PrEP efficacy – the evidence

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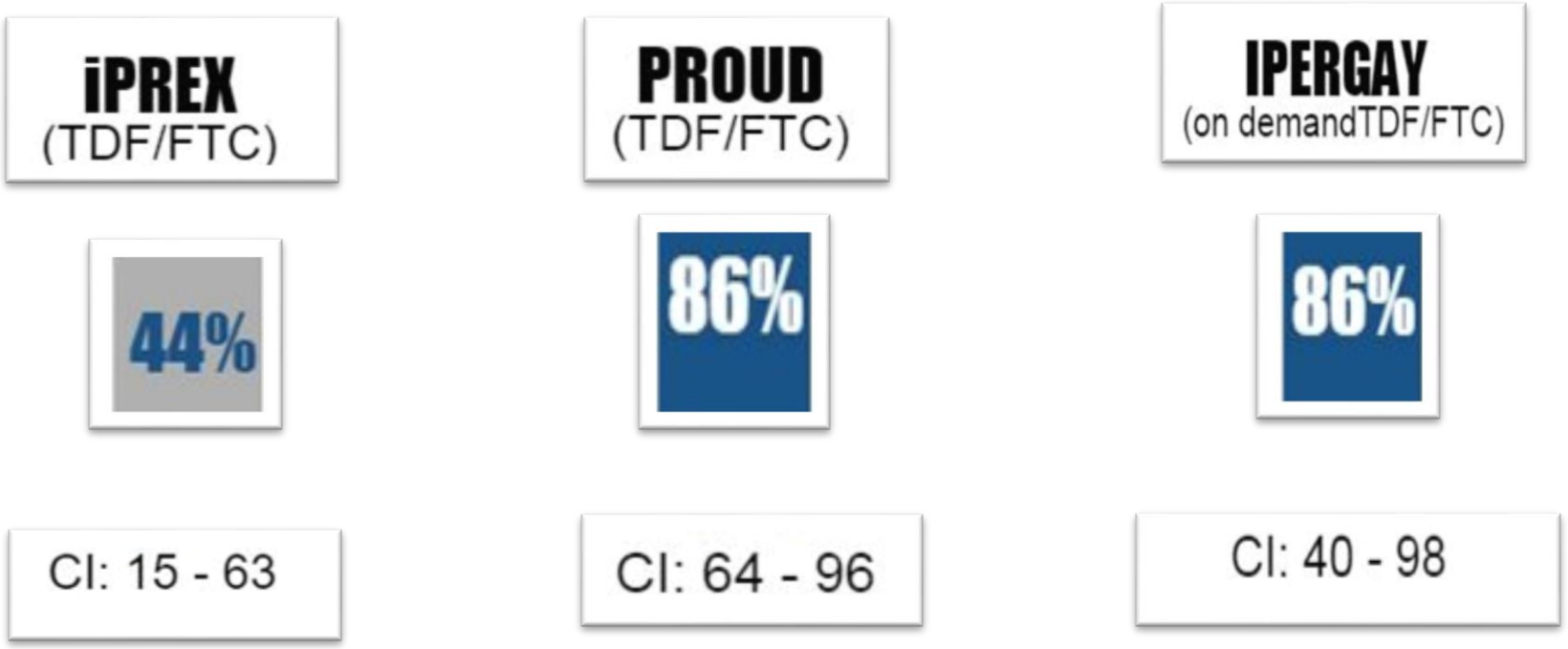
PrEP

- Pre-exposure prophylaxis
- Tenofovir and emtricitabine (TDF/FTC)
  - Branded (Truvada)
  - Generic

Effectiveness in clinical trials: MSM and TGW



- South America, US, SA
- 2499: MSM (88%) and TGW (12%)
- Adherence 50%

(Grant et al, NEJM, 2010)

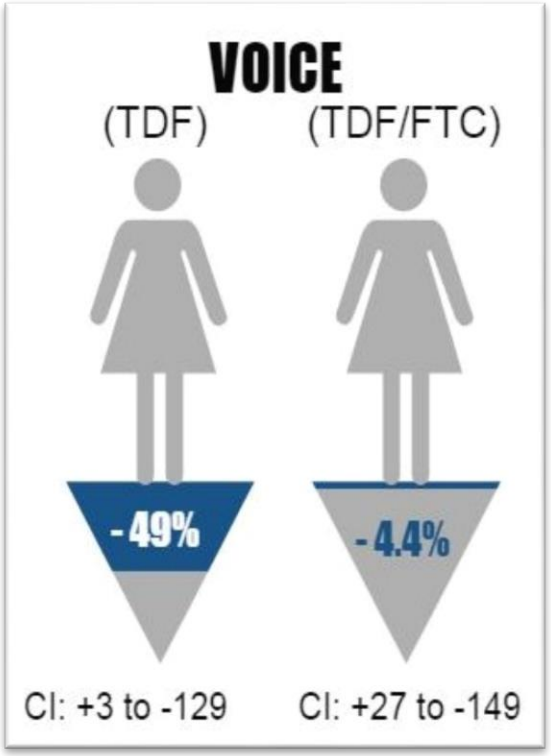
- UK
- 544 MSM (1 TGW)
- Adherence 88%

(McCormack et al, The Lancet, 2015)

- France
- 414 MSM
- Adherence 86%

(Molina et al, NEJM, 2015)

Effectiveness in clinical trials – Heterosexual



- South Africa, Uganda, Zimbabwe
- 5029 women, randomised to oral TDF, oral TDF/FTC, vaginal TFV gel, placebo
- Zero evidence effectiveness
- Adherence: 25-30%

(Marazzo et al. NEJM, 2015)

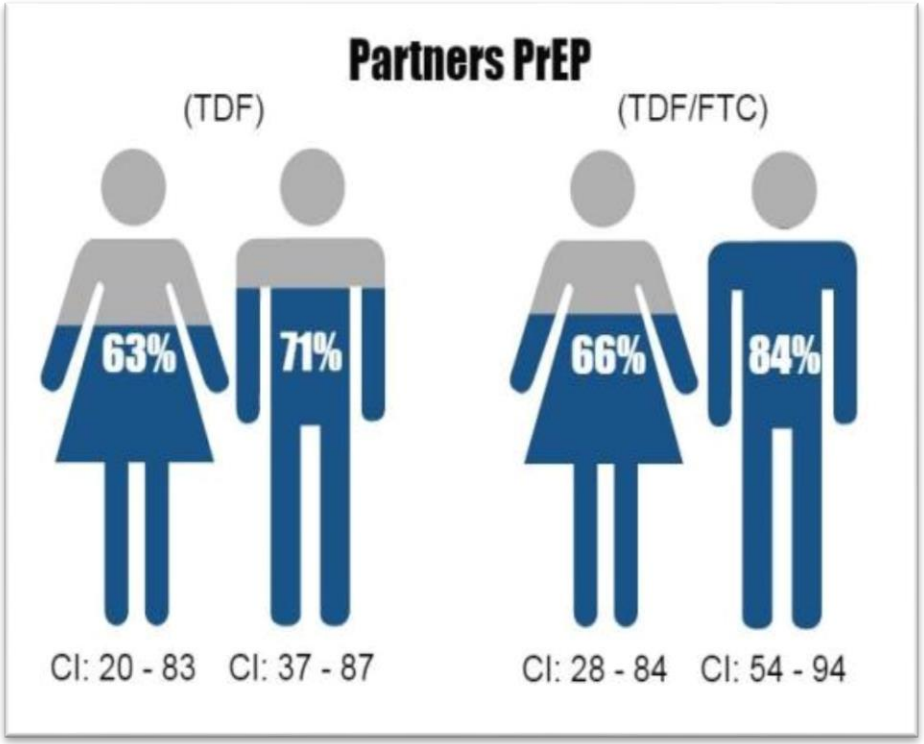
- South Africa, Kenya, Tanzania
- 2120 women
- Randomised 1:1 to TDF/FTC or placebo
- No evidence effectiveness
- Adherence <40%

(van Damme L et al. NEJM, 2012)

Effectiveness in clinical trials – Heterosexual

- Botswana
- HT men and women (n=1219)
- Randomised to TDF/FTC or placebo
- Adherence: 84%

(Karim et al. Lancet 2011)



- Kenya and Uganda
- Heterosexual men and women randomised to placebo (n=1586) or TDF (n=1589) or TDF/FTC (n=1583)
- Adherence: 92%

(Baeten et al. NEJM 2012)

Effectiveness in clinical trials – Trans women and PWID

- Subgroup analysis iPrEx trial[1]: 339 TGW
  - 11 infections PrEP arm and 10 in placebo
  (HR: 1.1, 95% CI: 0.5–2.7)
  - None of those infected had detectable TDF/FTC in blood
  - Reported higher rates of high HIV risk behaviours

- The Bangkok Tenofovir Study[2]: 1:1 male and female PWID randomised to TDF or placebo.
  - 48.9% reduction incidence (95% CI 9.6-72.2)
  - Adherence 83%

1. *Deutsch MB et al. HIV pre-exposure prophylaxis in transgender women: a subgroup analysis of the iPrEx trial. The Lancet HIV (2015)*
2. *Choopanya et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study). The Lancet (2013)*

Effectiveness in open label extension studies - MSM

iPrEx-OLE[1]

- 76% of 1603 iPrEX participants, MSM/TGW
- No seroconversions if drug levels compatible with ≥four pills/week

IPERGAY-OLE[2]

- 362 MSM
- 97% reduction in risk compared to the placebo arm of the IPERGAY randomised phase

1. *Grant RM et al. Uptake of PrEP, sexual practices, and HIV incidence in men and transgender women who have sex with men. The Lancet Infectious Diseases (2014)*
2. *Molina et al. Efficacy of "On Demand" PrEP in the ANRS IPERGAY Open-Label Extension Study. IAS, Durban (2016)*

Effectiveness in open label extension studies – Heterosexual

Partners PrEP OLE[1]

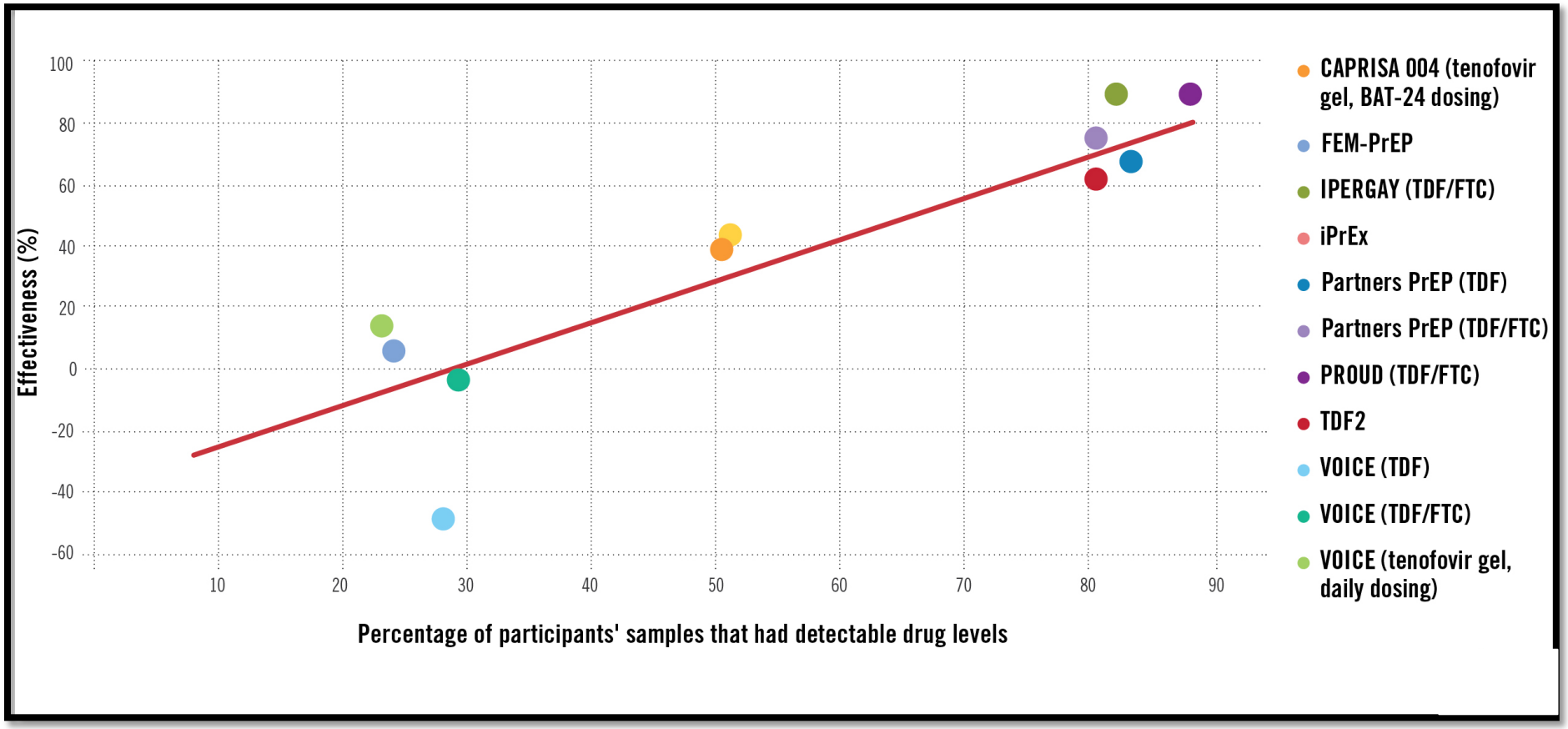
- 89% of 1418 heterosexual men and women
- Efficacy of TDF (67%) & FTC/TDF (75%)

TDF2 OLE[2]

- 229 men and women, 33% did not complete follow up
- No new HIV infections during the 12 month F/U
- 87% women and 96% men had detectable drug levels at visits

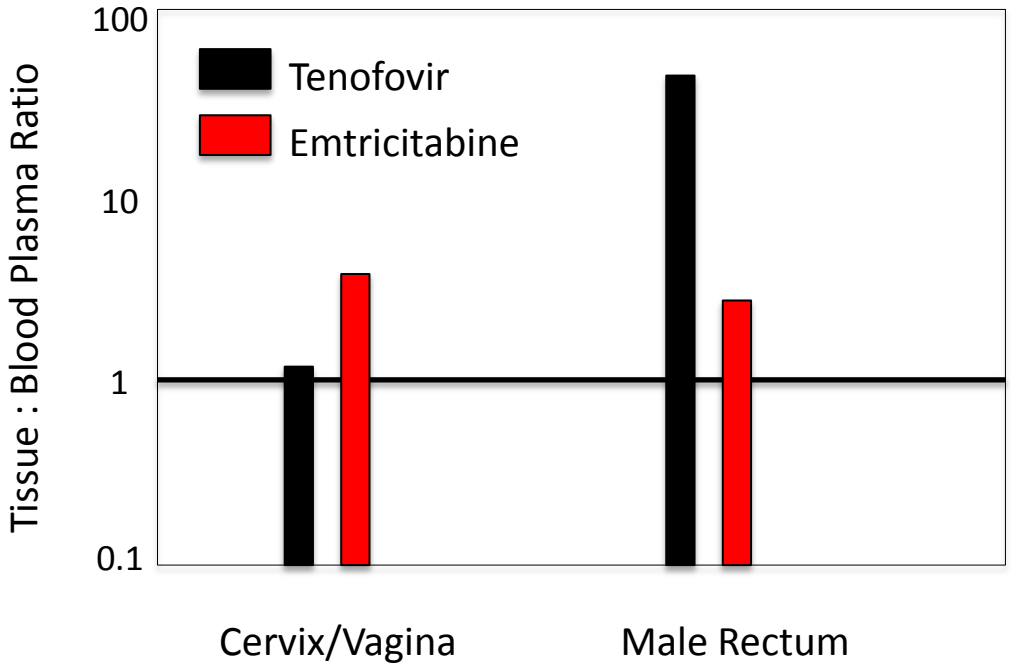
1. *Ndase P et al. Successful discontinuation of the placebo arm and provision of an effective HIV prevention product: the partners PrEP study experience. JAIDS. 2014*
2. *Chirwa LI et al. Enrollment into open-label phase of TDF2 PrEP Study. 20th IAC; 2014; Melbourne, Australia.*

Differences in efficacy largely explained by adherence



Tissue concentrations: male versus females

GENDER DIFFERENCE OR COMPARTMENT DIFFERENCE?



Different concentrations of membrane transporters explain a lot of the difference in genital tract tenofovir concentrations

Different tissue drug concentrations = different dose-response in males versus females

Need for: Different adherence patterns?

Different drugs/drug combinations?

Different dosing schedules?

[1] Patterson et al et al. 2011; [2] Nichol MR et al. J Clin Pharmacol. 2014

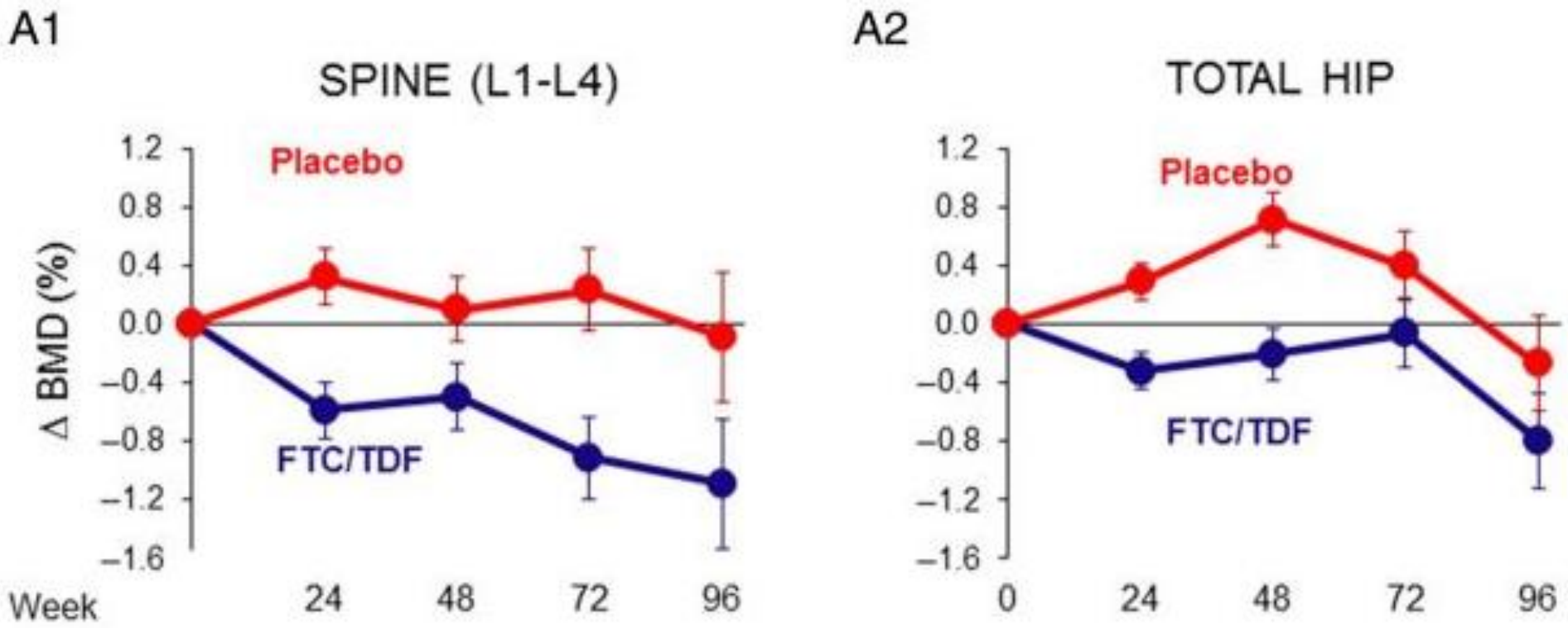
PrEP - dosing

- Daily dosing
  - For all
  - 7 day lead in to protection
- ‘On demand dosing’
  - For anal sex
  - 2 tablets 2 – 24 hours before sex lead in to protection
- Ts and Ss: Tuesday, Thursday, Saturday, Sunday
  - For anal sex

PrEP - safety

- **Renal function**
  - Where renal function has been affected PrEP was associated with mild, non-progressive and reversible reductions in renal function
  - Being aged >40 years or having impaired renal function at baseline are associated with a (small) risk of renal impairment.
- **Bone mineral density**
  - Where bone mineral density was studied, small net decreases have been noted in those taking PrEP.
  - There are no long-term data on bone health or evidence of increased fracture risk.

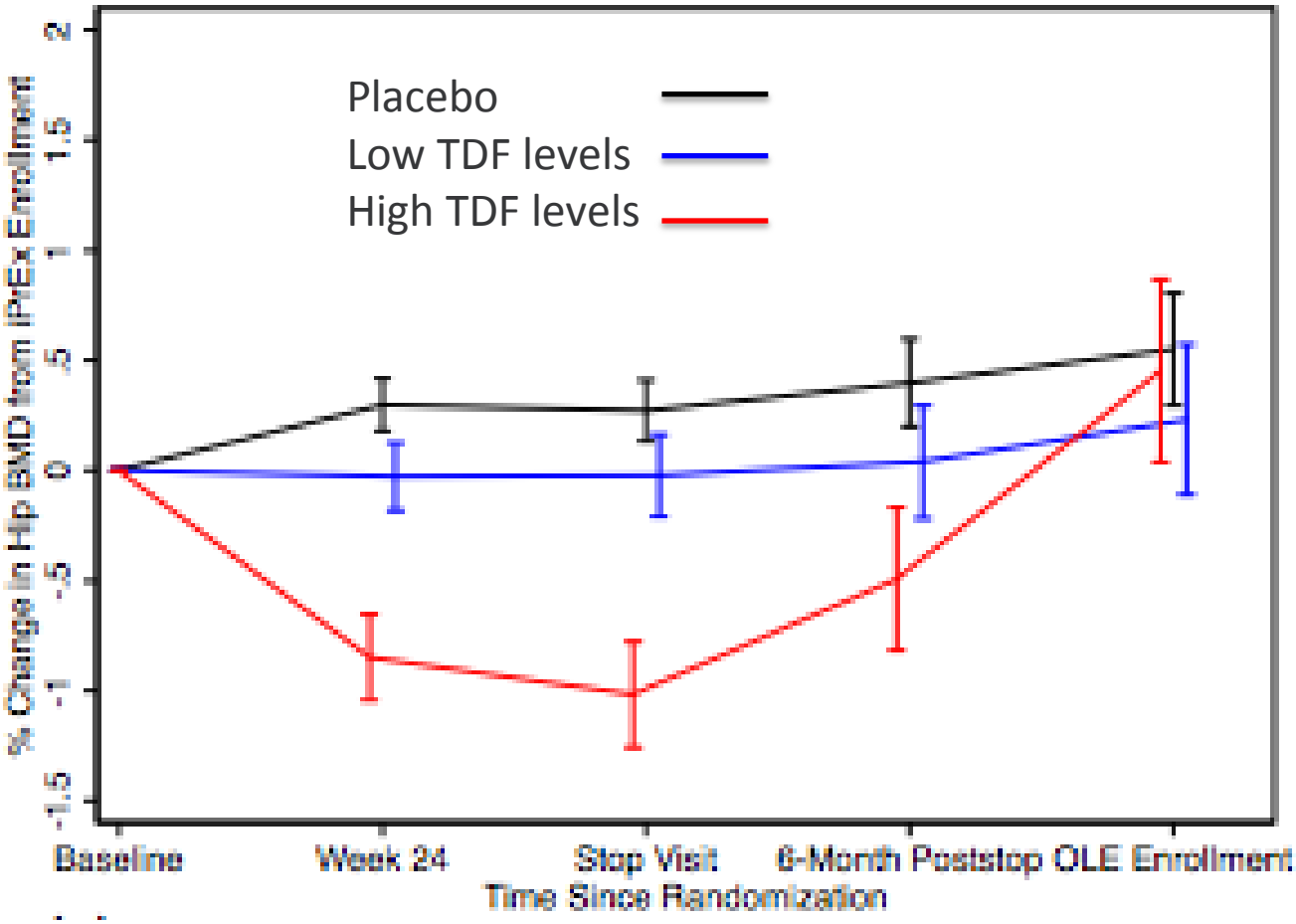
Bone safety: iPrEx



Decline significantly steeper in first 24 weeks vs later time periods

Mulligan K et al. Clin Infect Dis. 2015 Aug 15; 61(4): 572–580.

iPrEx BMD reversibility



On average, BMD returned to baseline levels by 1 year after PrEP stop. Recovery was consistent across age, baseline BMD z-score and treatment duration.

Glidden DV et alJ Acquir Immune Defic Syndr. 2017 Jun 19. doi: 10.1097/QAI.0000000000001475.

PrEP – drug resistance

- Ensuring individuals are HIV negative when starting PrEP is essential

- HIV drug resistance uncommon in clinical trials – but was seen in those starting PrEP with undiagnosed recently acquired HIV

- PROUD study:
  - **3** of **6** individuals who were seroconverting at baseline (immediate group) or month 12 (deferred group) developed resistance to emtricitabine

PrEP – identifying those at risk

- WHO:
  - "Offering PrEP should be a priority for populations with an HIV incidence of about 3 per 100 (3%) or higher"
- HIV incidence (MSM):
  - PROUD deferred arm: 9% incidence
  - IPERGAY placebo arm: 7% incidence

- How do we identify other groups with similarly high HIV incidence?

HIV incidence in STI Clinic Attendees

Estimated HIV incidence among sexual health clinic attendees in England (2012)		
Group of attendees	Estimated incidence	95% CI
All	0.15%	0.13% - 0.17%
MSM	1.34%	1.15% - 1.53%
Heterosexuals	0.03%	0.02% - 0.04%
Black African Heterosexuals	0.17%	0.08% - 0.27%

Ref: Sex Transm Infect 2015;91:A2 doi:10.1136/sextrans-2015-052126.4

HIV incidence in HIV negative MSM who re-attended at STI clinics (2012)		
Category	HIV incidence (per 100 py)	95% CI
HIV test 42-365 days prior to current attendance	2.4	2.0 – 2.8
Bacterial STI in previous year and/or at current attendance	3.3	2.8 – 4.0
Rectal bacterial STI in previous year and/or at current attendance	5.2	3.7 – 6.7
PEP in previous year	3.3	1.7 – 6.3

Ref: GUMCAD, PHE, HIV incidence analyses 2012

HIV risk assessment and PrEP - heterosexual

- Good evidence of PrEP efficacy if provided to those ***at high risk*** of HIV
- All trials in heterosexuals conducted in sub-Saharan Africa
- HIV incidence in black Africans attending GUM clinics is 0.17%[1], compared to the 2 – 5% incidence seen in the RCTs
- Difficult to identify, using specific clinical criteria, heterosexual people in the UK who would be at sufficient risk
- Insufficiently precise clinical criteria or application of criteria may result in people unnecessarily taking PrEP

[1]GUMCAD, PHE, HIV incidence analyses 2012

HIV risk assessment and PrEP - Trans people

It is estimated that worldwide, trans women are 49 times more likely to be infected with HIV than the general population

- 1 unplanned subgroup analysis of trans women (iPrex and iPrex OLE)
- Very small numbers of trans women in phase 3 trials (PROUD and Ipergay)
- Effectiveness poorer than MSM – adherence ……..and yet high HIV risk
- There are no PrEP studies in trans women which are specifically designed for and focussed on trans women and trans issues,
- There is no data at all in trans men

Summary: PrEP efficacy and safety

- PrEP is highly effective and safe
- We have the best evidence for MSM
- The challenge for other groups at risk of HIV is:
  - Awareness and knowledge
  - Engagement
  - Identifying those at risk
- There are dosing options for anal sex (daily vs on-demand)
- Daily dosing for other exposures
- Renal monitoring important – but mostly for those already at risk of renal disease
- Effect on bone ‘uncertain’ – but no evidence of harm so far from studies