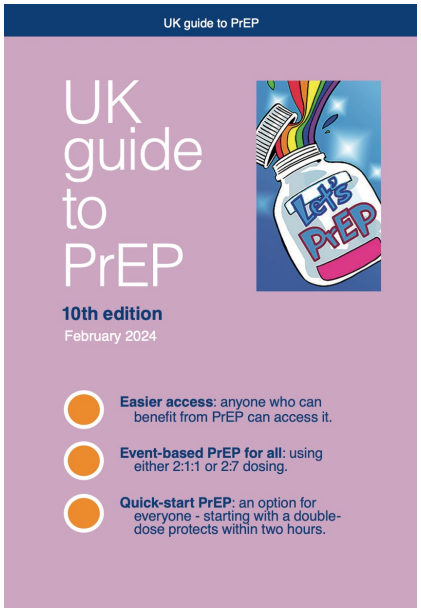
A community perspective on UK Guide to PrEP: 2024 update

C&W HIV GUM teaching, 9 July 2024

Simon Collins
HIV i-Base
i-Base.info



Introduction

- Background
- PrEP guidelines in 2024.
- New changes in the community PrEP guide.
- New evidence and references.
- Ongoing questions and choices.
- Transgender healthcare and rights

Introduction

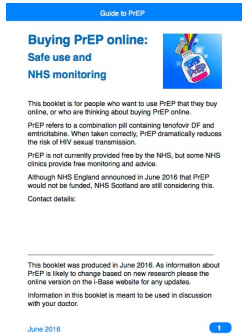
- Background: guidelines and this update.
- New changes (1) Double dose start. (2) New adherence data. (3) New options for event-based dosing: similar by sex and gender. (4) Easier access.
- New evidence and five key references.
- Ongoing questions and choices.
- How does this affects PrEP services?

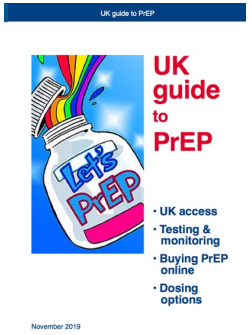
Background to the guide

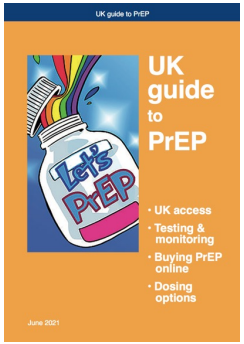
First produced in 2016.

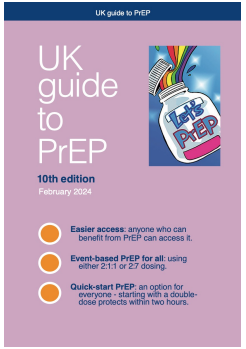
Community collaboration with leading PrEP researchers and providers to provide evidence-based information.

No funding, co-ordinated by i-Base.



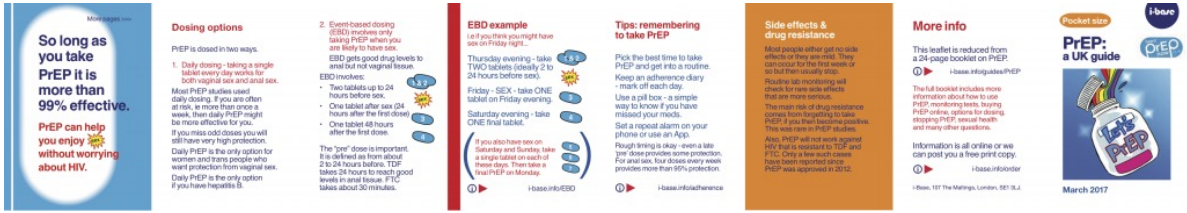






Pocket leaflets & PrEP for Women

Pocket guide
to PrEP



Sophia

Shona, Spanish, Swahili
Xhosa, French, Portuguese

PrEP guidelines

Guidelines depend on date, regulatory indication, with different recommendations for different drugs.

South Africa (2016) – WHO, SA

UK BHIVA/BASHH (2018) – EMA

WHO (2016, 2019, 2021) – All

US CDC (2012–2023) and IAS-USA (2021) – FDA

EACS (2019, 2021, 2023) – EMA

UK guidelines
(BHIVA/BASHH)

- Excellent UK guidelines in 2018 - included many more options before other guidelines.
- 6 years ago: No new RCTs but other studies since.
- Draft circulated mid-2023 *(delayed by CAB-LA?)*
- Expected in Nov/Dec 23/early 2024.

Guide was out of stock by Dec 23 with 6000 orders by Feb 2024. Worked with UK panel to include main expected changes.

Background: PrEP equity across UK

PrEP access in UK among those with need in 2022:

- 74% gay and bisexual men.
- 39% heterosexual men.
- 36% heterosexual and bisexual women.

Other differences by age and ethnicity.

- New research included much easier options for using PrEP and supported better equity.

UKHSA. HIV in the UK (Oct 2023).

New research (even though not RCTs)

Clearly effective in RCTs as daily or 2:1:1 but… PrEP is a very difficult scientific challenge.

- Target drug levels uncertain: which drugs at which levels in which parts of the body?
- Surrogate markers for adherence several weeks or months earlier before diagnosis. New cases may or may not have taken PrEP.

New: efficacy linked to drug levels in cells vs tissue.

Timing to start and stop

Example: significant differences in guidelines over time to protection – ie daily dosing before protected.

- 21 days (US).
- 7 days daily to start, 2 or 7 days to stop (UK).
- 7 days to start or stop (EACS).
- 7 days MSM, 20 days women; 28 days to stop (SA).

Event-based 2:1:1 vary, mostly since 2019.

New: double-dose to start – for all

Several PK studies show a new option for everyone to start oral PrEP with a double dose (2 pills).

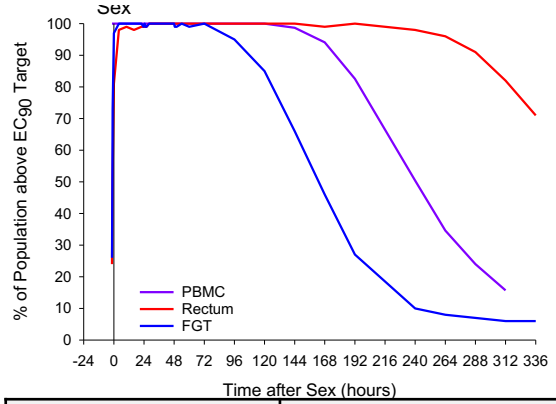
Protection in 2 hours vs 7-20 days

- Based on closer correlation between protection and drug levels in cells rather than genital/rectal tissue.
- More accurately predicts clinical outcome.
- Rapid/more durable drug levels with double dose.

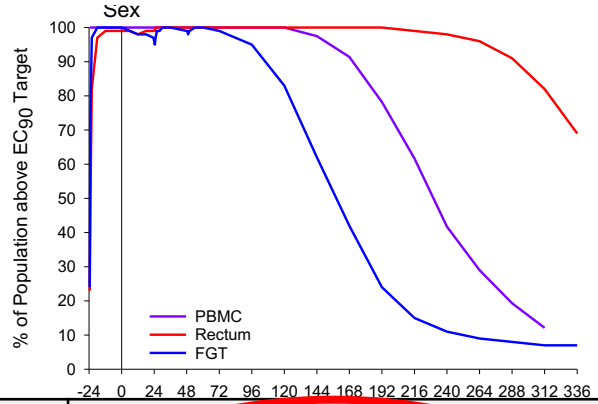
Where - EC_{90} in PBMCs FGT & rectal tissues after IPERGAY

Adapted from Cottrell et al. J Infect Dis. 2016 Jul 1;214(1):55-64 and Garrett et al. J Pharmacol Exp Ther. 2018 Nov;367(2):245-251.

IPERGAY start 2 hours before Sex



IPERGAY start 24 hours before Sex



Compartment	How Quickly Above Target?	How Long Above Target?
FGT	2 hours after double dose	4 days after sex
PBMC		7 days after sex
Rectum		12 days after sex

Adherence

New analyses are important for reducing the adherence threshold.

Recommendations were for trans and non-binary people and cis women to need strict daily adherence.

- New adherence: 4+ doses a week now also for cis women *(JAMA paper)*
- Some benefit for gay and bisexual men with 2-3 pills, though highest protection with 4+ doses.

Event-based 2:7 option for trans and nonbinary people and cis women

New data from PK studies and modelling studies now enable options other than daily PrEP.

Especially if there is no need for 24/7 protection 365 days a year.

Possible caution over post-dosing – continue daily PrEP for 7 days – ie 2:7 dosing for transgender and non-binary people and cisgender women.

Systemic protection

- Oral PrEP is distributed systemically and not locally.
- Although tissue concentrations warranted cautious approach to dosing by sex and gender, drug levels in cells (PBMCs) will be similar in all body sites.
- Route of exposure becomes irrelevant.
- Possibly important implications for route?

Reducing the barrier to access

UK guidelines will reduce the barrier for access: no longer will need tp be at higher risk.

Instead, being at risk is a more practical and equitable approach especially with event-based dosing options.

PrEP can increase QoL by reducing anxiety over risk.

Having PrEP at home can also be **starter PEP**.

Evidence

- Five key studies with accumulating evidence *(see additional slides 23 – 32).*
- Practical information in absence of clinical evidence from RCTs.
- Timeline from first evidence (1994), to large studies (iPrEX 2009-2012), to approval (FDA 2012, EU 2016) to guidelines (UK 2018).

Ongoing issues

- Data on the duration of event-based PrEP for trans and non-binary people and cis gender women.
- Target drugs levels
- Data in transgender and non-binary people.
- Data on transgender men: excluded or lost in ALL RCTs up to now.

Guidelines matter

"Guidelines are out of date before they are even published".

Mike Youle, 2005

"Vaginas do not demand perfection".

Jennell Stewert, Challenging the Dogma of Event-driven PrEP, CROI 2024.

Guidelines provide a minimum standard of care that people can reference when advocating for our care and their care.

References

1. **Zhang L et al.** Model-based predictions of protective HIV pre-exposure prophylaxis adherence levels in cisgender women. Nat Med. (November 2023). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10667095
2. **Cottrell ML et al.** A translational pharmacology approach to predicting outcomes of preexposure prophylaxis against HIV in men and women using tenofovir disoproxil fumarate with or without emtricitabine. J Infect Dis. (February 2016). https://pubmed.ncbi.nlm.nih.gov/26917574
3. **Garrett KL et al.** A pharmacokinetic/pharmacodynamic model to predict effective HIV prophylaxis dosing strategies for people who inject drugs. J Pharmacol Exp Ther. (August 2018). https://pubmed.ncbi.nlm.nih.gov/30150483
4. **Cespedes MS et al.** Gender affirming hormones do not affect the exposure and efficacy of F/TDF or F/TAF for HIV preexposure prophylaxis: a subgroup analysis from the DISCOVER trial Transgender Health (January 2024). https://www.liebertpub.com/doi/full/10.1089/trgh.2022.0048
5. **Marrazzo J et al.** HIV Preexposure Prophylaxis With Emtricitabine and Tenofovir Disoproxil Fumarate Among Cisgender Women. JAMA (1 March 2024). https://jamanetwork.com/journals/jama/fullarticle/2816036

Tsai C-C et al, Science 1995

Daily weight-based daily PMPA (tenofovir) SC for one month in 35 macaques inoculated IV with SIV (10 x 50% infectious dose): 5 arms, follow up 40-56 weeks.

Dose	Timing	n	% became SIV+
20 mg/kg	48 hrs pre	5	0/5
30 mg/kg	48 hrs pre	10	0/10
30 mg/kg	4 hrs post	5	0/5
30 mg/kg	24 hrs post	5	0/5
Control	48 hrs pre	10	10/10

Tsai C-C et al, Prevention of SIV Infection in Macaques by (R)-9-(2-Phosphonylmethoxypropyl)adenine. Science 1995. (NIH funded). https://pubmed.ncbi.nlm.nih.gov/7502044/

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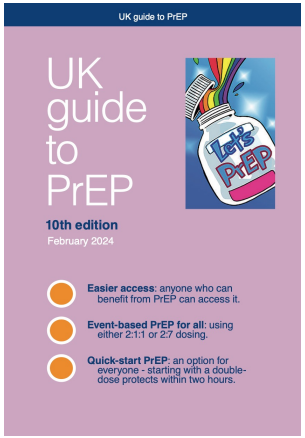
Thanks



Dan Clutterbuck, Sheena McCormack, Achyuta Nori, Will Nutland, Greg Owen, Mags Portman*, Michelle Ross, Sophie Strachan, Martina Toby, Laura Waters, Ashwin Caffery and Aedan Wolton.

**This guide is dedicated to our inspirational co-author Dr Mags Portman who was a leading advocate for PrEP in the UK. Mags died from mesothelioma in February 2019 aged 44 and we miss her deeply.*

Feb 2024 edition will be out of stock by August 2024.

Additional slides

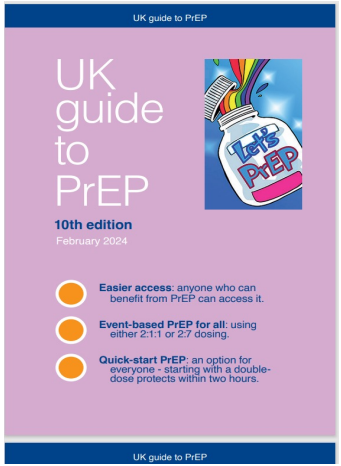
Dan Clutterbuck

What's New in HIV

Plenary talk, BHIVA Annual Conference, 29 April– 1 May 2024

https://www.bhiva.org/file/665da45a5391c/Daniel-Clutterbuck.pdf

PrEP equity- oral PrEP for receptive vaginal and neovaginal sex

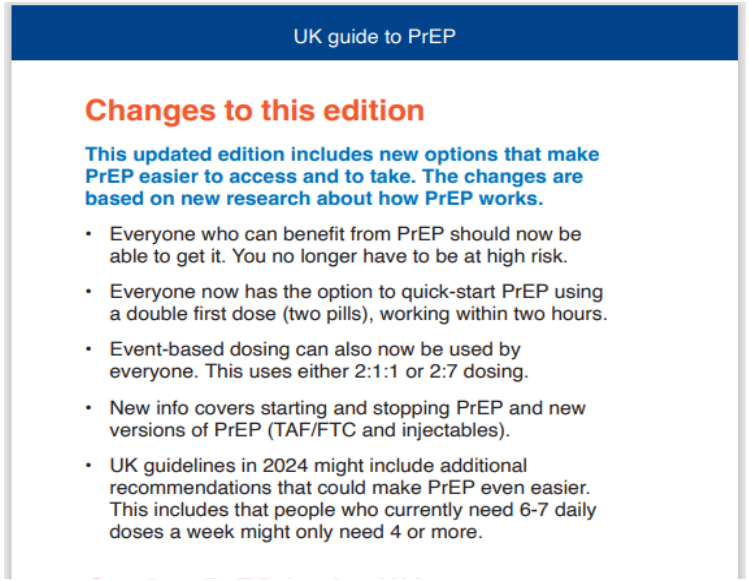


- Of five major RCTs of oral daily PrEP for women, two showed effect (TDF2 Partners-PrEP) and and three showed no benefit (VOICE, FEM-PrEP and HPTN 084).
- ADAPT study (CROI 2015) - ED PrEP in Bangkok, Cape Town and NYC. No further studies of event-based or quick start PrEP undertaken in cisgender women.

Stewart J. *Challenging the Dogma of Event-Driven PrEP.* CROI 2024, Oral abs 50.

Dan Clutterbuck, BHIVA 2024

What's new – oral PrEP ?



UK guide to PrEP

Changes to this edition

This updated edition includes new options that make PrEP easier to access and to take. The changes are based on new research about how PrEP works.

- Everyone who can benefit from PrEP should now be able to get it. You no longer have to be at high risk.
- Everyone now has the option to quick-start PrEP using a double first dose (two pills), working within two hours.
- Event-based dosing can also now be used by everyone. This uses either 2:1:1 or 2:7 dosing.
- New info covers starting and stopping PrEP and new versions of PrEP (TAF/FTC and injectables).
- UK guidelines in 2024 might include additional recommendations that could make PrEP even easier. This includes that people who currently need 6-7 daily doses a week might only need 4 or more.

- Limited new evidence. No new RCTs
- Control arms of dapivirine ring and cabotegravir trials (HTPN 084)
- Pooled analysis of daily PrEP data (Marrazzo 2024)
- Re-evaluation of PK data
- Modelling data refined and revised (Zhang 2023).

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Pooled analysis of PrEP studies

- Marrazzo: Pooled analysis of 6296 participants from 11 post-approval studies of PrEP in cisgender women: overall HIV incidence was 0.72 per 100 person-years.
- Mapped objective (DBS & plasma) to reported adherence levels and assigned an ordinal rank to each individual, repeated over time.
- HIV incidence rates per 100 person-years for different PrEP adherence trajectories were 0 for consistently daily (7 doses/week), 0.13 for consistently high (4-6 doses/week), 0.49 for a mean of 4-6 doses/week and then declining, and 1.27 for consistently low (less than 2 doses/week) adherence.
- Exactly comparable to trials in GBMSM & TGW and to the control arm of HTPN084

- Marrazzo J et al. HIV Preexposure Prophylaxis With Emtricitabine and Tenofovir Disoproxil Fumarate Among Cisgender Women. *JAMA*. doi:10.1001/jama.2024.0464. (1 March 2024).

Dan Clutterbuck, BHIVA 2024

Modelling: Zhang *Nature Medicine* 2023

nature medicine

Article

https://doi.org/10.1038/s41591-023-02615-x

Model-based predictions of protective HIV pre-exposure prophylaxis adherence levels in cisgender women

Received: 3 April 2023

Accepted: 26 September 2023

Published online: 13 November 2023

Check for updates

Lanxin Zhang[1,9], Sara Iannuzzi[1,2,9], Ayyappa Chaturvedula[3], Elizabeth Irungu[4], Jessica E. Haberer[5,6], Craig W. Hendrix[7] & Max von Kleist[1,8]

Most human immunodeficiency virus (HIV) infections occur in cisgender women in resource-limited settings. In women, self-protection with emtricitabine/tenofovir disoproxil fumarate pre-exposure prophylaxis (FTC/TDF-PrEP) constitutes a major pillar of HIV prevention. However, clinical trials in women had inconsistent outcomes, sparking uncertainty about adherence requirements and reluctance in evaluating on-demand

- '….In heterosexual women, the range in clinically estimated average efficacy of oral FTC/TDF-PrEP is particularly vast'
- Results dichotomised into those with some drug vs no drug (ie to include treatment arms)

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Zhang *Nature Medicine* 2023

- Top down (data) vs ‘bottom up’ models
- Model adherence, exposure site pharmacokinetics, exposure-site, effect site drug potency and exposure route

- Outcome variability between trials can solely be explained by adherence
- Any simulated scenario in which drug levels in PBMCs are used as a marker of efficacy closely matches observed clinical outcomes.

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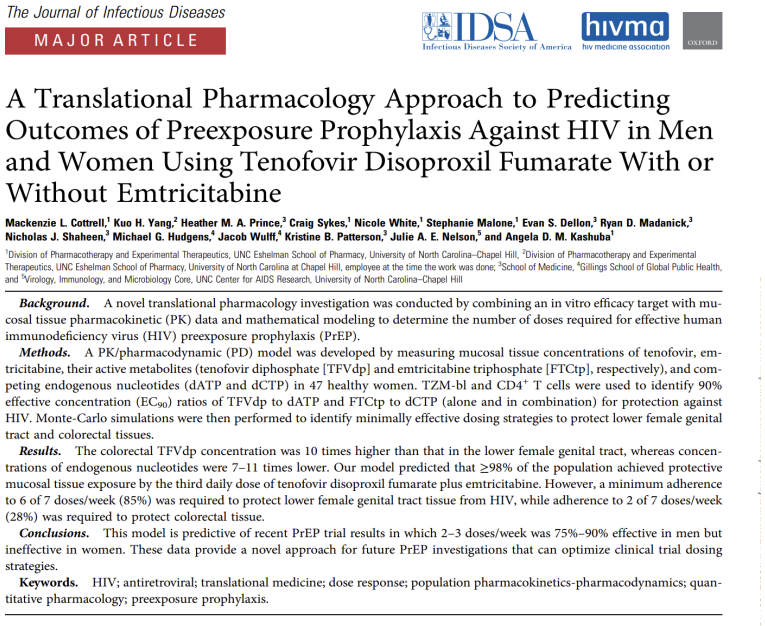
Pharmacodynamic studies

- 47 women received different single-doses of TDF and FTC with blood, rectal, vaginal and cervical tissue sampling over 48h.
- PK/PD model using tissue concentrations of TFV, FTC, and competing endogenous nucleotides
- CD4 T-cells used to identify 90% Effective Concentration (EC_{90}) ratios of TVF-DP to dATP and FTC-TP to dCTP
- Percentage of the population achieving the EC_{90} in colorectal tissue and female genital tract tissue
- Presented as models of single daily dosing or ED (2;1;1) dosing



The Journal of Infectious Diseases

MAJOR ARTICLE

A Translational Pharmacology Approach to Predicting Outcomes of Preexposure Prophylaxis Against HIV in Men and Women Using Tenofovir Disoproxil Fumarate With or Without Emtricitabine

Mackenzie L. Cottrell,[1] Kuo H. Yang,[2] Heather M. A. Prince,[3] Craig Sykes,[1] Nicole White,[1] Stephanie Malone,[1] Evan S. Dellon,[3] Ryan D. Madanick,[3] Nicholas J. Shaheen,[3] Michael G. Hudgens,[4] Jacob Wulff,[4] Kristine B. Patterson,[3] Julie A. E. Nelson,[5] and Angela D. M. Kashuba[1]

[1]Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, University of North Carolina–Chapel Hill, [2]Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, employee at the time the work was done; [3]School of Medicine, [4]Gillings School of Global Public Health, and [5]Virology, Immunology, and Microbiology Core, UNC Center for AIDS Research, University of North Carolina–Chapel Hill

Background. A novel translational pharmacology investigation was conducted by combining an in vitro efficacy target with mucosal tissue pharmacokinetic (PK) data and mathematical modeling to determine the number of doses required for effective human immunodeficiency virus (HIV) preexposure prophylaxis (PrEP).

Methods. A PK/pharmacodynamic (PD) model was developed by measuring mucosal tissue concentrations of tenofovir, emtricitabine, their active metabolites (tenofovir diphosphate [TFVdp] and emtricitabine triphosphate [FTCtp], respectively), and competing endogenous nucleotides (dATP and dCTP) in 47 healthy women. TZM-bl and $CD4^+$ T cells were used to identify 90% effective concentration (EC_{90}) ratios of TFVdp to dATP and FTCtp to dCTP (alone and in combination) for protection against HIV. Monte-Carlo simulations were then performed to identify minimally effective dosing strategies to protect lower female genital tract and colorectal tissues.

Results. The colorectal TFVdp concentration was 10 times higher than that in the lower female genital tract, whereas concentrations of endogenous nucleotides were 7–11 times lower. Our model predicted that ≥98% of the population achieved protective mucosal tissue exposure by the third daily dose of tenofovir disoproxil fumarate plus emtricitabine. However, a minimum adherence to 6 of 7 doses/week (85%) was required to protect lower female genital tract tissue from HIV, while adherence to 2 of 7 doses/week (28%) was required to protect colorectal tissue.

Conclusions. This model is predictive of recent PrEP trial results in which 2–3 doses/week was 75%–90% effective in men but ineffective in women. These data provide a novel approach for future PrEP investigations that can optimize clinical trial dosing strategies.

Keywords. HIV; antiretroviral; translational medicine; dose response; population pharmacokinetics-pharmacodynamics; quantitative pharmacology; preexposure prophylaxis.

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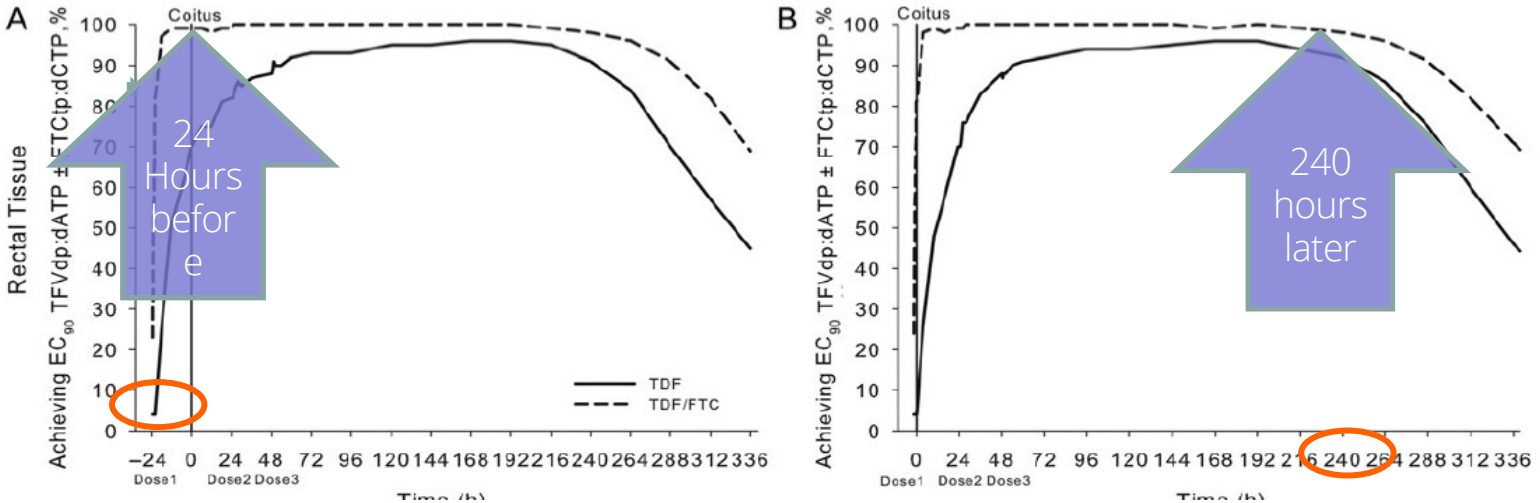

Event driven (2:1:1) PrEP – rectal tissue

- In rectal tissues, 98% of users have protective levels 24 hours after, 81% have protective levels 2 hours after dosing (double dose)
- Tenofovir levels remain protective for 10 days after exposure

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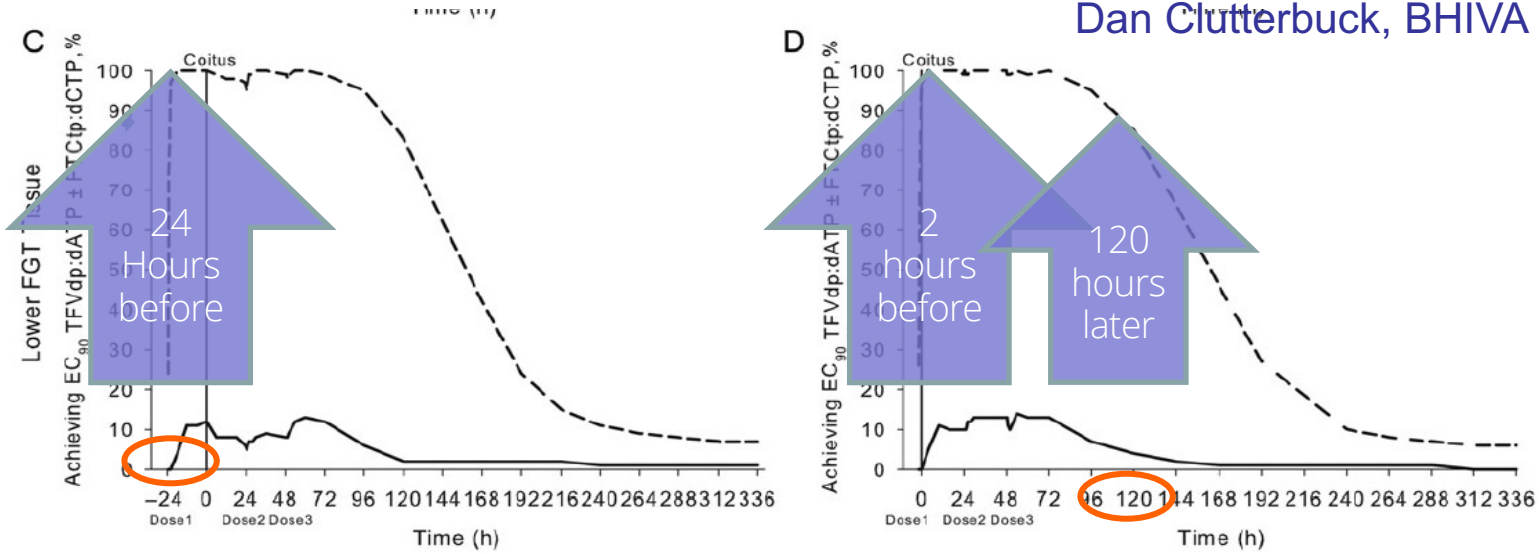
Dan Clutterbuck, BHIVA 2024



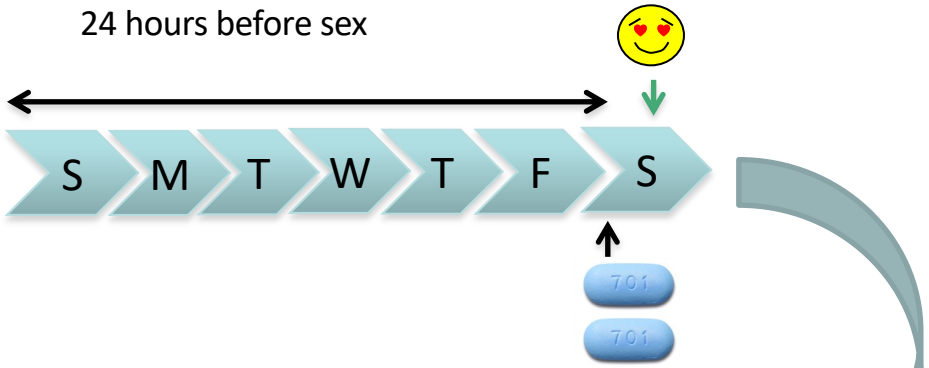
Event driven (2:1:1) PrEP – FGT tissue

- In female genital tract tissue, 99% of users have protective levels, even 2 hours after dosing. FTC-tp concentrates in FGT tissues
- But TDF never reaches protective levels, and TDF/FTC levels fall after 120 hours

Quick start PrEP - for receptive vaginal/neovaginal sex if you have not taken seven daily pills before sex

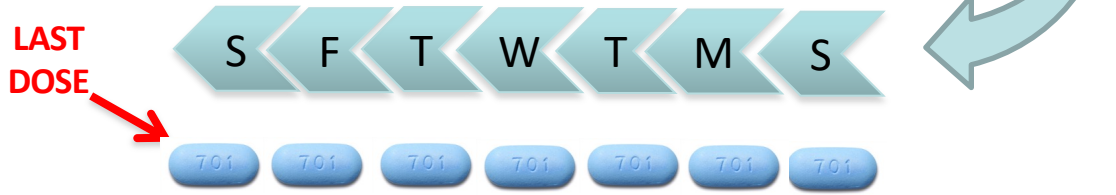
BEFORE SEX

Take a Double dose (two pills) at least 2 hours & not more than 24 hours before sex



AFTER SEX

Continue to take a pill every day for seven days after your last risk



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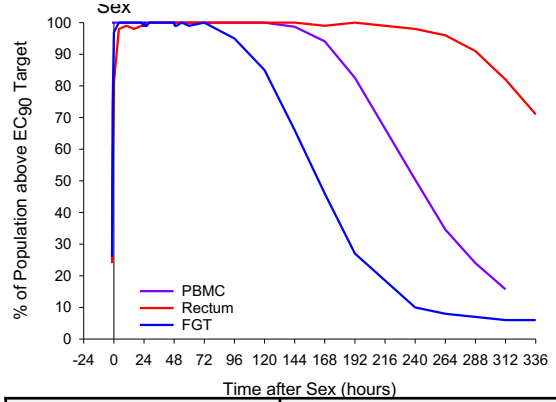
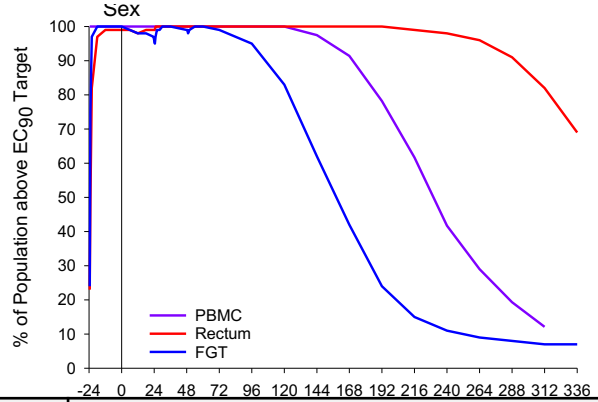
Where - EC_{90} in PBMCs FGT & rectal tissues after IPERGAY

Adapted from Cottrell et al. J Infect Dis. 2016 Jul 1;214(1):55-64 and Garrett et al. J Pharmacol Exp Ther. 2018 Nov;367(2):245-251.

IPERGAY start 2 hours before Sex



IPERGAY start 24 hours before Sex



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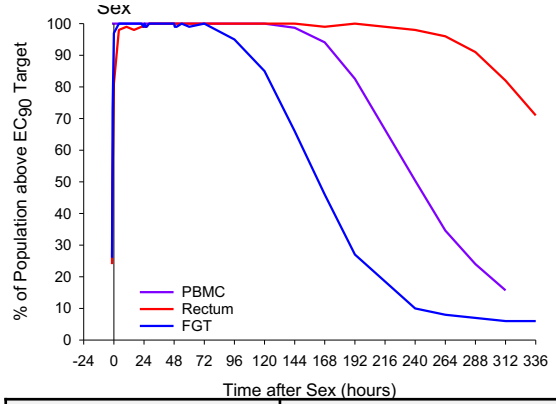
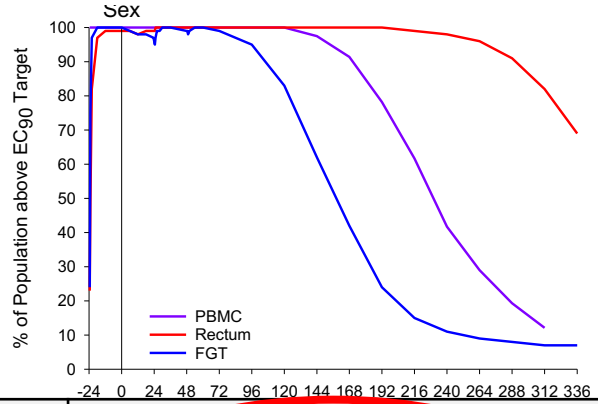


IPERGAY start 24 hours before Sex



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