Infezione da HIV:
uno sguardo al futuro

Indicazioni di efficacia e limiti della PrEP

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Disclosures

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- Speaker: Gilead, Merck
- Research grant: Gilead
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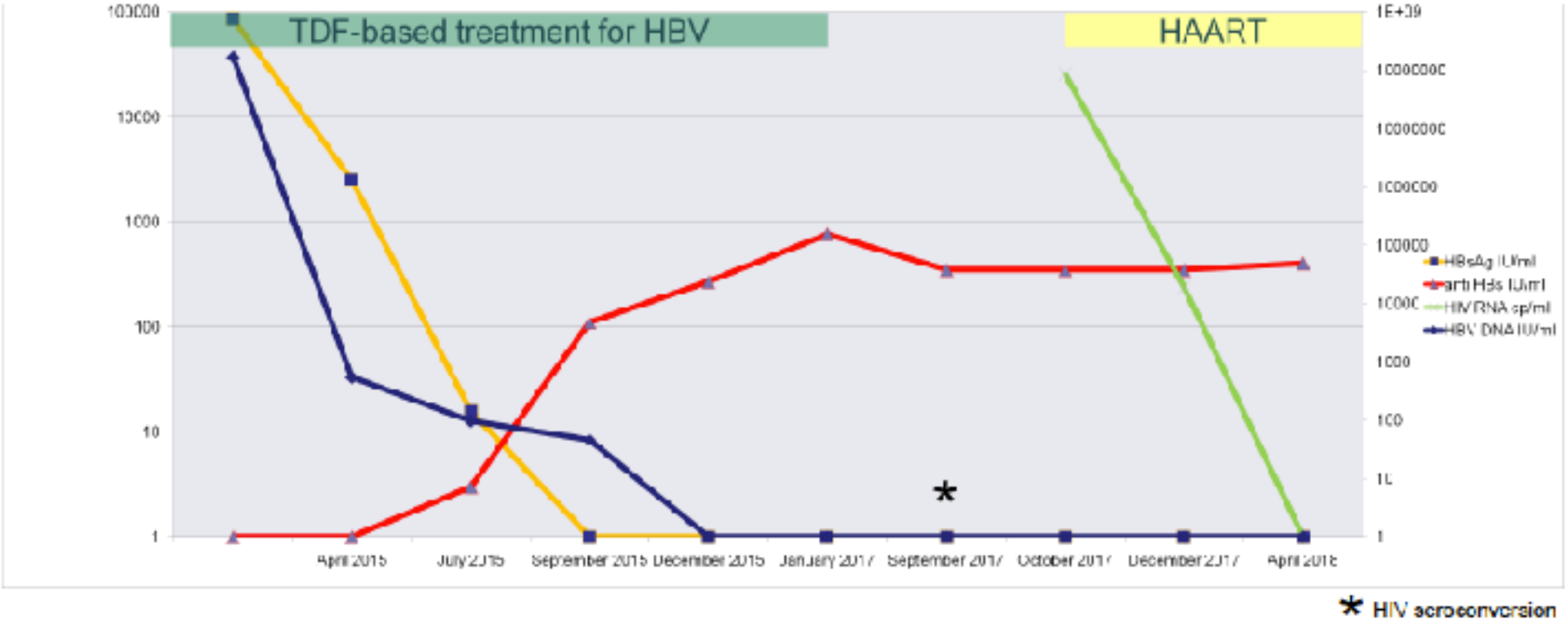
Why PrEP?

HIV seroconversion after stopping TDF-based treatment for HBV



HIV seroconversion was documented early after stopping TDF in a subject at high risk for HIV acquisition. TDF alone had probably protected the patient from acquiring HIV during the cumulative two years when it was administered for HBV. It is our opinion that the patient would have benefit from receiving PrEP with TDF/FTC (Tenofovir Disoproxil/Emtricitabine) after stopping TDF for HBV and the likelihood of acquiring HIV infection would have been reduced by over 90%.

Tazza B. et al, ICAR2018, P110

PrEP works

Efficacy results from PrEP clinical trials

Studies supporting TVD label for PrEP

Clinical trial	Participants	Number	Drug	mITT [a] efficacy of % reduction in acquisition of HIV infection [b]		Adherence-adjusted efficacy based on TDF detection in blood [c]	
				%	(95% CI)	%	(95% CI)
iPrEx[1]	Men who have sex with men (MSM)	2499	TVD*	44	(15-63)	**92**	(40-99)
Partners PrEP [2]	HIV discordant couples	4747	TDF	67	(44-81)	**86**	(67-94)[9]
			TVD*	75	(55-87)	**90**	(58-99)[9]
TDF2 [3]	Heterosexually active men and women	1219	TVD*	62	(21-83)	**78**	(41-94)
Bangkok Tenofovir Study [4]	IDU	2413	TDF	49	(10-72)	**84**	(73-99)
PROUD [5]	MSM	544	TVD*	86	(64-96)	-----	-----
IPERGAY [6]	MSM	400	on demand TVD*	86	(40-98)	-----	-----
Fem-PrEP [7]	Heterosexually active women	2120	TVD*	NS	-----	**< 40%**	-----
VOICE [8]	Heterosexually active women	5029	TVD*	NS	-----	**<30%**	-----

1. Grant RM & al. *N Engl J Med* 2010; 363:2587-99
2. Baeten JM & al. *N Engl J Med* 2012;367:399-410
3. Thigpen M, et al. *N Engl J Med* 2012;367:423-34
4. Choopanya K & al. *Lancet* 2013;381, 2083-90
5. McCormack S. & al. *Lancet* 2016;387,53-60
6. Molina JM & al. *N Engl J Med* 2015;373,2237-46
7. Van Damme L, et al. *N Engl J Med* 2012;367:411-22
8. Van der Straten A, et al. *AIDS* 2012;26(7):F13-F19
9. New York State Department of Health AIDS Institute PrEP Guidance 2015, Available at http://www.hivguidelines.org/wp-content/uploads/2016/02/PrEP-Guidance_10-14-15.pdf
10. MarrazzoJM et al. *N EnglJ Med*. 2015 Feb 5;372(6):509-18

***TVD = FTC/TDF**

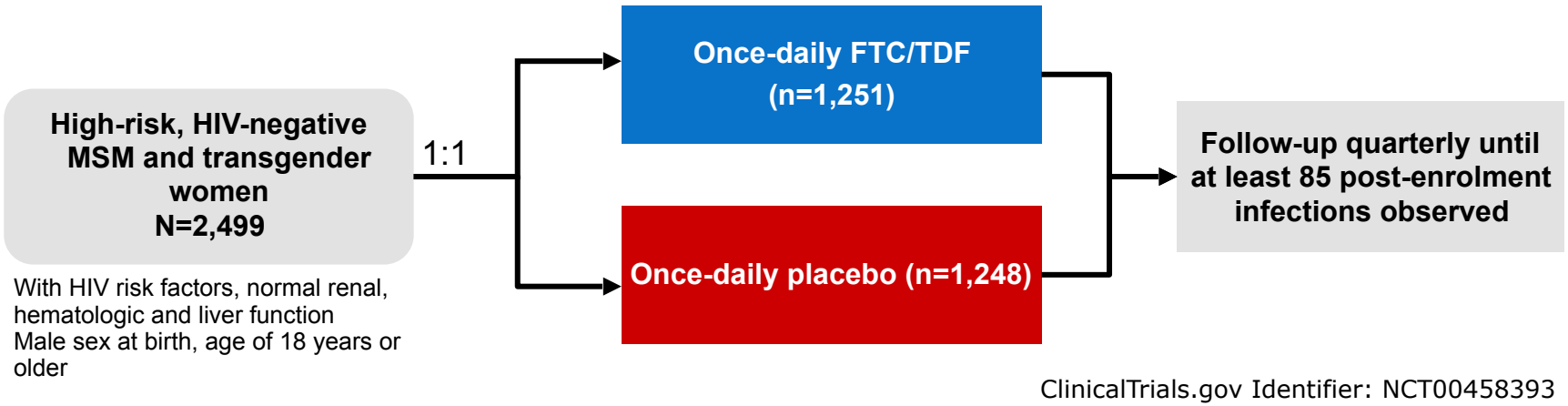
a. Modified Intent to Treat
b. Excluded only those enrolled patients later found to be infected at randomization and those with no follow-up visit or HIV test
c. The percentage of reduction in HIV incidence among those with TFV detected in blood, compared with those without detectable TFV

"On-demand" regimen constitutes: FTC/TDF or 2 placebo < 24 hrs prior to sexual intercourse exposure 1 FTC/TDF or placebo dose 24 hrs after; and a final dose 48 hrs after sexual intercourse

TDF is not licensed for PrEP
FTC/TDF is only licensed as a daily dosage for PrEP

iPrEx : Preexposure Prophylaxis Initiative trial

Placebo-controlled, double-blind, randomised, multicentre study in the Americas, South Africa, and Thailand



With HIV risk factors, normal renal, hematologic and liver function
Male sex at birth, age of 18 years or older

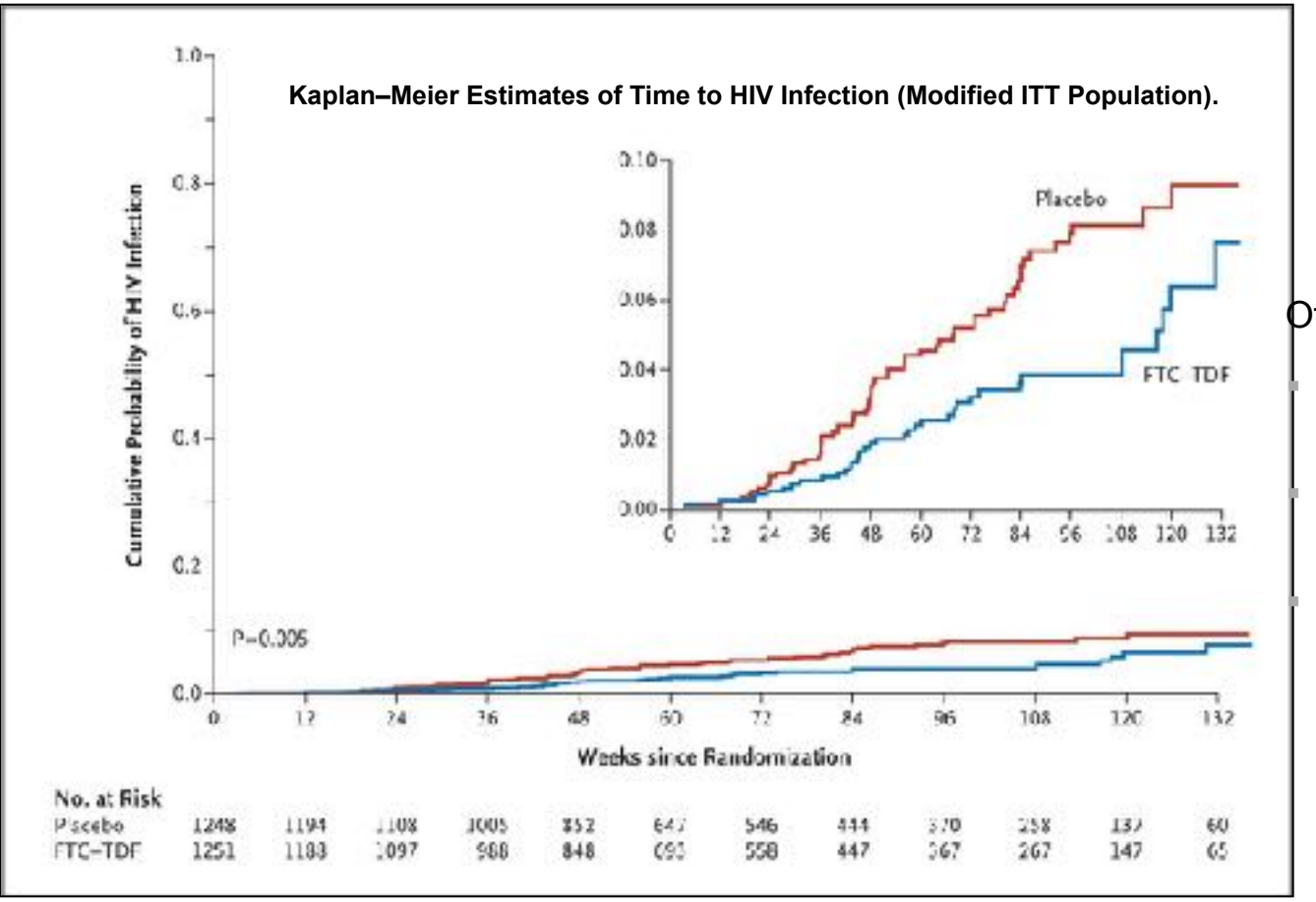
ClinicalTrials.gov Identifier: NCT00458393

- **Objective** : to determine whether once-daily use of FTC/TDF versus placebo can prevent HIV-1 infection in 2,499 MSM who also receive HIV counselling, condoms, and treatment for STIs
- **Primary endpoint**: HIV seroconversion between randomisation and Month 12
- **Secondary endpoints**: safety, adherence, sexual behaviour, resistance development

Grant RM et al. *N Engl J Med* 2010;363:2587–2599
Michael NL. *N Engl J Med* 2010;363:2663–2664

MSM : Men who have Sex with Men

Efficacy results



Of the 100 incident infections:

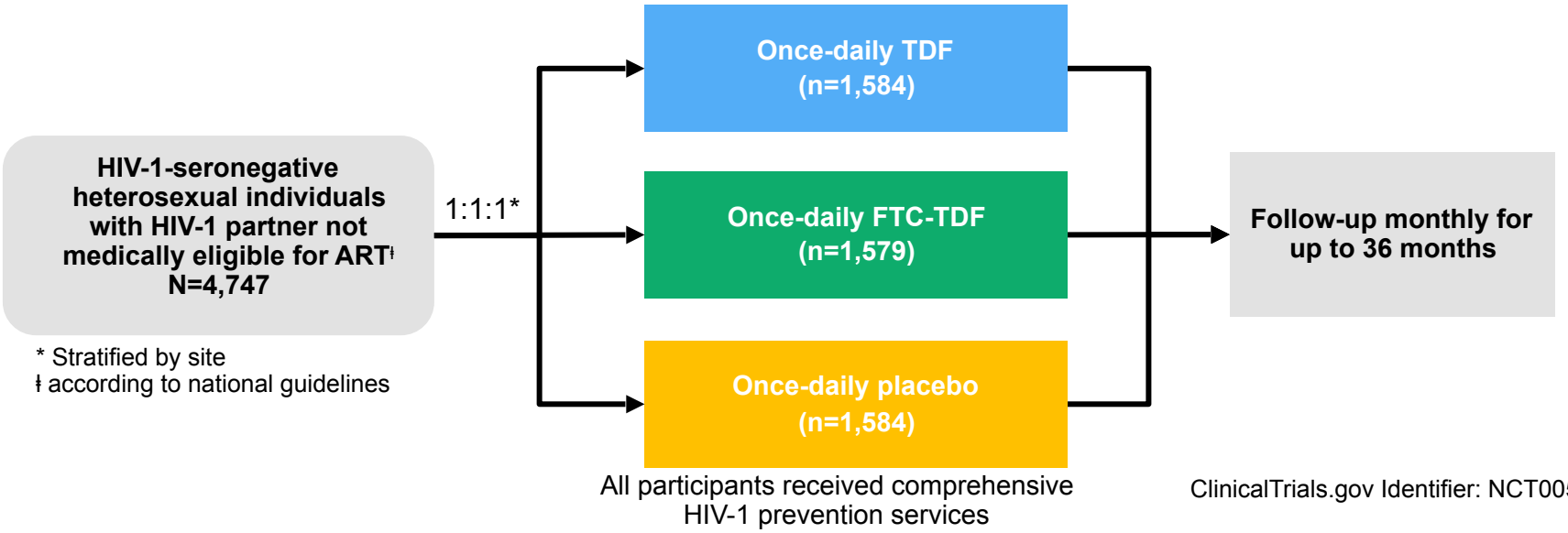
- **64** infections in the placebo group
- **36** infections in the FTC/TDF group
- No resistance to FTC or TDF was detected among these individuals

Once-daily oral FTC/TDF provided 44% additional protection from HIV among MSM who received a comprehensive package of prevention services

Grant RM & al. *N Engl J Med* 2010; 363:2587-99

Partners PrEP

Randomised, double-blind, placebo-controlled study in Africa (Kenya and Uganda)



- **Study objective**: to determine whether once-daily use of FTC/TDF vs placebo can decrease the acquisition of HIV-1 infection in 4,747 serodiscordant heterosexual couples
- **Primary endpoints**: incidence of HIV-1 seroconversion among HIV-1-negative participants, adherence
- **Secondary endpoints**: safety, sexual behaviour, resistance development, sexual transmitted infections (STI)

Baeten JM et al. *N Engl J Med* 2012;367:399-410

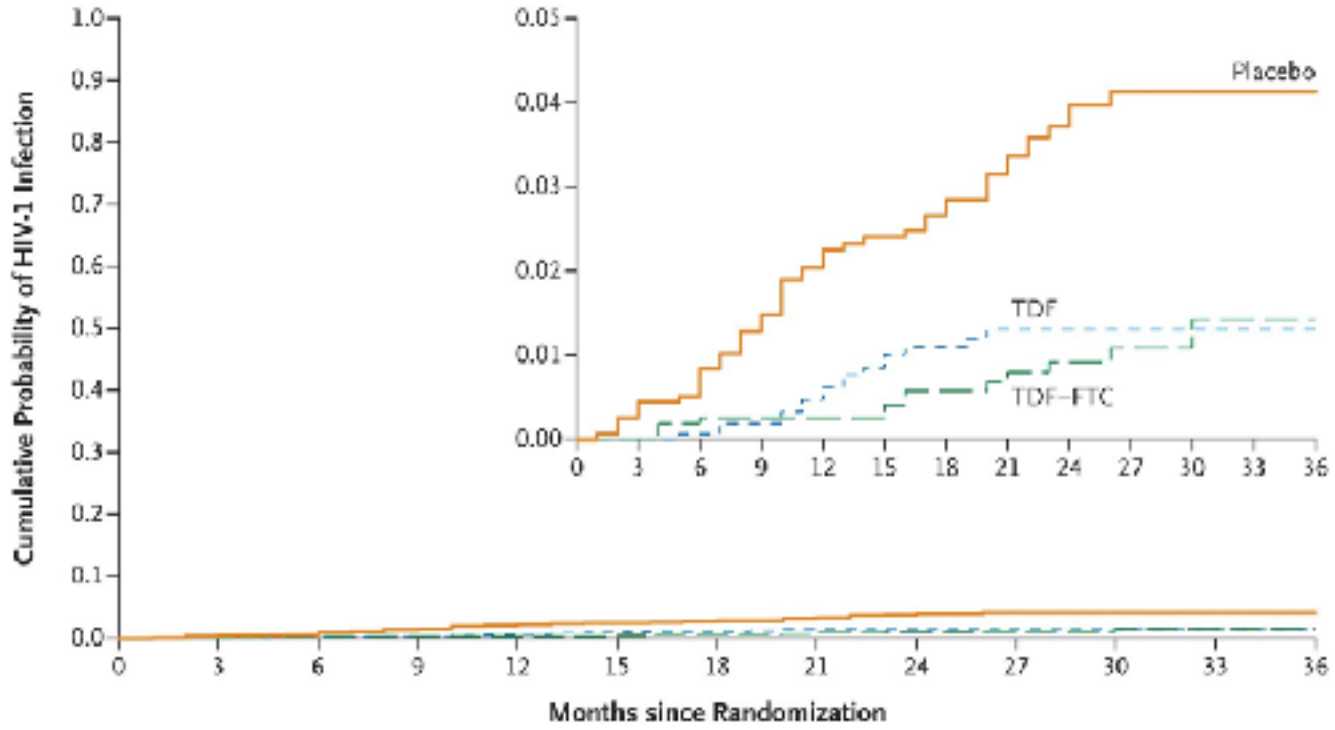
TDF is not licensed for PrEP

Efficacy results

Of the **82** incident infections:

- **17** occurred in TDF group
- **13** in the FTC/TDF group
- **52** in the placebo group

Kaplan–Meier Estimates of the Primary End Point in the Modified ITT Analysis, according to study treatment.



No. at Risk													
TDF	1572	1559	1547	1498	1350	1223	1062	902	735	510	287	108	15
TDF–FTC	1568	1557	1546	1493	1371	1248	1059	901	743	525	291	114	16
Placebo	1568	1557	1544	1487	1347	1224	1061	902	744	523	295	120	18

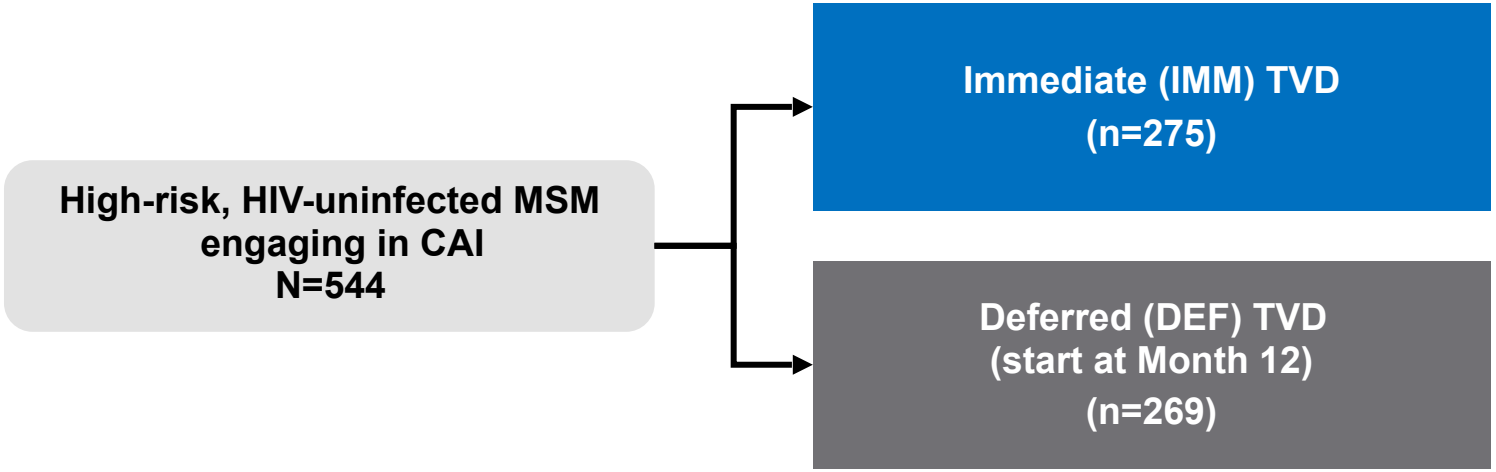
TDF and FTC/TDF were efficacious in preventing HIV-1 acquisition among negative individuals part coupled with an HIV-1 positive partner

Baeten JM et al. *N Engl J Med* 2012;367:399-410

TDF is not licensed for PrEP

PROUD

Randomised, multicentre, open-label pilot study in the UK



ClinicalTrials.gov Identifier: NCT02065986

All subjects received comprehensive HIV prevention services, including condoms, risk-reduction counseling, testing and treatment for sexually transmitted infections, and HIV pre- and post-test counseling

Primary endpoint: HIV seroconversion between randomisation and Month 12

Secondary endpoints: Safety, adherence, sexual behavior, resistance development

Oct 2014: the PROUD Trial Steering Committee announced that participants on the deferred arm of the study, who had not yet started PrEP, would be offered the opportunity to begin PrEP ahead of schedule

McCormack S. & al. *Lancet* 2016;387,53-60

CAI: Condomless anal intercourse

Efficacy results

HIV Incidence

Group	Infections, n	Follow-up (PY)	Incidence/100 person-years (90% CI)
Overall	23	465	- *
Immediate	3	243	1.2 (0.4-2.9)
Deferred	20	222	9.0 (6.1-12.8)

* The overall incidence was 4.9 infections/100 person-years, 90%CI (3.4-6.8) at 1st communication in McCormack S, et al. CROI 2015; Seattle, WA. #22LB

- Use of post-exposure prophylaxis by arm:
  - IMM: 12 subjects (4.4%); 14 prescriptions
  - DEF: 85 subjects (31.5%); 174 prescriptions

86% (90% CI: 64-96) Relative Risk Reduction; *p*=0.0001

Number needed to treat to avert one HIV infection = 13 (90% CI: 9-23)

McCormack S. & al. *Lancet* 2016;387,53-60

IPERGAY

Randomised, multicentre, double-blind study in France and Québec

High-risk, HIV-uninfected MSM with Condomless anal sex with ≥2 partners within 6 months
N=400

eGFR > 60 mL/min

- **« On-demand » TVD (n=199)**
- **« On-demand » TVD placebo (n=201)**

All participants received a package of preventative measures:
- counseling
- repeated HIV testing
- screening & treatment for other STIs
- HBV and HAV vaccination
- condoms and gel

"On-demand" regimen constitutes:
- 2 TVD or 2 placebo 2 - 24 hrs prior to sexual intercourse exposure
- 1 TVD or placebo 24 hrs after first intake
- 1 TVD or placebo 48 hrs after first intake

Primary endpoint: HIV seroconversion

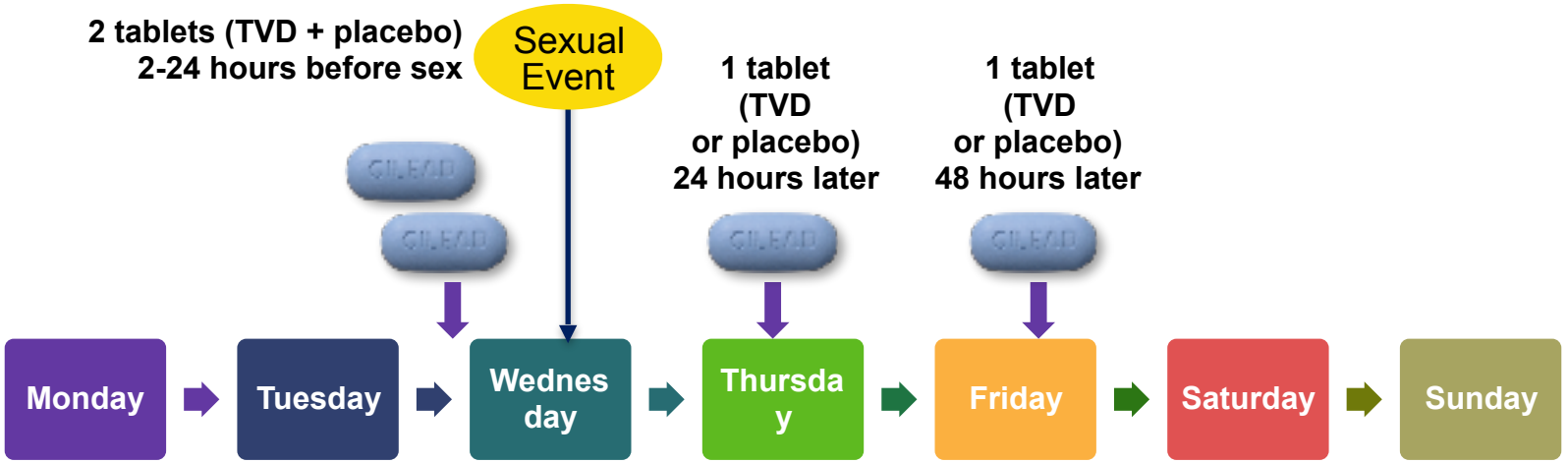
Secondary endpoints: Sexual behavior, safety events, adherence

Oct. 2014, the DSMB recommended that the placebo arm be discontinued and patients be offered switching into the treatment arm.

Molina JM et al. CROI 2015; Seattle, WA. #23LB
Molina JM & al. *N Engl J Med* 2015;373,2237-46

FTC/TDF is only licensed as a daily dosage for PrEP

Event-driven PrEP



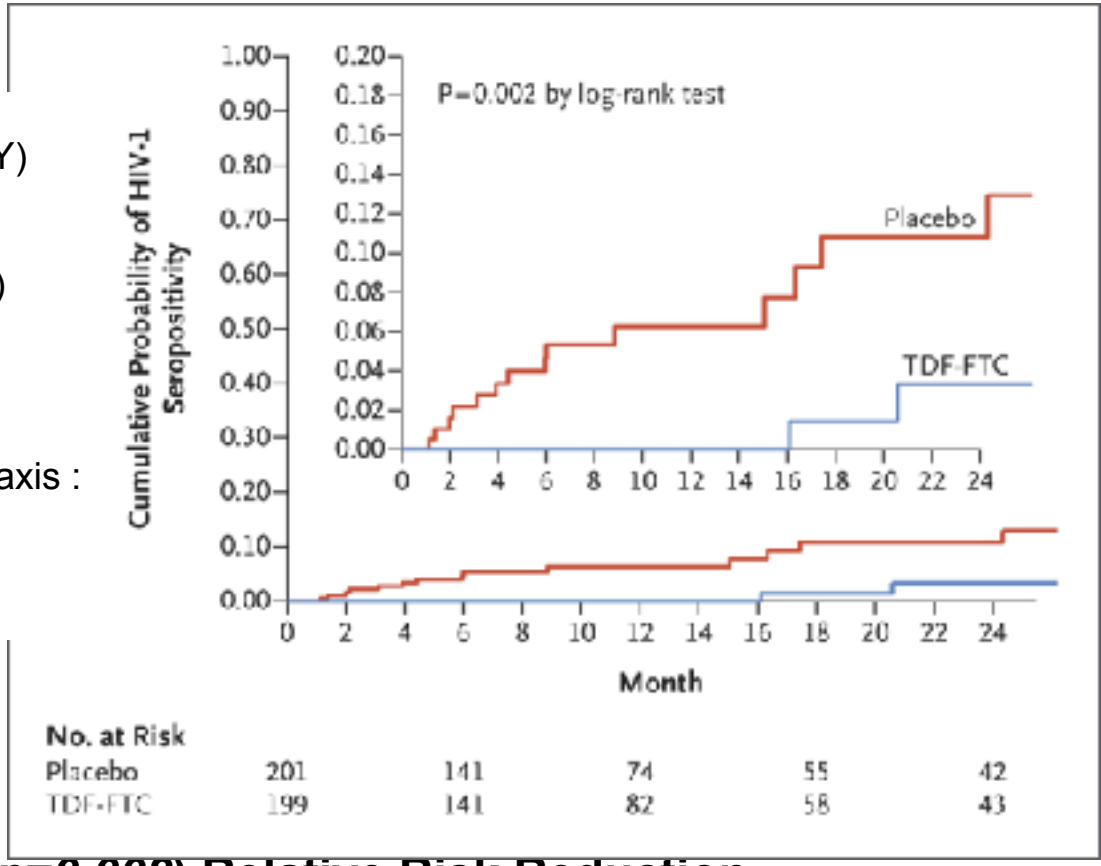
- IPERGAY results provide the first evidence that an event-driven regimen was effective among high-risk MSM with frequent sex (median of 10 sex acts per month and 8 partners every two months).
  - In this study overall, available data suggest that men were taking PrEP an average of three to four days per week.
- CDC cautions that researchers do not yet know if this regimen will work among MSM who have sex less frequently or among other populations at high risk for HIV infection.
- CDC continues to recommend daily dosing of PrEP and urges people at substantial risk for HIV infection and their health care providers to continue to follow current CDC guidelines

Molina JM et al. CROI 2015; Seattle, WA. #23LB
Molina JM & al. *N Engl J Med* 2015;373,2237-46
http://www.cdc.gov/nchhstp/newsroom/2015/IPERGAY-2015-Media-Statement.html

FTC/TDF is only licensed as a daily dosage for PrEP

Efficacy results

- **16 subjects infected**
  - **Placebo = 14** (incidence: 6.60/100 PY)
  - **FTC/TDF =2** (incidence: 0.91/100 PY)
- Mean follow-up= **9.3 months** (IQR 4.9-20.6)
- Average **15 pills / month**
  (TVD : IQR 11-21; PBO : IQR 9-21)
- 56 subjects received post-exposure prophylaxis :
  - PBO = 25
  - TVD = 31 *p=0.37*



86% (95% CI: 40-98, *p=0.002*) Relative Risk Reduction
Number needed to treat for 1 year to avert 1 HIV infection: 18 (95% CI : 11-50)

Molina JM et al. CROI 2015; Seattle, WA. #23LB
Molina JM & al. *N Engl J Med* 2015;373,2237-46

FTC/TDF is only licensed as a daily dosage for PrEP

IPERGAY Sub-Study

On-Demand PrEP in MSM with High Risk and Less Frequent Sexual Intercourse

Sub-analysis in IPERGAY trial to assess the effectiveness of on-demand PrEP in MSM at high risk for HIV infection but with less frequent sexual intercourse

- Retrospective analysis of a sub-group of patients (N=269, 134 PYFU)
  - Who reported a PrEP use ≤ 15 pills/month
  - Systematically or often during sexual intercourse
  - Considering potential bias as variability of sexual activity across the trial and the date determination of a potential infection

	Patient-Years	HIV infections, n	IR/100 PY (95%CI)	RRR* (95%CI)	P-value
Placebo	64.8	**6**	**9.3** (3.4, 20.1)	-	-
FTC/TDF	68.9	**0**	**0.0** (0.0, 5.4)	**100%** (39, 100)	0.013
Median pills/month: 9.5 (IQR: 6-13) Median number sexual intercourse/month: 5 (IQR: 2-10)					

These data suggest on-demand PrEP with FTC/TDF may be an adequate alternative to daily PrEP for MSM at high risk of HIV acquisition but with less frequent sexual intercourse

*RRR, Relative Risk Reduction
IQR, Interquartile range
IR=incidence ratio
PYFU=person-years of follow-up

Seroconversion rates in demonstration projects
(July 2012 to May 2016)

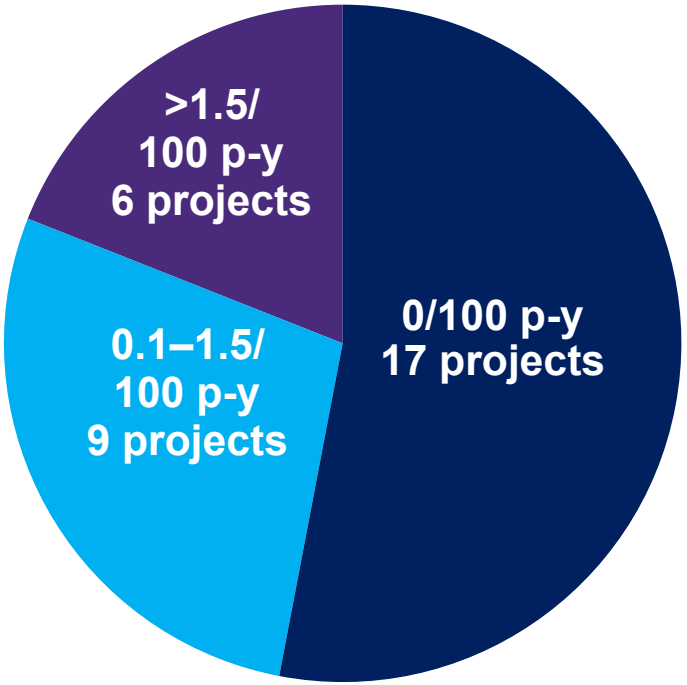
32 individual studies of FTC/TDF for PrEP

- 8,478 participants:
  - 7,002 men
  - 1,388 women
  - 76 transgender
- 7,061 cumulative person-years of FTC/TDF exposure

Results

- 67 HIV-1 seroconversions
- 0.95/100 p-y seroconversion rate (95% CI: 0.74, 1.21)

Seroconversion Rates From 32 Projects



IPERGAY control arm: 6.6/100 p-y
PROUD control arm: 9/100 p-y

Mera, R. AIDS 2016. Durban, South Africa. Oral #TUAX0105LB
McCallister, ASM Microbe 2016, Abs 371LB

Characteristics of Seroconverters in Demonstration Projects

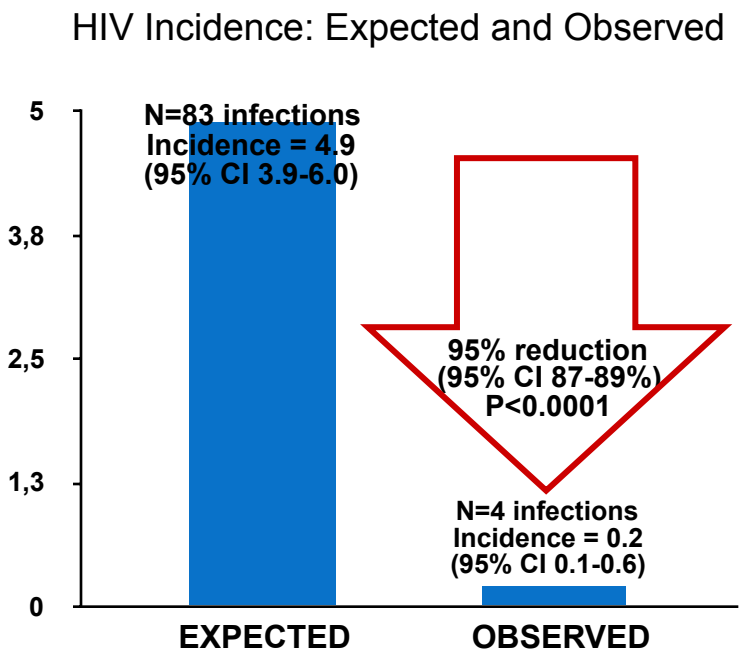
Seroconversion Rates By Sex/Gender

	 Men n=7002	 Women n=1388	 Transgender Women* n=76
Total exposure, p-y	6214	788	48
Number of HIV-1 seroconversions	64	2	1
Rate/100 p-y (95% CI)	**1.03** (0.80-1.32)	**0.25** (0.03-0.92)	**2.07** (0.05-11.52)

Mera, R. AIDS 2016. Durban, South Africa. Oral #TUAX0105LB
McCallister, ASM Microbe 2016, Abs 371LB

*Includes genderqueer, androgynous designations.

Integrated delivery of PrEP and ART: sustained near elimination on HIV transmission in African HIV serodiscordant couples



4 incident HIV seroconverters :

- No TFV detected in plasma (n=3) or PrEP declined (n=1)
- No resistance for TFV or FTC

- **Integrated delivery of ART and PrEP in HIV serodiscordant couples demonstrated,**
  - **95% reduction in observed HIV incidence compared to expected**
  - **time-limited PrEP as a bridge to ART is feasible and highly effective in preventing HIV transmission**

Baeten J, et al. AIDS 2016. Durban, South Africa. Oral #WEAC0105

Renal and bone safety

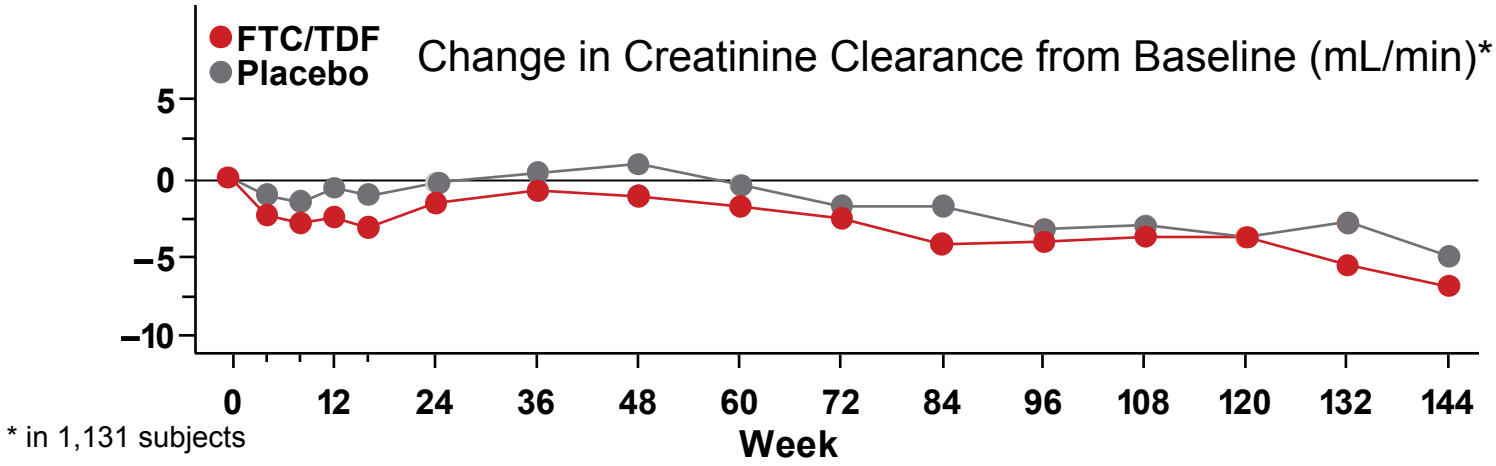
Renal Safety

Renal safety assessment of 2499 HIV-negative subjects in iPrEx study

- A mild, non-progressive decrease in creatinine clearance (Cockcroft-Gault), that was reversible and readily managed with routine monitoring
  - Did not vary by race, age, or HTN history
  - Affected by NSAID use
    - -3.4 mL/min (+NSAID) vs. -0.3 mL/min (no NSAID), *p* = 0.04

Mean Change in CrCL (mL/min)

	TVD	Placebo	*p-value*
Wk 4	-2.4	-1.1	0.02
Last visit on treatment	+0.3	+1.8	0.02
Post stopping treatment	-0.1	0.0	0.83

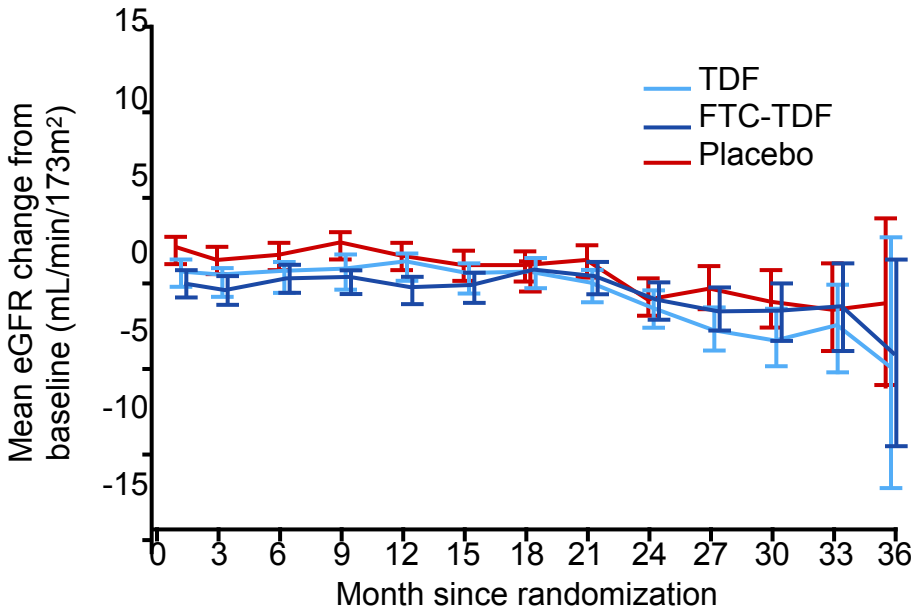


* in 1,131 subjects

Solomon M, et al. *AIDS* 2014;28(6):851-9

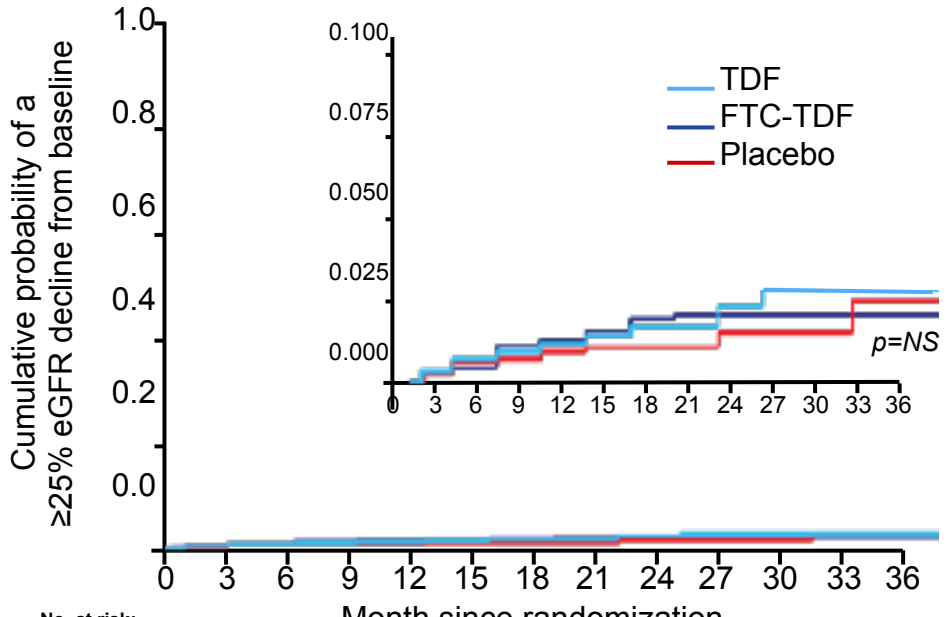
Renal safety

Variation over time in crude mean eGFR change from baseline, according to treatment group



TDF	1568	1523	1495	1443	1307	1187	1029	872	717	502	286	107	15
FTC-TDF	1558	1522	1498	1448	1334	1204	1029	870	727	516	288	112	16
Placebo	1570	1530	1511	1446	1317	1190	1037	885	737	516	295	119	18

Cumulative probability of a ≥25% eGFR decline from baseline, according to study treatment



No. at risk:

TDF	1548	1479	1399	1305	1146	1019	872	724	579	400	237	86	10
FTC-TDF	1545	1491	1420	1326	1191	1063	893	740	602	420	235	89	12
Placebo	1547	1480	1409	1311	1166	1039	893	752	613	425	233	97	16

- **Both TDF** (-1.23mL/min/1.73m², 95%CI, -2.06 to-0.40, p=0.004) **and FTC/TDF** (−1.59 mL/min/1.73m², 95%CI, −2.44 to −0.74; P < .001) **were associated with significant decline in eGFR vs placebo after a median follow-up of 18 months**
- **The difference in mean eGFR between PrEP and placebo appeared by 1 month after randomisation and was stable through 12 months**

FTC/TDF as PrEP resulted in a small but non-progressive decline in eGFR

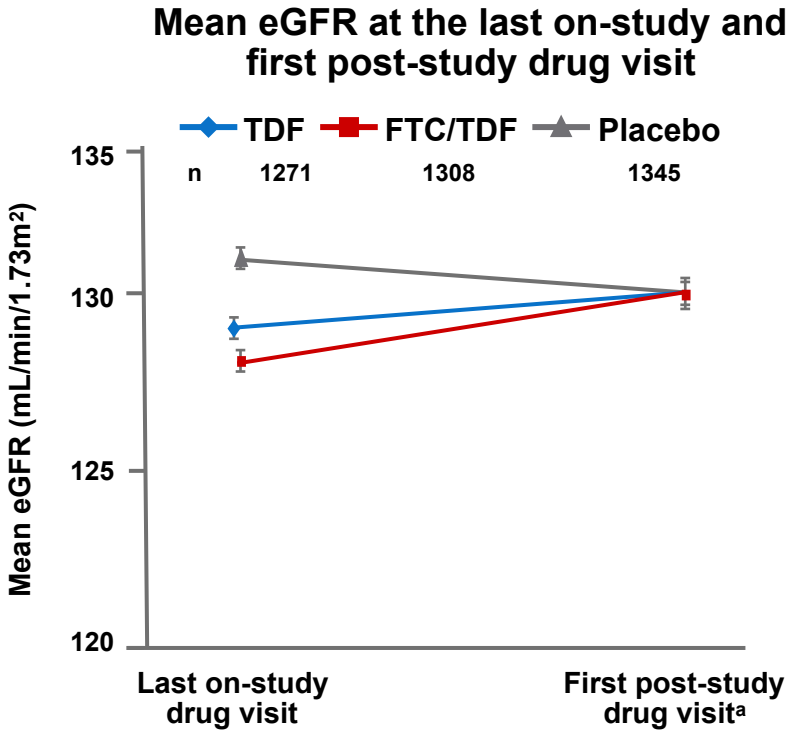
Mugwanya K et al. *JAMA* Intern Med 2015;175(2):246–254

TDF is not licensed for PrEP

Decline in eGFR resolves within weeks of discontinuing TDF or FTC/TDF for PrEP

- Phase 3, randomised trial of daily oral TDF PrEP vs. FTC/TDF PrEP vs. PBO among African HIV-negative men and women (N=4747) with normal baseline renal parameters
  - SCr was assessed quarterly while on study medication, and at 2 monthly visits after d/c
  - eGFR was calculated using CKD-EPI[a]

- **Mean eGFR was 2-3 mL/min lower on PrEP vs. PBO (*P*<0.01) at first post-study drug visit**
- **>96% of participants had >75% eGFR reversion to baseline levels by 8 weeks of study drug discontinuation**



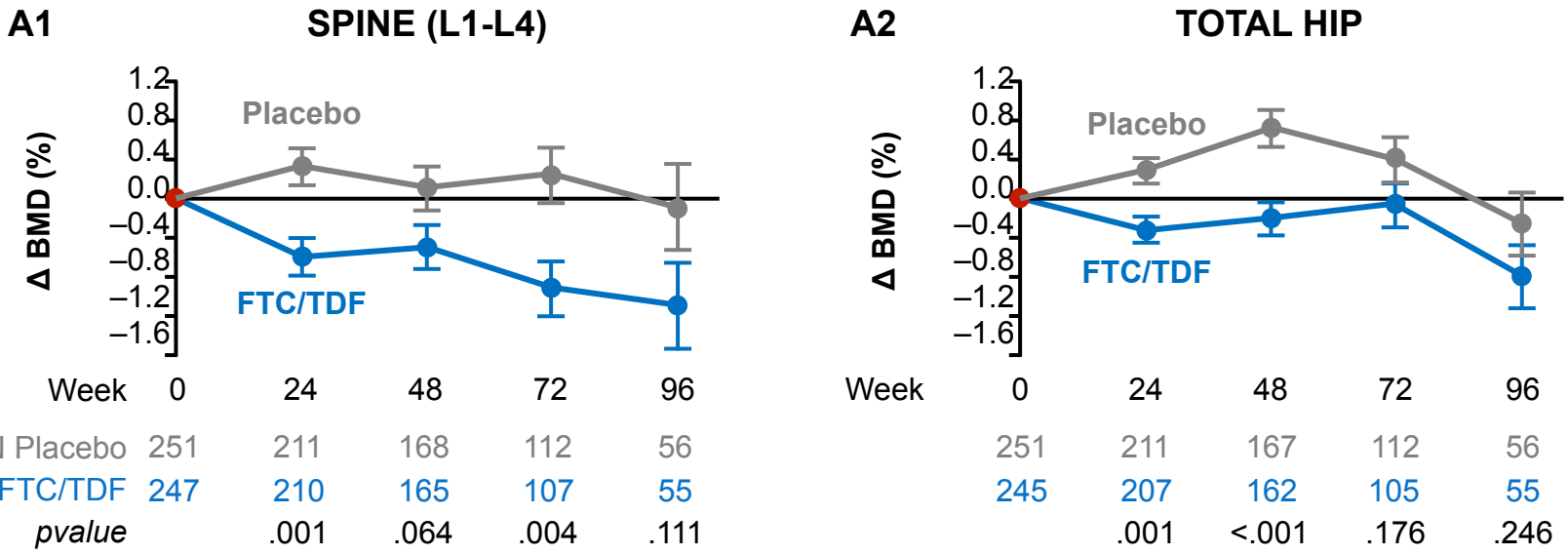
[a] Chronic Kidney Disease Epidemiology Collaboration Equation.
[b] Median time from the last on-study drug visit to the first post-study drug visit was 4 weeks (IQR: 3 - 5), which was similar across treatment groups.

Mugwanya, K. CROI 2015, Seattle, WA #981

TDF is not licensed for PrEP

Change from baseline in bone mineral density (BMD)

Changes from baseline in BMD during treatment in the spine and hip



A decrease in BMD was observed for both spine (p=0.001) and hip (p=0.001) in the FTC/TDF group vs placebo within 24 weeks

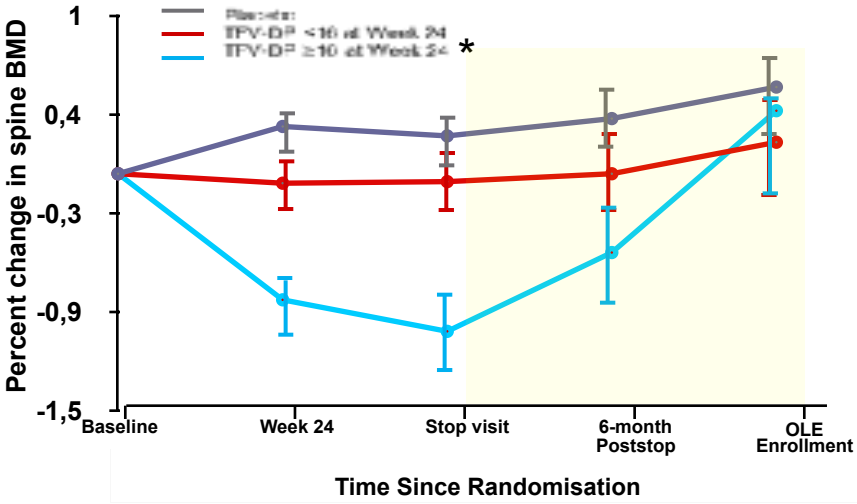
There were no differences in bone fractures between the FTC/TDF and placebo groups (p=0.62)

DEXA, dual-energy X-ray absorptiometry
Mulligan K et al. *Clin Infect Dis* 2015;61(4):572–580

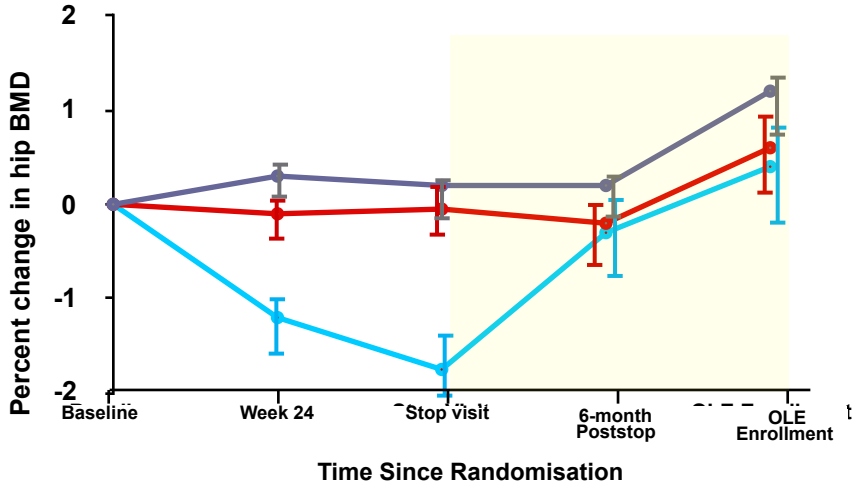
Bone mineral density (BMD) extension study

498 MSM and TGW, BMD measured every 24 weeks during the iPrEx study, 24 weeks after stopping PrEP and at the beginning of the iPrEx open-label extension (OLE)

Change in spine BMD from iPrEx enrolment



Change in hip BMD from iPrEx enrolment



* Drug concentration in PBMCs to evaluate adherence. (fmol/M viable PBMCs)

16 fmol/M viable PBMCs is the TDF concentration associated with a 90%-reduction in HIV infection risk (EC_{90})

- **BMD recovered (to placebo levels) by 6 months in spine when TVD discontinuation**
- **BMD recovered completely by enrolment in iPrEx OLE (median 73 weeks) in both spine and hip**

Grant R et al. CROI 2016, Boston, MA, Oral #48LB: http://betablog.org/9038-2/ (accessed June 2016)

BMD changes in 18-24yo MSM after discontinuing TVD PrEP

Extension Phase (EPH)

- DXA scans at 48 weeks after discontinuing PrEP study, i.e. 48 weeks on FTC/TDF followed by 48 weeks off FTC/TDF
- N=72 individuals followed-up through the EPH

BMD change (mean)	From BL to Wk 48 (on FTC/TDF)	From Wk 48 to end of EPH (off FTC/TDF)	Overall change from BL to end of EPH
Hip	**-1.43%***	**+1.02%***	-0.35%
Whole Body	**-0.63%***	**+0.64%***	-0.11%
Lumbar Spine 1-4	-0.25%	**+1.15%***	**+0.87%***

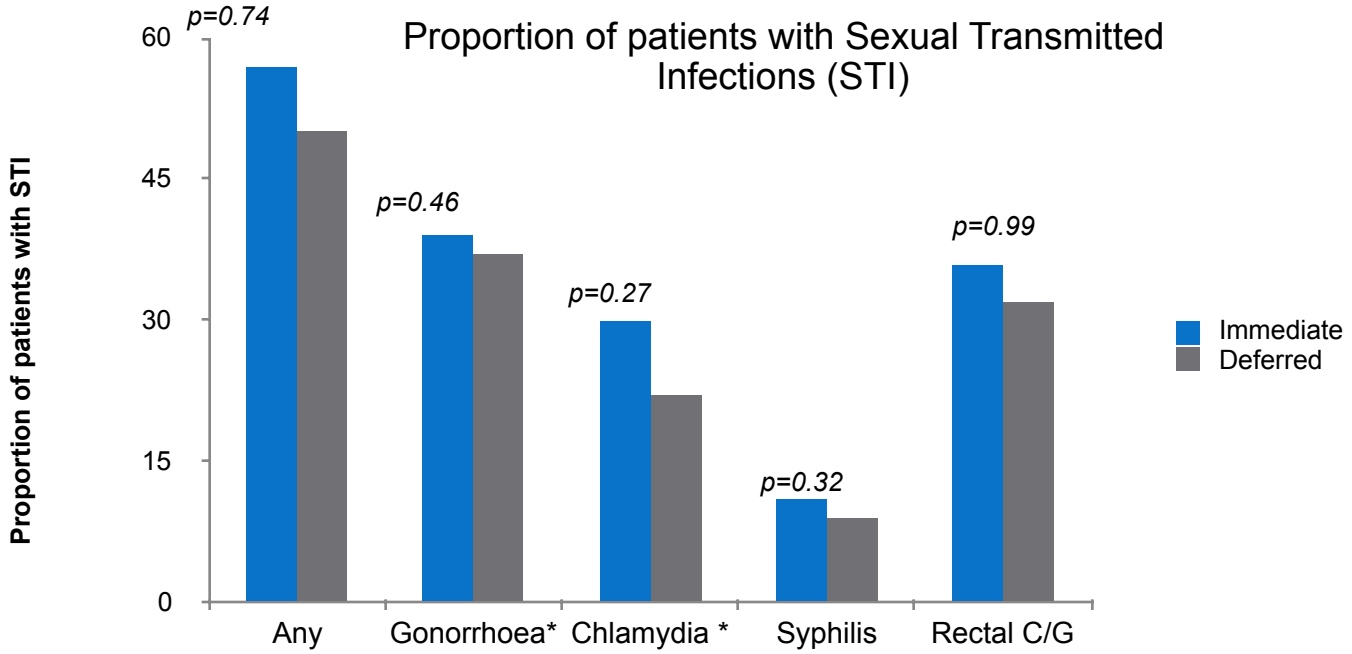
***p<0.05**

- **There is evidence of impact on bone density caused by exposure to TDF/FTC used as PrEP over 48 weeks in 18-22 year old males**
- **Discontinuation of exposure to TDF/FTC leads to a trend to recovery of bone density changes over a 48 week follow-up period**

Mulligan K, et al. AIDS 2016, Durban, South Africa. Oral #WEAC0305LB

Risk compensation

Risk compensation



- **The proportion of sexually transmitted infections did not differ significantly between groups** despite a suggestion of risk compensation among a small proportion of PrEP recipients.
- However, the number of screens differed between groups, eg. rectal C/G :
  - 974 in immediate arm
  - 749 in deferred arm
- 6 incidents Hepatitis C (3 in each group)

STI, Sexuallly Transmitted Infections
C/G Chlamydia or Gonorrhoea
* Detected in throat, urethra or rectum
McCormack S, et al. CROI 2015; Seattle, WA. #22LB
McCormack S. & al. PROUD_Lancet 2016;387,53-60

‡

HIV incidence (mITT analysis), adherence and sexual behavior

	Open-label	Double-blind	
	FTC/TDF	FTC/TDF	PBO
HIV Incidence per 100py (95%CI)	**0.19** (0.01-1.08)	**0.91** (0.11-3.30)	**6.60** (3.60-11.1)
Total Follow-up, py	515	219	212
Median follow-up, months (IQR)	18.4 (17.5-19.1)	9.3 (4.9-20.6)	
Adherence Measures:			
Median pills/month, no. (IQR)	18 (11-25)	15 (11-21)	
Participants with plasma TFV >40ng/ml, %	55	46	
Correct* PrEP use at last sexual intercourse, %	50 *p=0.007*	42	
Sexual Behavior:			
Change in No. reporting condomless AI, %	77→86 (p=0.0003)	No significant change	
Incidence rate of first STI , /100py	40.6	35.2	
Participants with any STI, %	58	37	

*At least one pill 24h before and one pill 24h after sex event

mITT, Modified Intention-to-Treat Population
py, patient years
STI, sexually transmitted infection

On Demand PrEP with oral TDF/FTC remained highly effective in at-risk MSM
97% relative reduction in HIV incidence vs. Placebo

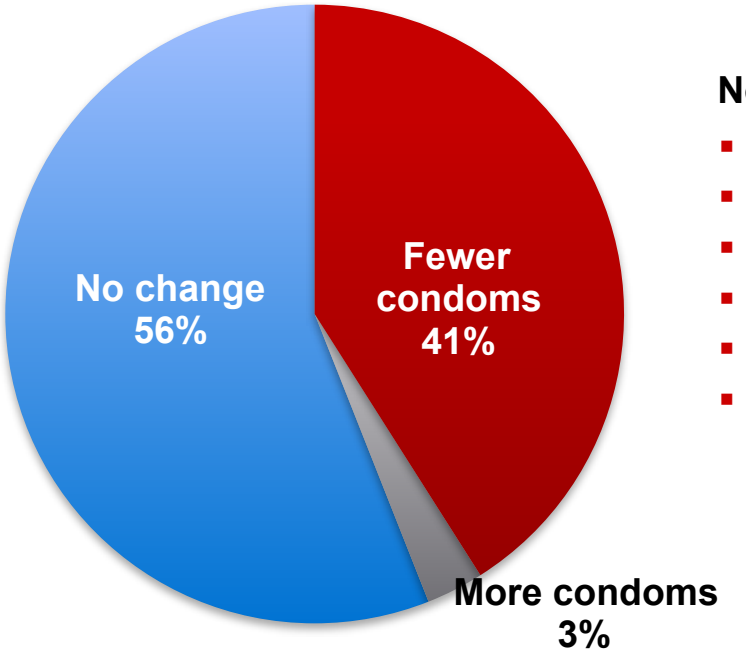
Molina JM, et al. AIDS 2016. Durban, South Africa. Oral #WEAC0102
Molina JM. N Engl J Med 2015; 373:2237-2246.

FTC/TDF is only licensed as a daily dosage for PrEP

Behaviour change after starting PrEP

A total of 143 individuals taking PrEP completed a survey relating to use of condoms after 6 months of PrEP use

Changes in reported condom use after starting PrEP (n=143)



No association with:

- Age
- STI history
- Condoms 3 months before PrEP use
- HIV-positive partner
- Methamphetamines/cocaine
- Adherence

A decrease in self-reported use of condoms was observed in PrEP users

Volk JE et al. *Clinical Infectious Diseases* 2015;61(10):1601–1603

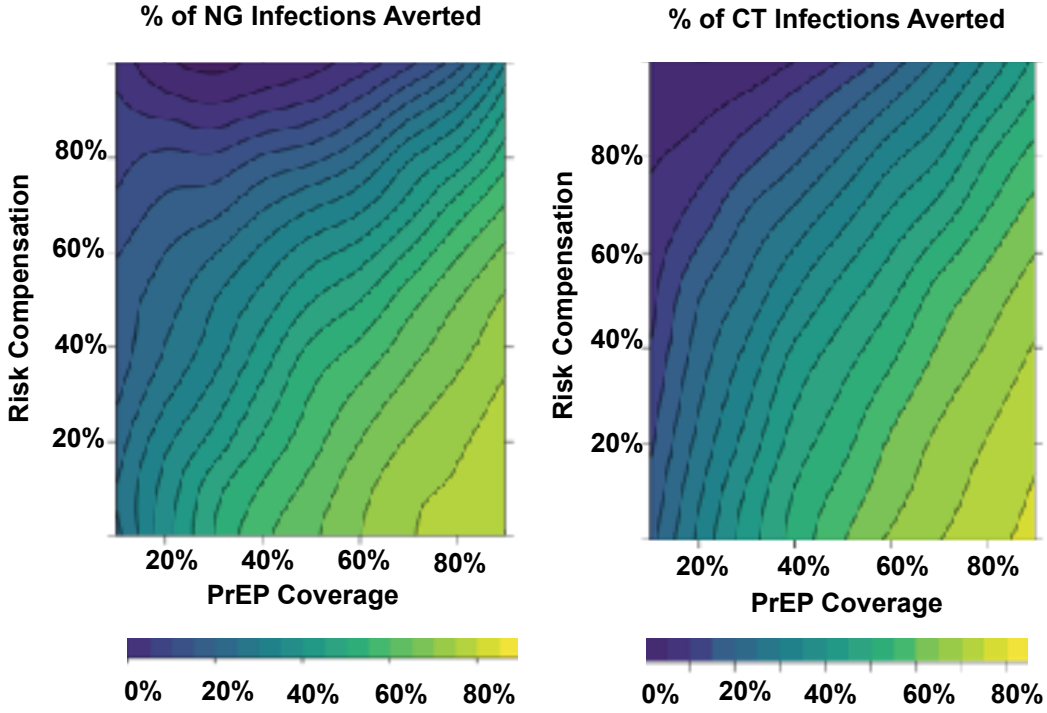
Combining TRUVADA for PrEP with STI Screening Could Decrease STI Rates

Model of co-circulating HIV, gonorrhea (NG), and chlamydia (CT) infections among MSM in the United States based on social networks

Method: TRUVADA indications modeled based on CDC guidelines, adherence based on the PrEP Demo Project, efficacy based on iPrEx.

Results:

- At 40% TRUVADA coverage and 40% Risk Compensation 42% of GC and 40% of CT infections would be averted over 10 years
- A doubling in risk compensation would still result in net STI prevention relative to no TRUVADA
- Performing STI screening at quarterly vs. biannual intervals would result in a further 50% reduction in incidence



The study suggests that the high STI rates among PrEP users may not be attributable to Risk compensation, and may be a result of selection bias (i.e. higher risk population at baseline combined with more frequent screening). Increased uptake of TRUVADA coupled with routine STI screening and treatment could lead to strong and sustained declines in gonorrhea and chlamydia incidence and prevalence among MSM

Jenness SM, et al. CROI 2017. Seattle, WA. Poster #1034

Drug resistance and drug-drug interactions

Drug resistance

	Individuals Uninfected at Baseline Who Acquired HIV-1 on Study, n		Unrecognized Baseline Infections, n	
Study	**HIV Infections**	**Resistant to FTC or TDF**	**HIV Infections**	**Resistant to FTC or TDF**
iPrEx	100 (36 on FTC/TDF, 64 on placebo)	0	10 (2 on FTC/TDF, 8 on placebo)	2 on FTC/TDF (M184V/I); 1 on placebo (M184V/I)
Partners PrEP	65 (13 on FTC/TDF, 52 on placebo)	0	9 (3 on FTC/TDF, 6 on placebo)	1 on FTC/TDF (M184V) 2 on TDF (M184V)

Resistance development to FTC or TDF was more likely to occur when FTC/TDF for PrEP was given during unrecognised/acute infection.

US Public Health Services. Preexposure Prophylaxis For The Prevention Of HIV Infection In The United States, 2014. http://www.cdc.gov/hiv/pdf/guidelines/PrEPguidelines2014.pdf. Accessed June 13, 2014.

Infection with Multidrug Resistant HIV Despite Use of FTC/TDF for PrEP

43 y/o MSM (no IDU) on PrEP (FTC/TDF) X 2 years, with high adherence by self report

- Multiple, condomless, anal sexual exposures in 2-4 weeks prior to HIV diagnosis
- Day 0: 4th Gen+, p24+, Western blot-

- FTC/TDF levels:
  - FTC and TDF detected at Day 0 (by LC-MS)
  - Based on DBS data, TFV-DP level were consistent with being adherent to PrEP >8 weeks
- Transmission of multidrug, class-resistant HIV
  - 4 TAMs, M184V, phenotypic resistance to INSTI EVG (FC >100x)
  - Clade B, CCR5-tropic

Resistance Testing Results

Class	Mutation	Resistance Analysis (est. IC50 FC)
NRTI	41L, 67G, 69D, 70R, 184V, 215E	ABC 1.9x 3TC resistant FTC resistant TDF 1.3x
NNRTI	181C	NVP resistant
PI	10I	
INSTI	51Y, 92Q	RAL 2.7x EVG resistant DTG 9.6x

First reported case of breakthrough HIV infection with a virus carrying TFV and FTC resistance, in a patient with evidence of long-term adherence to FTC/TDF for PrEP

LC-MS - Liquid Chromatography-Mass Spectroscopy
DBS – Dried Blood Spot

Knox D, et al. CROI 2016. Boston, MA. #169aLB

Amsterdam PrEP Project

Acquisition of Wild Type HIV Infection While on TRUVADA for PrEP

- Case Study: 50 yo MSM on daily TRUVADA
- HIV negative at TRUVADA initiation (HIV RNA and Ag/Ab) and at Months 1, 3 and 6 (Ag/Ab)
- HIV risk
  - Multiple concurrent sexual partners (12-75 partners/month)
  - Frequent condomless anal intercourse (3-21 days/month)
  - STIs on PrEP: rectal gonorrhea x 2, rectal chlamydia trachomatis x 1
  - Reported drugs during sex:
    - amphetamine, cocaine, GHB/GBL, mephedrone and ketamine
    - self reported clean needle use
- At Month 8: fever and dysuria

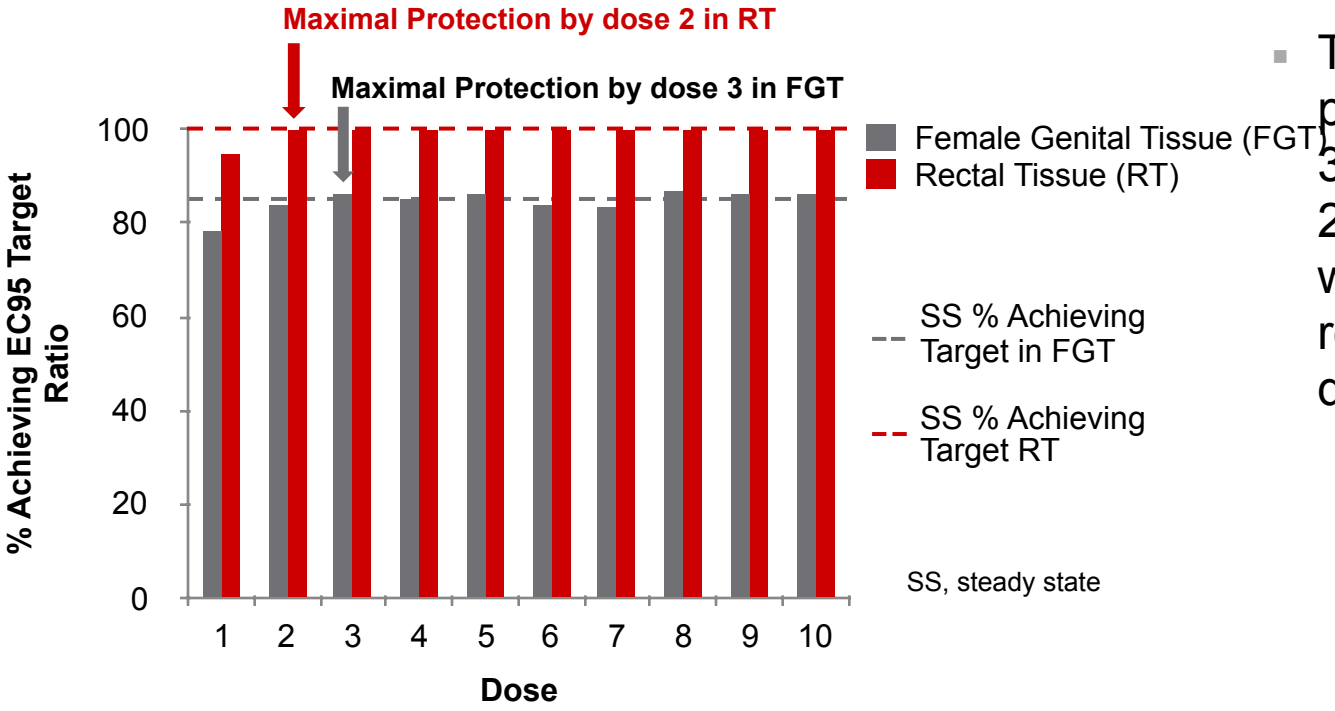
- Verified adherence with Adequate TRUVADA levels in dried blood spots
  - 6 Months after start = 2234 fmol/punch
  - 8 Months after start = 2258 fmol/punch
- HIV diagnostics:
  - 4th Gen: Ab+/Ag-
  - HIV RNA (-)
  - WB: gp160 only
  - VL/bcDNA-
  - Sigmoid bx– for HIV
- TRUVADA discontinued
- Detectable VL at 3 weeks off TRUVADA
  - No resistance mutations seen.
- ART initiated (DRV+RTV, DTG, F/TDF) and VL undetectable after 1 month

MSM on TRUVADA acquired wild-type HIV virus.
TRUVADA may be >90% effective when taken daily along with a comprehensive HIV prevention strategy.

Hoornenborg E, et al. CROI 2017. Seattle, WA. Poster #953

Time to Protection with Daily Dosing of Truvada® for PrEP

- WHO recommends additional HIV prevention measures should be used for 7 days after starting daily PrEP[1]
- Target ratios have been defined for TFV and FTC for adequate cellular protection in genital tissue[2]



- Time to maximal protection is achieved by 3rd dose in FGT and by 2nd dose in RT[3], well within the WHO recommendation of 7 days post-PrEP initiation

1. WHO Implementation tool for pre-exposure prophylaxis (PrEP) of HIV infection. Module 1: Clinical.Geneva: World Health Organization; 2017 (WHO/HIV/2017.17)
2. Cottrell M, et al J Infect Dis. 2016 Jul 1;214(1):55
3. Kashuba A, IAS 2017, France, Paris. Symposium #MOSY0803

Is FTC/TDF for PrEP safe for use in transgender women taking hormones?

- HIV rates among transgender women (TGW), especially TGW of color, are very high (14-38%)[1,2]
- No drug interaction data has been specifically obtained with regard to hormone use in transgender women or transgender men
  - No DDI is expected between FTC/TDF and estradiol or testosterone, both of which are mainly metabolized by CYP3A4[1]
- In iPrEx, FTC/TDF was generally well-tolerated among TGW. Moderate and severe adverse events were similar between the active and placebo arms

1. Pitasi M, et al. National HIV Prevention Conference 2015; Atlanta, GA. #1193;
2. Bukowski L. National HIV Prevention Conference 2015; Atlanta, GA. #2062.

Conclusions

- FTC/TDF as PrEP is highly effective when taken as prescribed, daily
- On-demand schedule is a feasible option for MSMs
- Risk Assessment tools may best identify those at highest risk
- FTC/TDF for PrEP has been proven safe in uninfected individuals, but regular monitoring is key
- More data are needed in women, trans persons, elderly
- Education and awareness of PrEP for both providers and individuals at risk of HIV infection are vital components of PrEP delivery

Studio SEX-CHECK

- Studio osservazionale sui comportamenti sessuali degli MSM e TG, in collaborazione AUSL BO - Azienda Ospedaliera S. Orsola - PLUS Onlus