

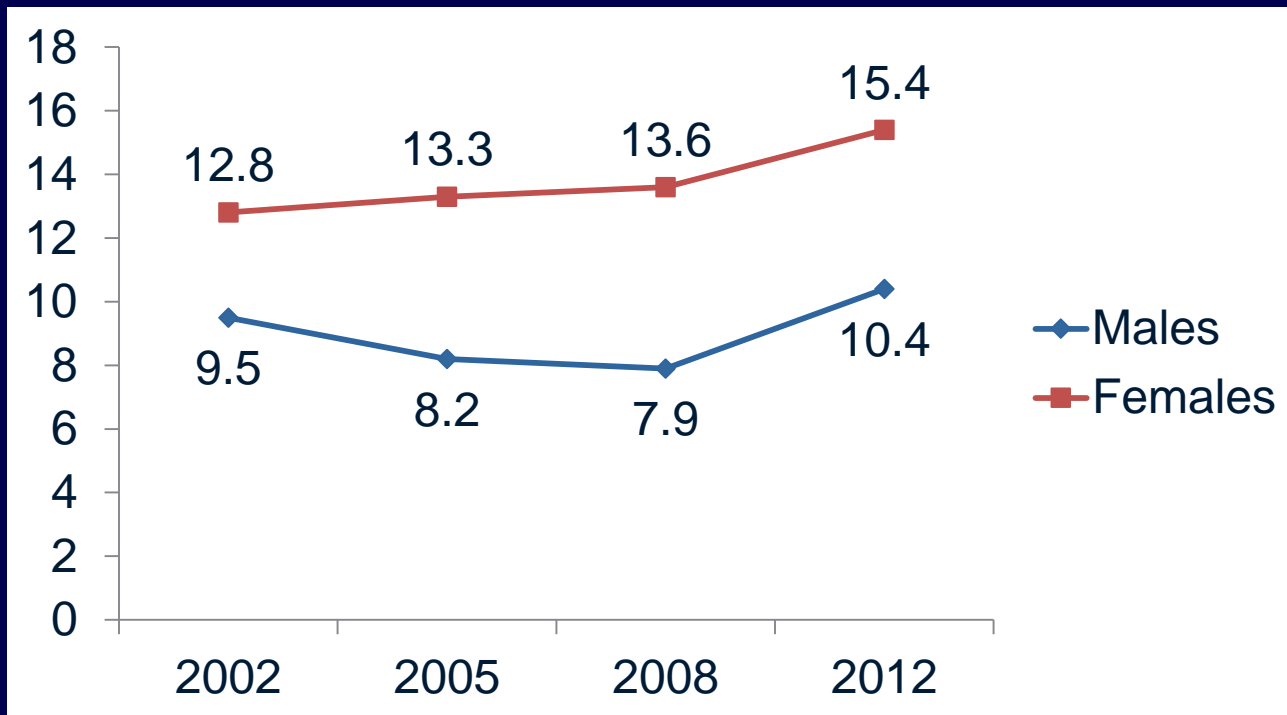
The Science behind Preexposure Prophylaxis (PrEP)

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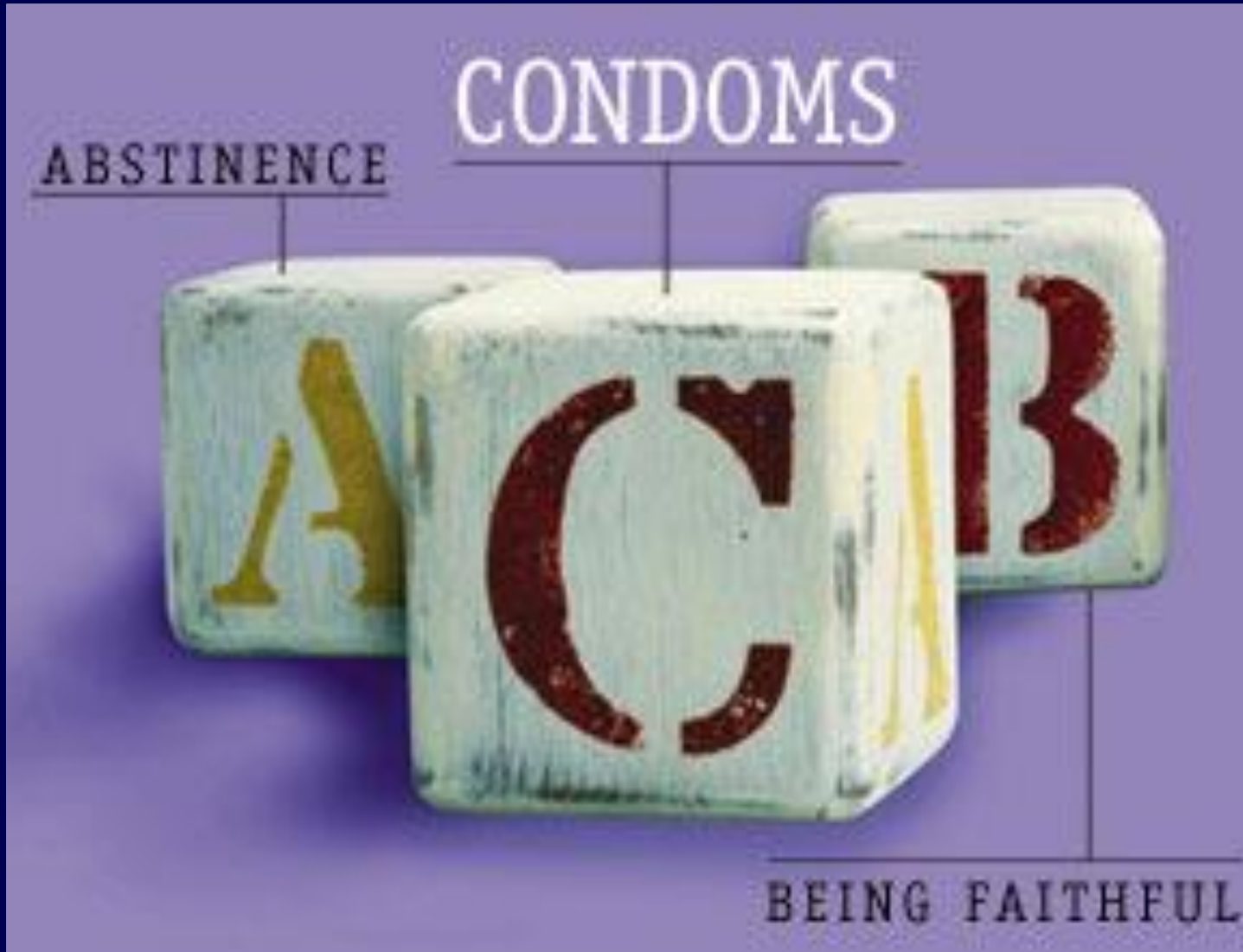
UKZN

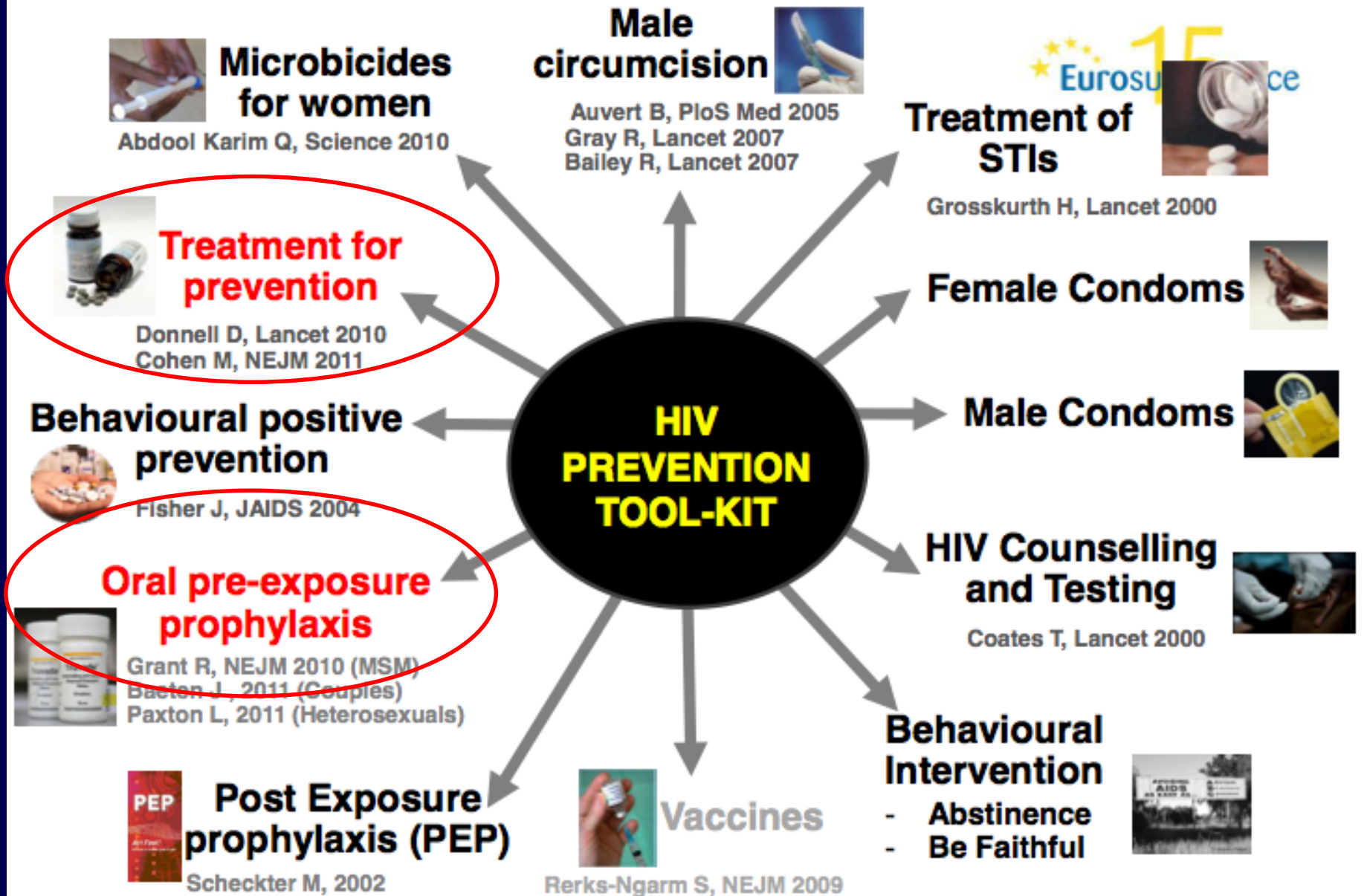
Ongoing HIV transmission despite expanding access to ART – SA



Source: HSRC, 2012

Prevention Package





Note: PMTCT, Screening transfusions, Harm reduction, Universal precautions, etc. have not been included – this is focused on reducing sexual transmission

Have you prescribed PrEP in you Practice

A. Yes

B. No

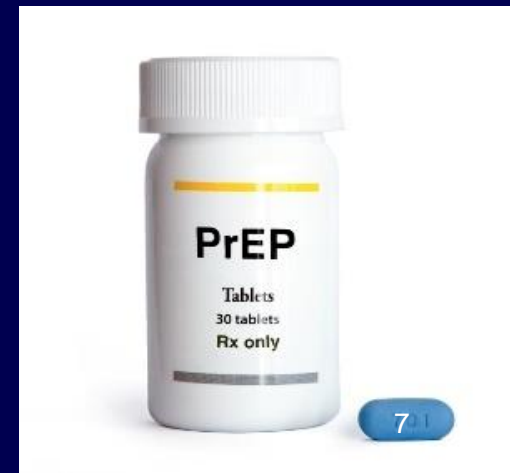
Do you think you will prescribe PrEP

A. Yes

B. No

Pre-exposure prophylaxis (PrEP)

- Taking a pharmaceutical agent prior to an exposure to prevent an outcome.
- In HIV
 - Use existing ARVs
 - Novel agents: long-acting injectable formulations
 - Different delivery systems
 - Topical gels,
 - Microbicide vaginal rings



- In the absence of a vaccine PrEP is an important prevention tool
- PrEP – malaria, surgical prophylaxis

Why TDF or TDF/FTC for PrEP?

- High level of activity in inhibiting HIV replication
- Acceptable safety profile
- Relative high barrier to resistant virus
- Low levels of side-effects
- Efficacy in animal models
- Best efficacy when both agents combined

Outline of Talk

- Rationale
- Proof of Concept in animal models
- ART penetration in genital tract
- Overview of trials:
 - Adherence
 - Sexual behavior/Risk compensation
 - Side effects and toxicities
 - Outcomes: efficacy/effectiveness
 - Resistance in seroconverters
 - Risk benefit balance: NNT

ART - A preventative Strategy

- Effective treatment prevents transmission
- Post-exposure prophylaxis
- Pre-exposure prophylaxis

What level of Efficacy is required for PrEP to work as an effective strategy

- A. 30%
- B. 40%
- C. 50%
- D. 60%
- E. 70%
- F. 80%
- G. 90%
- H. 100%

Is PrEP a Rational Approach?

- Mathematical models estimate that over the next 10 yrs., an effective PrEP program could prevent 2.5 to 3.5 million new HIV-1 infections in Africa
- Requires PrEP efficacy $\geq 50\%$

Proof of Concept: macaques \Rightarrow systemic ART before rectal exposure prevents infection

- Controls: most became infected within 4 rectal challenges
- 4 Different PrEP regimens: all protected to some extent
- Grp. 3 high dose daily PrEP
- Grp. 4 high dose intermittent 2 hrs. before and 24 hrs. after

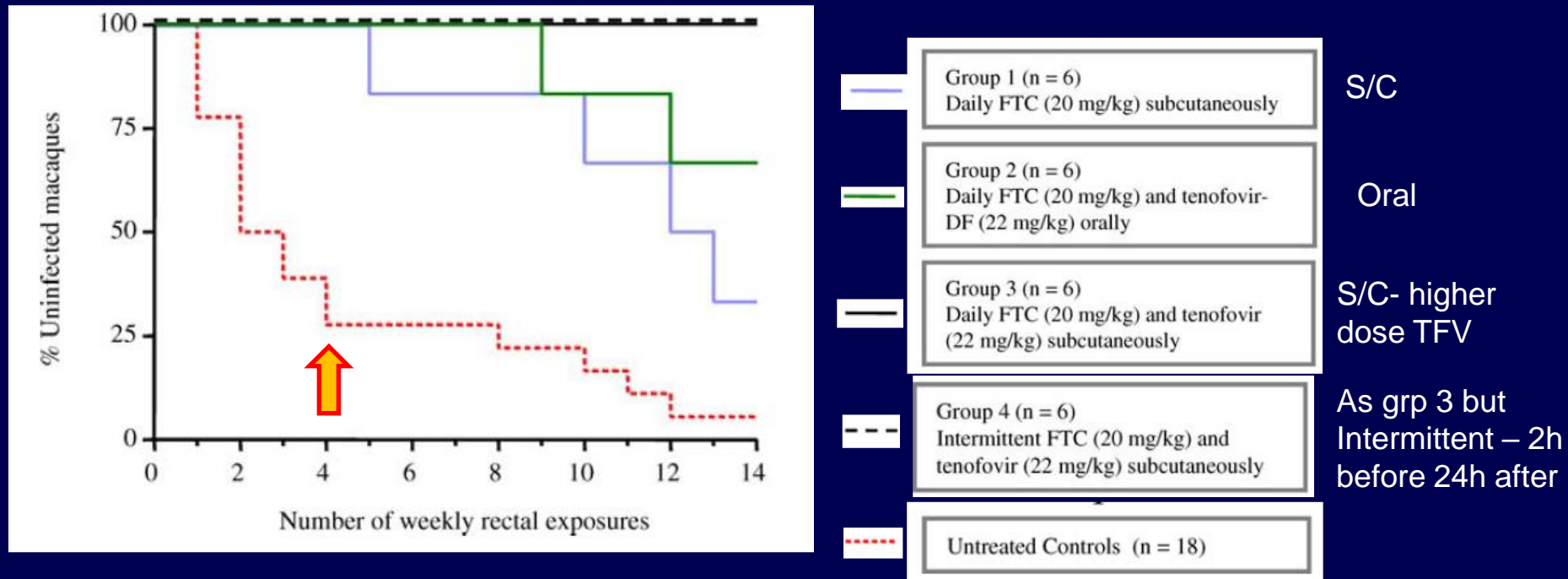


Figure 2. Protection against Repeated Rectal Virus Exposures by Daily or Intermittent PrEP

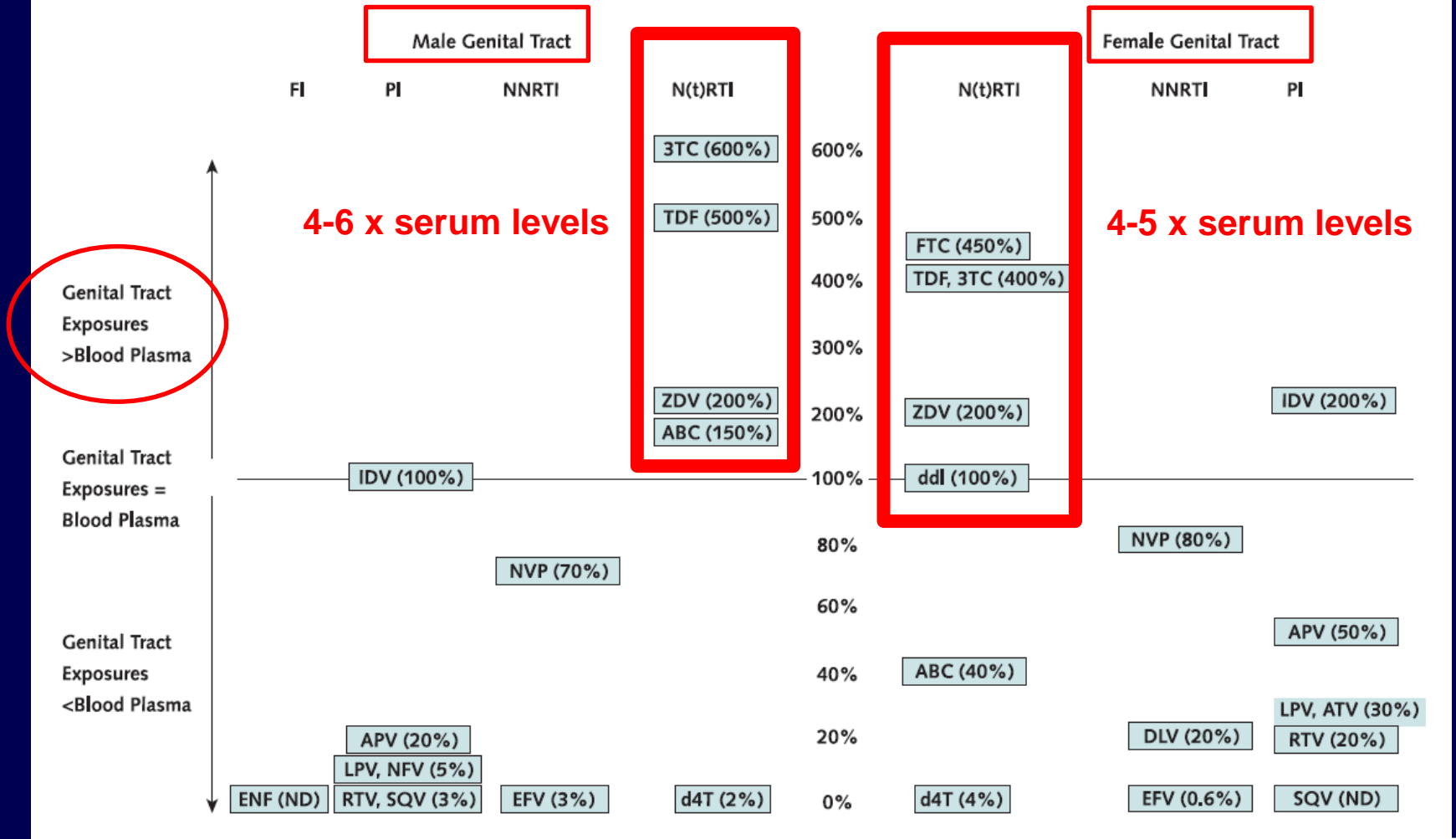
Does Drug Get to the Site?

Which drugs you think best penetrate the Genital Mucosa

- A. AZT
- B. TDF
- C. LPV/r
- D. EFV

Penetration of ART into Genital Tract relative to blood

Figure 1. Antiretroviral drug concentrations in the male and female genital tract relative to blood plasma concentrations (ratio of genital to blood plasma concentrations).

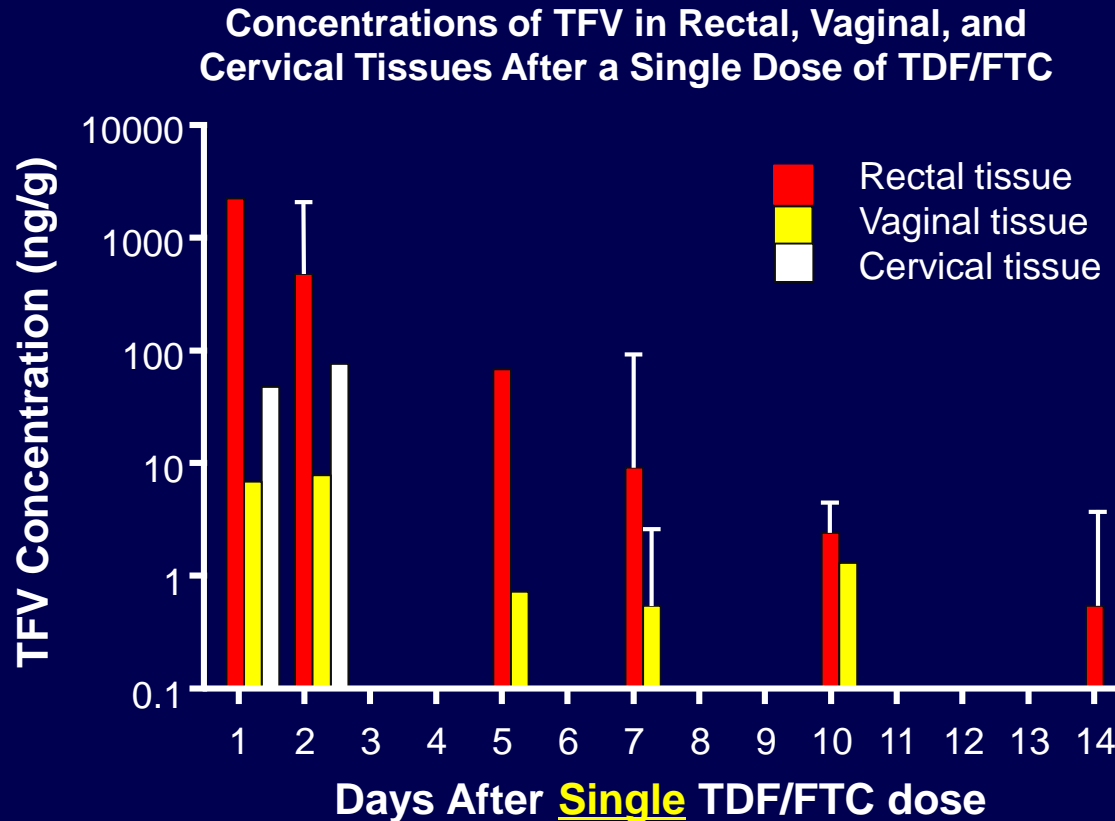


Which Mucosa has highest drug penetration and retention

- A. Rectal
- B. Vaginal
- C. Cervical
- D. Oral

Dynamics of TDF Penetration into Mucosal Tissues

- Exposure and retention varies in different mucosal tissues
- Rectal tissue- higher levels and longer retention
- implications for adherence in women



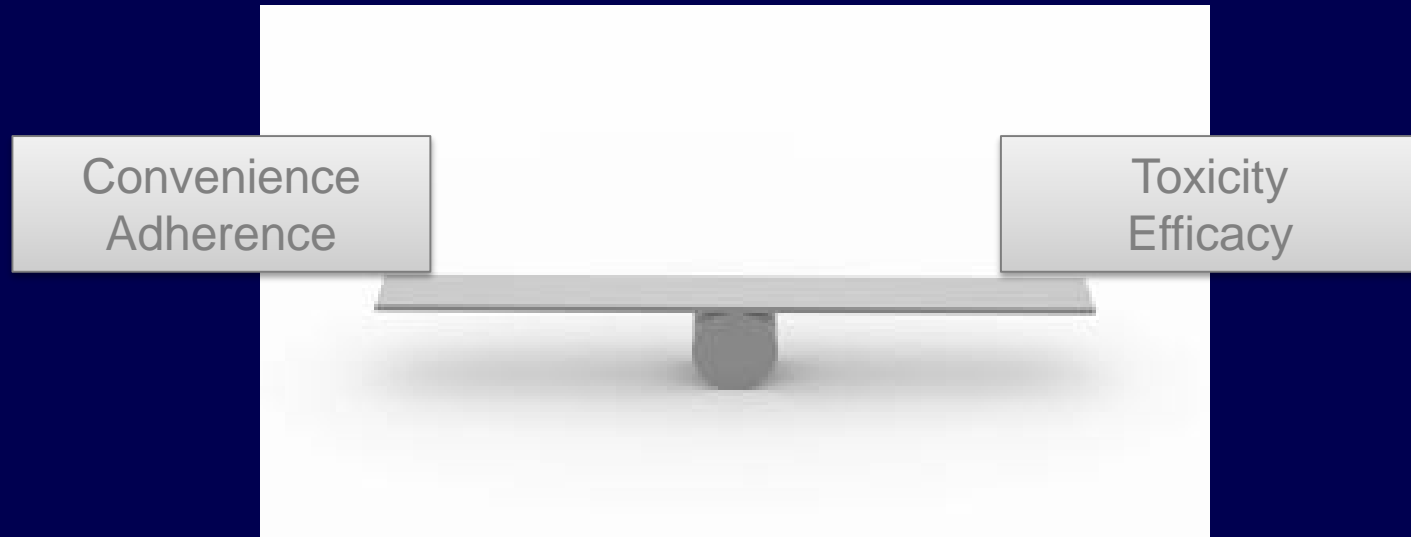
Rationale

During sexual transmission HIV replicates at low levels at mucosal entry point providing a brief period of virus vulnerability to block HIV from establishing infection

Critical Question

Will therapy that gets to the genital tract and effectively suppresses HIV replication prevent sexual transmission

Getting The Right Balance



Will Review a few relevant studies

- Partners PrEP
- TDF2
- VOICE
- FEM PrEP
- iPrEX
- PROUD
- Ipergay

2 Studies from Africa showed high level protection

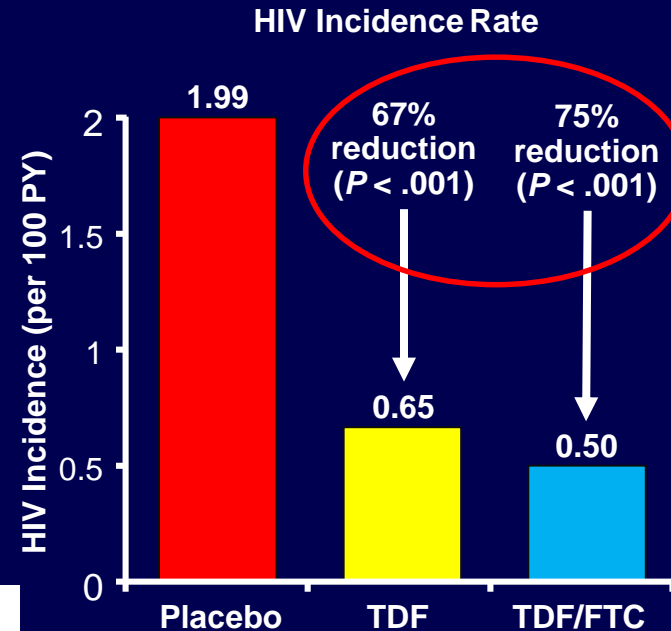
- The Partners PrEP study
 - TDF2 trials
- 
- Daily PrEP
 - Heterosexual
 - Males & Females

Partners PrEP Study

- RCT - oral PrEP among HIV–sero-discordant heterosexual couples: Kenya and Uganda.
- Seronegative partner randomly assigned to
 - Daily oral TDF
 - Daily oral TDF/FTC
 - Daily matched placebo
- Monthly follow up x 36 months.
- Eligible if positive partners not eligible ART

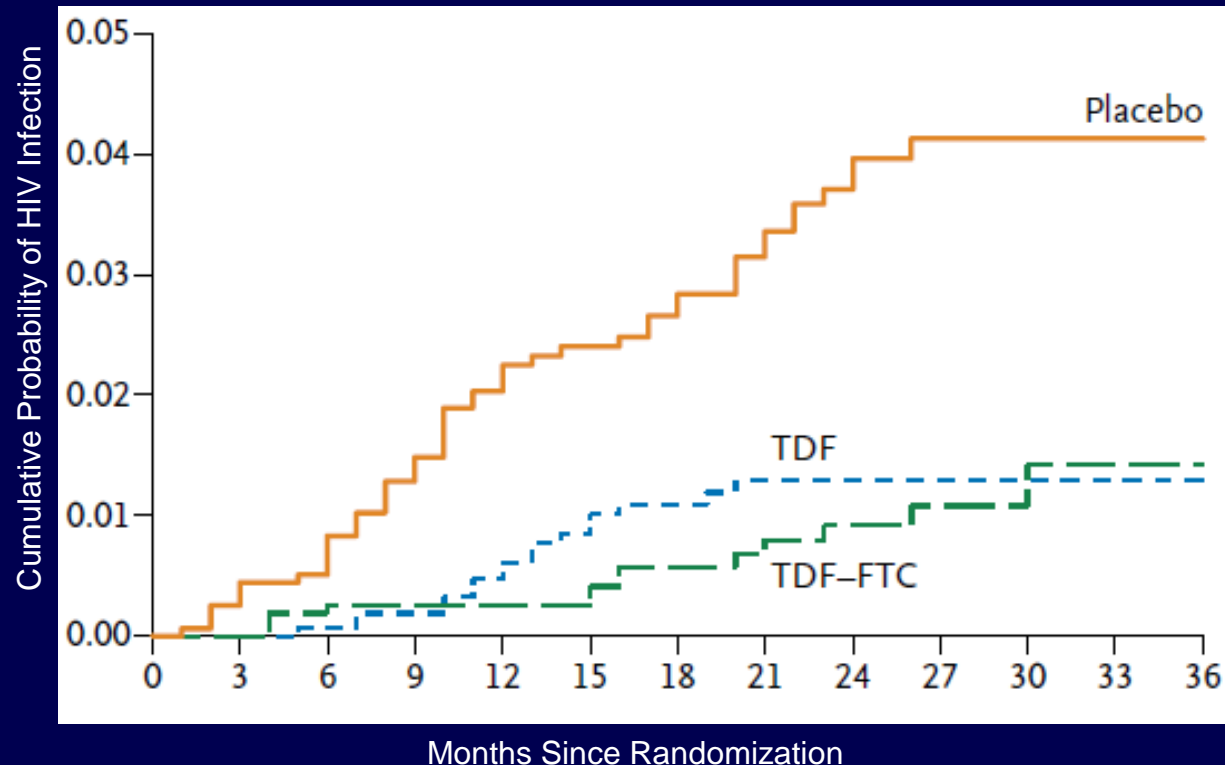
Partners PrEP Study: Efficacy

- 4758 couples - 1584 TDF, 1579 TDF/FTC, 1584 placebo.
- 62% of couples – male negative partner
- Median CD4 was 495 in infected
- 82 infections:
- 17 TDF (0.65/100 pyr.), 13 TDF/FTC (0.50/100 pyr) 52 placebo (1.99/100 pyr)
- Incidence was reduced in both men & women.



TDF: $1.99 - 0.65 / 1.99 \times 100 = 67\%$

TDF/FTC: $1.99 - 0.05 / 1.99 \times 100 = 75\%$




Partners PrEP Study : Adverse Events

Table 3. Adverse Events, According to Study Group.*

Adverse Event	TDF (N=1584)	P Value vs. Placebo	TDF-FTC (N=1579)	P Value vs. Placebo	Placebo (N=1584)
	<i>no. (%)</i>		<i>no. (%)</i>		<i>no. (%)</i>
Any adverse event	1350 (85)	1.00	1362 (86)	0.42	1350 (85)
Any serious adverse event	118 (7)	1.00	115 (7)	0.89	118 (7)
Death†	8 (1)	0.80	8 (1)	0.80	9 (1)
Any grade 4 event	34 (2)	0.64	44 (3)	0.58	39 (3)
Any grade 3 event	289 (18)	0.35	293 (19)	0.24	268 (17)
Confirmed laboratory events‡					
Elevated creatinine§					
Grade 1	16 (1)	0.57	18 (1)	0.28	12 (1)
Grade 2 or 3	3 (<1)	0.62	2 (<1)	0.62	1 (<1)
Decreased phosphorus¶					
Grade 2	134 (8)	0.56	128 (8)	0.79	124 (8)
Grade 3	8 (1)	0.50	12 (1)	1.00	12 (1)

Partners PrEP Study: Sexual Behavior

- No evidence of risk compensation
- **Condom-less sex**: seronegative partners:
 - At enrollment 27%
 - At 12 months 13%
 - At 24 months 9%
- Similar proportion reported **relations outside their partnerships**
- Similar rates of **STIs** during follow-up

Antiretroviral Pre-exposure Prophylaxis for Heterosexual HIV Transmission in Botswana: TDF2 Study

- Double-blind, placebo controlled RCT
- Daily TDF/FTC vs. placebo
- Enrolled men & women in 2 Botswana cities
- Participants HIV-seronegative, sexually active adults, 18 to 39 years of age

TDF2 Outcome

- 1219 (45.7% women) F/U 1563 pyrs (median 1.1 years; max 3.7 years).
- 33 infect: 9 TDF/FTC (1.2/100 pyrs) 24 placebo (3.1/100 pyrs)
- Efficacy - 62.2%
- TDF/FTC PrEP effective in heterosexual

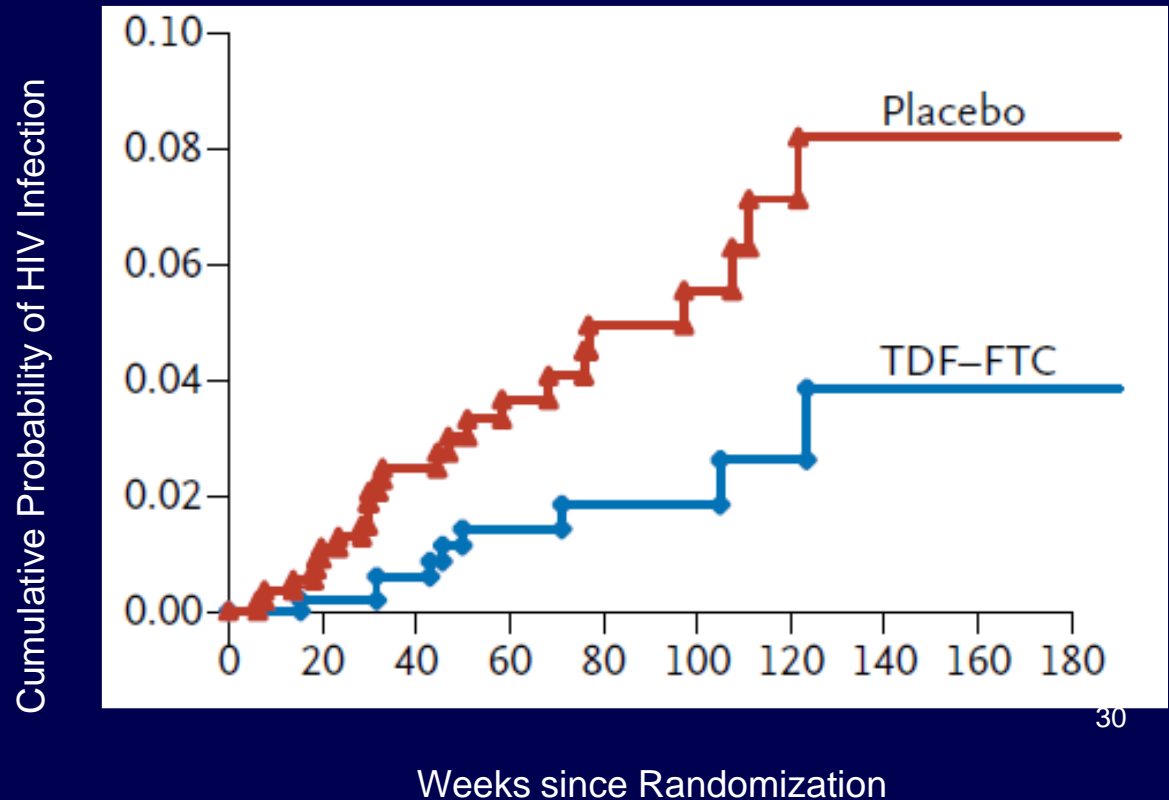


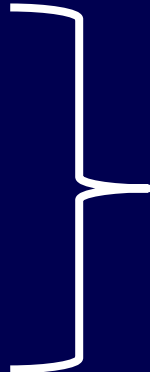
Table 2. Adverse Events, According to Treatment Group.*

Adverse Event	TDF-FTC (N = 611)		Placebo (N = 608)		P Value†
	<i>no. of participants (%)</i>	<i>no. of events</i>	<i>no. of participants (%)</i>	<i>no. of events</i>	
Any	557 (91.2)	4357	536 (88.2)	4390	0.003
Any serious	63 (10.3)	68	66 (10.9)	79	0.90
Grade 3 or 4 only	19 (3.1)	21	29 (4.8)	32	0.17
At least possibly related to study drug	20 (3.3)	21	27 (4.4)	29	0.35
Upper respiratory tract infection	231 (37.8)	385	241 (39.6)	439	0.84
Headache	227 (37.2)	390	226 (37.2)	411	0.73
Dizziness	92 (15.1)	109	67 (11.0)	82	0.03
Abdominal pain	155 (25.4)	215	156 (25.7)	217	0.78
Nausea	113 (18.5)	132	43 (7.1)	48	<0.001
Vomiting	69 (11.3)	87	43 (7.1)	47	0.008
Diarrhea	76 (12.4)	93	65 (10.7)	76	0.22
≥5% Weight loss	75 (12.3)	113	61 (10.0)	72	0.13
Back pain	57 (9.3)	72	68 (11.2)	90	0.37
Rash	39 (6.4)	44	42 (6.9)	48	0.81
Fracture	7 (1.1)	7	6 (1.0)	8	0.74
Elevated creatinine	1 (0.2)	1	0	0	1.00
Hypophosphatemia	142 (23.2)	219	159 (26.2)	245	0.65
Hyperamylasemia	315 (51.6)	997	302 (49.7)	1017	0.45
Elevated AST	36 (5.9)	43	38 (6.2)	42	0.90
Elevated ALT	38 (6.2)	48	43 (7.1)	66	0.57
Death‡	2 (0.3)	2	4 (0.7)	4	0.45

What do you think is the main reason for poor efficacy of PrEP

- A. Poor Adherence
- B. Drug interactions
- C. Poor absorption
- D. High Metabolism

2 Studies from Africa showed NO protection

- VOICE study
 - FEM PrEP
- 
- Daily PrEP
 - Females

TNF-Based PrEP in African Women: VOICE

Vaginal & Oral Interventions to Control the Epidemic

Randomized, placebo-controlled trial

- Daily oral TDF
- Daily oral TDF-FTC
- 1% tenofovir (TFV) vaginal gel

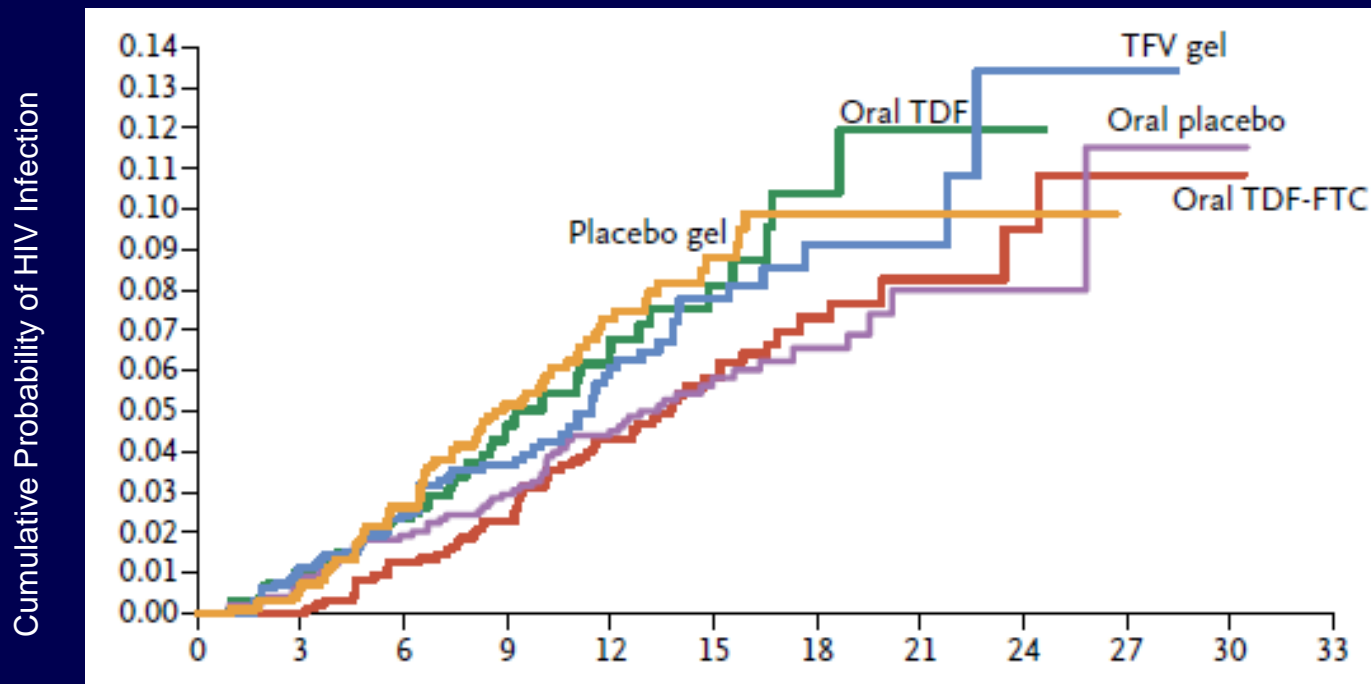
Participants: women in SA, Uganda, Zimbabwe.

- HIV-1 testing monthly
- Plasma TFV levels quarterly.

VOICE: no impact on HIV incidence

Table 3. Primary Efficacy Results.

Result	Oral TDF*		Oral TDF-FTC	Oral Placebo	TFV Gel	Placebo Gel
	Active Agent	Placebo				
Person-years	823	838	1284	1308	1024	1030
Number of HIV-1 infections	52	35	61	60	61	70
HIV-1 incidence — cases per 100 person-years (95% CI)	6.3 (4.7–8.3)	4.2 (2.9–5.8)	4.7 (3.6–6.1)	4.6 (3.5–5.9)	6.0 (4.6–7.6)	6.8 (5.3–8.6)
Hazard ratio (95% CI)	1.49 (0.97–2.29)	—	1.04 (0.73–1.49)	—	0.85 (0.61–1.21)	—
P value	0.07	—	0.81	—	0.37	—



VOICE: Different measures of Adherence

Table 2. Adherence to Study Products.*

Measure of Adherence	Total (N=5007)	Oral TDF (N=1002)	Oral TDF-FTC (N=994)	Oral Placebo (N=1008)	TFV Gel (N=1003)	Placebo Gel (N=1000)
Mean rate of adherence (%)						
Assessed by clinic-based <u>product count</u> †	86	84	88	90	83	84
Assessed by <u>face-to-face interview</u> ‡	90	91	90	91	90	90
Assessed by ACASI§ ←	88	87	87	88	88	89
Mean proportion of quarterly plasma samples with TFV detected (%)¶	NA	30	29	NA	25	NA
Proportion of women with TFV not detected in any quarterly plasma samples (%)¶	NA	58	50	NA	57	NA
Mean proportion of vaginal swab samples with TFV detected (%)	NA	NA	NA	NA	49	NA
Proportion of women with TFV not detected in any vaginal swab samples (%)	NA	NA	NA	NA	41	NA

ACASI: audio computer-assisted self-interview

Preexposure Prophylaxis for HIV Infection among African Women

Lut Van Damme, M.D., Amy Corneli, Ph.D., Khatija Ahmed, M.Med.,

Engl J Med 2012;367:411-22.

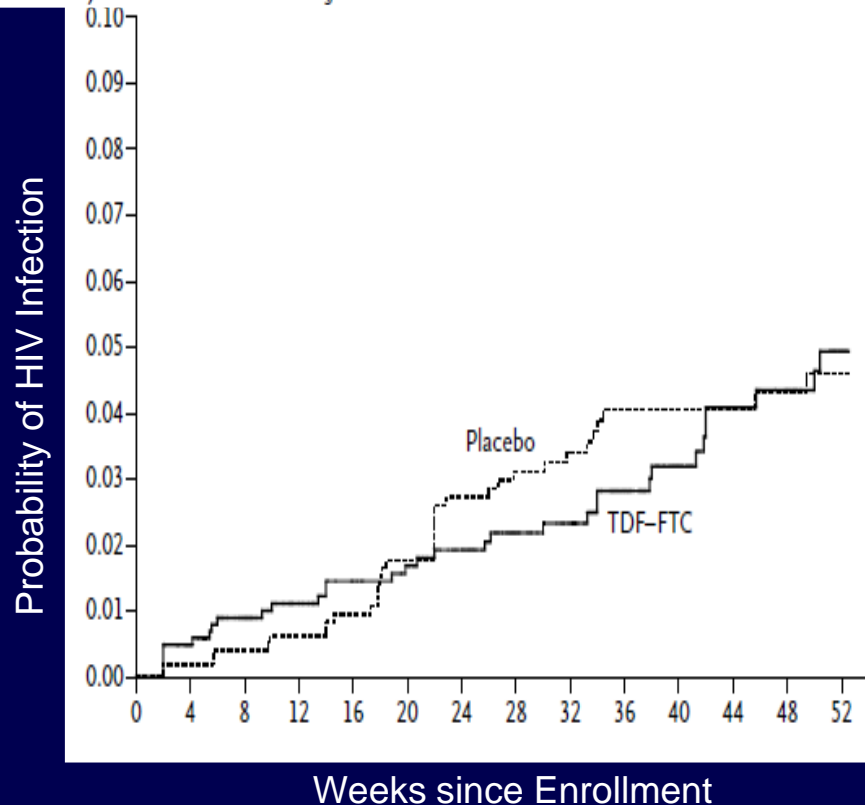


- Double blinded, placebo controlled RCT
- 2120 HIV negative women- Kenya, SA, Tanzania
- TDF–FTC once daily.
- Primary objective: Prevention of HIV & safety.

FEM PrEP

Table 2. Effectiveness Results.*

Variable	TDF-FTC			Placebo			Hazard Ratio (95% CI) [†]	P Value
	No. of Participants	No. of Events	Rate <i>no. of events/ 100 person-yr</i>	No. of Participants	No. of Events	Rate <i>no. of events/ 100 person-yr</i>		
Type of analysis								
Primary analysis	1024	33	4.7	1032	35	5.0	0.94 (0.59–1.52)	0.81
Data censored when study drug was last available for use‡	1025	27	4.2	1031	34	5.1	0.82 (0.49–1.36)	0.44
After adjustment for covariates§	1020	33	4.7	1028	34	4.9	0.95 (0.59–1.54)	0.84



No difference in incidence of HIV

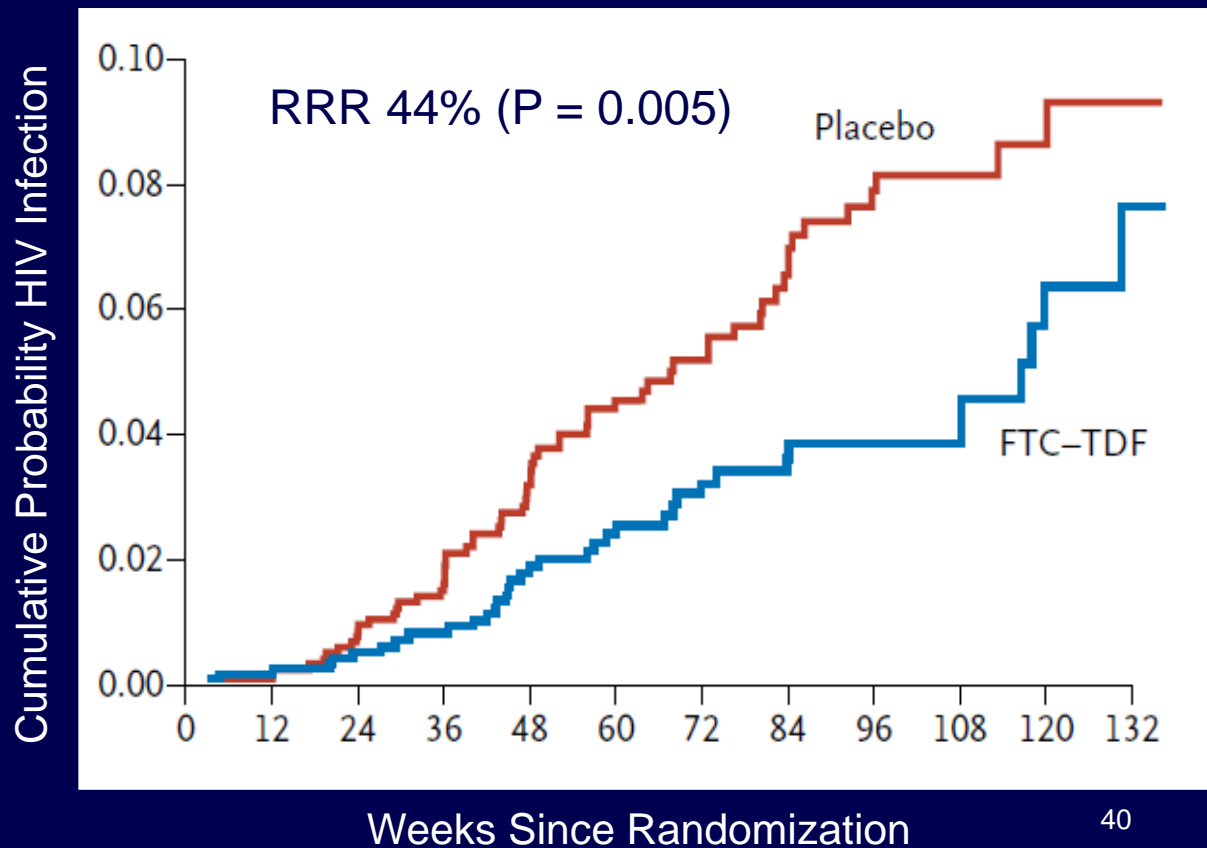
Low adherence based on drug blood levels- unable to assess the effectiveness/safety

PrEP in MSM & TGW

- iPrEx trial - first RCT
- PROUD study
- IPERGAY - 'on-demand' dosing strategy.

iPrEX: Daily Oral TDF/FTC PrEP for MSM

- Double-blind RCT of TDF/FTC vs PBO
- 2499 MSM/TGW – daily Oral TDF/FTC PrEP vs. placebo



Outcome Dependent on Adherence

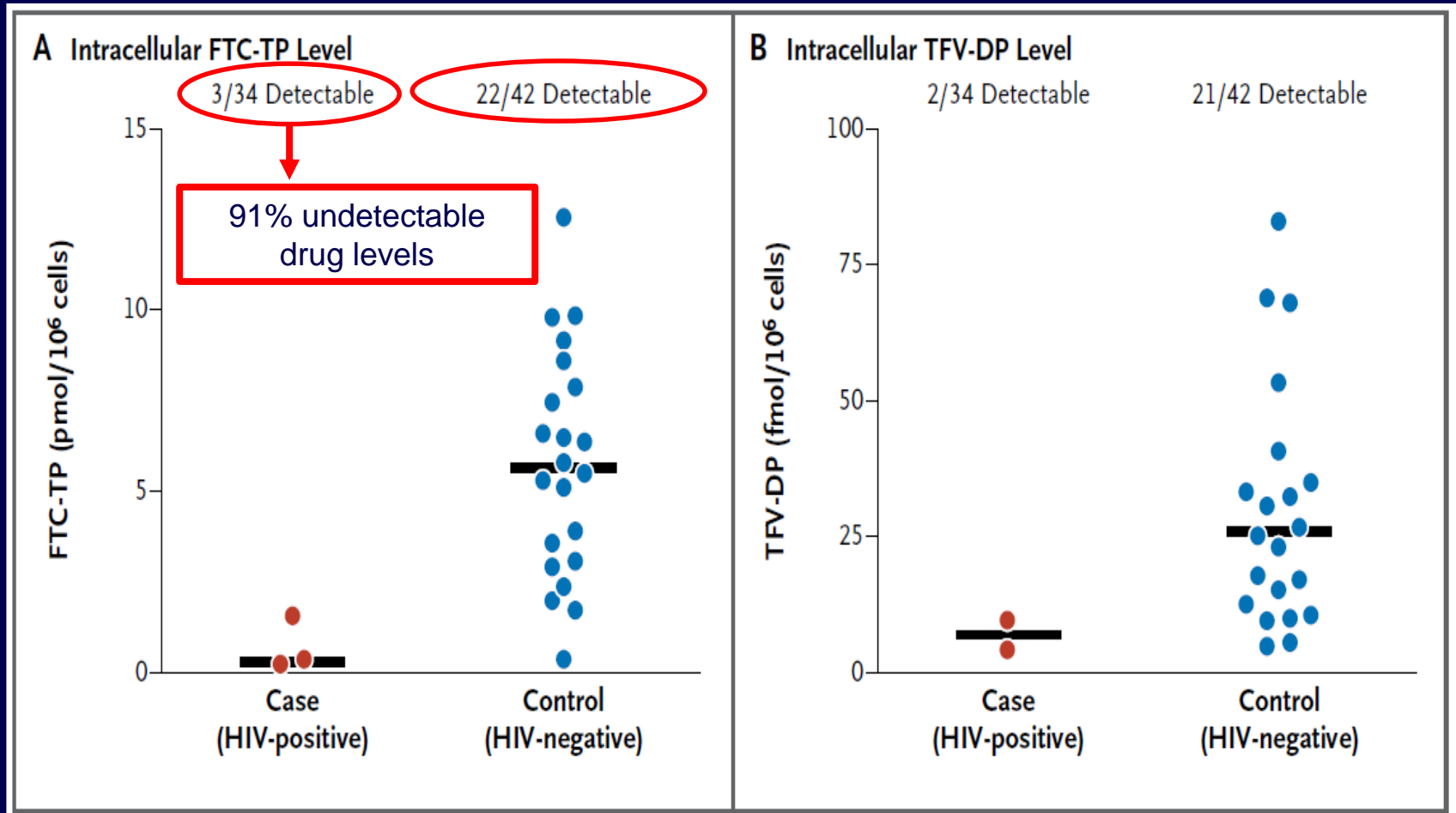
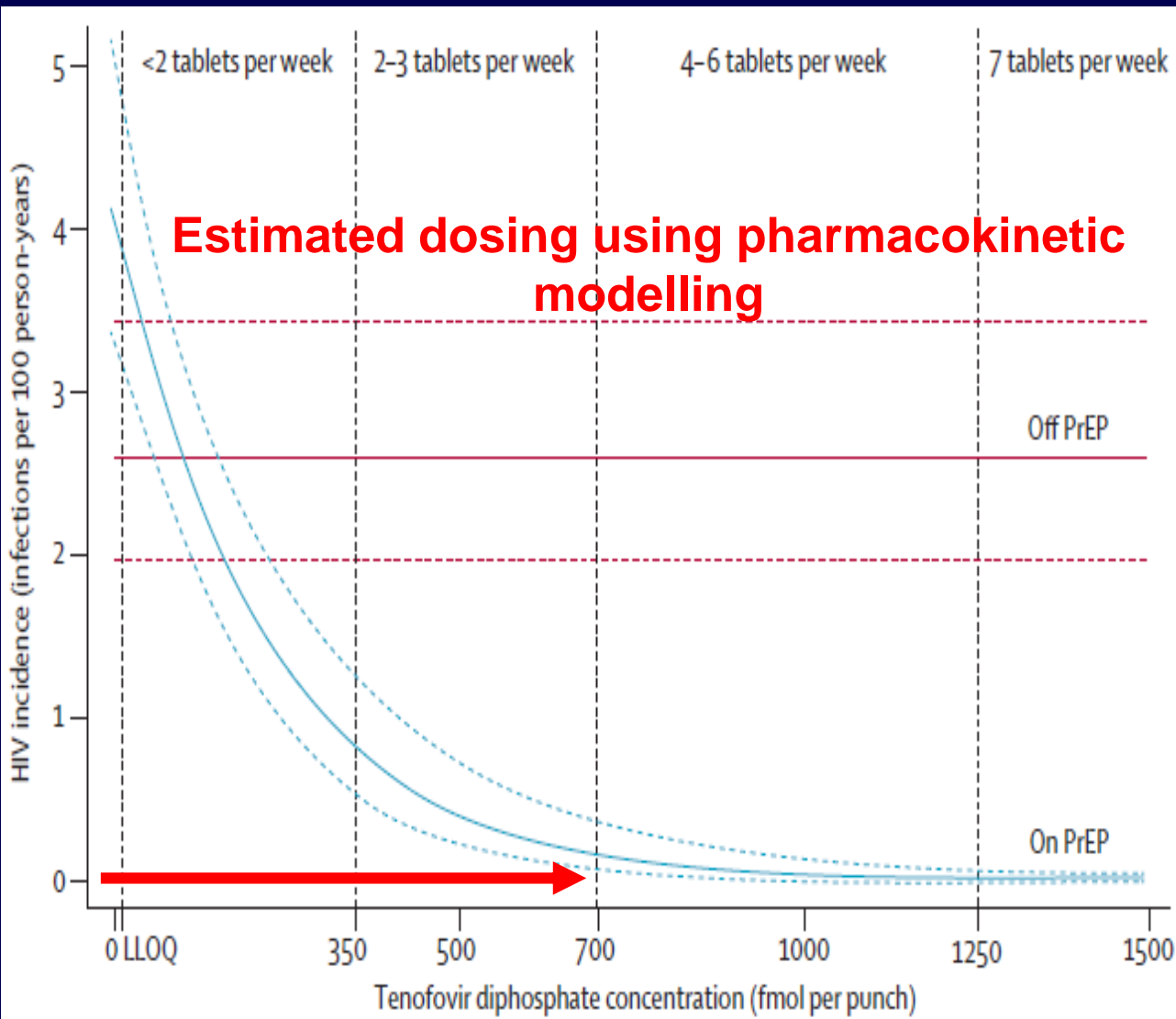


Figure 4. Levels of Study-Drug Components in Blood of Subjects Receiving FTC-TDF, According to HIV Status.

Perfect adherence not required: iPrEx – open label extension



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

Sexual Risk Compensation: RAI (iPrEx)

Two groups based on perception of PrEP

Mean no. of RAI partners decreased from baseline and remained stable both

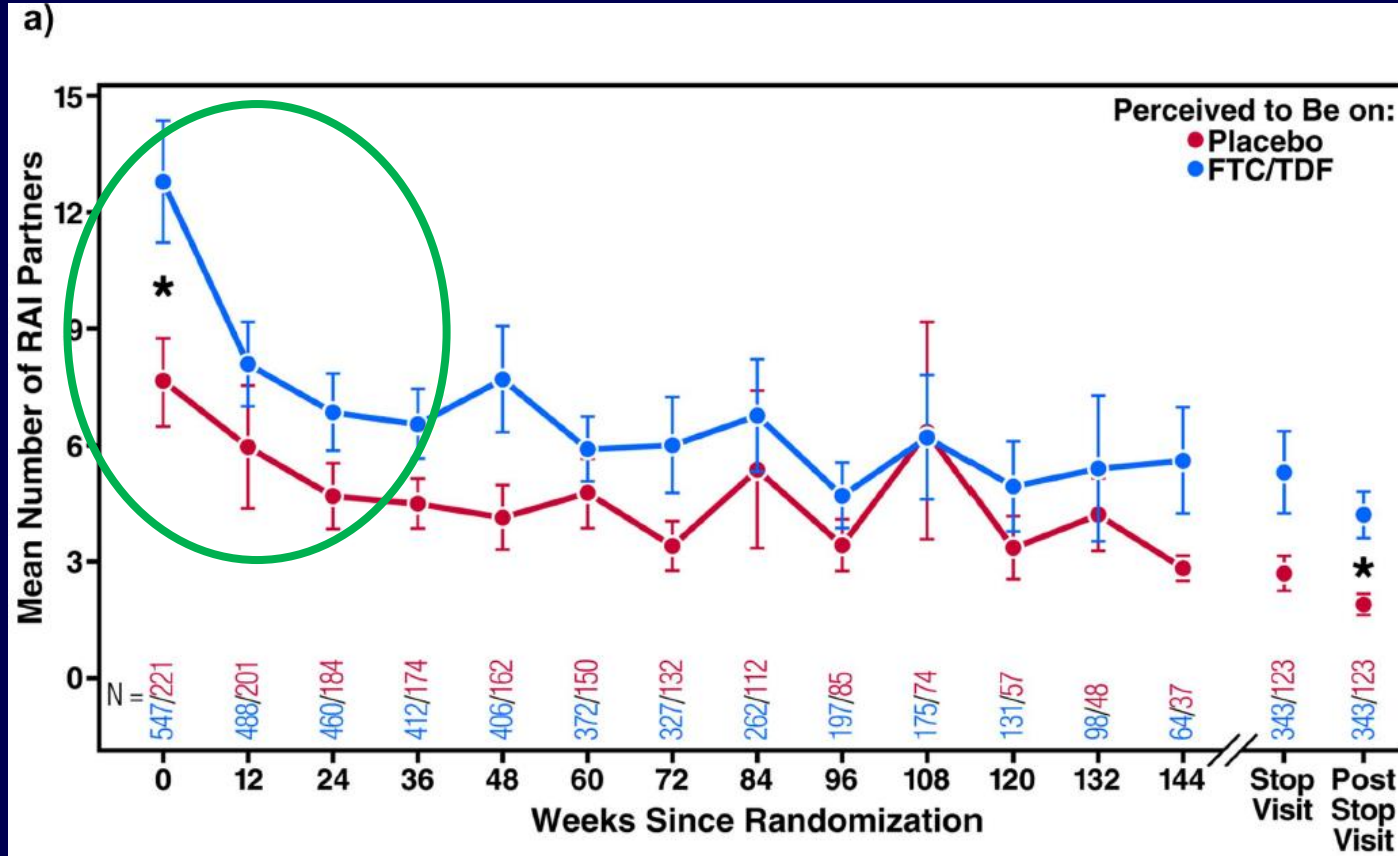


Figure 1. Sexual behavior by perceived treatment group. Figure 1a shows the mean number of receptive anal intercourse (RAI) partners in the past 3 months by perceived treatment group at 12 weeks. Figure 1b shows the percent of those partners using a condom by perceived treatment group at 12 weeks. Asterisks indicate $P < 0.05$ by t-test.

Sexual Risk Compensation: Condom Use (iPrEx)

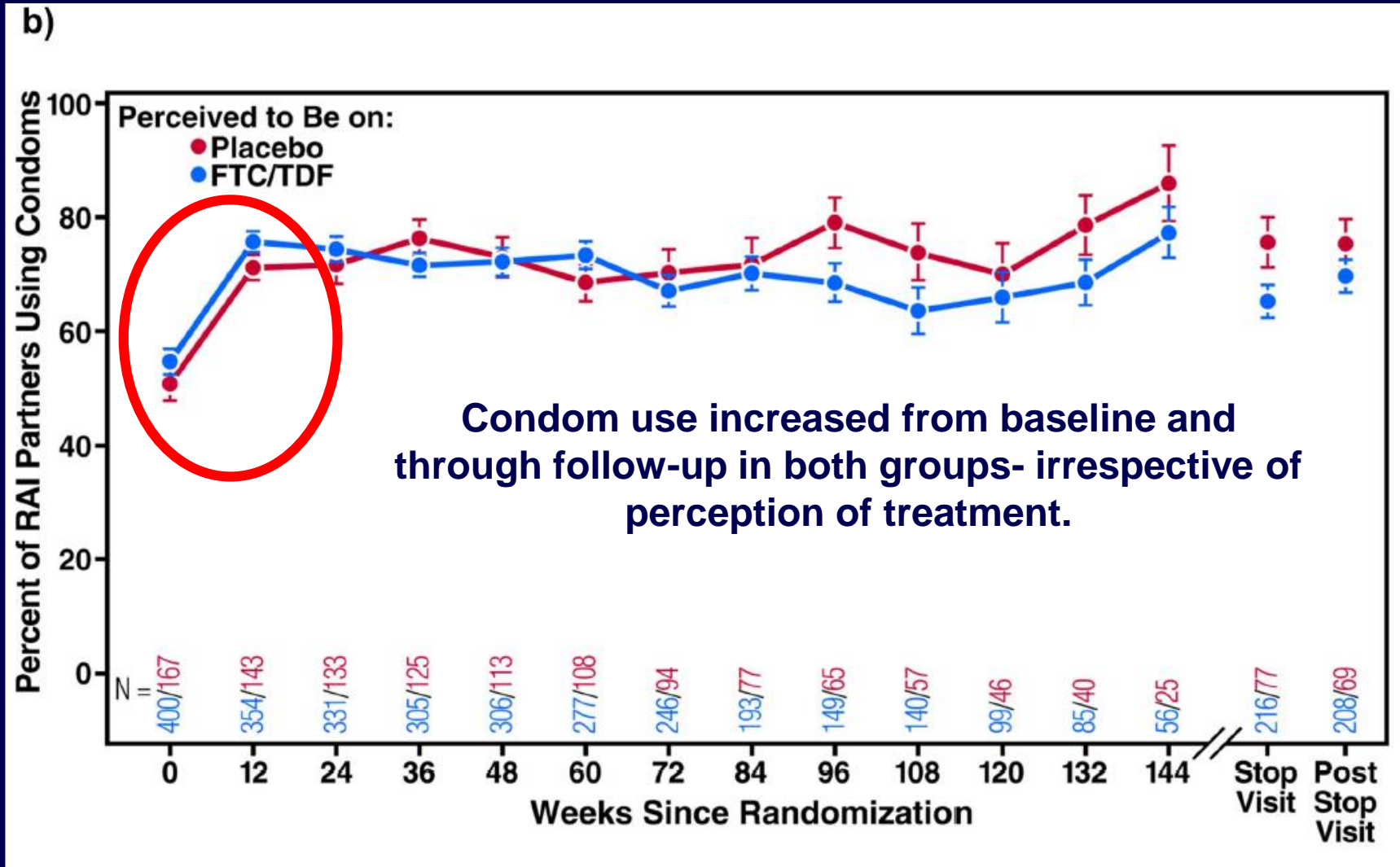


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Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial

Sheena McCormack, David T Dunn*, Monica Desai, David I Dolling, Mitzy Gafos, Richard Gilson, Ann K Sullivan, Amanda Clarke, Iain Reeves,*

- **Open-label RCT- TDF/FTC**
- MSM: condomless anal sex in last 90 days.
- Immediate or deferred initiation (after 1 year)
- 24 months Follow up.
- Study stopped early by DSMB- d/t high efficacy

PROUD Study UK: Efficacy

- 544 subjects (275 immediate, 269 deferred)
- Early evidence of effectiveness all offered PrEP
- 2 infections immediate grp (1.2/100 pyrs) vs. 20 in deferred grp (9.0/100 pyrs)
- RRR 86%, (90% CI 64–96, $p=0.0001$)
- ARR 7.8/100 pyrs
- 13 men need to take PrEP for 1 yr to avert one HIV infection.

Risk Compensation

STIs surrogate for risky behavior- no change

	Immediate	Deferred	Unadjusted odds ratio	Adjusted odds ratio (90% CI)*	p value
Any	152/265 (57%)	124/247 (50%)	1.33	1.07 (0.78–1.46)	0.74
Gonorrhoea†	103/261 (39%)	89/242 (37%)	1.12	0.86 (0.62–1.20)	0.46
Chlamydia†	77/261 (30%)	54/242 (22%)	1.46	1.27 (0.89–1.80)	0.27
Syphilis	30/263 (11%)	22/247 (9%)	1.32	1.29 (0.79–2.10)	0.39
Rectal gonorrhoea or chlamydia	93/258 (36%)	77/238 (32%)	1.18	1.00 (0.72–1.38)	0.99

Infections diagnosed during deferral phase of follow-up. Analysis based on participants with at least one screen.

*Adjusted for the number of screens for specific infection. †Detected in throat, urethra, or rectum.

Table 3: Bacterial sexually transmitted infections

PROUD Study UK

- No serious reactions attributable to study drug
- Most common nausea, headache, arthralgia, resulted in interruption of PrEP.
- 5 participants in the immediate group had HIV infection
 - 3 with undetected acute infection at enrolment - 2/3 developed resistance mutations
 - 2 seroconverted on PrEP - no resistance
- The use of Truvada for PrEP was safe

On Demand PrEP vs. Daily PrEP Ipergay Trial

- Long term adherence to daily PrEP is challenging
- Another option is “on demand” PrEP
- Intermittent sex-based dosing: 2 pills 2h to 24h before sex, another 24h later and 4th pill 48h after first (4 or more doses).

On Demand PrEP -Oral TDF-FTC in MSM (Ipergay Trial)

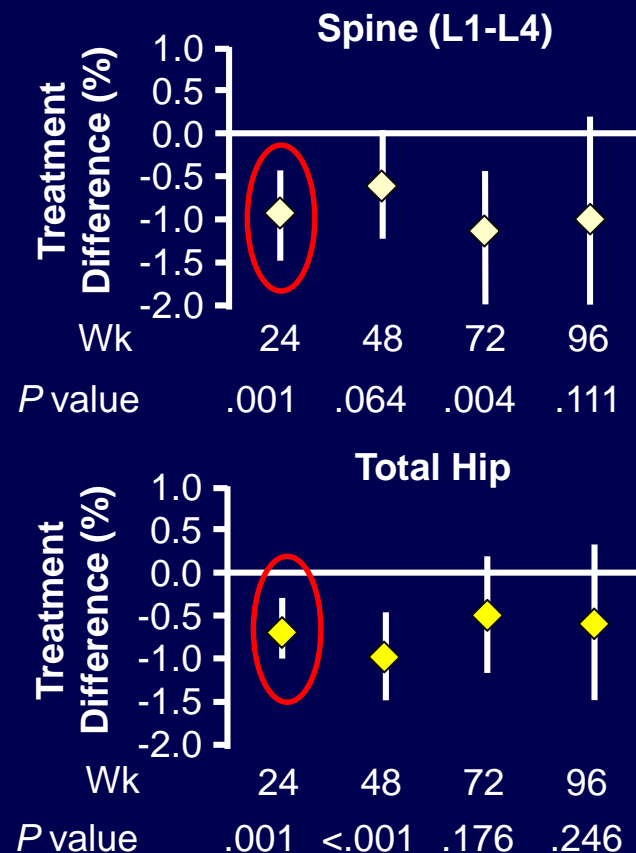
- Prospective double blind RCT of Truvada vs. placebo- 400 highly sexually active MSM
 - Stopped early by DSMB due to high efficacy
 - Incidence: 14 vs. 2 infections
 - Incidence rate:
 - 6.75/100 pyr placebo arm
 - 0.94/100 pyrs TDF/FTC arm
- RRR 86%** (95% CI 40% to 99%, P = 0.002)
- N, V, D abdominal pain with TDF-FTC (13% vs 6%, p=0.02).
 - NNT for 1 year to prevent 1 infection was 18

Bone and Renal Toxicity

iPrEx: Bone Mineral Density Sub study

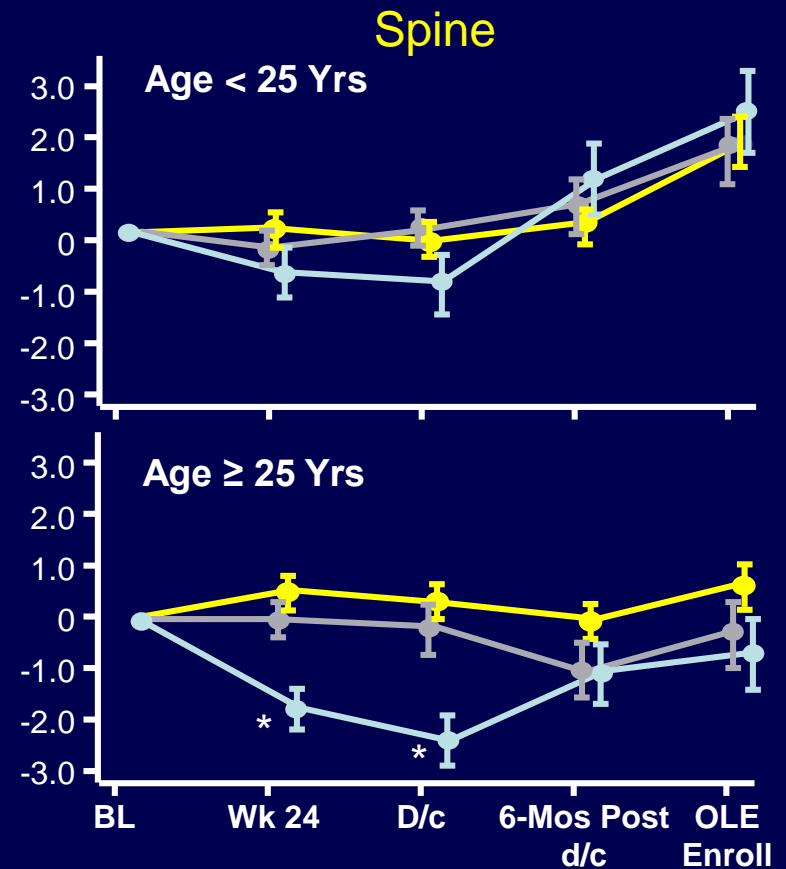
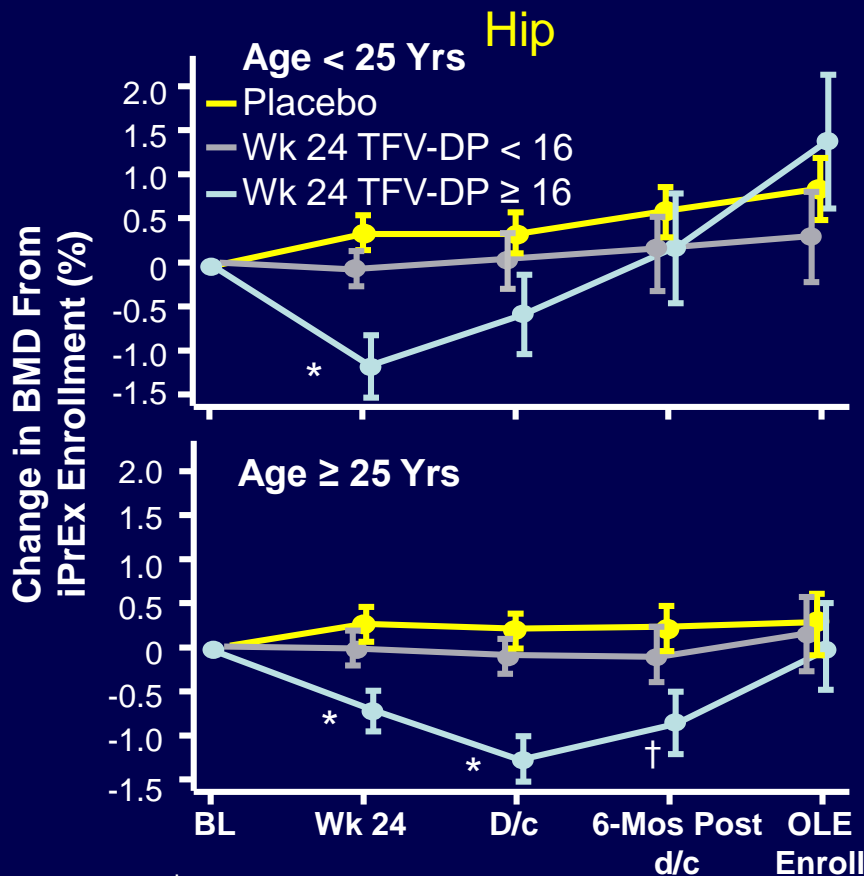
- DEXA scan assessment (N = 498)
- **Small net decrease in spine and total hip BMD** with TDF/FTC at wk. 24 (-0.91% & -0.61%, respectively; $P = .001$ for both)
- **No difference in fracture rate** between groups ($P = .62$)
- **Clinical significance of BMD loss** (1.42% spine or 0.85% hip) in healthy young & middle-aged is unknown

Mean Net Treatment Difference in BMD Change, Placebo – TDF/FTC (95% CI)



iPrEx BMD Sub study: BMD Recovery After Discontinuing TDF/FTC PrEP

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



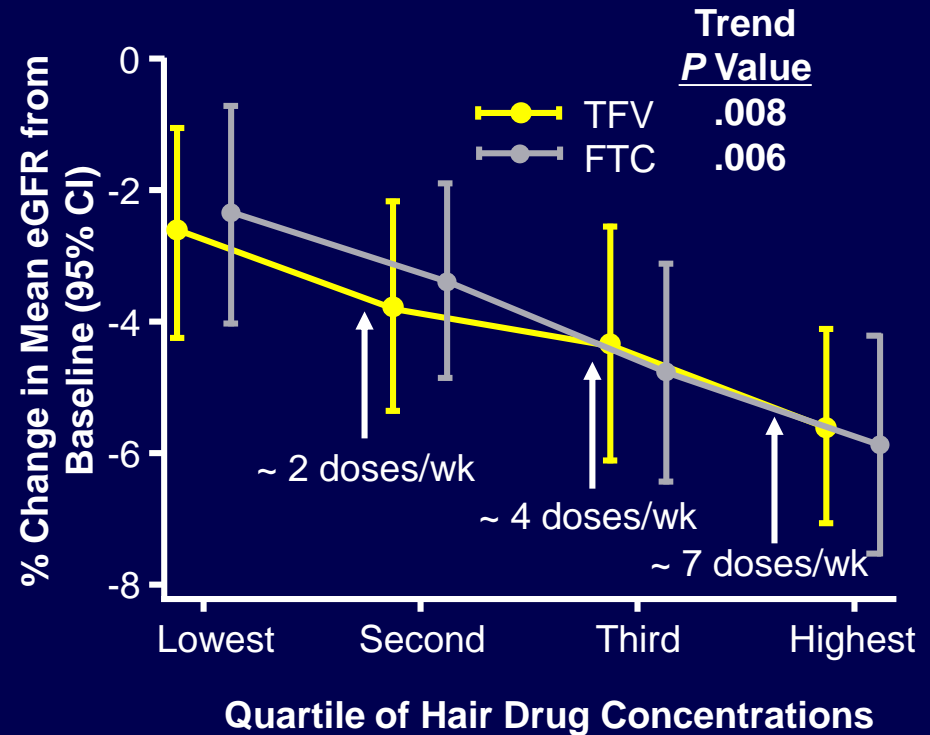
* $P < .001$; † $P < .05$



Cumulative Decline in Renal Function on TFV/FTC PrEP

- Higher TFV exposure associated with greater eGFR decreases
 - iPrEx OLE^[1] (n = 202): 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 **age > 40-45 yrs.**

%Change in eGFR from baseline vs Concentration FTC in Hair^[1]



1. Gandhi M, et al. CROI 2016. Abstract 866.

2. Liu AY, et al. CROI 2016. Abstract 867.

Summary Slides

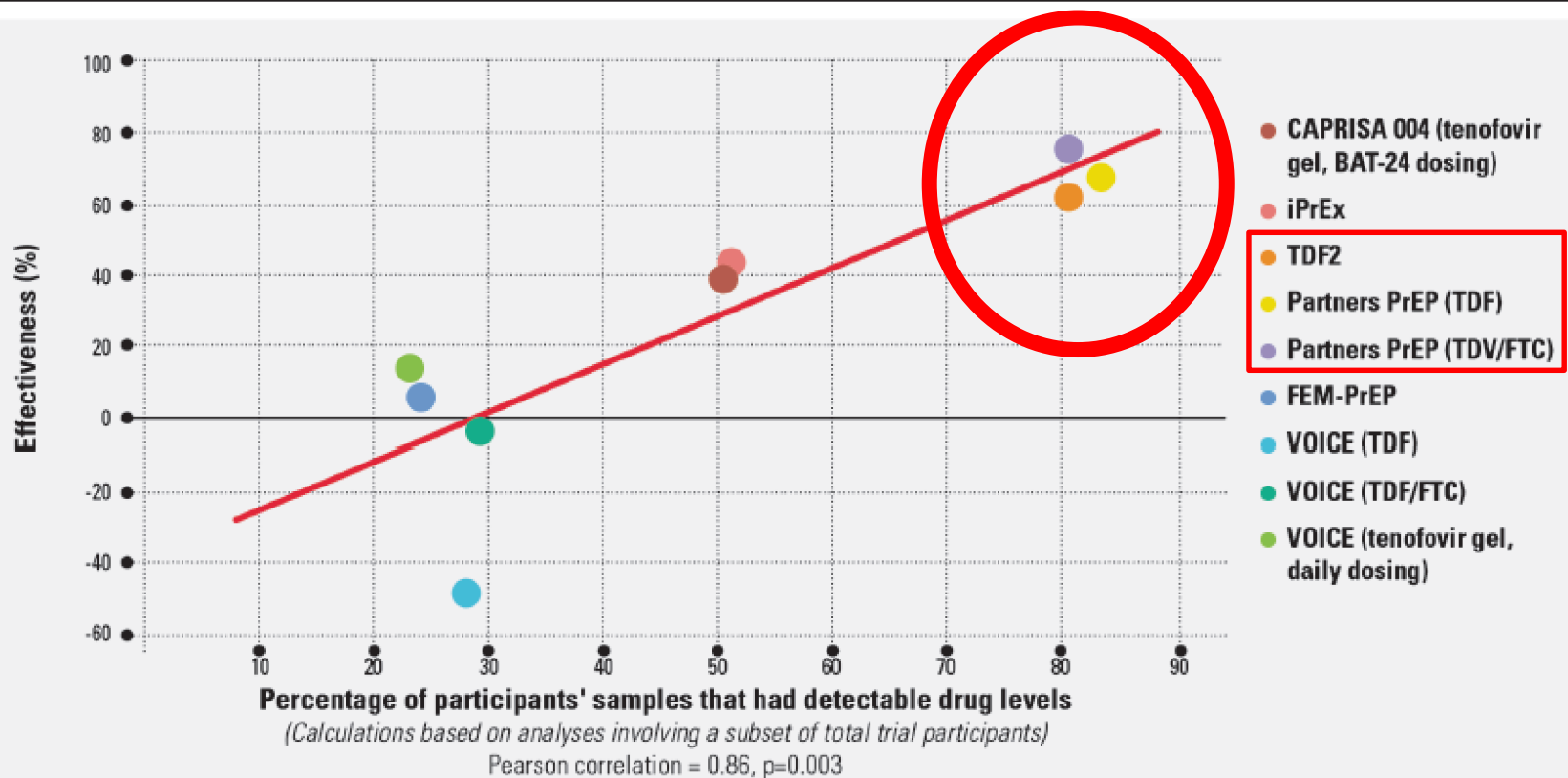
Table 3: Evidence Summary—HIV Incidence Findings

Study	Outcome Analyses— HIV incidence (mITT)		Effect — HR [Efficacy Estimate] (95% CI)		
	Agent	Control			
iPrEx (MSM)	36 infections among 1224 persons	64 infections among 1217 persons	0.56 [44%] (0.37–0.85)		
US MSM Safety Trial	3 infections among 201 persons (all 3 in delayed arm, not on TDF)	4 infections among 199 persons (1 acute infection at enrollment)	Not Reported		
Partners PrEP (heterosexual men and women)	TDF 17 infections among 1572 persons	52 infections among 1568 persons		TDF	TDF/FTC
	TDF/FTC 13 infections among 1568 persons		All	0.33 [67%] (0.19–0.56)	0.25 [75%] (0.13–0.45)
			Women	0.29 [71%] (0.13–0.63)	0.34 [66%] (0.16–0.72)
			Men	0.37 [63%] (0.17–0.80)	0.16 [84%] (0.06–0.46)
TDF2 (heterosexual men and women)	9 infections among 601 persons 1.2 infections/100 person-years	24 infections among 599 persons 3.1 infections per 100 person-years	0.38 [62%] (0.17–0.79)		
FEM-PrEP (heterosexual women)	33 infections among 1024 persons 4.7 infections per 100 person-years	35 infections among 1032 persons 5.0 infections per 100 person-years	0.94 [6%] ^a (0.59–1.52)		
West African Trial (heterosexual women)	2 infections among 427 persons 0.86 infections per 100 person-years	6 infections among 432 persons 2.48 infections per 100 person-years	0.35 [65%] ^a (0.03–1.93)		
VOICE (heterosexual women)	TDF 52 infections among 993 persons 6.3 infections per 100 person-years	35 infections among 999 persons 4.2 infections per 100 person-years	TDF	TDF/FTC	
	TDF/FTC 61 infections among 985 persons 4.7 infections per 100 person-years		1.49 [-50 %] ^a (0.97–2.3)	1.04 [-4%] ^a (0.73, 1.5)	
BTS (injection drug users)	17 infections among 1204 persons 0.35 infections per 100 person-years	33 infections among 1207 persons 0.68 infections per 100 person-years	0.51 [49%] (9.6, 72.2)		

mITT: modified intent to treat analysis; HR: hazard ratio.

^a Not statistically significant.

PrEP works if you take it



Trials of oral and topical tenofovir-based PrEP show that these strategies reduce risk of HIV infection if they are used correctly and consistently. Higher adherence is directly linked to greater levels of protection.

Source: Salim S. Abdool Karim, CAPRISA

PrEP and ARV Resistance

Using standard sequencing resistance from PrEP rare.
Mostly seen with undetected acute infection at time PrEP of initiation.

	Number of HIV seroconverters on PrEP with resistance	
	HIV infected after enrollment	Seronegative acute HIV infection at enrollment
Partners PrEP	0 / 30	3 / 8
iPrEx	0 / 36	2 / 2
TDF2	0 / 10	1 / 1

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

Partners PrEP: Resistance

- Risk of resistance during breakthrough infections on PrEP
- Ultradeep sequencing in 121 converters

Table 1. Drug Resistance Present at Levels of >1%, According to Treatment Arm at the Time of Seroconversion

Group	Subjects With Resistance Frequencies >1%, Proportion (%), by Treatment Arm			
	FTC/TDF	TDF	Placebo	Overall
All patients	5/25 (20)	2/38 (5.3)	2/58 (3.5)	9/121 (7.4)
Among subjects retrospectively found to be HIV positive at enrollment or rerandomization ^a Seroconverting at enrollment	2/4 (50)	1/8 (12.5)	0/6 (0)	3/18 (16.7)
Among subjects who acquired HIV after enrollment or rerandomization ^a	3/21 (14.3)	1/30 (3.3)	2/52 (3.8)	6/103 (5.8)

- Resistance during breakthrough infections on PrEP rare
- Resistance could be due to:
 - Resistance selected by PrEP during breakthrough infections
 - Resistance from undetected infection at PrEP initiation
 - Transmitted resistance
- Need vigilance at initiation of PrEP and during PrEP

Conclusion

- PrEP is a highly effective & safe
- Adherence is critical / more forgiving for MSMs
- Does not impact on sexual risk behavior
- Toxicity is low but long term impact unclear
- Excluding seroconversion illness at initiation is critical to prevent resistance.
- PrEP should be tailored to populations at highest risk
- PrEP may be used intermittently during periods of perceived risk