PrEP Dosing Strategies

Outline

- Background
  - PrEP absorption and tissue penetration
- Oral versus topical
- Lead in and lead out dosing
  - Time to protection
- Cycling on and off PrEP
- Balancing toxicity and adherence

ART-Based PrEP

How are antiretrovirals used?	• **Oral pill**
	• Topical gel (microbicide)
	  •Rectal
	  •Vaginal
	• Injection
	• Intravaginal ring

How often are the antiretrovirals used?	• **Daily** • Intermittently • Coitally (before/sex)
How many antiretrovirals are used?	• **Combination** • Monotherapy
What antiretrovirals are used?	• **Truvada** • Tenofovir • (Cabotegravir /miraviroc)

Post Exposure prophylaxis (PEP)

Treatment as Prevetion (TasP)

Combination Prevention with existing and new technologies

Four Early Trials Demonstrating PrEP Efficacy in Diverse Geographic and Risk Populations

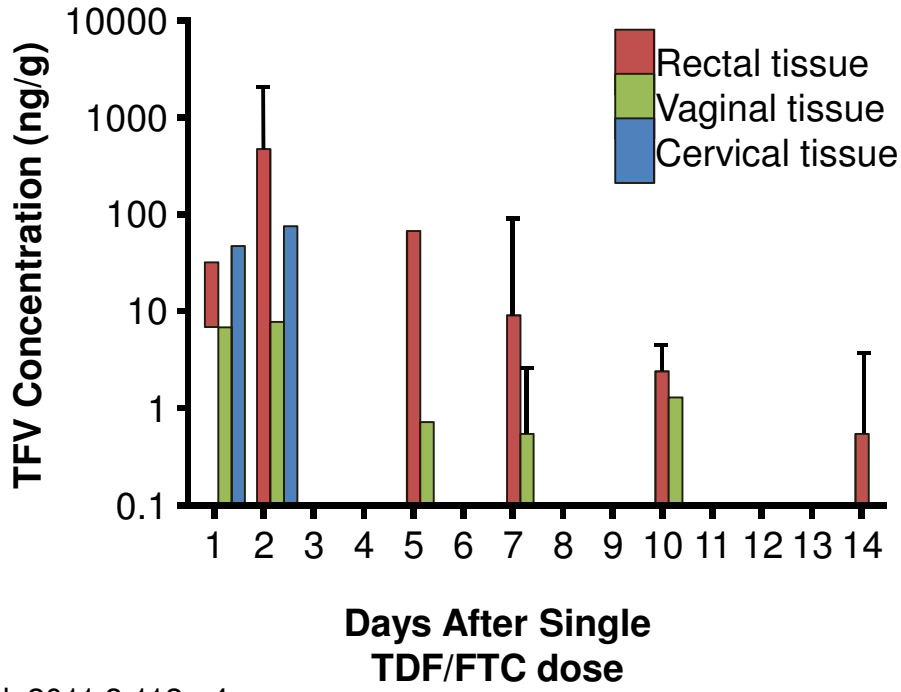
Study, population	PrEP agent	# of HIV infections		PrEP efficacy (95% CI) publication
		PrEP	placebo	
Partners PrEP Study Heterosexual couples Kenya, Uganda (n=4758)	TDF/FTC	13	52	**75%** (55-87%)
	TDF	17		**67%** (44-81%) Baeten et al. N Engl J Med 2012
TDF2 Study Heterosexuals Botswana (n=1219)	TDF/FTC	10	26	**62%** (16-83%) Thigpen et al. N Engl J Med 2012
Bangkok Tenofovir Study (BTS) IDUs Thailand (n=2413)	TDF	17	33	**49%** (10-72%) Choopanya et al. Lancet 2013
iPrEx MSM Brazil, Ecuador, Peru, South Africa, Thailand, US (n=2499)	TDF/FTC	36	64	**44%** (15-63%) Grant et al. N Engl J Med 2010

Penetration of TDF in Mucosal Tissues

Slide credit: clinicaloptions.com

- Exposure to TFV, TFV-DP, FTC, FTC-TP varied widely in different mucosal tissues
- Women may need to be more adherent to PrEP than MSM

Concentrations of TFV (A) and TFV-DP (B) in Rectal, Vaginal, and Cervical Tissues After a Single Dose of TDF/FTC



Patterson KB, et al. Sci Transl Med. 2011;3:112re4.

Lead In and Out Doses

…Or Time to Protection

7 days for anal tissue levels to reach high level steady state

→ Protects against anal aquisition of HIV

20-30 days for vaginal tissue levels to reach high level steady state

→ Protection againt vaginal aquisition of HIV

→ May need higher adherence levels for women

28 day lead out time (cf. PEP)

Cycling On or Off PrEP

- PrEP is not a lifelong drug-taking intervention
- PrEP should be used only if there is possible exposure to HIV
  - Risk levels expected to change
  - People will use PrEP for variety of reasons
  - Case example e.g. student / CSW
- People can cycle off PrEP
- This is NOT non-adherence
- Remember lead in and lead out times

Getting The Right Balance

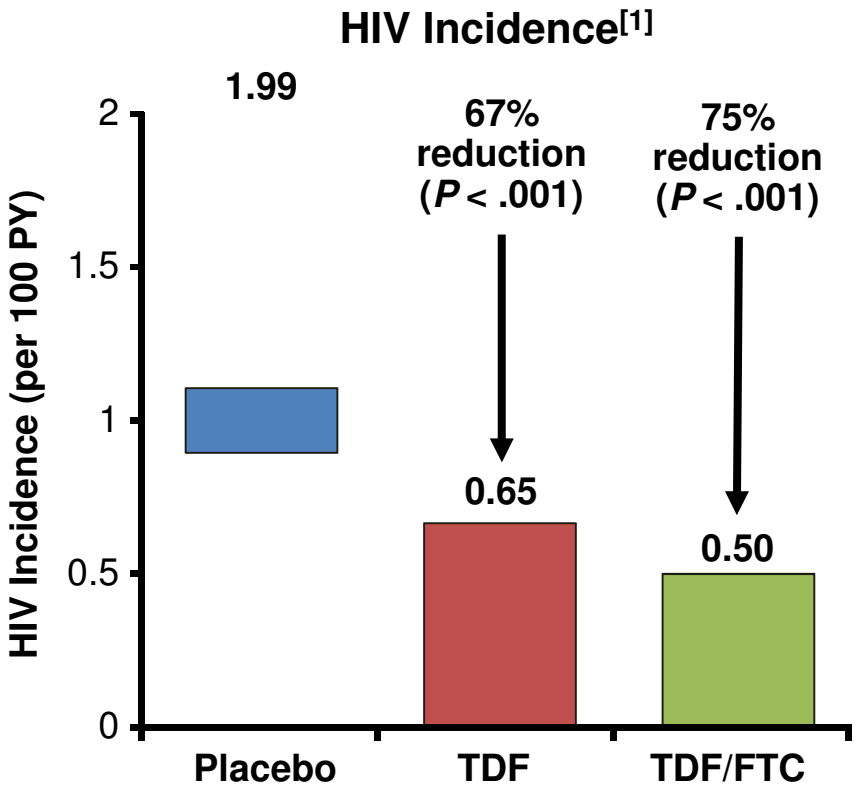
Convenience
Adherence

Toxicity
Efficacy

Partners PrEP: Efficacy and Resistance Results

Slide credit: clinicaloptions.com

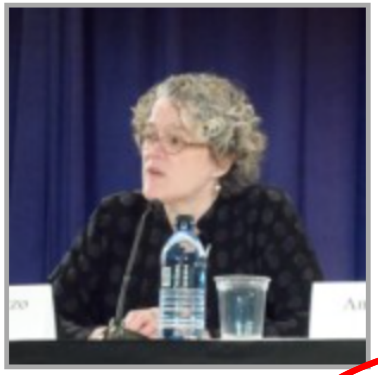
- Both PrEP arms significantly reduced HIV acquisition risk; similar efficacy in men and women[1]
  - TDF levels correlated with HIV protection
- No differences in serious AEs, creatinine abnormalities across arms
- No evidence of risk compensation
- Ultradeep sequencing in 121 HIV seroconverters (25 TDF/FTC, 38 TDF, 58 placebo)[2]
  - Overall resistance: 7.4% (9/121)
  - In 26 pts, drug levels suggested PrEP use during or after HIV acquisition; in 5/26, resistance detected



1. Baeten JM, et al. N Engl J Med. 2012;367:399-410.
2. Lehman DA, et al. J Infect Dis. 2015;211:1211-1218.
3. Mujugira A, et al. CROI 2015. Abstract 989.

CROI 2013: VOICE Trial Results on Daily HIV Prevention for Women

March 4, 2013, by Reilly O'Neal



Dr. Jeanne Marrazzo at CROI 2013 (photo: Reilly O'Neal)

Highly anticipated results were reported today from the VOICE trial, which looked at the safety and efficacy of daily oral PrEP and drug-containing vaginal microbicide gel in more than 5,000 women in South Africa, Uganda, and Zimbabwe.

Jeanne Marrazzo, MD, MPH, explained to a packed auditorium at the 20th Retrovirus Conference that these approaches did not prevent new HIV infections in this particular study because most participants didn't actually use them.

When VOICE—short for Vaginal and Oral Interventions to Control the Epidemic—began enrolling women in September 2009, it had five study groups. Participants were randomized to use one of the following products daily:

- tenofovir gel
- placebo gel
- oral tenofovir tablet
- oral Truvada (the tenofovir/emtricitabine combination)
- oral placebo pill

The NEW ENGLAND JOURNAL of MEDICINE
August 2, 2012

ORIGINAL ARTICLE

Preexposure Prophylaxis for HIV Infection among African Women

Van Damme, L et al

FEM-PrEP

- RCT of 2120 HIV negative women in Kenya and Tanzania
- TDF/FTC PrEP versus placebo
- Objectives: effectiveness and safety

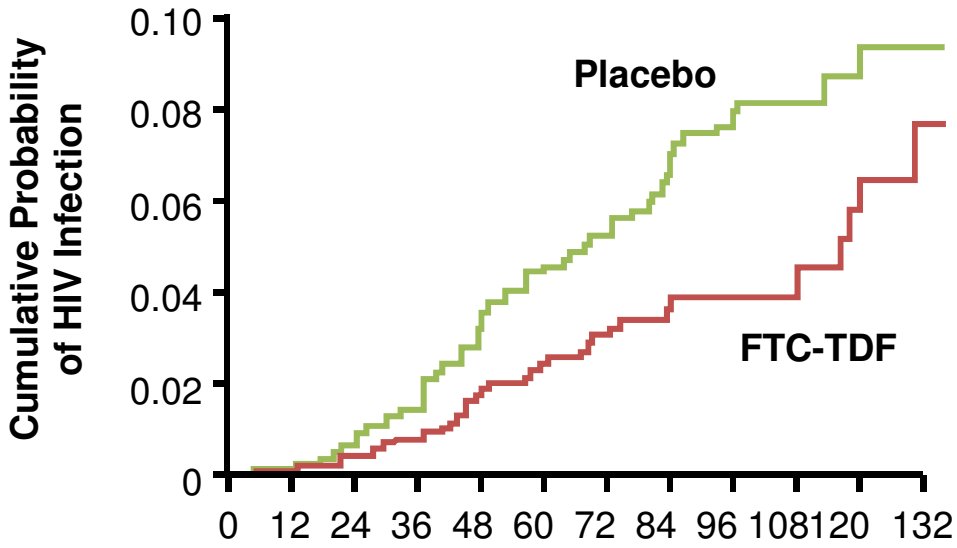
Results

- HIV incidence 4,7% PrEP and 5.0% placebo → no difference
- Significantly higher side effects in intervention arm (GIT)

CONCLUSIONS

Prophylaxis with TDF–FTC did not significantly reduce the rate of HIV infection and was associated with increased rates of side effects, as compared with placebo. Despite substantial counseling efforts, drug adherence appeared to be low. (Supported by the U.S. Agency for International Development and others; FEM-PrEP ClinicalTrials.gov number, NCT00625404.)

iPrEX: Daily Oral TDF/FTC PrEP for MSM



- Double-blinded, randomised trial of oral TDF/FTC QD PrEP vs PBO for HIV-negative MSM/TGW at high risk for HIV infection (N = 2499)
- Relative reduction in cumulative risk of HIV infection: 44% with TDF/FTC vs PBO (*P* = .005)[1]

1. Grant RM, et al. N Engl J Med. 2010;363:2587-2599.
2. Marcus JL, et al. PLoS One. 2013;8:e81997.
3. Liegler T, et al. J Infect Dis. 2014;210:1217-1227.

Slide credit: clinicaloptions.com

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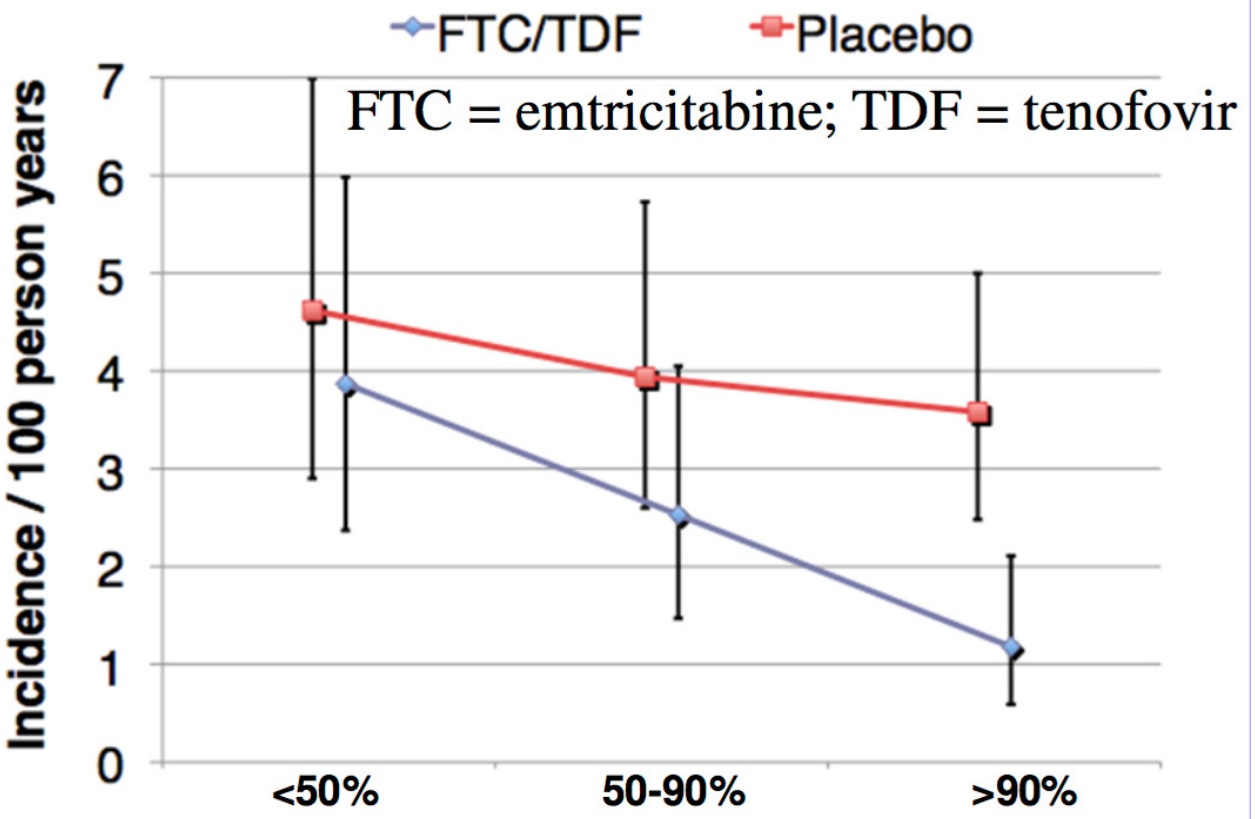
Summary
Efficacy of Oral FTC/TDF PrEP

	Efficacy	95% CI	P Value
Intention to Treat	47%	22-64	P=0.001
Modified Intention to Treat	44%	15-63	P=0.005
As Treated (50%)	50%	18-70	P=0.006
As Treated (90%)	73%	41-88	P<0.0006
Unprotected RAI at Baseline	58%	32-74	P<0.0006

New England Journal of Medicine, online Nov 23, 2010

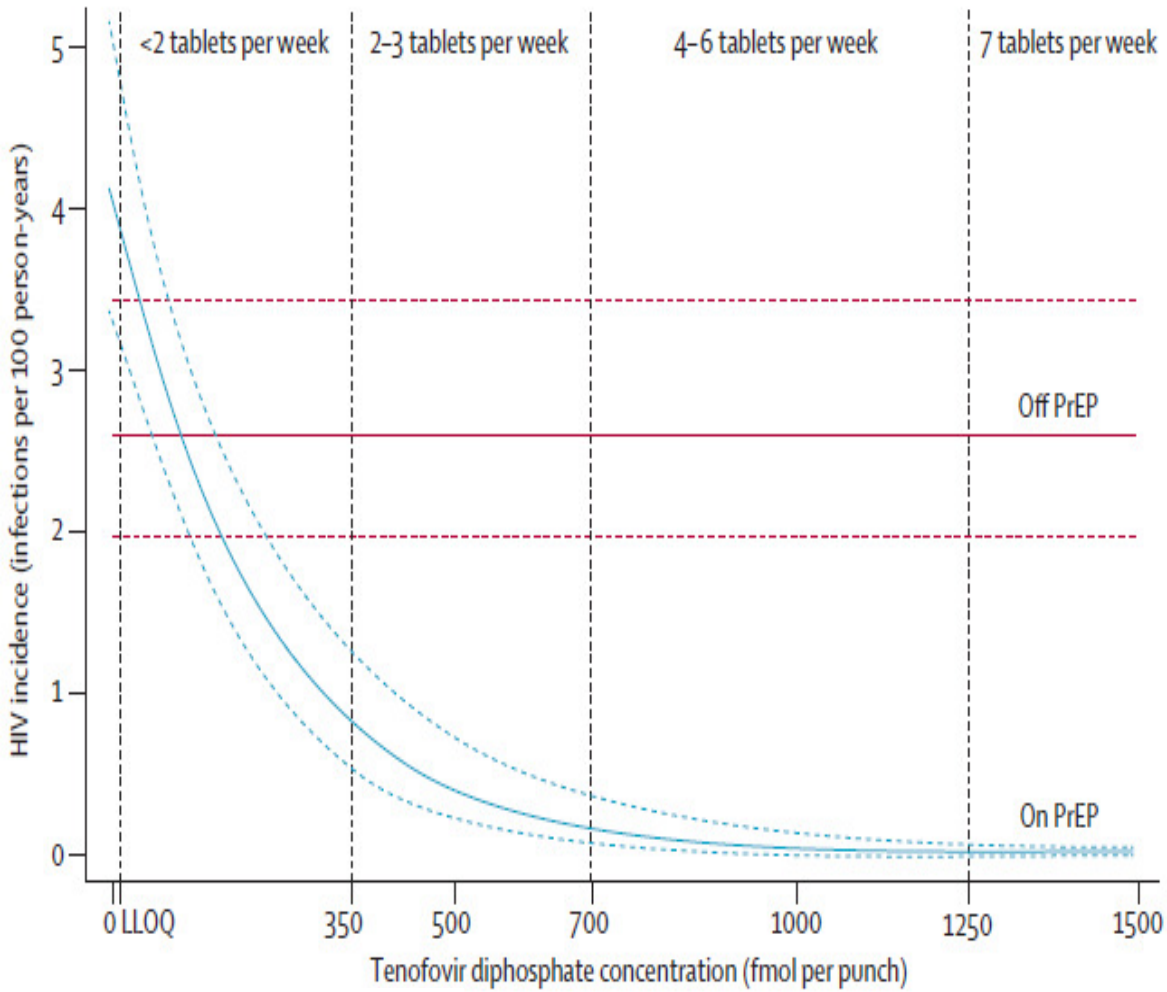
iPrEX: Adherence and Efficacy



	<50%	50-90%	>90%
% of Visits	18%	33%	49%
Efficacy	**16%**	**34%**	**68%**
95% CI	-54 - 54	-20 - 64	36 - 84

Grant, R et al. CROI, 2010

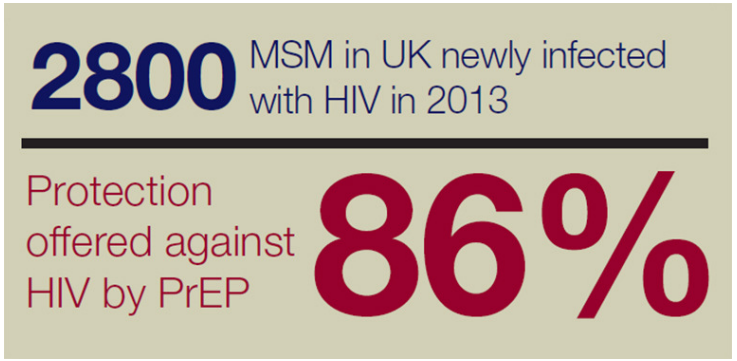
Perfect adherence is not required: iPrEx OLE



100% HIV protection was seen with adherence consistent with ≥4 tablets per week

Grant et al. Lancet ID 2014

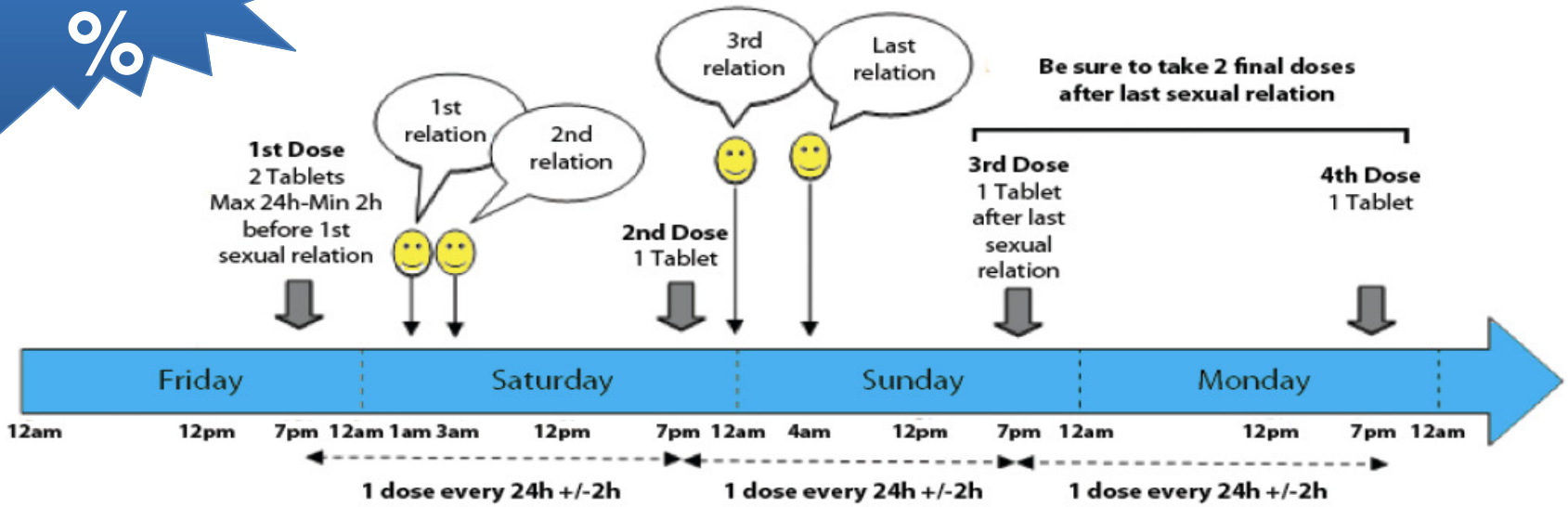
PROUD Study UK



- 545 MSM recruited to take Truvada PrEP
- Immediate or delayed initiation with 24 months follow up
- Study stopped early by DSMB as efficacy dictates that continuing would be unethical
- **Efficacy =86% (90% CI: 58 – 96%) P-value =0.0002**
- **Number Needed to Treat =13 (90% CI: 9 – 25)**
- HIV incidence amongst gay men in England is much higher than what was thought
- There was no difference in the rate of STIs other than HIV
- The use of Truvada for PrEP was safe and concerns about resistance are minimal
- PrEP can be delivered as part as routine HIV reduction package

86 %

IPERGAY France



- RCT of Truvada versus placebo in 400 recruited high risk MSM
- Sex-based dosing (4 or more doses)
- Relative RR of HIV incidence was 86% (95% CI 40% to 99%, P = 0.002)
- Number needed to treat for 1 year to prevent 1 infection was 18
- Also stopped early by DSMB because of high efficacy
- Very sexually active
- Self-reported adherence: 43% took tablets correctly; 29% took tablets sub-optimally
- Did they not get almost daily dosing by default?

On-Demand PrEP: Points for Discussion

Slide credit: clinicaloptions.com

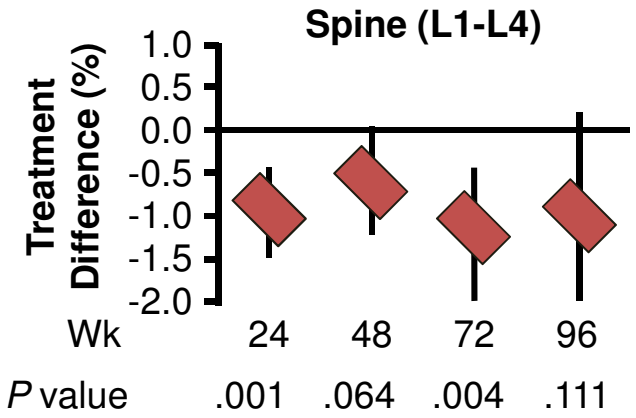
- Risk if patient not adherent (poor coverage)?
- Risk if patient infrequently having sex?
- Does median monthly number of pills in IPERGAY translate to “on demand”?
- Do pharmacokinetics affect whether results can be extrapolated to women?

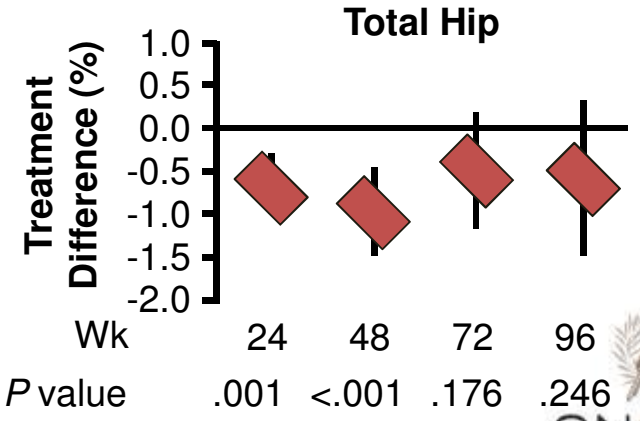
Current evidence supports daily dosing

iPrEX: Bone Mineral Density Sub study

Slide credit: clinicaloptions.com

- iPrEX substudy: dual-energy x-ray absorptiometry assessment (N = 498)
- Small net decrease in spine and total hip BMD with TDF/FTC vs PBO at Wk 24 (-0.91% and -0.61%, respectively; *P* = .001 for both)
- No difference in fracture rate between groups (*P* = .62)

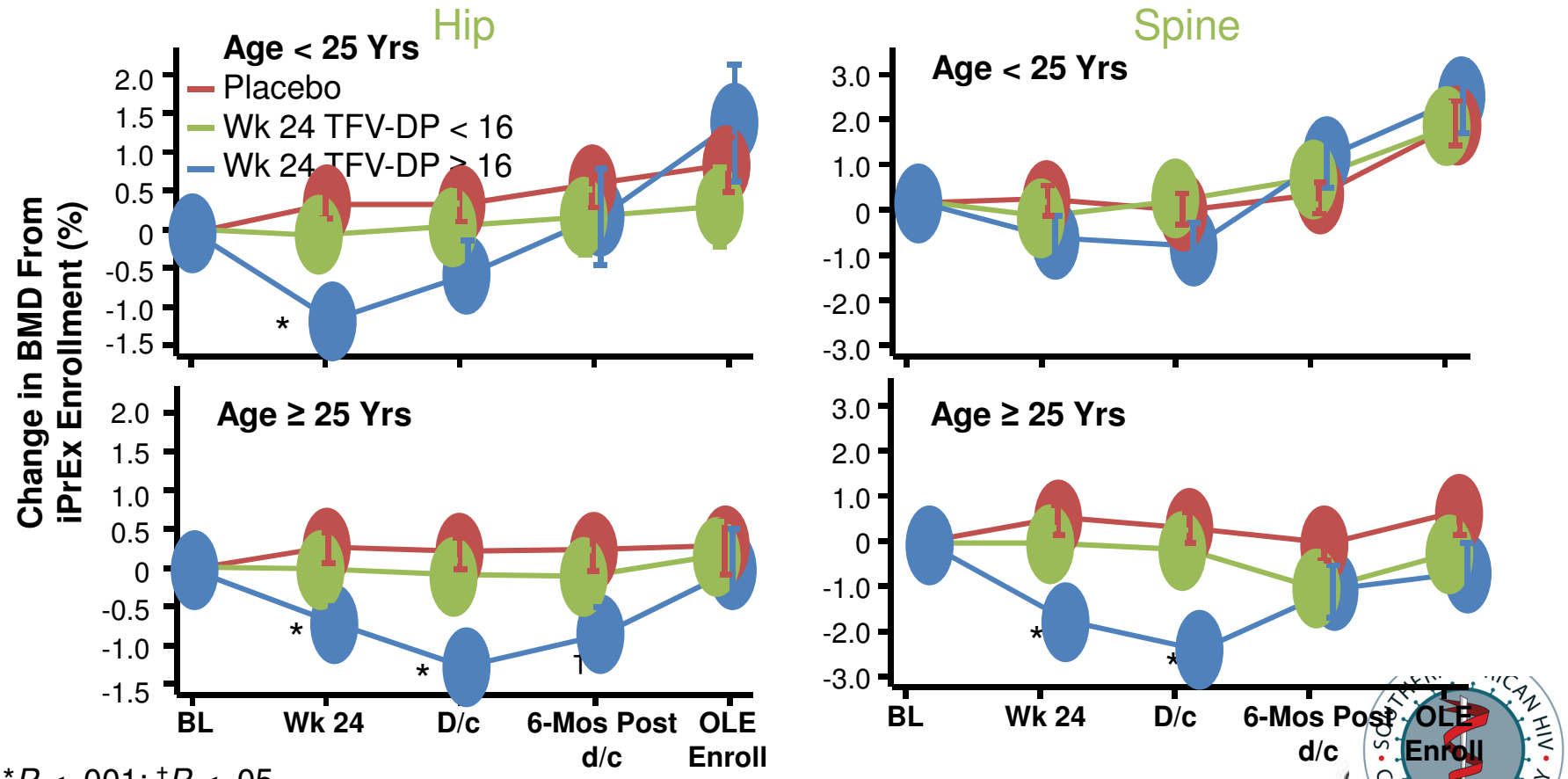




Mulligan K, et al. Clin Infect Dis. 2015;61:883-92.

iPrEx BMD Sub study: BMD Recovery After Discontinuation of TDF/FTC PrEP

- Data compared for TFV-DP < or ≥ 16 fmol/M



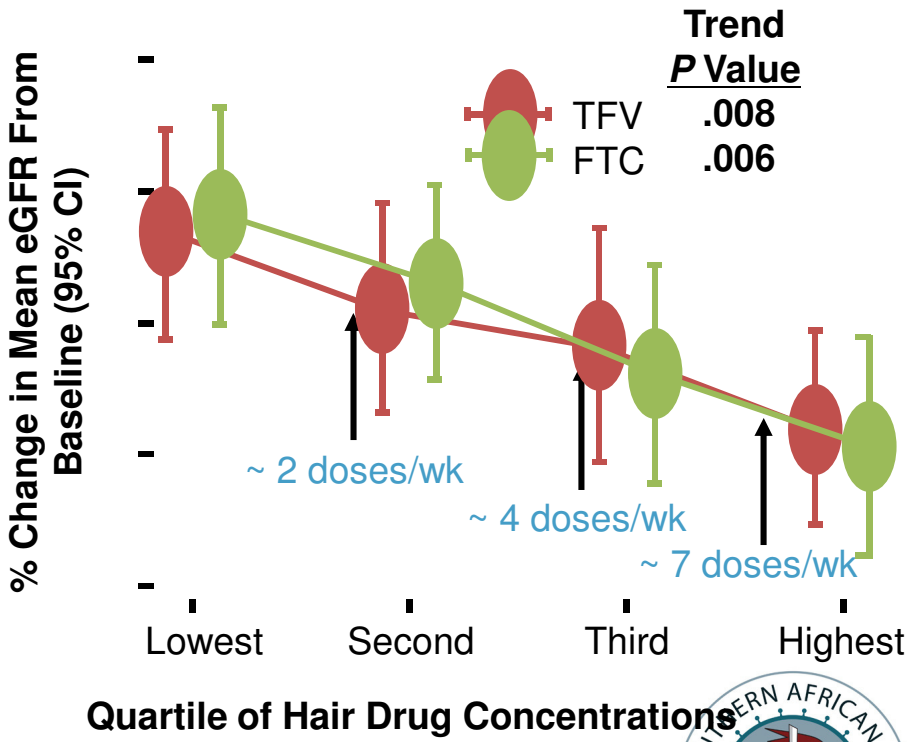
*$P < .001$; †$P < .05$

Grant R, et al. CROI 2016. Abstract 48LB.

Cumulative Decline in Renal Function on TFV/FTC PrEP

- Higher TFV exposure associated with greater eGFR decreases in 2 studies
  - iPrEx OLE[1] (n = 220): hair sampling for exposure
  - US Demo Project[2] (n = 557): dried blood spot sampling for exposure
- In both studies, eGFR decrease to < 70 mL/min more frequent among those with BL eGFR < 90 mL/min and older persons (older than 40-45 yrs)

Change in eGFR From BL vs Concentration of TFV or FTC in Hair[1]



1. Gandhi M, et al. CROI 2016. Abstract 866.
2. Liu AY, et al. CROI 2016. Abstract 867.

Slide credit: clinicaloptions.com

Adherence and HIV protection

	% of blood samples with tenofovir detected	HIV protection efficacy in randomized comparison	HIV protection estimate with high adherence
Partners PrEP TDF/FTC arm	81%	75%	90% (tenofovir in blood)
TDF2	79%	62%	78% (prescription refill)
BTS	67%	49%	70% - 84% (tenofovir in blood / pill count)
iPrEx	51%	44%	92% (tenofovir in blood)
FEM-PrEP & VOICE	<30%	No HIV protection	N/A

When adherence was high HIV protection is consistent and high

Baeten et al N Engl J Med 2012; Thigpen et al N Engl J Med 2012; Choopanya et al Lancet 2013; Grant et al N Engl J Med 2010; Van Damme et al N Engl J Med 2012; Marrazzo et al CROI 2013

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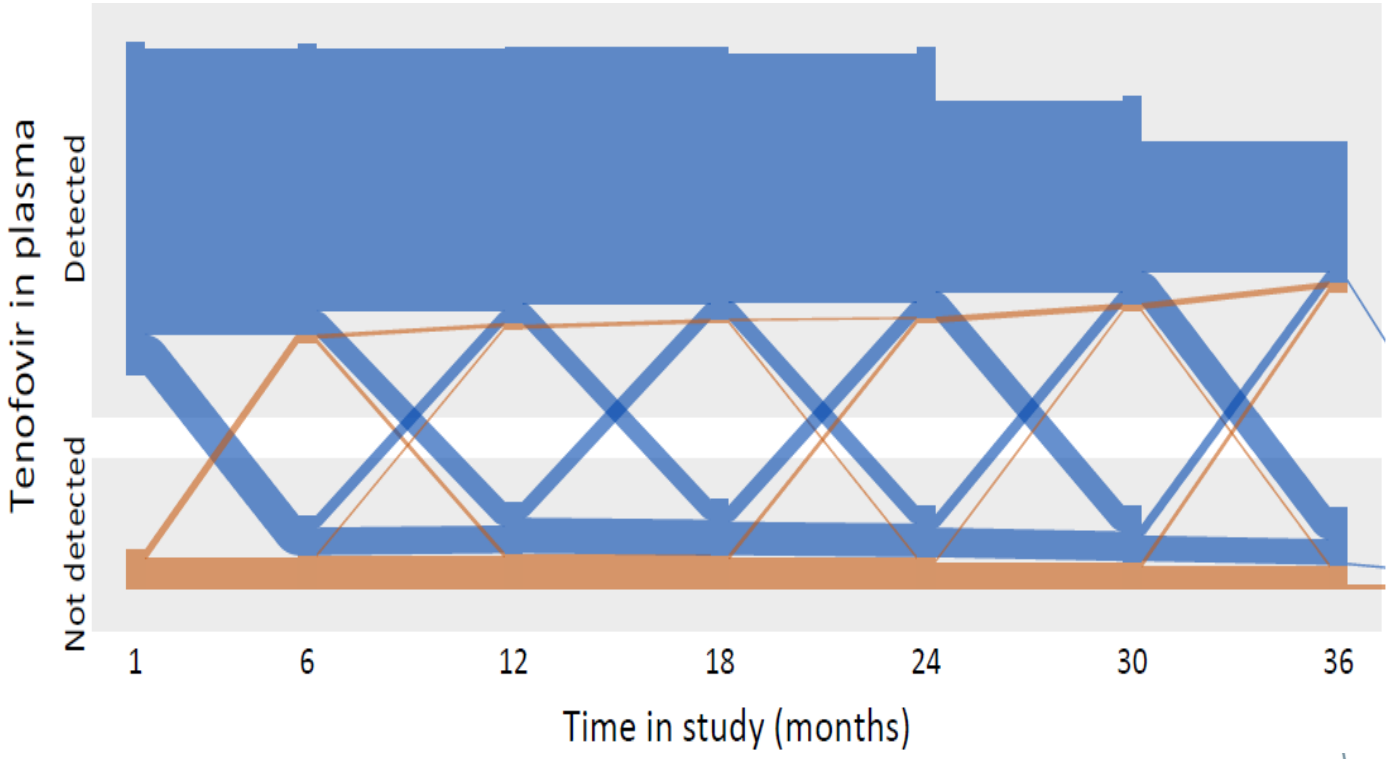
Oral PrEP Adherence

Longitudinal analysis of tenofovir detection in blood samples from persons on PrEP has shown that, for those who were taking PrEP, adherence was frequently consistent over time:



Partners PrEP Study, Baeten et al., Lancet ID 2014

US PrEP Demonstration Project

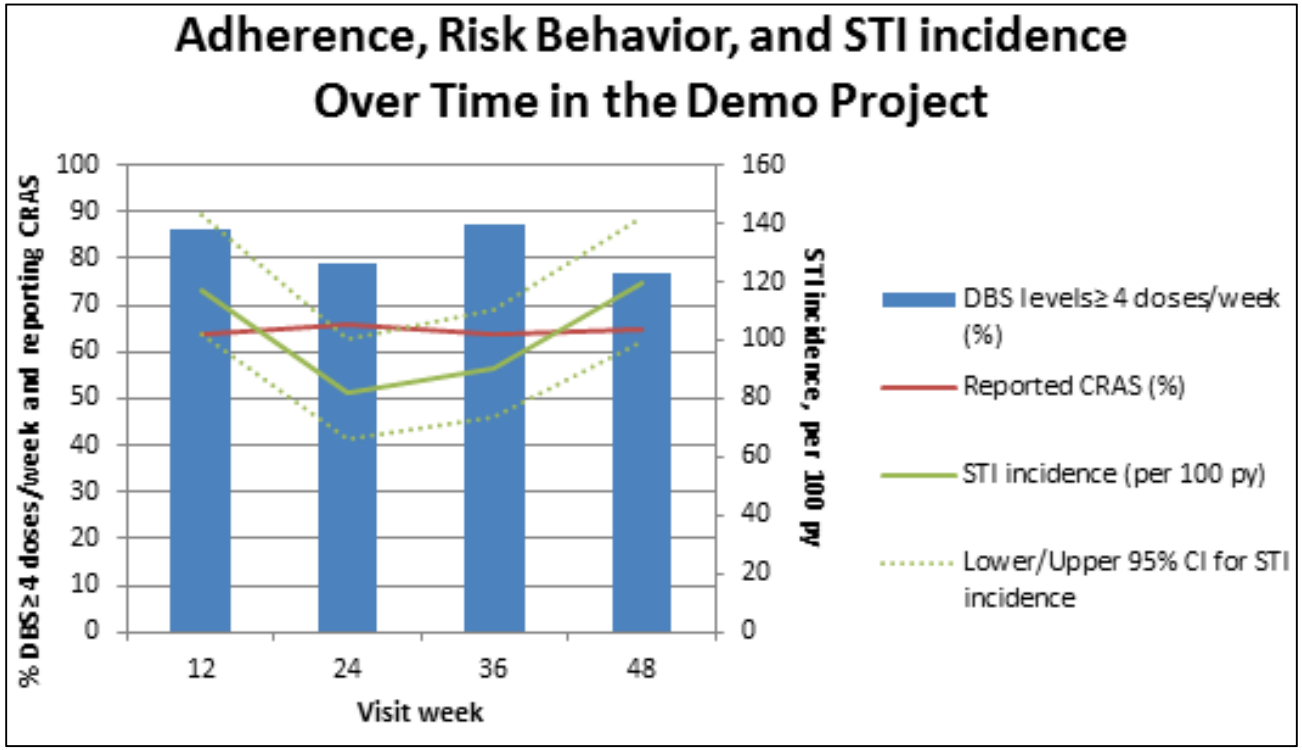
- Launched in Sep 2012
- Fully enrolled Mar 2014
- Eligible: At risk, HIV and HBV negative

PrEP eligibility and uptake, by site

	SF	Miami	DC	Total
Approached for pre-screening	581	312	176	1069
Declined	233	76	55	364
Ineligible (behavioral or medical)	48	79	21	148
Enrolled	300	157	100	557
Uptake among potentially eligible	**56%**	**67%**	**65%**	**60%**

Fuchs, J et al. Lessons learned from the US PrEP Demonstration Project: Moving from the "real world" to the "real, real world".

http://federalaidspolicy.org/wp-content/uploads/2015/04/Fuchs-FAPP-15-April-15.pdf



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PrEP and ARV Resistance

Resistance from PrEP was very rare; with only a small number who had acute infection at the time they were started on PrEP

	# of HIV seroconverters assigned PrEP with HIV resistance	
	HIV infected after enrollment	**Seronegative acute HIV infection at enrollment**
Partners PrEP	0 / 48	2 / 10
iPrEx	0 / 36	2 / 2
TDF2	0 / 10	1 / 1

Resistance = K65R (TDF) or M184V/I (FTC) mutations

PrEP in Pregnancy

Slide credit: clinicaloptions.com

- PrEP use at conception and during pregnancy by the uninfected partner may offer an additional tool to reduce the risk of sexual HIV acquisition[1]
- Data directly related to the safety of PrEP use for a developing fetus are limited
- Potential risks and limited information should be discussed
- TDF and FTC are classified as FDA Pregnancy Category B medications[2]

1. CDC. PrEP Guideline. 2014. 2. DHHS. HIV Perinatal Guideline. 2014.

Future PrEP Agents

Drug	Mechanism	Dosing Route	Dosing Frequency	Research Stage
Rilpivirine LA	NNRTI	SC Injection	1 Monthly	Phase 1
GSH 1265744	Integrase inhibitor	SC Injection	1 Monthly	Phase 1
Ibalizumab	CD4 attachment inhibitor	SC Injection	1-4 Weekly	Phase 1

Alternate drug mechanisms
Alternate delivery methods
Alternate dosing frequencies

Thank You

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www.wethebrave.co.za

Contact:

- Johan Hugo
- 021 447 2844
- hugo@anovahealth.co.za

- Ben Brown
- 021 421 6127
- bbrown@anovahealth.co.za

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