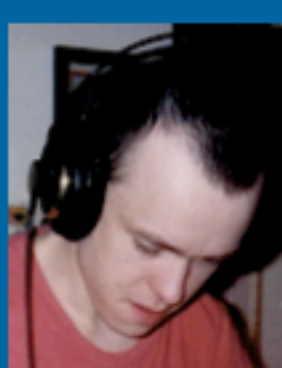
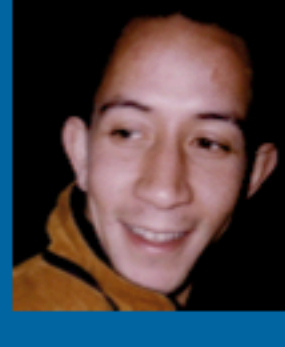


PrEP: a community perspective



Simon Collins
www.i-Base.info



Andrew, Andy B, Andy C, Chris M, Chris P, Richard, Chris W, Space, Nick, Dolly, Wesley, Colvin, Jimi, Kevin, Mike, Paul, Mark, Steve.

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	Day started	n	% infected
20mg/kg	48 hrs pre	n=5	0
30mg/kg	48 hrs pre	n=10	0
30mg/kg	4 hrs post	n=5	0
30mg/kg	24 hrs post	n=5	0
Control	48 hrs pre	n=10	100

1. Tsai C-C et al, Prevention of SIV Infection in Macaques by (R)-9-(2-Phosphonylmethoxypropyl)adenine. Science 1995. (NIH funded).

PrEP timeline

1995–2005: First macaque data with tenofovir. [1, 2, 3]

- Other ARVs may work but AZT did not.
- Driven by independent research & community needing alternatives to condoms.
- Never an industry priority.

2002: Tenofovir approved as ARV.

- Question to Bill Gates at CROI: “When I have sex with my HIV positive boyfriend should I take an HIV drug to protect me” – Dr Mike Youle. [4]
- Largest studies public/private funded. [5]

2012: US approval for tenofovir/FTC as PrEP.

1. Tsai C-C et al, Science 1995; 2. Van Rompay K et al, AIDS Res Hum Retroviruses 1998; 3. Otten R et al. J Vir, 2000. 4. Keynote lecture, CROI 2002, Seattle; 5. NIH, Gates Foundation. US CDC and Thailand MOPH.

People at high risk: women, transwomen, gay men, PWID

Situations when many people are at especially high risk. Option that is not partner dependent.

“... chemoprophylaxis against HIV could benefit those who are less empowered to insist on condom use... HIV serodiscordant couples, sex workers, women wishing to conceive, and individuals unwilling to use condoms are groups that are regularly at significantly higher risk of HIV infection than the general population” – Mike Youle, 2003

1. Youle M, JIAPAC, 2(3) 102-105, 2003. PWID: People Who Inject Drugs

Background

- Holy grail of HIV prevention has been a vaccine: 50% efficacy would be sufficient. [1, 2]
- Daily PrEP when taken significantly higher. [3]
- ~2 million globally are infected each year. [4]
- Condom-based prevention programmes continue to fail people at high risk.
- Low PrEP awareness: ~25% of 1500 MSM age 18-24 in US online survey in 2013. [5]

1. RV144 ALVAC/AIDSVAX trial; 2. IAVI Policy Brief 2007; 3. Grant et al, iPrEX-OLE; 4. UNAIDS, 2013 data; 5. Bauermeister JA, Curr HIV Res, 2013.

Myth 1: pharma marketing

- Not pharma-driven: often donated ARV compounds.
- Limited commercial benefit.
- No PrEP marketing in US by Gilead.
- % use via patient assistance programmes.
- Broad use unlikely until after tenofovir patent expires in 2017.
- Target price close to condoms + lube or oral birth control or Viagra etc

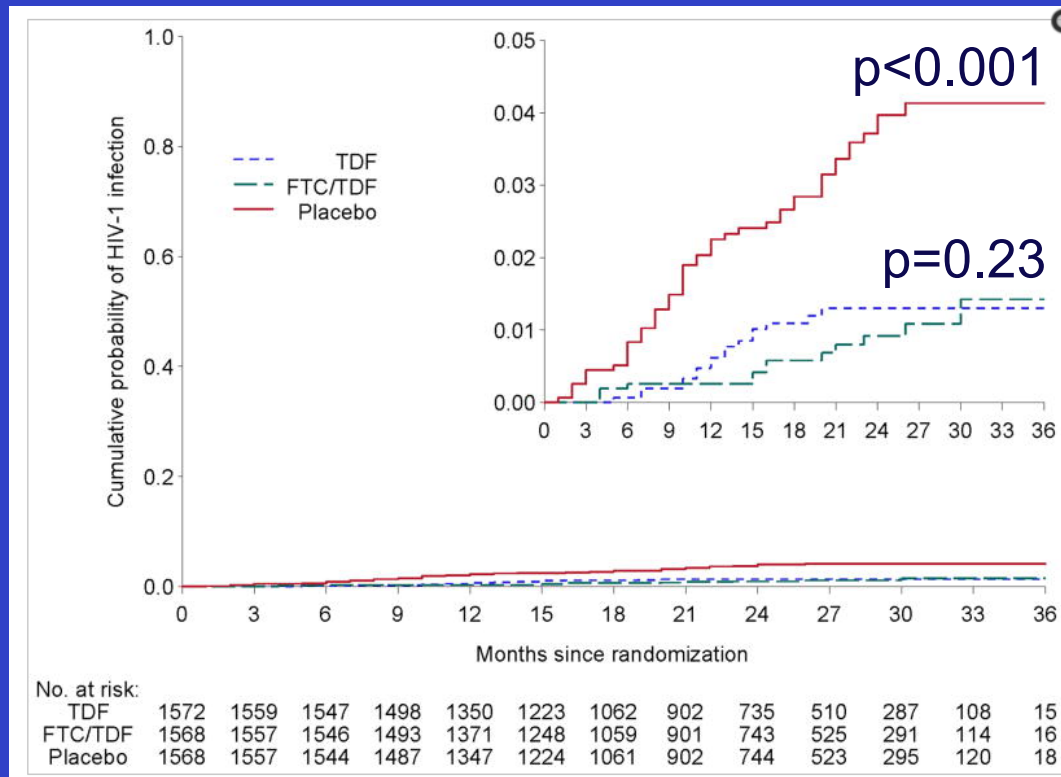
Myth 2: PrEP is not effective

- Efficacy: does PrEP work if you take it?
- Macaque data with intermittent dosing. [1, 2]
- iPrEX >95% with 4 doses a week – more relevant than 42% ITT rate. [3]
- FEM-PrEP and VOICE showed no benefit: challenge of low incidence and adherence. [4, 5]
- Post-efficacy studies: PROUD and IPERGAY report efficacy-based changes based on DSMB reviews – need full results. [6, 7]

1. Garcia-Lerma JG et al, PLoS Med, 2008; 2. Radzio J et al, PLoS One 2012. 3. Grant R et al, IAS 2014, Melbourne. 4. Van Damme L et al, NEJM, 2012; 5. Marrazzo J et al, CROI 2013.; 6. www.proud.mrc.ac.uk; 7. www.ipergay.fr.

Efficacy in Partners PrEP^[1]

Table 2: Kaplan-Meier curve for the primary modified ITT analysis



Heterosexual study in Kenya and Uganda. N=4758. 38% HIV neg partners were women.

	+ve
PCB	52
75% TDF/FTC	13
67% TDF	17

31% vs 81% detectable TNF at seroconversion visit

1. Baeten JR et al, NEJM, 2012.

Funding: Bill & Melinda Gates

Safety in Partners PrEP [1]

	FTC/TDF	TDF	Placebo
Neutropenia			
Grade 1 or 2	15%	2%	2%
Grade 3 or 4	4%	2%	2%
Serum creatinine			NS
phosphorus abnormalities			NS
SAEs			NS
Deaths			NS

Modest GI and fatigue in active arms during month 1.

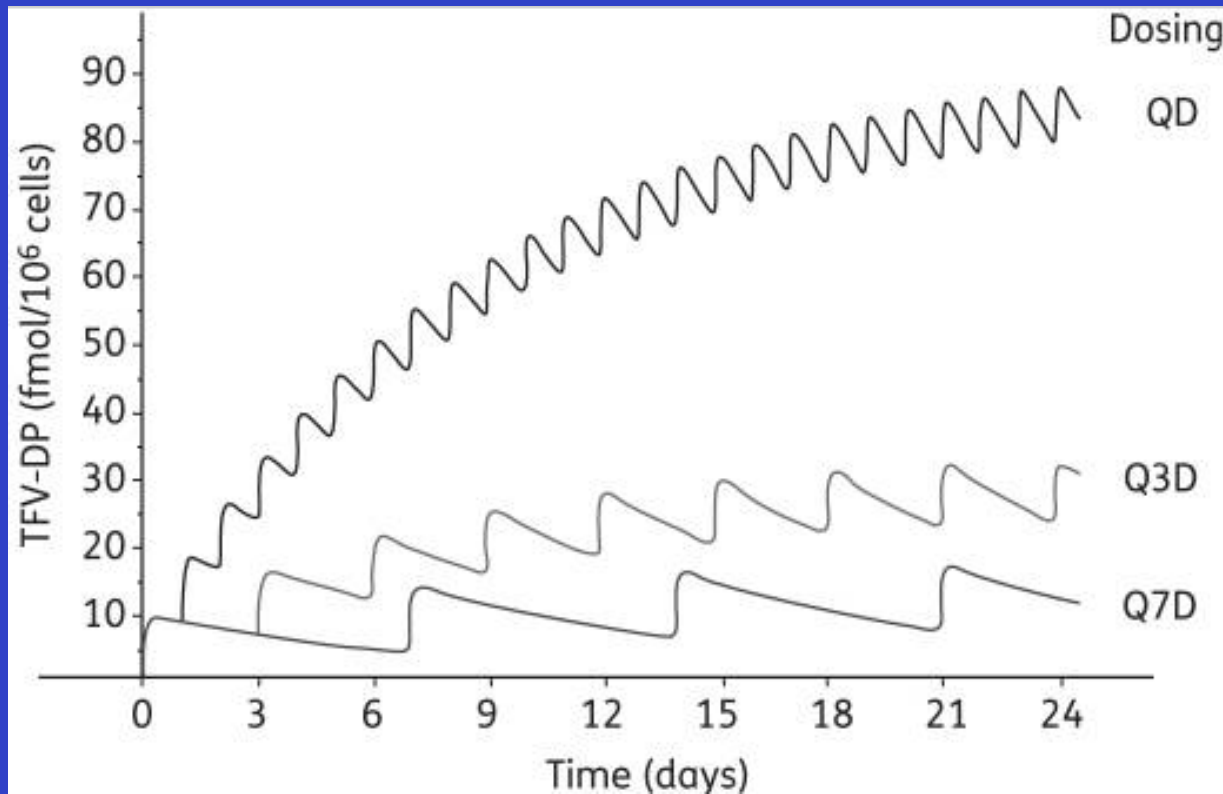
1. Baeten JR et al, NEJM, 2012.

PK - complex

- Two drugs with different PK profiles.
- Intracellular level (active DP/TP), half life
- Absorption in different tissue and cell types:
rectal >> vaginal/cervical >> plasma.
- Defining target levels – interpatient variability.
- Efficacy seems to overcome this complexity.
- Time to protection:
Does absorption require intensive dosing to reach intracellular steady state?

1. Personal communication : Saye Khoo

Predicted TFV-DP accumulation to steady state [1]



TFV
Daily (QD)

Every 3 days
(Q3D);

Once weekly
(Q7D).

In iPrEX – 4 doses a week ~16 fmol/M (95%CI 3-28) [2]

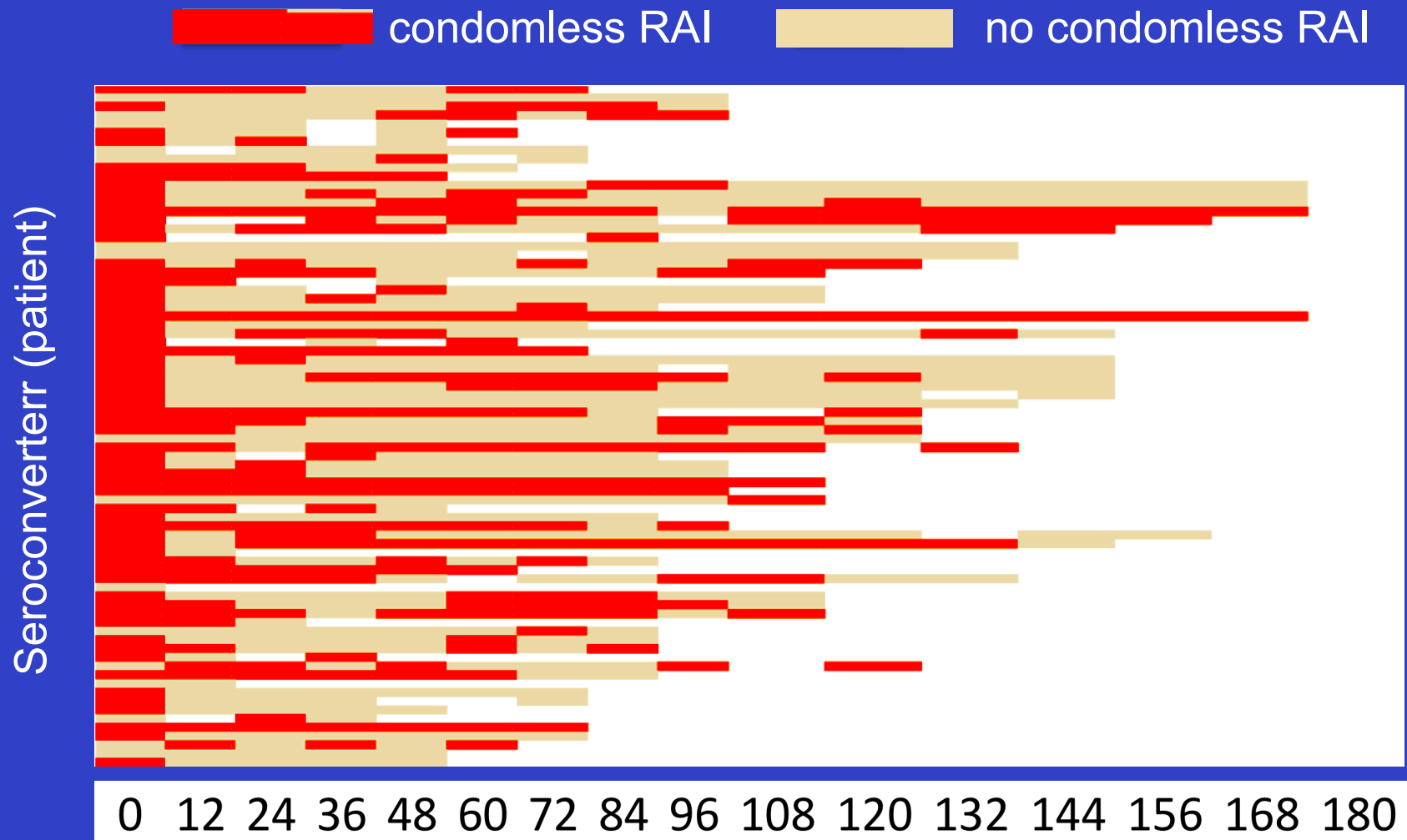
1. Anderson PL, J Antimicrob Chemother 2011; 66: 240–250; 2. Anderson P et al, CROI 2012.

Myth 3: “medicalising sex”

- PrEP not for everyone: ~ 50% interest. [1, 2]
- Not to universally replace condoms.
- Not as lifelong treatment.
- **OPTION = CHOICE.**
- Aim to “come through a higher risk period without HIV complicating the rest of life”.

1. Aghaizu A, BHIVA 2012. 2. Thng C, BHIVA 2012.

iPrEX: HIV risk is not constant



Grant R et al, CROI 2013, Atlanta.

Randomised Phase Study Week

Efficacy vs. effectiveness

- Efficacy = does it work if I take it?
- Effectiveness = the impact on a population-based response?
- A highly effective treatment will have low effectiveness if:
 - 1) it is widely-used in a population with low risk.
 - 2) poorly used by a population at high risk.

Bangkok tenofovir study

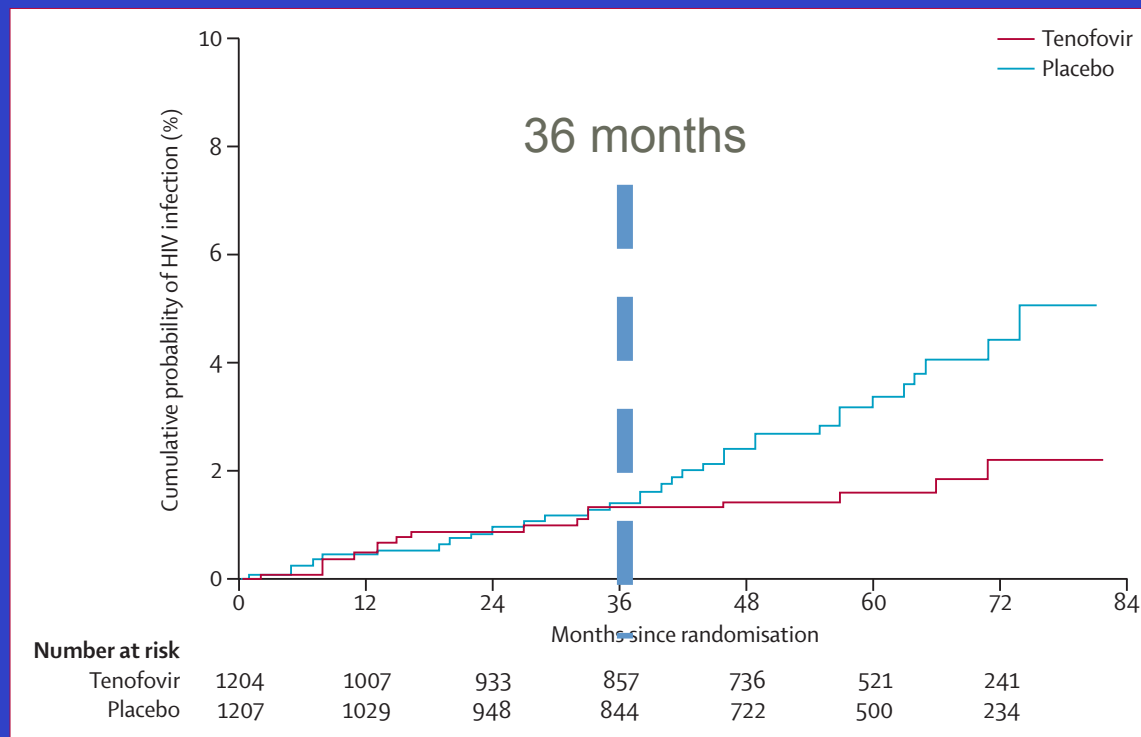
- n=2413 people who inject drugs (PWID). [1]
- randomised to TDF vs placebo
- ~4 years follow-up: 50 infections (17 vs 33)
- 48·9% reduced incidence (95% CI 9·6-72·2; p=0·01);
- 78% reduced incidence with detectable TNF.
- 16 infections averted overall.
- CDC recommendation for PrEP use in PWID

1. Choopanya K et al, Lancet (2013).

Funding: US CDC and the Bangkok Metropolitan Administration

Bangkok tenofovir study

Figure 2: Kaplan-Meier estimates of time to HIV infection (modified ITT)



3 years follow-up:
27 infections (13 vs 14)

5 years follow-up:
50 infections (17 vs 33)

16 infections averted
overall

15 infection averted in
final two years (4 vs 19)

1. Choopanya K et al Bangkok tenofovir study (Lancet 2013).

Matching need

- Categorising **people** as a risk is unhelpful. [1, 2]
- **Situation-related risk** is more useful:
 - relationship status/change in status?
 - sexual history: STIs, history of abuse?
 - recent PEP?
 - recent receptive anal sex without a condom?
 - home life, employment, lifestyle stress?
 - alcohol and drug use, etc.

1. US CDC guidelines, 2014; 2. WHO guidelines, 2014.

Cost-effectiveness

- Price determines access in all populations.
- Generics are dramatically cheaper.
- TDF - \$54 or TDF/3TC - \$66 /year, daily dosing (5-fold mark up ~ \$250-300/year).^[1]
- Depending on background incidence PrEP is already cost-effective based on NNT.^[2, 3]
- Must be cheap enough to not compromise adherence (\$25 a month in Western setting).

1. CHAI, ARV Ceiling Price List, August 2014; 2. Hill A et al, CROI 2006; 3. . Buchbinder SP et al. Lancet, June 2014.

Condoms & language

- Optimal use of PrEP is NOT with condoms or in serodifferent couples with VL <50 c/mL: (may have QoL benefit for individuals)
- Recommending both is not helpful. [1, 2]
- The biggest impact comes from reducing the greatest number of infections.
- No risk compensation in PrEP studies (used as a reason not to publicise condoms).
- Other STIs are important but the primary short term aim is to dramatically reduce HIV.

1. US CDC PrEP guidelines, 2014; 2. WHO PrEP guidelines, 2014,

Quality of life

- For three decades the impact of the fear of infection on QoL has been difficult to measure: before, during and after sex.
- PrEP and TasP can change this.
- Potential to normalise HIV: stigma remains high in high risk groups.
- Control over HIV risk is a motivation.
- Intimacy is a motivation.

Reduce anxiety

- “I’m a physician and I’ve started PrEP” [1]

“I am a 60-year-old gay man who has spent those same three decades trying to keep myself from becoming infected with HIV. I am tired of being scared, so I am starting on PrEP”.



“If there is something out there that can reduce my risk of getting HIV by 95%, I will use it. I'm tired of being scared of HIV.” — Dr Howard Grossman, July 2014

1. Grossman H, I'm an HIV Physician. And I'm Starting PrEP. TheBody.com. July 2014.

Safety concerns

- Safety is a serious risk.
- HIV testing & safety monitoring essential.
- Potential for acute toxicity, interactions with NSAIDs (diclofenac). [1, 2]
- Risk:benefit will change depending on HIV risk.
- Potential pressure on sex workers to use PrEP instead of condoms. [3]
- Monitoring impact on STIs is important.
- If PrEP works street versions may become available similar to Viagra.

1. Morelle J et al, Clin Nephrol 2009; 2. Bickel M et al, HIV Med 2013; 3. US working group on PrEP and women, 2103.

Adherence

- Develop adherence support – worked for ART.
- IF 4 doses is good - TTFN = TaTa For Now:
 - T - Tuesday
 - T - Thursday
 - F - Friday
 - N – NOW
- Or “Truvada Tuesday” (for mid-week dose)
- Long-acting formulations could overcome many adherence problems and warrant public investment as an urgent priority

Research: drugs and dosing

- PROUD & IPERGAY studies changed due to early efficacy of active arms. Need further data before any further comment – especially on “as needed” double-dose schedule. [1, 2]
- HPTN067 (ADAPT) Intermittent PrEP. [3]
- ‘NEXT PrEP’ study: maraviroc [4]
- Long-acting injections may overcome adherence (rilpivirine, cabatotegravir). [5, 6]
- Gels, rings, film, TAF?

1. www.proud.mrc.ac.uk; 2. www.ipergay.fr; 3. www.hptn.org; 4. NCT01505114; 5. NCT02165202; 6. Ford SL ICAAC 2014.

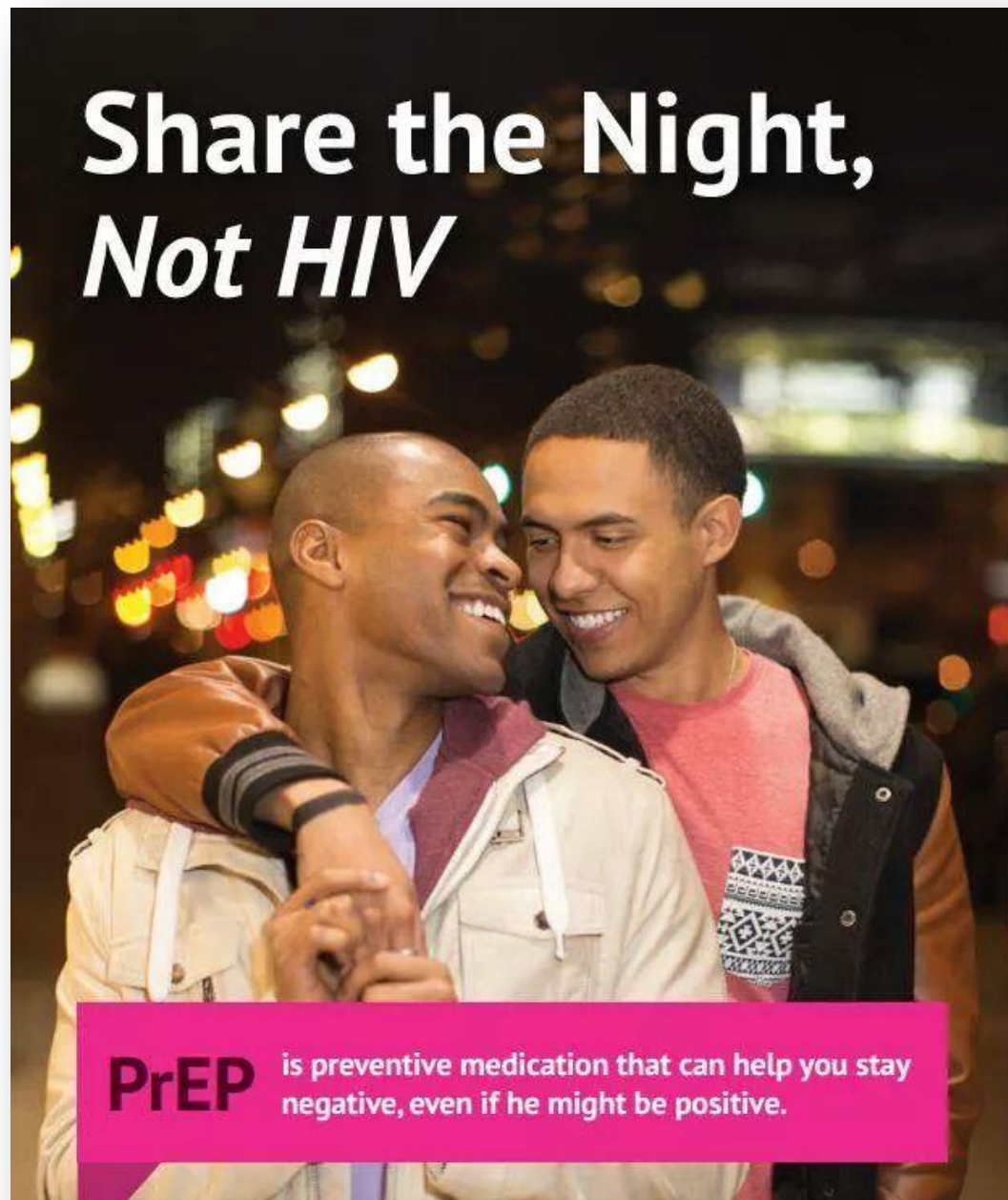
Conclusion

- PrEP works if you take it.
- Cost effective if risk is high: low NNT.
- Generic price could make PrEP affordable for all.
- Signs for low adherence.
- Education: awareness and mechanism.
- EU regulatory block: why this bottleneck? On whose behalf are the EMA to suggest low priority?
- Marketing challenge in the community.

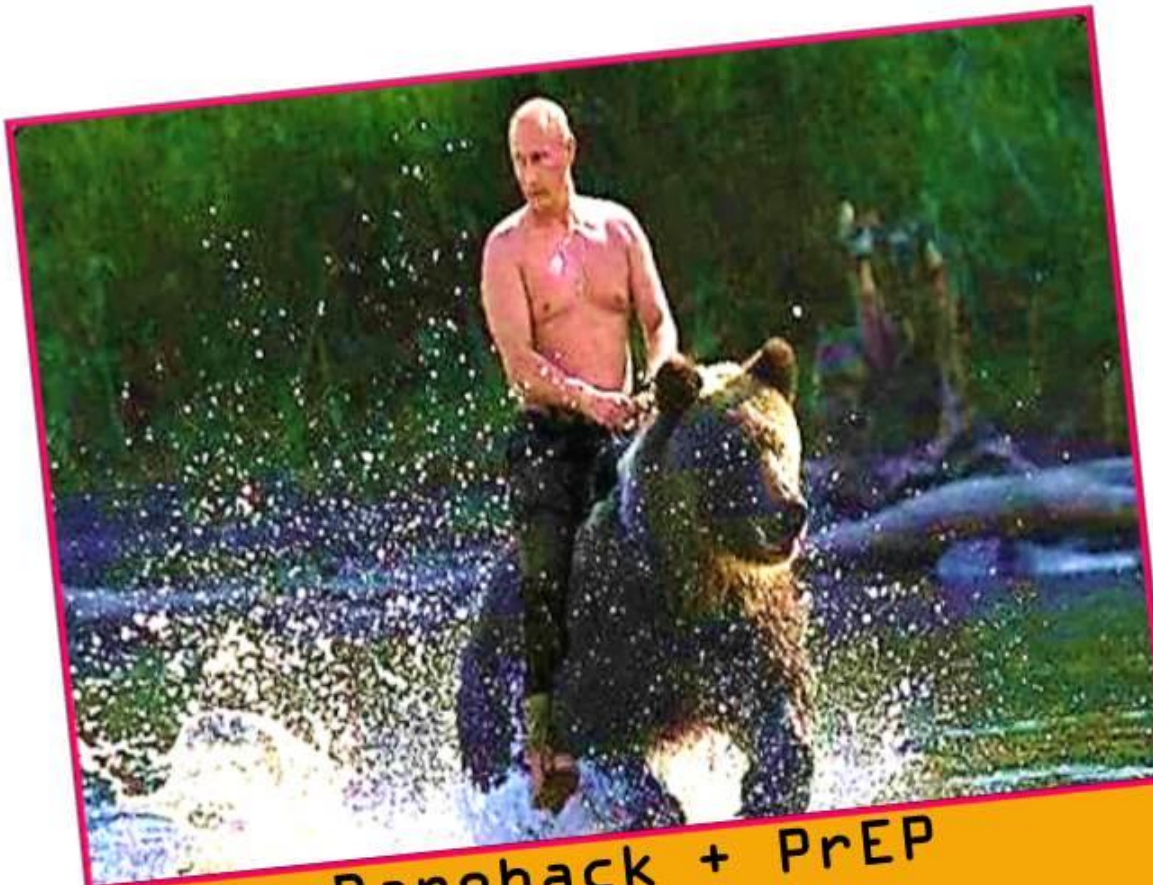
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Share the Night, *Not HIV*



PrEP is preventive medication that can help you stay negative, even if he might be positive.



**Bareback + PrEP
= Safer Sex**

Learn about PrEP
click myprepexperience.blogspot.com



**My PrEP
experience**

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A photograph of a man with short dark hair, smiling broadly, lying in a hospital bed. He is wearing a light grey t-shirt and has his arms crossed over his chest. The background is slightly blurred, showing another person in a hospital bed. The text is overlaid on the image.

Name a common side
effect from taking PrEP.

Peace of mind.

Learn about PrEP – www.myprepexperience.blogspot.com



*In this sample of men
who are in a
relationship with a
perceived HIV-negative
man, we found that
**intimacy motivation was
the strongest predictor
of adopting PrEP.***

**“Intimacy Motivations and Pre-exposure
Prophylaxis (PrEP) Adoption Intentions Among
HIV-Negative Men Who Have Sex with Men
(MSM) in Romantic Relationships”
– Annals of Behavioral Medicine
August 2014**

Thank you

Polly Clayden

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Mike Youle

Robert Grant

Mark Harrington

Richard Jefferys

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