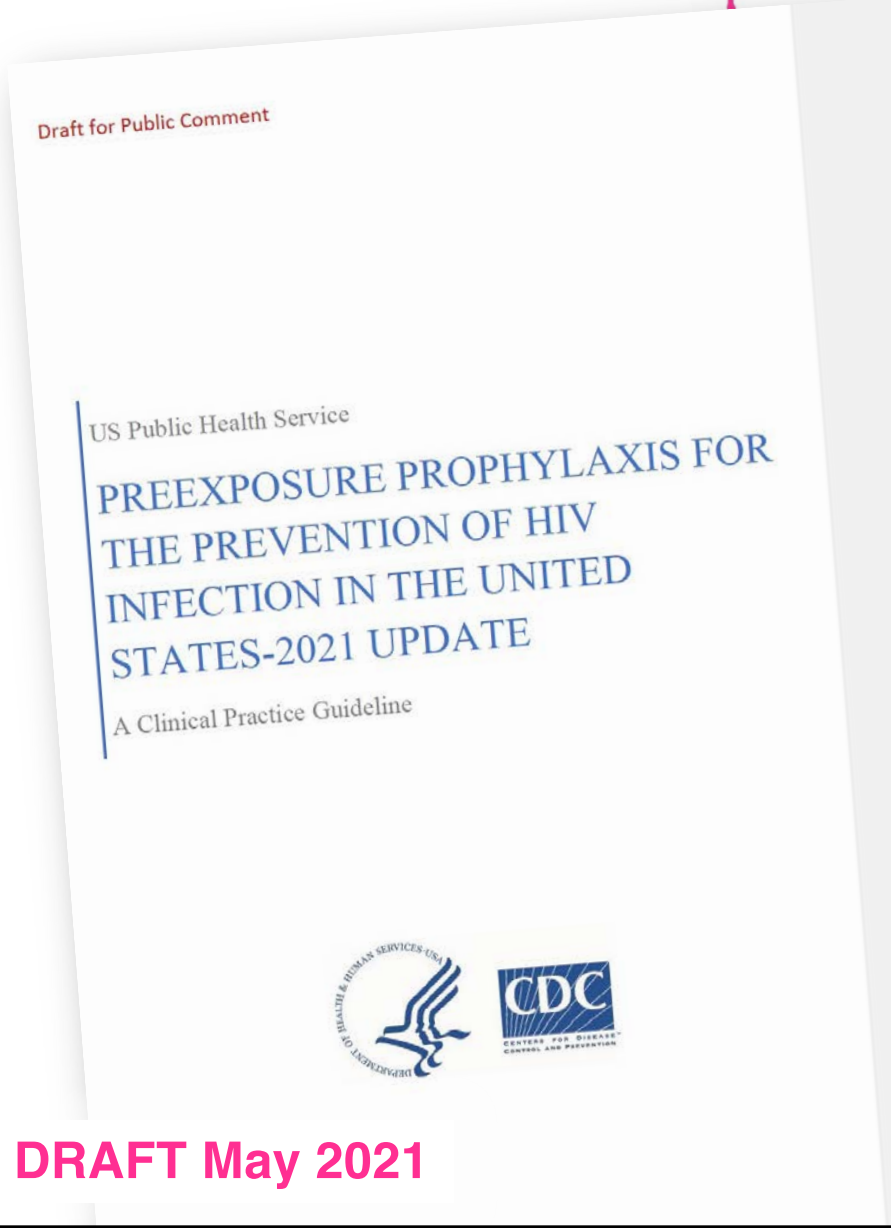


DRAFT May 2021

"While not an FDA-approved regimen… [IPERGAY & Prévenir studies demonstrated] the HIV prevention efficacy of 2-1-1 dosing only with F/TDF and only for MSM."

…but it's NOT recommended in the US

yet



DRAFT May 2021

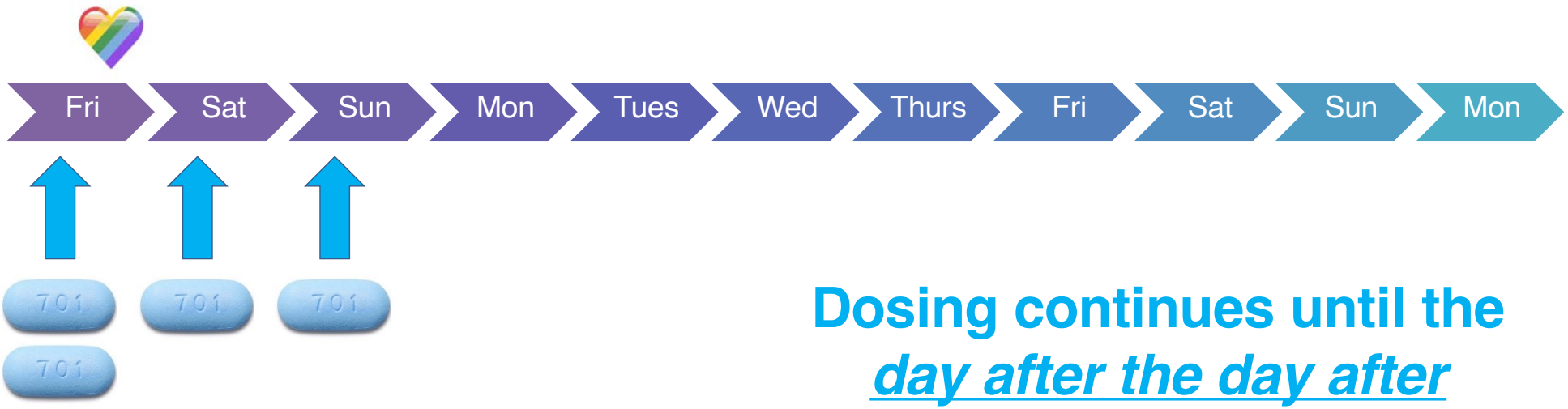
Guidance for off-label prescribing is provided for clinicians who choose to offer 2-1-1 with FTC/TDF to eligible MSM…

A big date on Friday night

Two FTC/TDF tablets 2-24h before sex

One FTC/TDF tablet 24h after first two tablets

One FTC/TDF tablet 48h after first two tablets



Dosing continues until the *day after the day after* the last "sex day"

Adapted from → Saberi, P., Scott, H.M. *J Gen Intern Med* 35, 1285–1288 (2020)

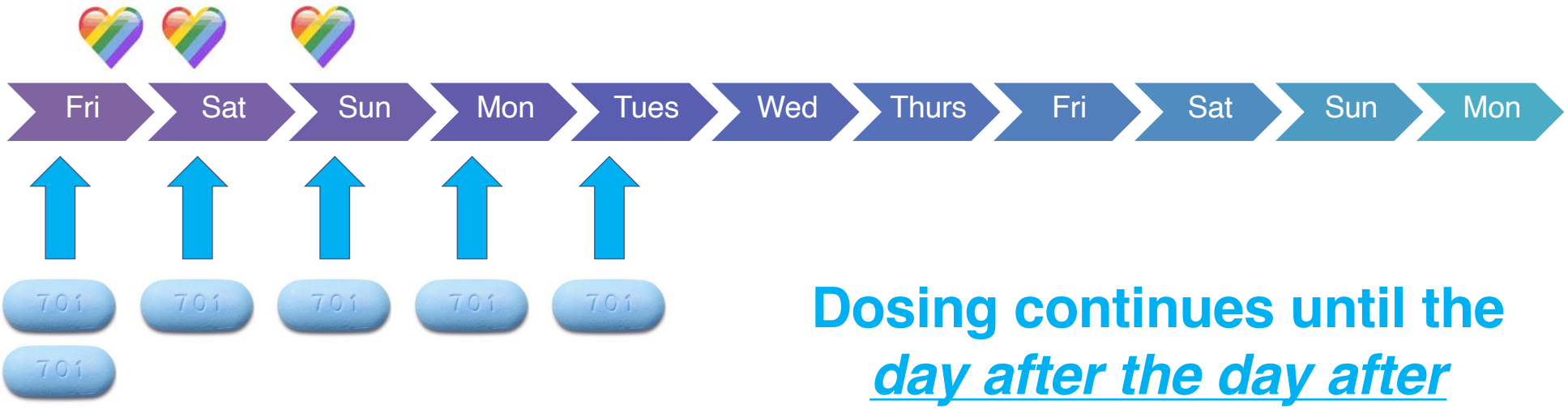
Things go really well Friday night

Two FTC/TDF tablets 2-24h before sex

One FTC/TDF tablet 24h after first two tablets

One FTC/TDF tablet 48h after first two tablets

Continue taking one tablet every 24h until until 2 days have passed since last "sex day"



Dosing continues until the *day after the day after* the last "sex day"

Adapted from → Saberi, P., Scott, H.M. *J Gen Intern Med* 35, 1285–1288 (2020)

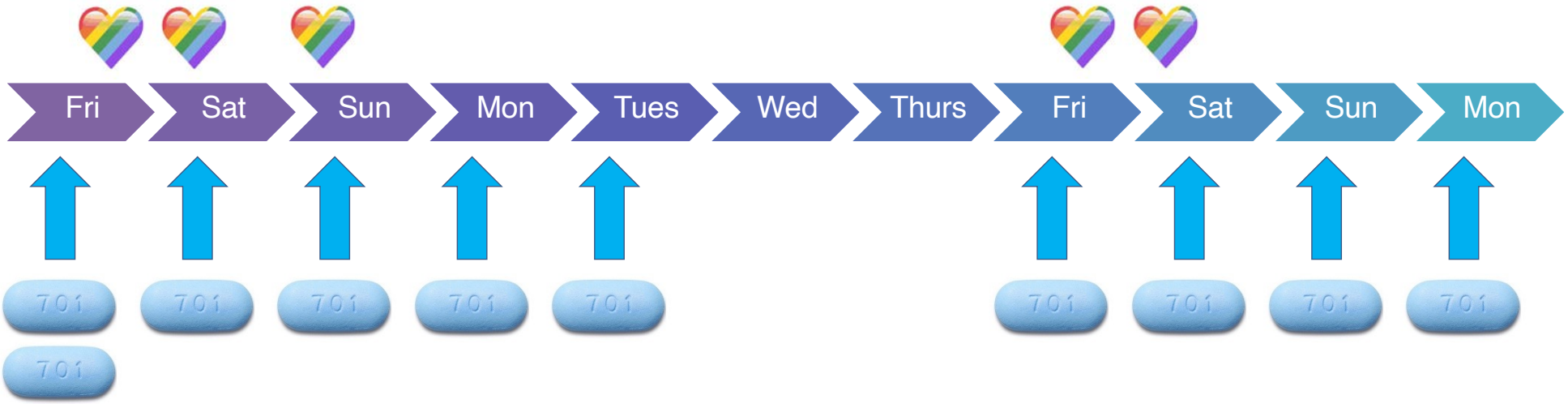
Less than 7d? One tab, not two!

Two FTC/TDF tablets 2-24h before sex

One FTC/TDF tablet 24h after first two tablets

One FTC/TDF tablet 48h after first two tablets

If less than 7 days elapse between end of one dosing period and start of next, ONE tablet to restart



Adapted from → Saberi, P., Scott, H.M. *J Gen Intern Med* 35, 1285–1288 (2020)

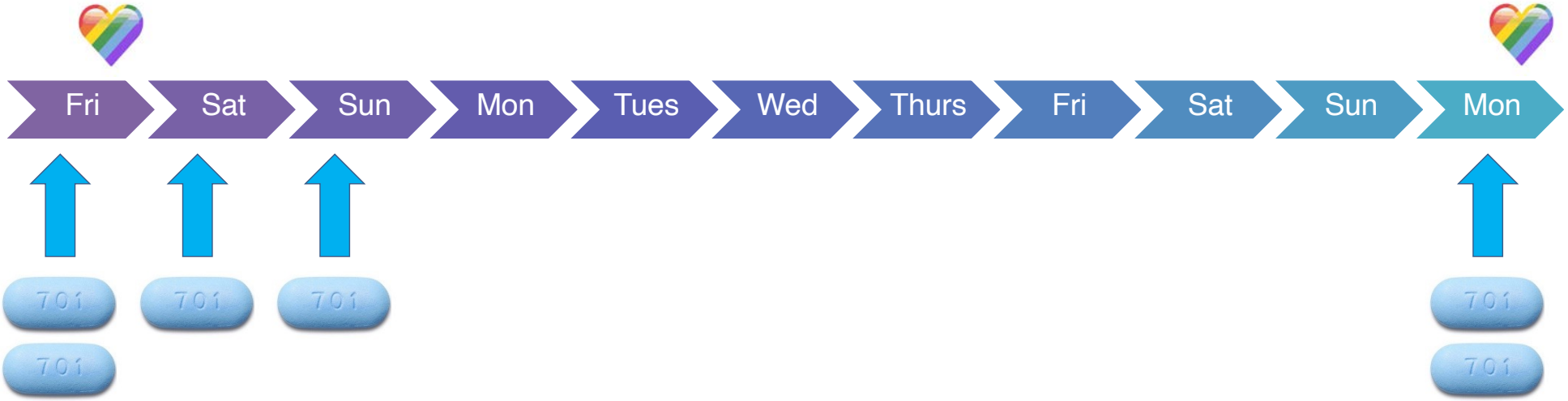
More than 7d? Start 2-1-1 over!

Two FTC/TDF tablets 2-24h before sex

One FTC/TDF tablet 24h after first two tablets

One FTC/TDF tablet 48h after first two tablets

If less than 7 days elapse between end of one dosing period and start of next, ONE tablet to restart

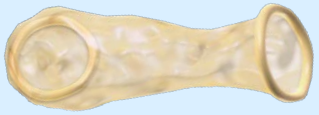
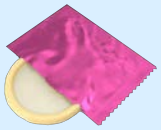
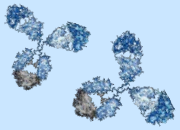
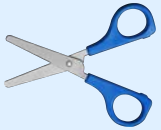


If more than 7 days elapse between end of one dosing period and start of next, TWO tablets to restart

Adapted from → Saberi, P., Scott, H.M. *J Gen Intern Med* 35, 1285–1288 (2020)

Summary

- Daily PrEP is the default for most patients.
- Pharmacologically, on-demand PrEP is only an option for protection during anal sex.
- On-demand PrEP is a viable option that is as effective as daily PrEP for MSM at risk.
- **ONLY FTC/TDF CAN BE USED FOR 2-1-1!**
  We have no data with FTC/TAF (Descovy).
- On-demand PrEP can get complicated fast.
  It's not bad to be selective with recommending it.

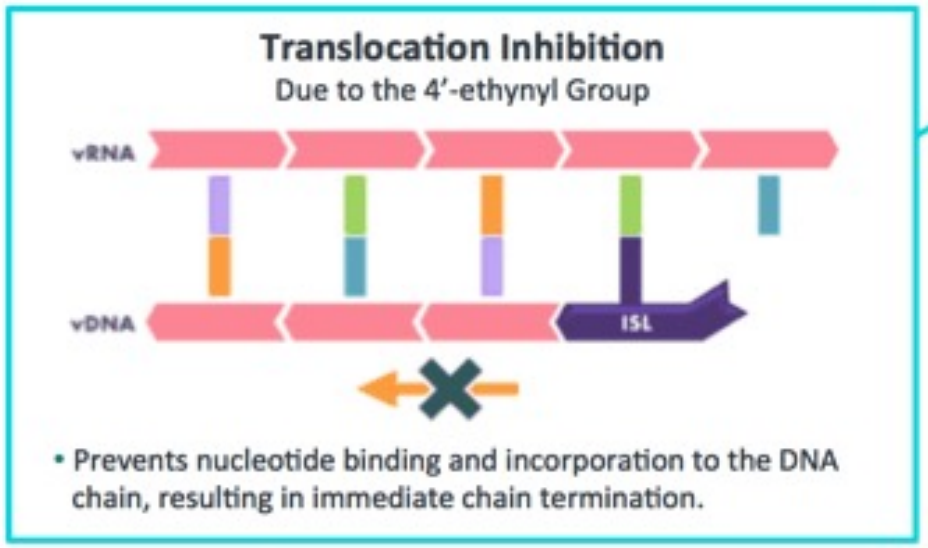
Pregnancy Prevention	HIV Prevention
Education & behavior modification	Education & behavior modification
Condoms 	 Condoms
Rings 	 Rings
Birth control pill & injection 	 PrEP (oral & injectable)
"Morning-after pill" 	 Post-exposure prophylaxis
Spermicide 	 Topical microbicides
Implantable birth control 	  Broadly neutralizing Abs Implantables
Vasectomy Tubal Ligation 	  U=U / TasP Vaccination

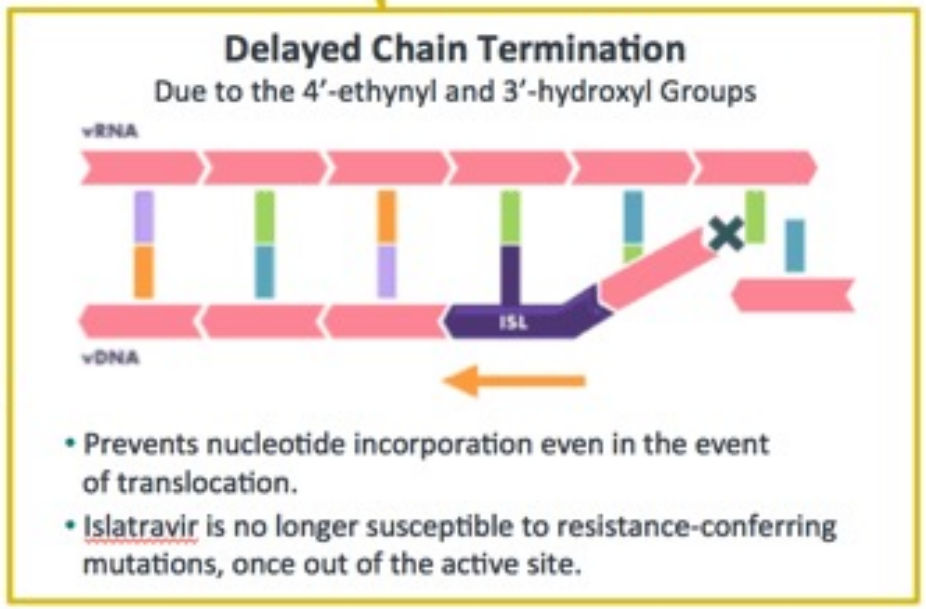
Adapted from HPTN

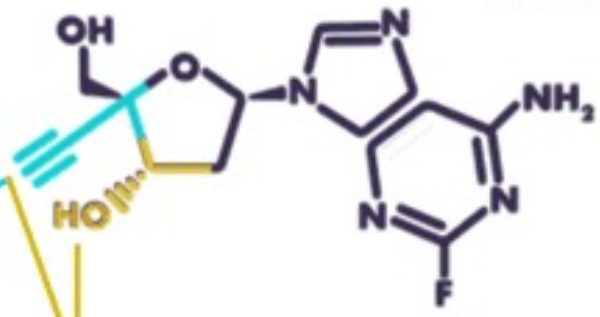
Islatravir

First-in-class nucleoside reverse transcriptase **translocation** inhibitor [NRTTI]
Formerly known as MK-8591 or EFdA

Two mechanisms of action



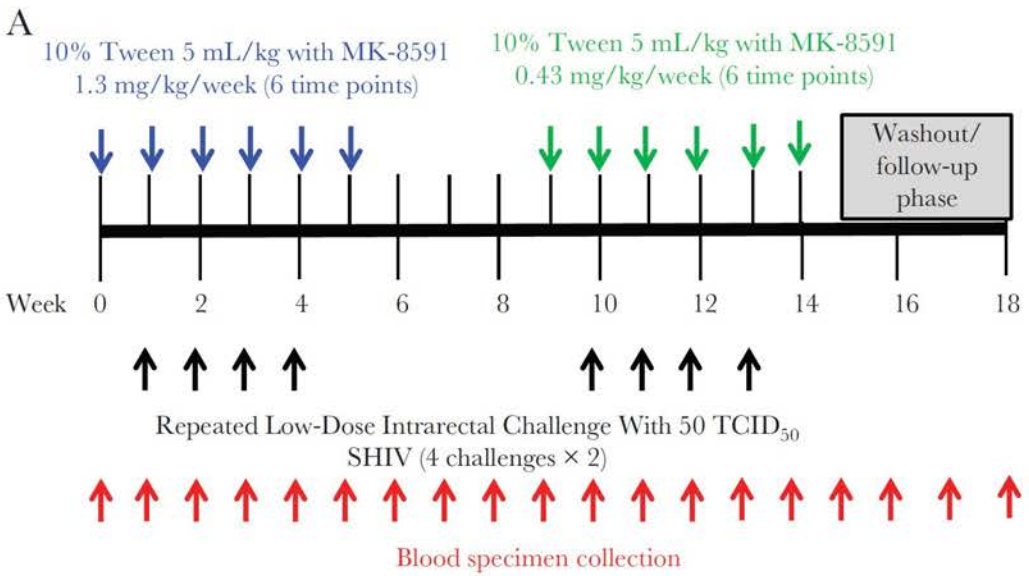


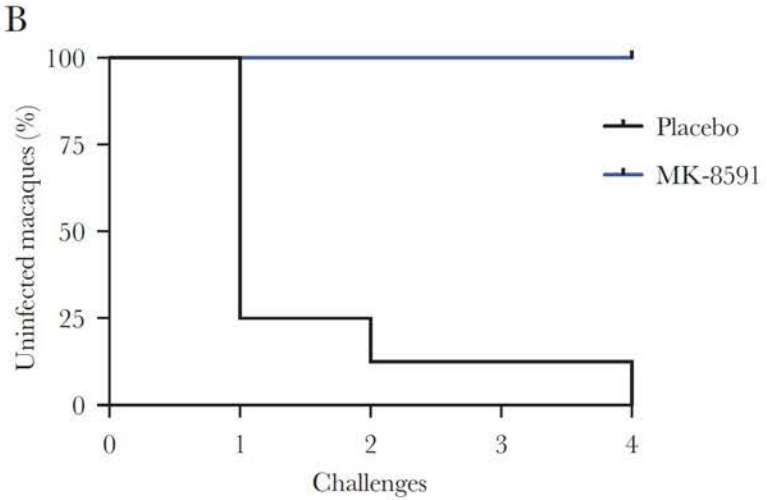


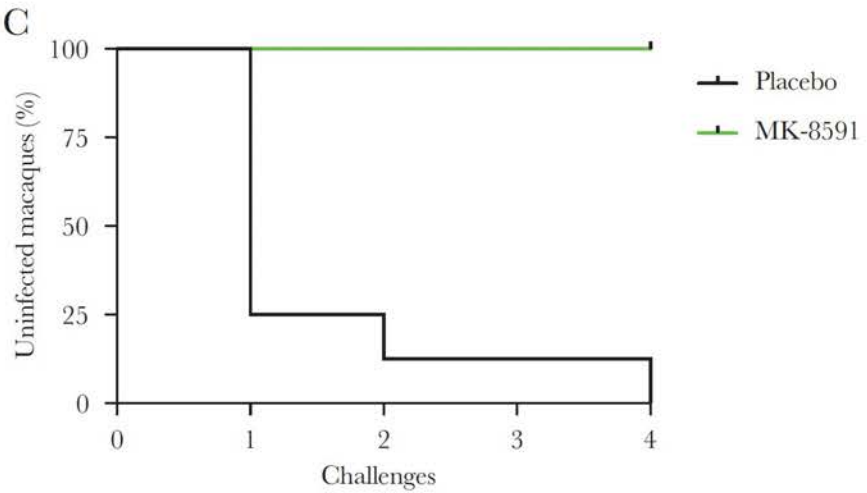
Essentially, it's "sticky" and once incorporated, it keeps the entire RT "machine" from ratcheting forward (strong interaction with dNTP binding site of RT)

https://www.natap.org/2019/EACS/EACS_81.htm
Markowitz M, Sarafianos SG. Curr Opin HIV AIDS. 2018;13(4):294-299 ← for more on the mechanism of action

Islatravir PO once <u>weekly</u> protects macaques

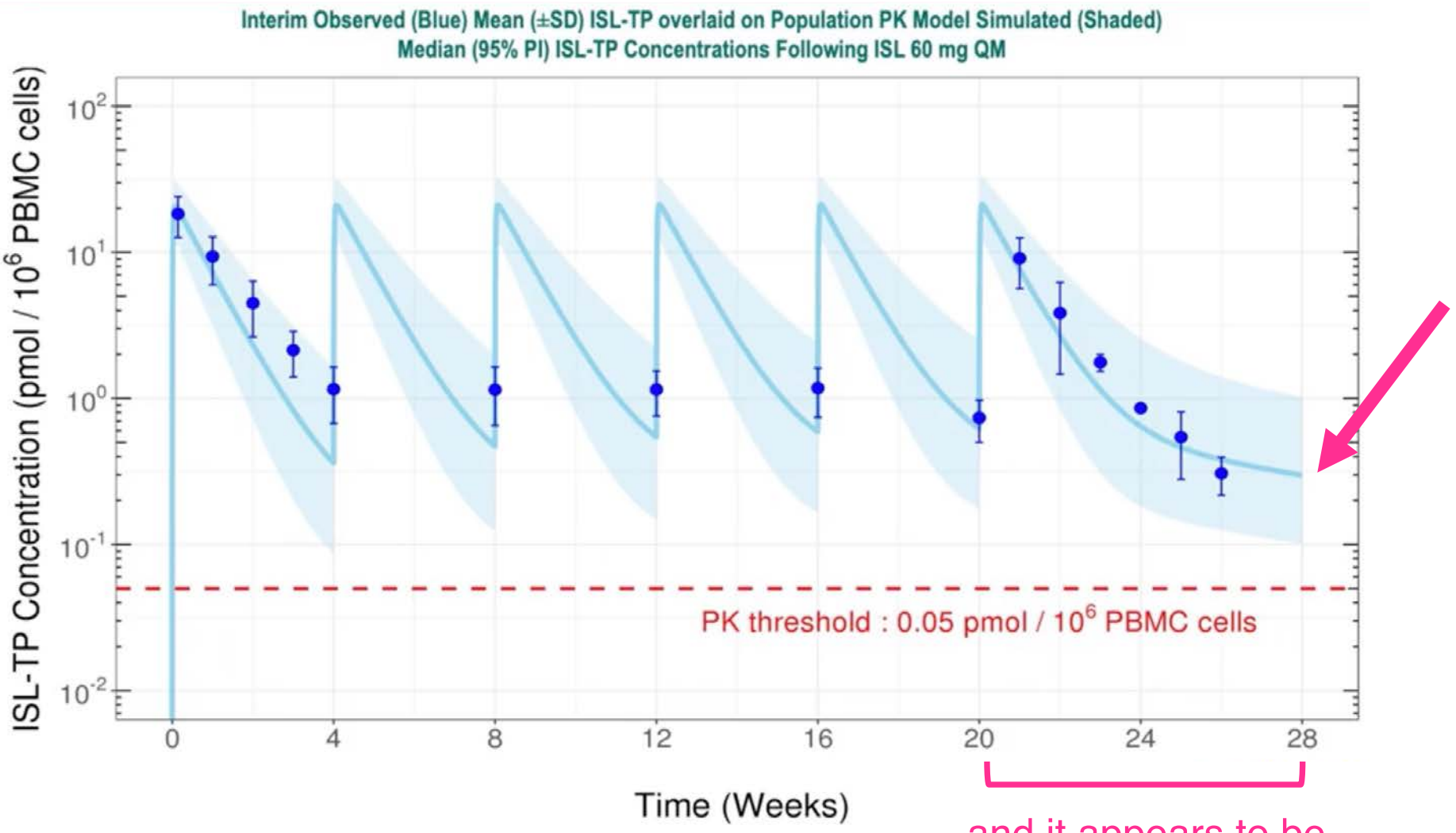






Markowitz M, et al. J Infect Dis. 2020;221(9):1398-1406

Islatravir PO once monthly maintains levels

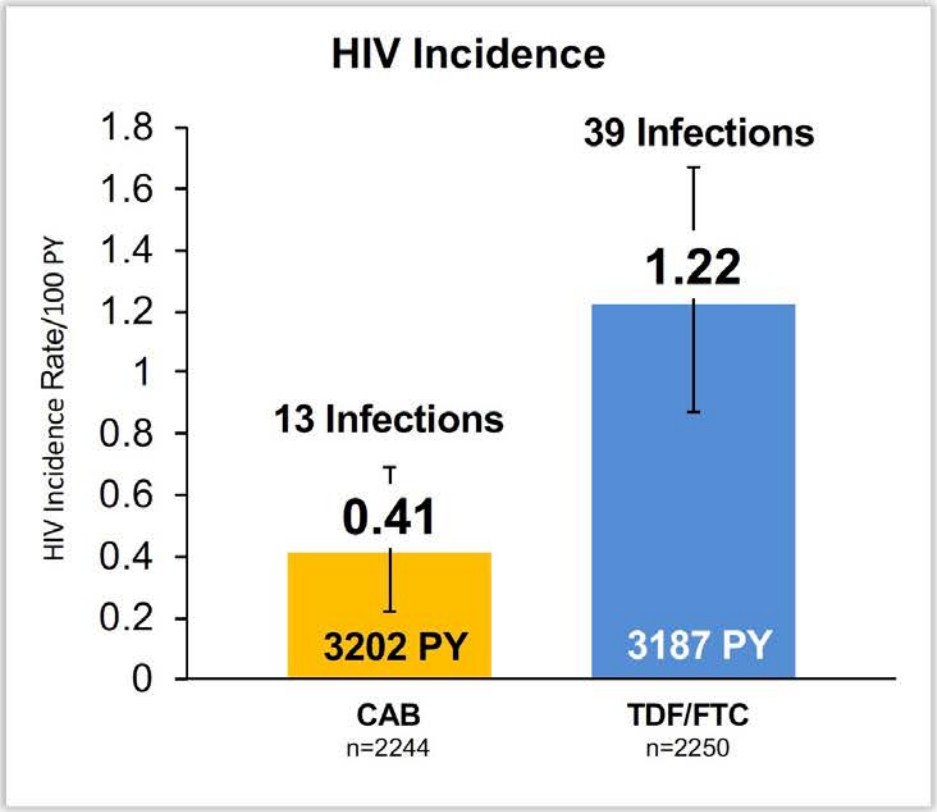


https://www.croiconference.org/abstract/islatravir-pk-threshold-dose-selection-for-monthly-oral-hiv-1-prep/
Figure from: Hillier S, et al. HIV R4P 2021. Abstract OA04.05LB. Accessed at https://programme.hivr4p.org/Abstract/Abstract/1363


PrEP
PrEP
PrEP
PrEP
PrEP
SINGLE USE ONLY

HPTN 083

Oral FTC/TDF vs Injectable CAB-LA for MSM & TGW



CI, confidence interval

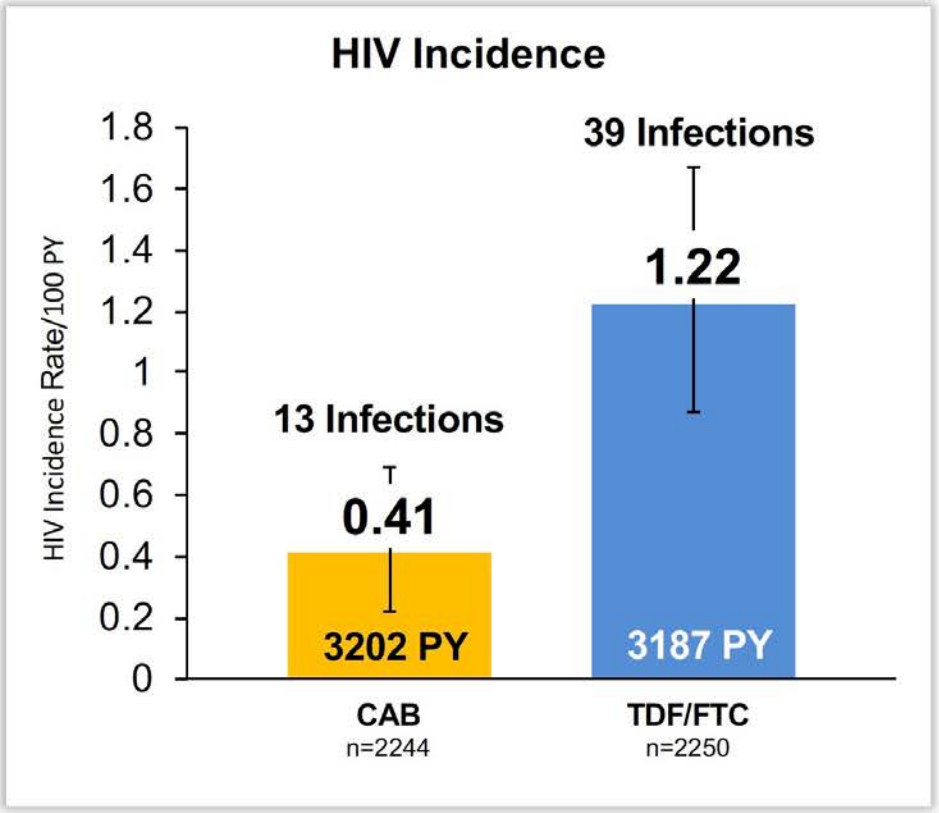
52 infections
6389 PY of follow-up

Landovitz RJ, et al. AIDS 2020. Abstract OAXLB01
Landovitz RJ, et al. N Engl J Med. 2021 Aug 12;385(7):595-608

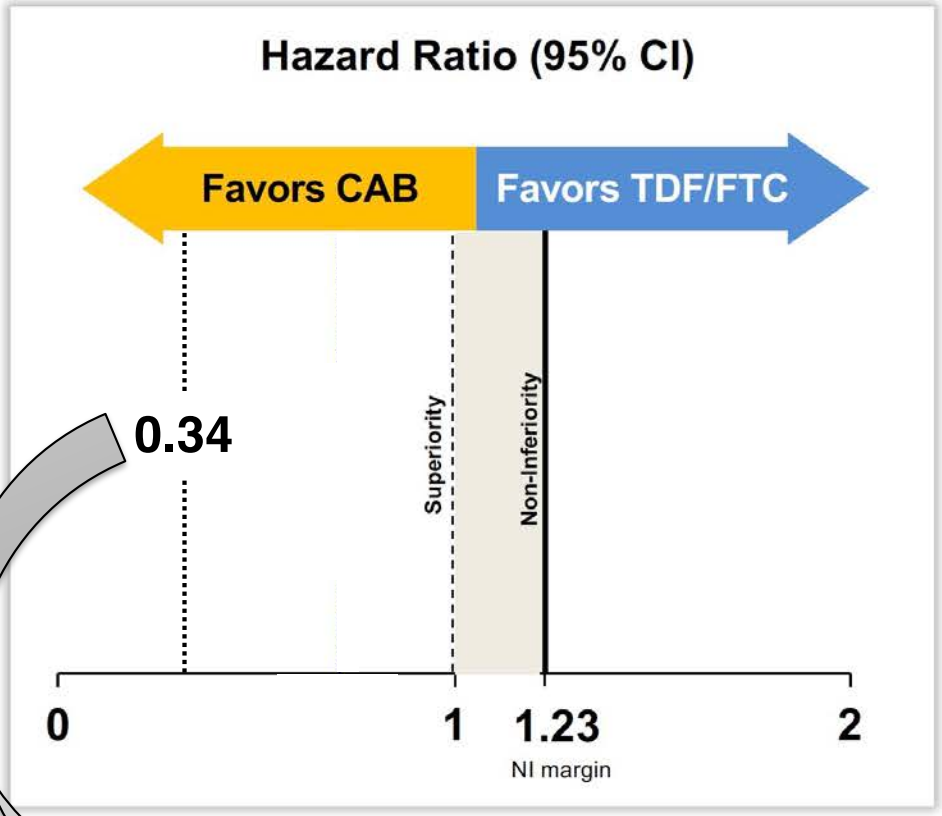
HPTN 083

Oral FTC/TDF vs Injectable CAB-LA for MSM & TGW

IM CAB-LA was statistically superior to oral FTC/TDF for preventing HIV



CI, confidence interval



52 infections
6389 PY of follow-up

66%

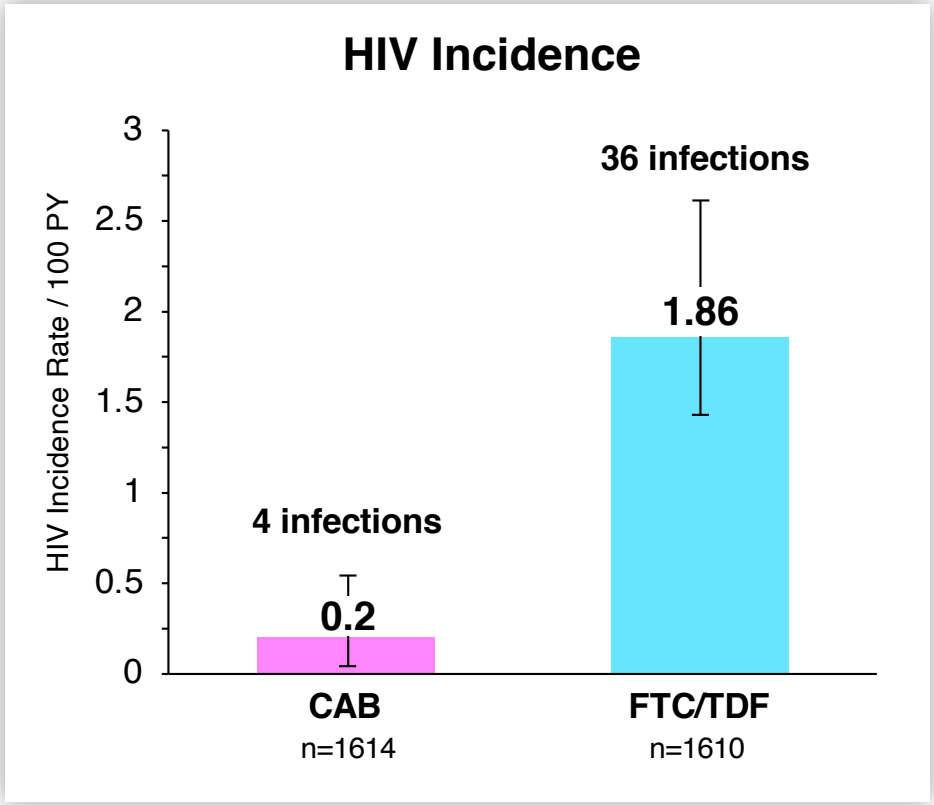
reduced hazard of HIV among CAB recipients, compared with FTC/TDF
(95%CI: 18%, 62%; p=0.0005)

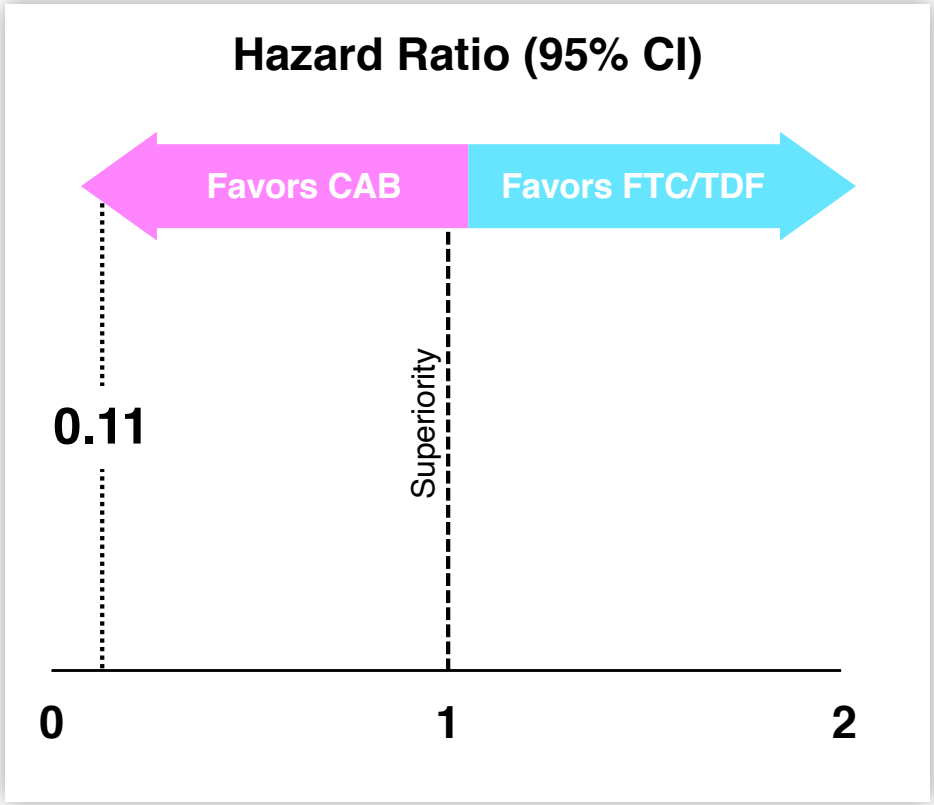
Landovitz RJ, et al. AIDS 2020. Abstract OAXLB01
Landovitz RJ, et al. N Engl J Med. 2021 Aug 12;385(7):595-608

HPTN 084

Oral FTC/TDF vs Injectable CAB-LA for Cisgender Women

IM CAB-LA was statistically superior to oral FTC/TDF for preventing HIV





40 infections
3892 PY of follow-up

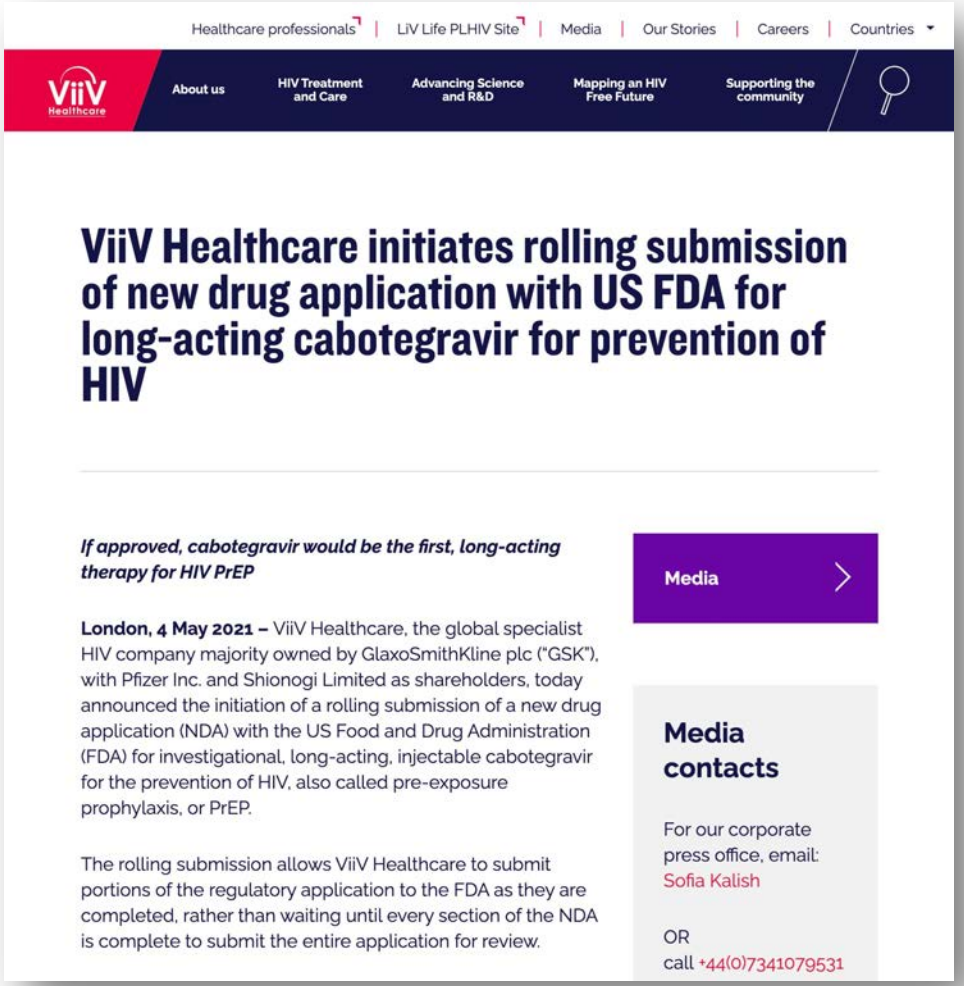
89%

reduced hazard of HIV among CAB recipients, compared with FTC/TDF
(95%CI: 69%, 99%; p=0.000027)

Figures (re)constructed from data presented in Delany-Moretlwe S, et al. R4P 2020. Abstract LB1479

What's the timeline for CAB?

- FDA submission opened May 2021
- Final elements submitted to FDA in summer 2021
- ViiV anticipates word from FDA by January 24, 2022
  (but it could be December 2021)



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ViiV Healthcare

About us | HIV Treatment and Care | Advancing Science and R&D | Mapping an HIV Free Future | Supporting the community

ViiV Healthcare initiates rolling submission of new drug application with US FDA for long-acting cabotegravir for prevention of HIV

If approved, cabotegravir would be the first, long-acting therapy for HIV PrEP

London, 4 May 2021 – ViiV Healthcare, the global specialist HIV company majority owned by GlaxoSmithKline plc ("GSK"), with Pfizer Inc. and Shionogi Limited as shareholders, today announced the initiation of a rolling submission of a new drug application (NDA) with the US Food and Drug Administration (FDA) for investigational, long-acting, injectable cabotegravir for the prevention of HIV, also called pre-exposure prophylaxis, or PrEP.

The rolling submission allows ViiV Healthcare to submit portions of the regulatory application to the FDA as they are completed, rather than waiting until every section of the NDA is complete to submit the entire application for review.

Media

Media contacts

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OR call +44(0)7341079531

Questions?

Please email me!

Christopher Hurt, MD

churt@med.unc.edu