NEWS FROM ASHM CONFERENCE BRISBANE, 16-18/09/2015

Focus on PrEP: from the world to Australia to New Zealand

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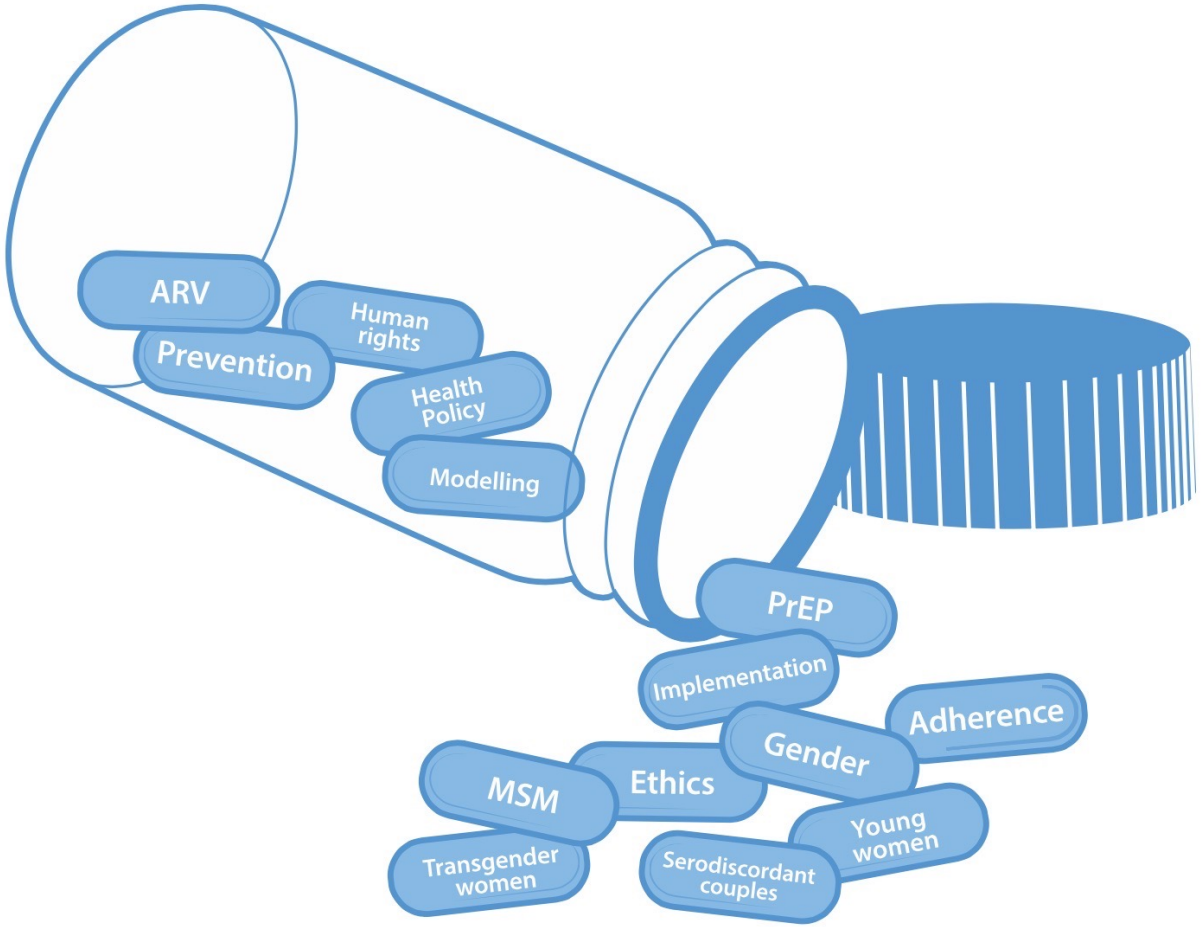
PrEP works - but how much exactly?



PrEP works - but how much exactly?

- At its best, comparably to condoms
- Condoms, used 100% of the time, provide protection of about 85% against HIV (95% C.I. = 76 - 93%)
  - *National Institute of Allergy and Infectious Diseases (NIAID) Scientific Evidence on Condom Effectiveness for Sexually Transmitted Disease (STD) Prevention. NIAID, 2001*
  - *Holmes KK et al. Effectiveness of condoms in preventing sexually transmitted infections. Bulletin of the World Health Organization 82:454-461, 2004*

First generation PrEP RCTs

Clinical trial	Participants	Type of medication	mITT efficacy*		Adherence-adjusted efficacy based on TDF detection in blood	
			%	(95% CI)	%	(95% CI)
Bangkok Tenofovir Study	Injecting drug users	TDF	49	(10–72)	70	(2–91)
Partners PrEP	HIV discordant couples	TDF	67	(44–81)	86	(67–94)
		TDF/FTC	75	(55–87)	90	(58–98)
TDF2	Heterosexually active men and women	TDF/FTC	62	(22–83)	84	NS
iPrEx	Men who have sex with men	TDF/FTC	42	(18–60)	92	(40–99)
Fem-PrEP	Heterosexually active women	TDF/FTC	NS	—	NA	—
VOICE	Heterosexually active women	TDF	NS	—	NA	—
		TDF/FTC	NS	—	NA	—

CI, confidence interval; FTC, emtricitabine; mITT, modified intent to treat analysis, excluding persons determined to have had HIV infection at enrolment; NA, data not available; NS, not statistically significant; TDF, tenofovir disoproxil fumarate

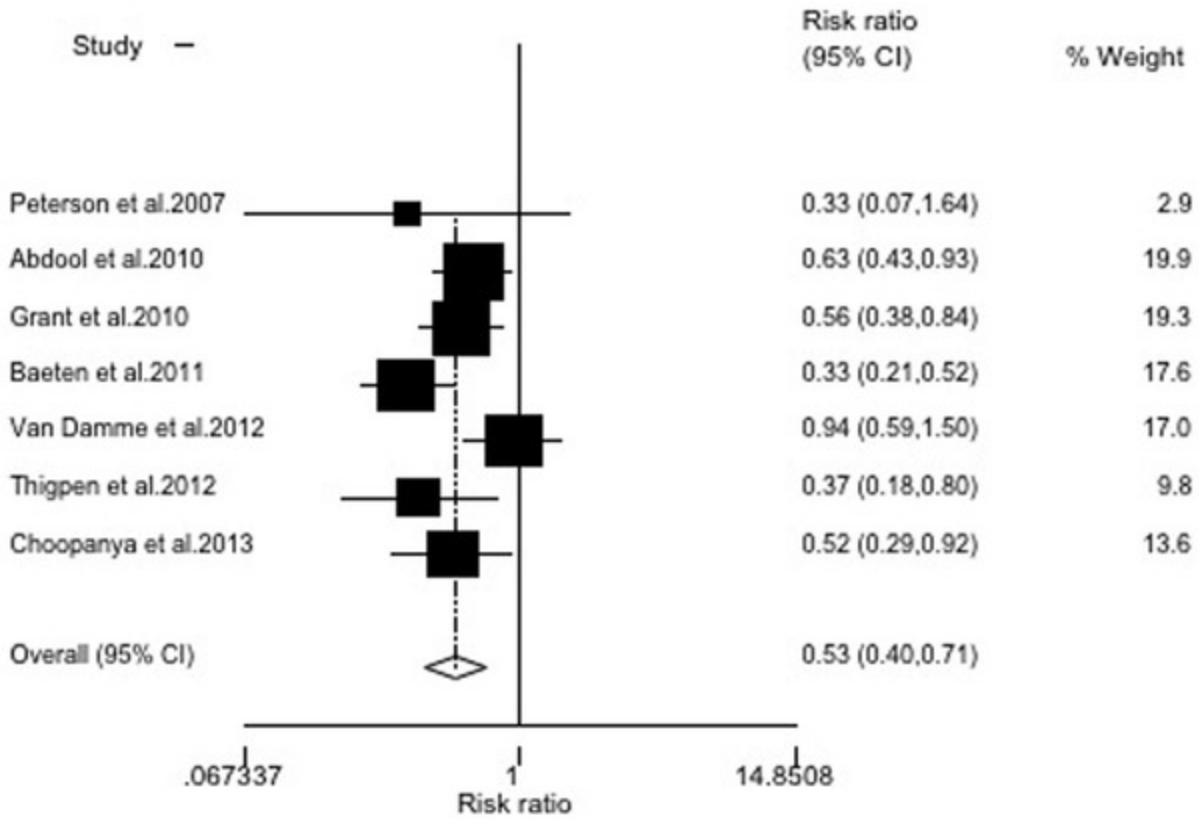
* % reduction in acquisition of HIV infection

PrEP RCTs: Overall Evidence Quality (per GRADE* Criteria)

Study	Design[a]	Participants		Limitations	Quality of Evidence (See Table 14, Appendix 2)
		Agent	Control		
Among Men Who have Sex with Men					
iPrEx Trial	Phase 3	TDF/FTC (n = 1251)	Placebo (n = 1248)	Adherence	High
US MSM Safety Trial	Phase 2	TDF (n = 201)	Placebo (n = 199)	Minimal	High
Among Heterosexual Men and Women					
Partners PrEP	Phase 3	TDF (n = 1589) TDF/FTC (n = 1583)	Placebo (n = 1586)	Minimal	High
TDF2	Phase 2	TDF/FTC (n = 611)	Placebo (n = 608)	High loss to follow-up; modest sample size	Moderate
Among Heterosexual Women					
FEM-PrEP	Phase 3	TDF/FTC (n = 1062)	Placebo (n = 1058)	Stopped at interim analysis, limited follow-up time; very low adherence to drug regimen	Low
West African Trial	Phase 2	TDF (n = 469)	Placebo (n = 467)	Stopped early for operational concerns; small sample size; limited follow-up time on assigned drug	Low
VOICE	Phase 2B	TDF (n = 1007) TDF/FTC (n = 1003)	Placebo (n = 1009)	TDF arm stopped at interim analysis (futility); very low adherence to drug regimen in both TDF and TDF/FTC arms	Low
Among Injection Drug Users					
BTS	Phase 3	TDF (n = 1204)	Placebo (n = 1207)	Minimal	High

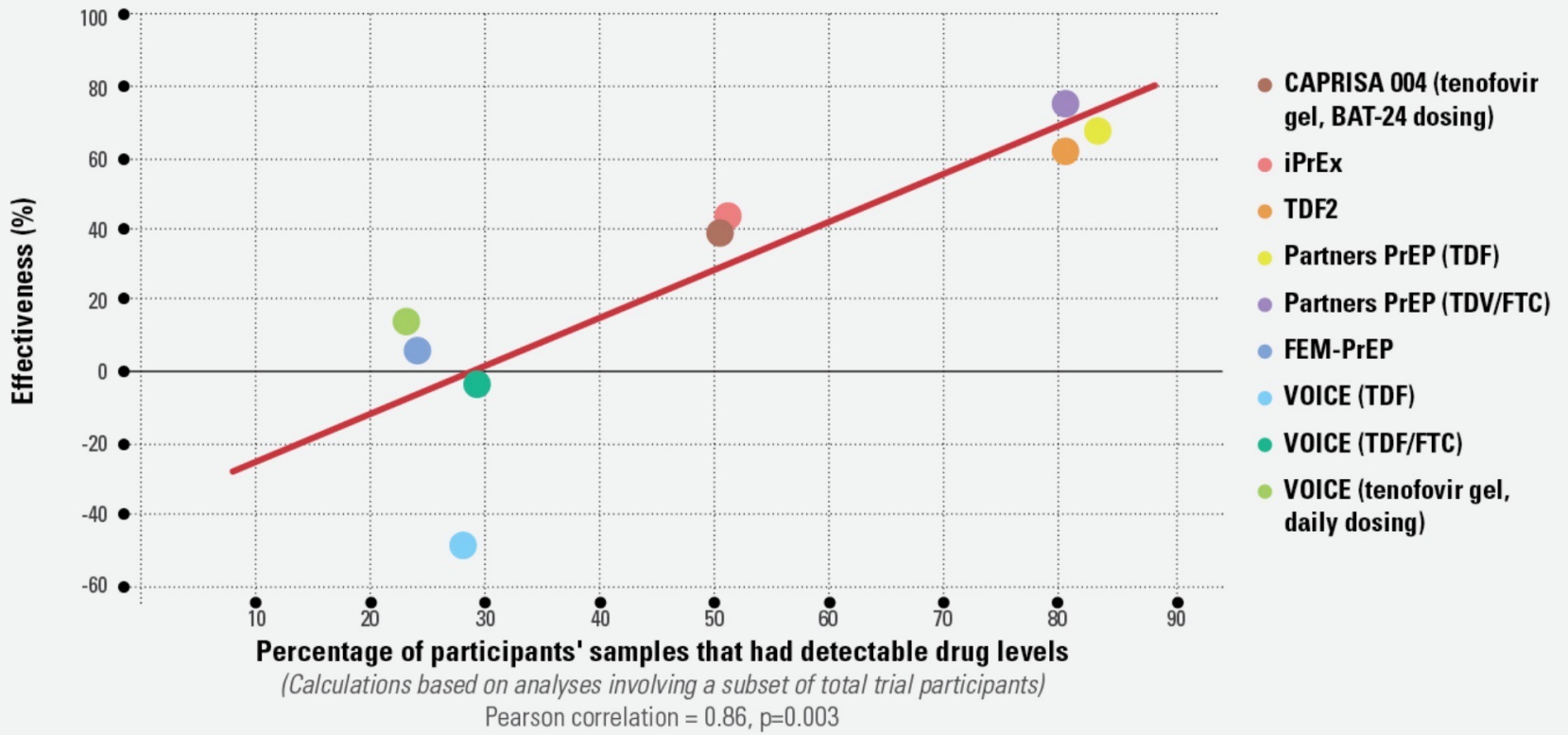
*GRADE quality ratings:
high = further research is very unlikely to change our confidence in the estimate of effect;
moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate;
low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate;
very low = any estimate of effect is very uncertain.

PrEP Effectiveness: Meta-analysis of RCTs by ITT



Jiang at al., PLOS ONE 2014

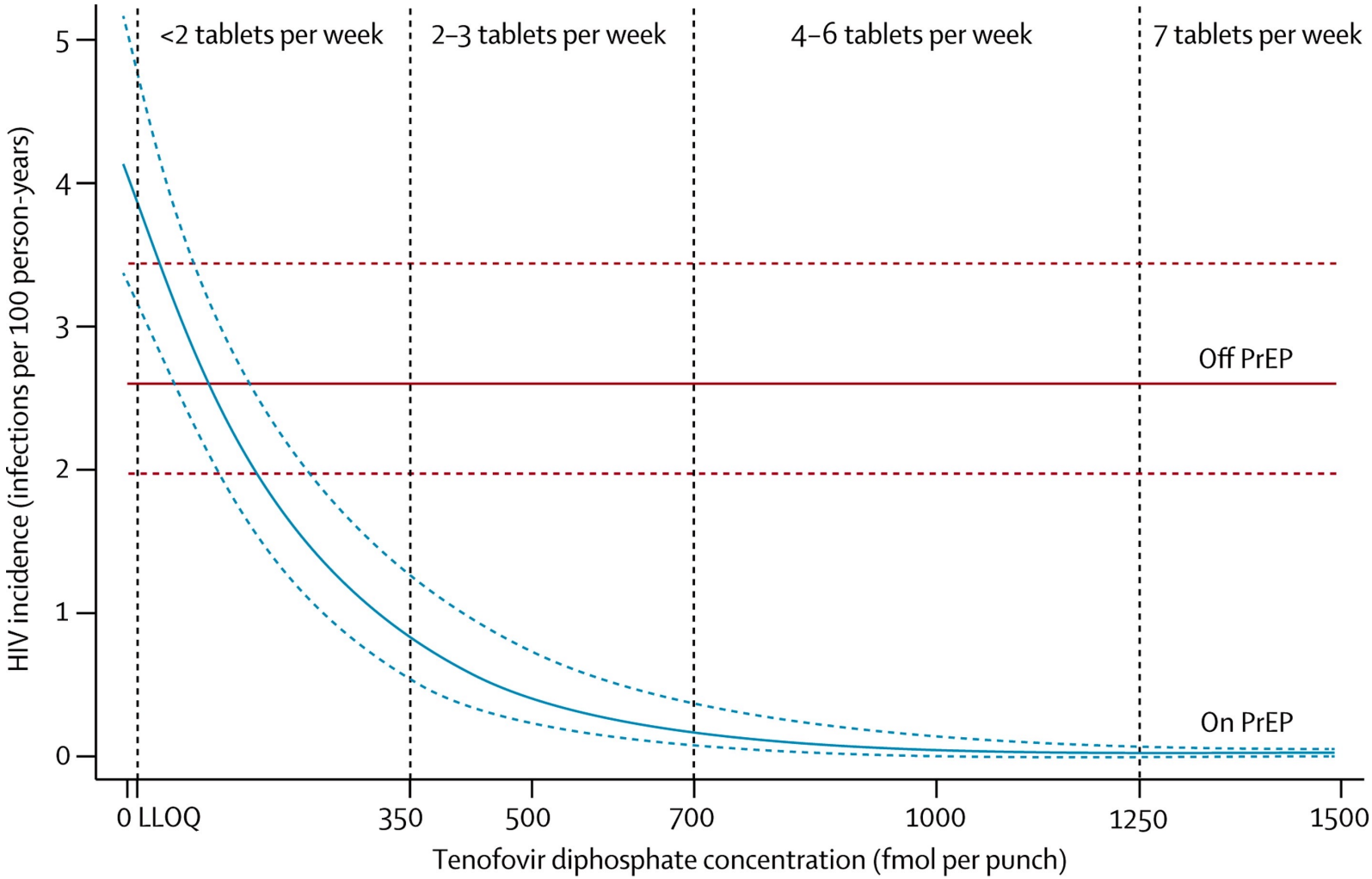
PrEP Adherence and Effectiveness among RCTs



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

iPrEx OLE - adherence vs. efficacy



Grant et al., Lancet Inf Dis 2014

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www.ipergay.fr

Study Design

Double-Blinded Randomized Placebo-Controlled Trial

- HIV negative high risk MSM
- Condomless anal sex with ≥ 2 partners within 6 m
- eGFR > 60 mL/mn

→ **Full prevention services* TDF/FTC before and after sex**

→ **Full prevention services* Placebo before and after sex**

* Counseling, condoms and gels, testing and treatment for STIs, vaccination for HBV and HAV, PEP

- End-point driven study : with 64 HIV-1 infections, 80% power to detect a 50% relative decrease in HIV-1 incidence with TDF/FTC (expected incidence: 3/100 PY with placebo)
- Follow-up visits: month 1, 2 and every two months thereafter

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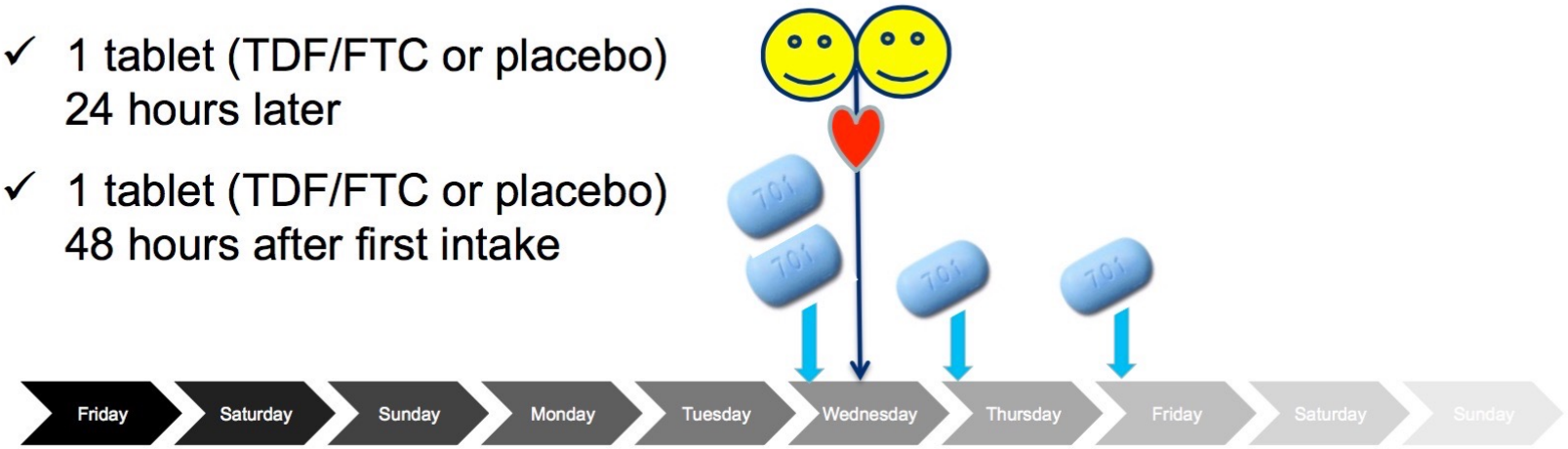
Ipergay : Event-Driven iPrEP

- ✓ 2 tablets (TDF/FTC or placebo) 2-24 hours before sex
- ✓ 1 tablet (TDF/FTC or placebo) 24 hours later
- ✓ 1 tablet (TDF/FTC or placebo) 48 hours after first intake



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Baseline Characteristics

Characteristics (Median, IQR) or (n, %)	TDF/FTC n = 199	Placebo n = 201
Age (years)	35 (29-43)	34 (29-42)
White	190 (95)	184 (92)
Completed secondary education	178 (91)	177 (89)
Employed	167 (85)	167 (84)
Single	144 (77)	149 (81)
History of PEP use	56 (28)	73 (37)
Use of psychoactive drugs*	85 (44)	92 (48)
Circumcised	38 (19)	41 (20)
Infection with NG, CT or TP**	43 (22)	59 (29)
Nb sexual acts in prior 4 weeks	10 (6-18)	10 (5-15)
Nb sexual partners in prior 2 months	8 (5-17)	8 (5-16)

* in last 12 months: ecstasy, crack, cocaine, crystal, speed, GHB/GBL
** NG: Neisseria gonorrhoeae, CT: Chlamydia trachomatis, TP: Treponema pallidum

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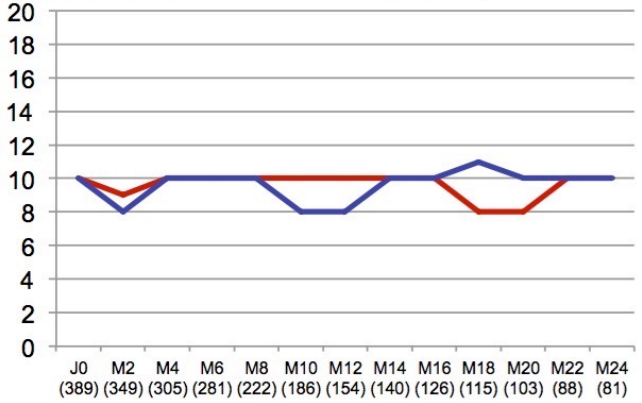
Sexual Behavior

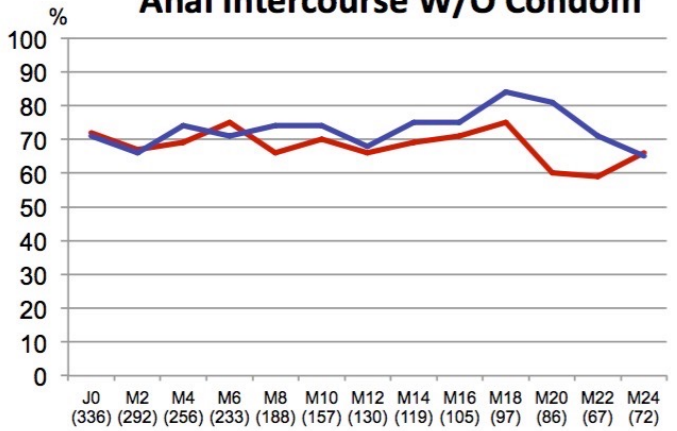
Median Nb of Sexual Acts (last 4 weeks)



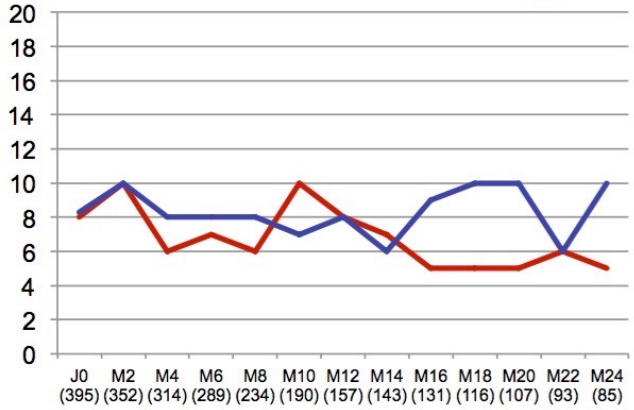
TDF/FTC

Placebo

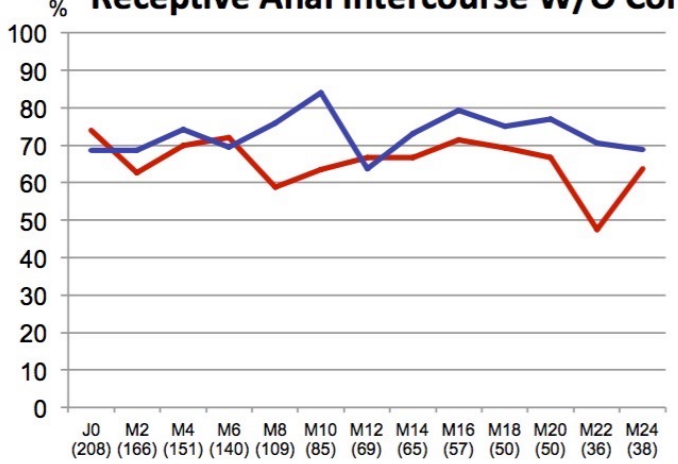
Anal Intercourse W/O Condom



Median Nb of Sexual Partners (2 months)



Receptive Anal Intercourse W/O Condom



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Sexually Transmitted Infections

- 276 STIs were diagnosed in 141 participants

	TDF/FTC n=199		Placebo n=201		P value
	Nb Pt (%)	Nb Events	Nb Pt (%)	Nb Events	
Chlamydia	43 (22)	61	34 (17)	48	0.23
Gonorrhoeae	38 (19)	50	45 (22)	67	0.42
Syphilis	19 (10)	19	19 (10)	25	0.98
HCV	3 (<2)	3	3 (<2)	3	1.00
Any STI	76 (38)	133	65 (32)	143	0.22

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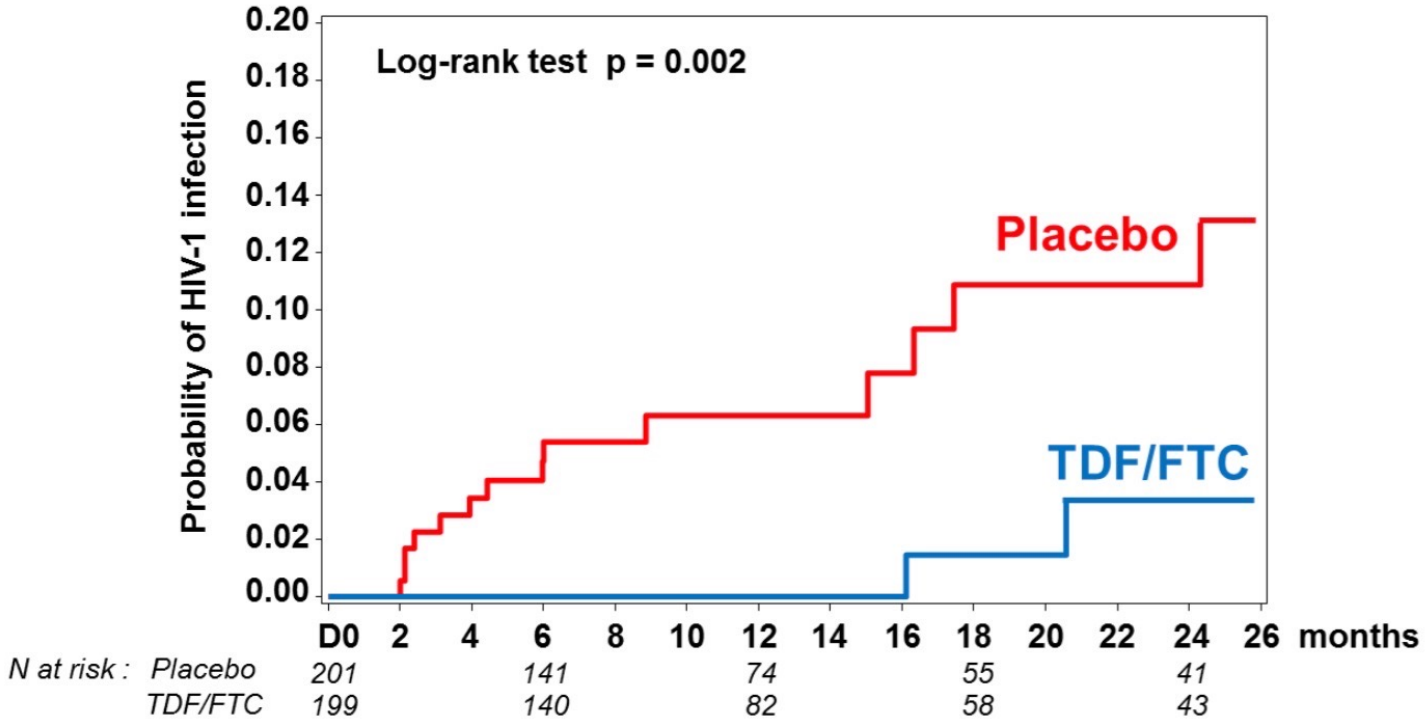
KM Estimates of Time to HIV-1 Infection (mITT Population)



Mean follow-up of 13 months: 16 subjects infected
14 in placebo arm (incidence: 6.6 per 100 PY), **2 in TDF/FTC arm** (incidence: 0.94 per 100 PY)

86% relative reduction in the incidence of HIV-1 (95% CI: 40-99, p=0.002)
NNT for one year to prevent one infection : 18

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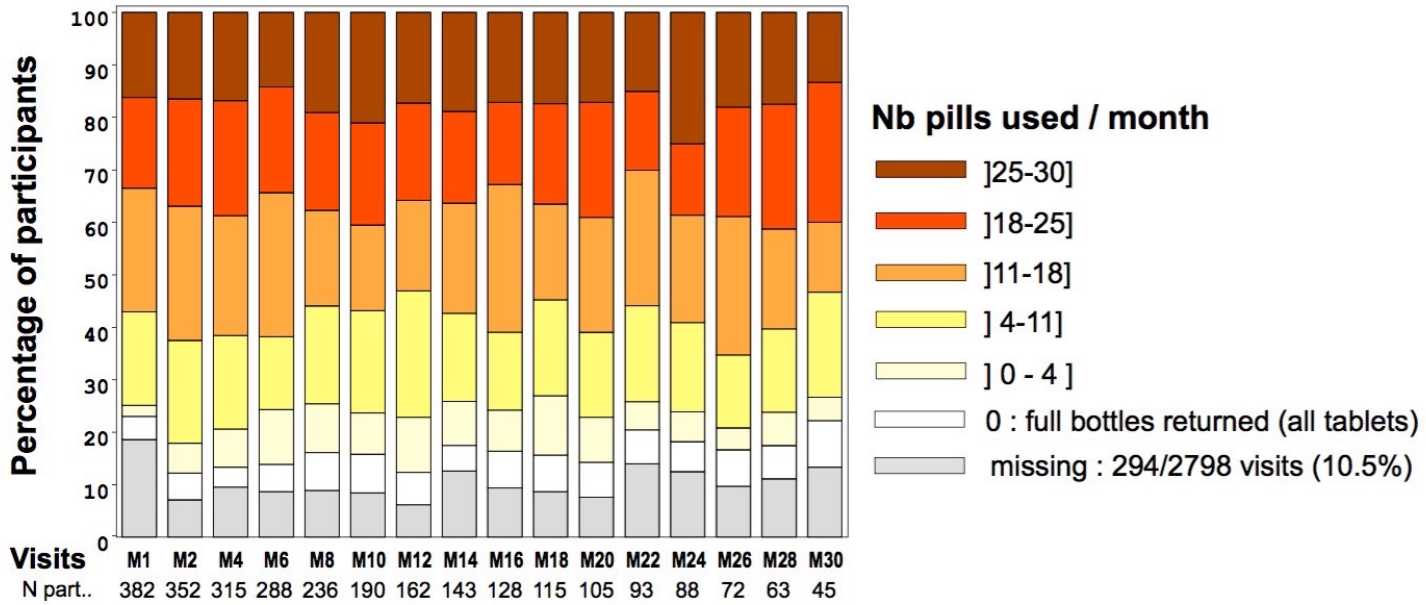
Adherence by Pill Count



- **Median number of pills/month (IQR):** 16 pills (10-23) in the placebo arm and 16 pills (12-24) in the TDF/FTC arm (p=0.84)
- **48 participants (12%) received PEP**
  25 (13%) in the TDF/FTC arm and 23 (11%) in the placebo arm (p=0.73)

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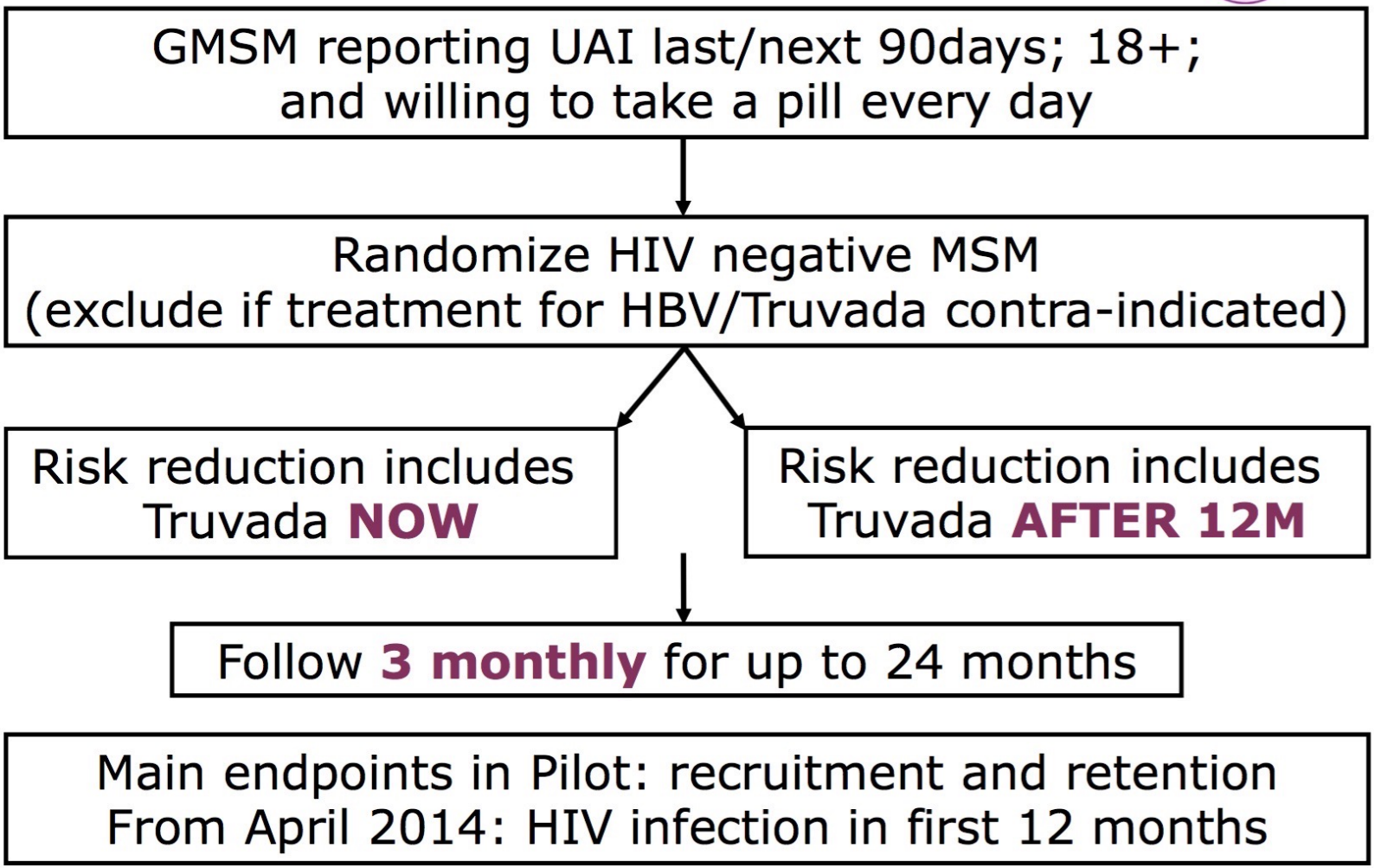
PROUD Pilot



www.thelancet.com Published online September 10, 2015 http://dx.doi.org/10.1016/S0140-6736(15)00056-2

Baseline demographics[1]

Characteristics		Immediate	Deferred
Age, median (IQR)		35 (30 – 43)	35 (29 – 42)
Ethnicity	White	80%	82%
Born UK	No	40%	40%
Education	University	59%	60%
Employment	Full-time	70%	73%
Sexuality	Gay	96%	94%
Current relationship	No	53%	55%
Recreational drug use[2]	Yes	76%	64%

[1] 539/545 (99%) questionnaires returned
[2] in the last 90 days

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HIV Incidence

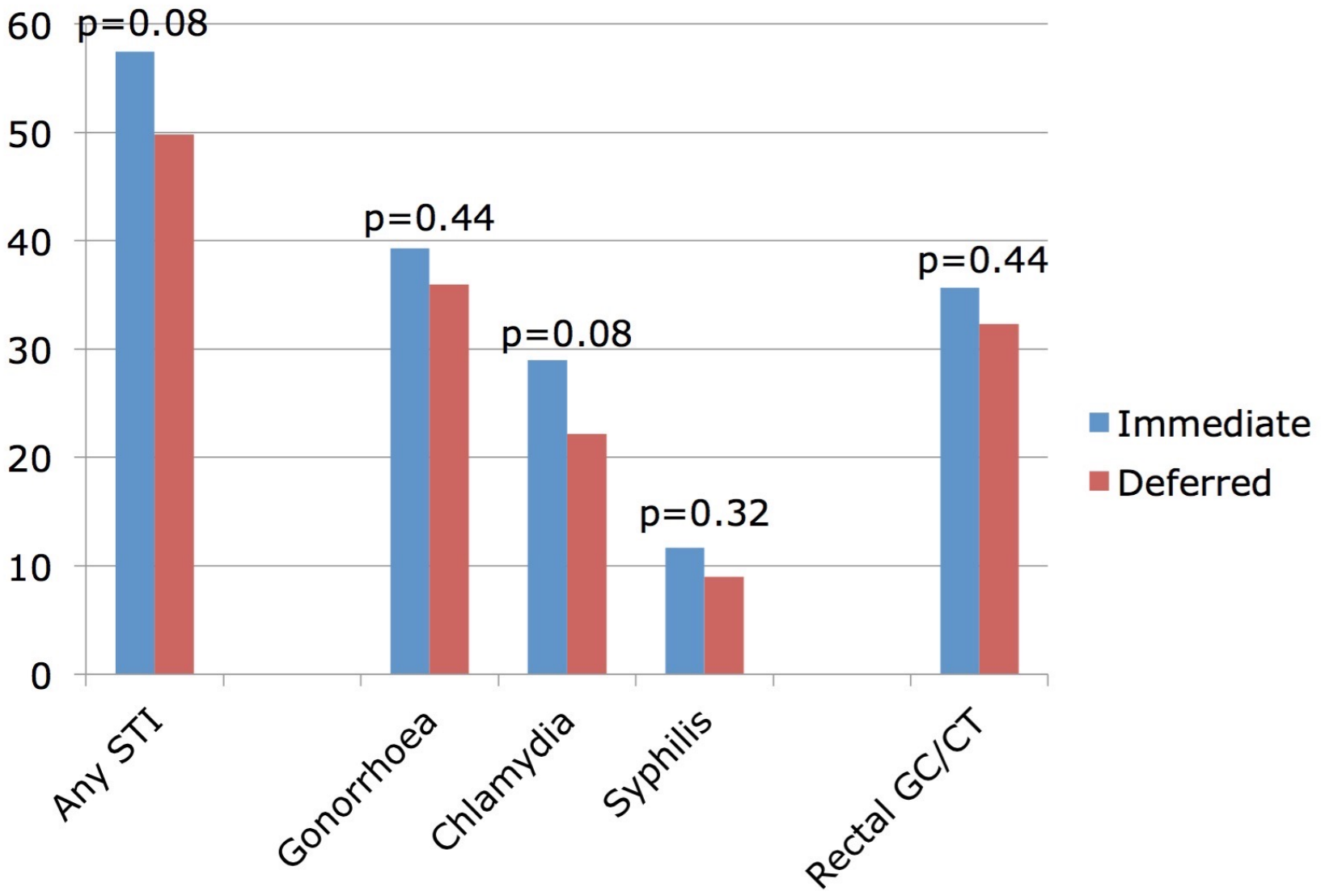
Group	No. of infections	Follow-up (PY)	Incidence (per 100 PY)	90% CI
Overall	22	453	4.9	3.4–6.8
Immediate	3	239	1.3	0.4–3.0
Deferred	19	214	8.9	6.0–12.7

Efficacy =86% (90% CI: 58 – 96%)
P value =0.0002

Rate Difference =7.6 (90% CI: 4.1 – 11.2)
Number Needed to Treat =13 (90% CI: 9 – 25)

www.thelancet.com Published online September 10, 2015 http://dx.doi.org/10.1016/S0140-6736(15)00056-2

STIs



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Reported sexual behaviour (preliminary)

Anal sex partners in last 90 days **BASELINE n=539**	**Immediate** Median (IQR)	**Deferred** Median (IQR)
Total number of partners	10.5 (5-20)	10 (4-20)
Condomless partners, participant receptive	3 (1-5)	2 (1-5)
Condomless partners, participant insertive	2.5 (1-6)	3 (1-7)

Anal sex partners in last 90 days **MONTH 12 n=349**	**Immediate** Median (IQR)	**Deferred** Median (IQR)
Total number of partners	10 (3-24)	8 (3-15)
Condomless partners, participant receptive	3 (1-8)	2 (1-5)
Condomless partners, participant insertive	3 (1-8)	3 (1-6)

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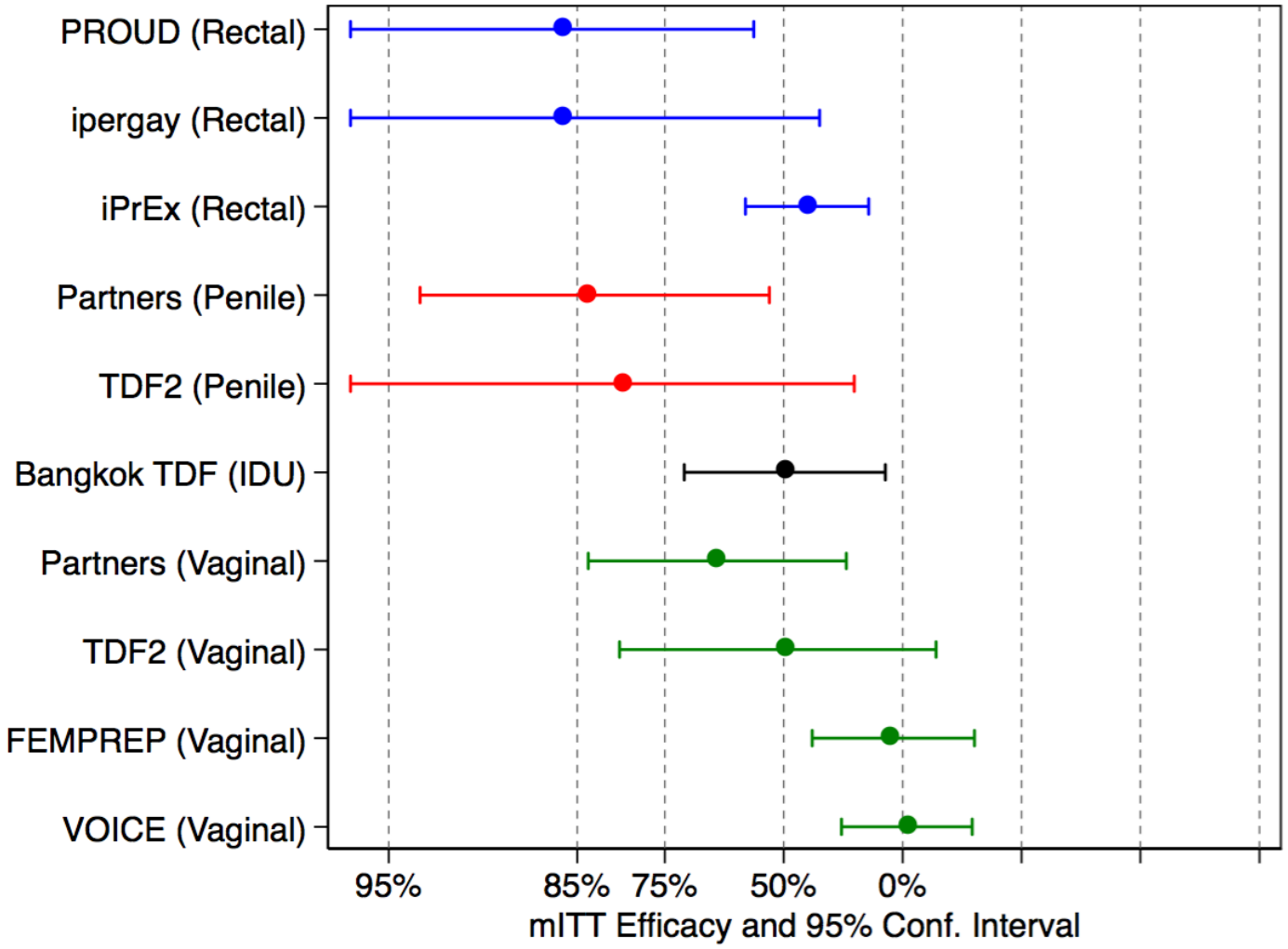
PrEP Protection by Major HIV Exposure Site



Dosing → Tissue Concentration → Efficacy

PrEP practical issues

- IPERGAY data not adequate to recommend intermittent use - they took so much “on-demand” PrEP that it was equivalent to continuous PrEP
- We are not going to get any more good quality data - future RCTs would be unethical
- Therefore we are stuck with 50% overall efficacy from the meta-analysis of the available RCTs
  - however, the data from iPrex (92% risk reduction with adequate adherence) and IPERGAY + PROUD (86% risk reduction) are pretty consistent
  - we can therefore assume that PrEP, in adherent (>4 doses/week) MSM is as effective as condoms in real-life.

PrEP practical issues

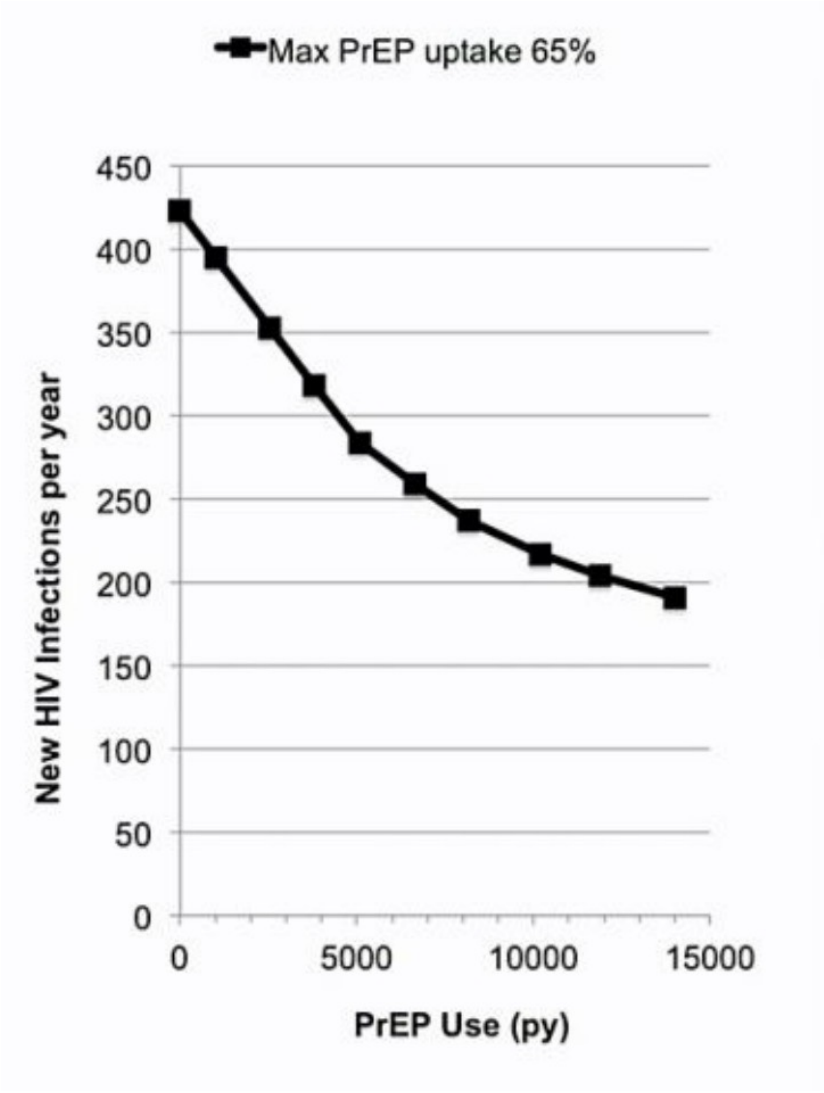
- TDF or TDF/FTC? can't say - no statistically significant difference from RCTs but in animal models TDF/FTC was more effective
- Rectal protection starts 5 days after starting continuous PrEP (10 days or more for vaginal protection)
- How to start PrEP when someone presents with very recent exposure risk?
  - option 1: delay and re-screen 4-6 weeks later - no risks in the meantime
  - option 2: start as PEP with TDF/FTC/INSTI
    - if neg 4 weeks later, stop the INSTI and continue TDF/FTC as PrEP
    - if pos 4 weeks later, continue triple therapy as ART.

PrEP practical issues

- Renal toxicity: creatinine/eGFR 3-monthly for the 1st year, then annually
- Bone toxicity: thought not to be relevant at this stage - future will tell
- HBV co-infection: limited data, seems to be safe
  - potential issues with stopping/starting: hepatitis B flares.

Real-life data: Projecting PrEP impact in San Francisco

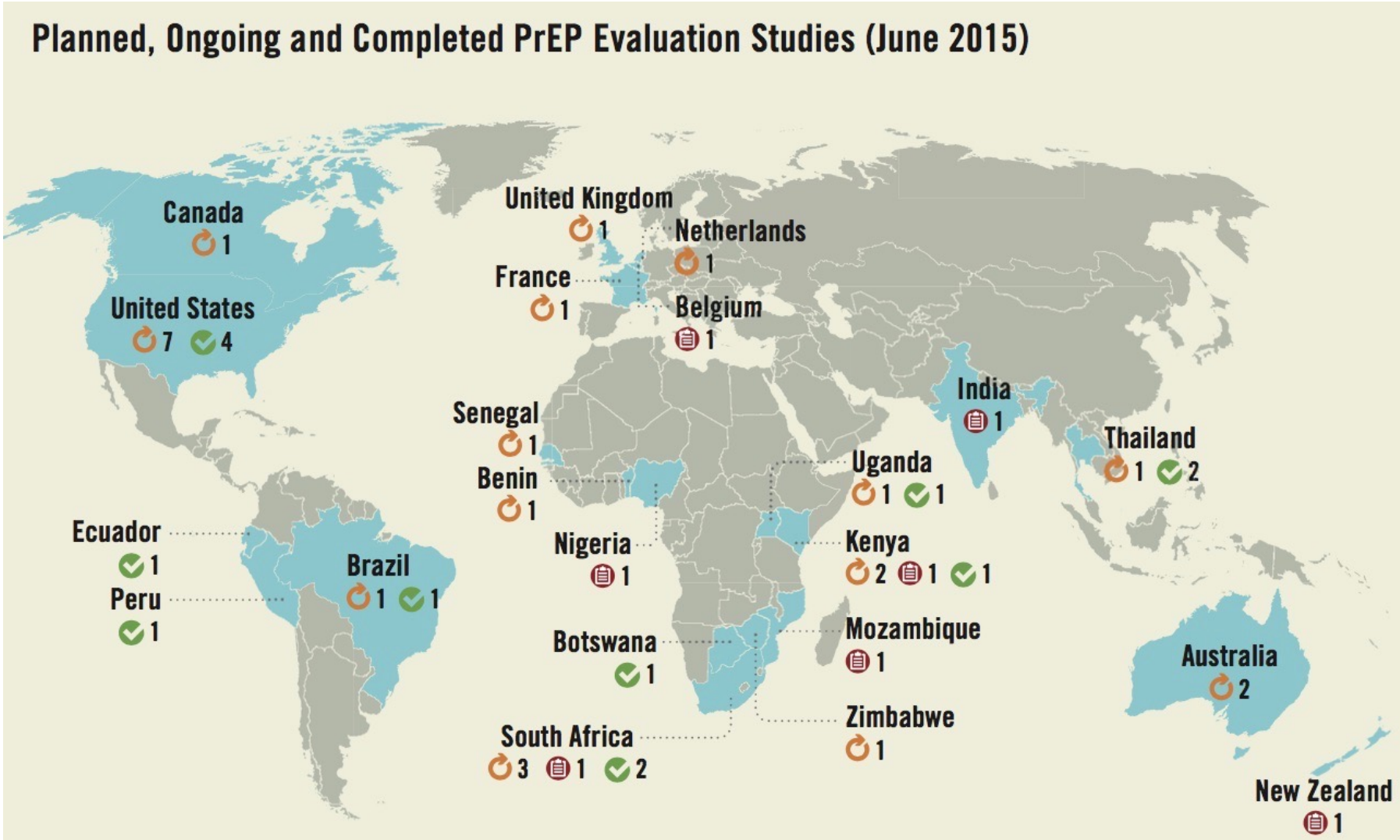
- Assuming:
  - HIV diagnosis rate = 94%
  - Viral suppression = 62%
  - Current PrEP intake increases proportionately to a maximum of 65% in the highest risk strata.



Adapted from Grant CROI Abstract 25 Seattle 2015

Real-life data: the Kaiser Permanente cohort

- Kaiser Permanente: big health insurer and healthcare provider in California, serves approx. 4.5M customers
- 657 customers on PrEP (almost all MSM), 0 HIV infections over 2 years
- >40% reported less condom use since on PrEP
- 74% said had the same number of partners before and after starting PrEP
- 50% STI incidence
  - *Clin Infect Dis. (2015) doi: 10.1093/cid/civ778 first published online: September 1, 2015*
- PrEP uptake in other US sites: 25% (Seattle) to 31% (San Francisco City Clinic).



For the latest on these studies, visit *www.avac.org/prep/track-research.*

Data from demonstration projects and open-label extension studies are beginning to come in. So far, the findings suggest that people want and will take daily oral PrEP correctly outside of a clinical trial setting. Expanded and faster rollout is key.

PrEP Implementation in Australia

- TRUVADA® not approved by TGA as PrEP
  - application lodged by Gilead on 01/04/2015
- Access to affordable PrEP is possible if preventive TRUVADA® is covered under the PBS
  - need to define who should be covered
  - prove that it is cost-effective
- Access to PrEP through feasibility studies
  - VicPrEP (100 MSM, Victoria, started in 2014)
  - PRELUDE (300 SM, NSW, started in 2014)
  - QPrEP (50 MSM, Queensland, started in 2015)
- “Informal use” (self-funded, purchased online): 2.5% of men according to the Sydney Gay Periodic Survey.

ASHM 2015: Australia and PrEP

- Eligibility criteria for MSM:
  - High risk - recommend prescribing daily PrEP if the client acknowledges any of the following in the last 3 months and likely to continue in the next 3 months:
    - HIV-positive RMP with whom condoms are not consistently used
    - URAI with any CMP of HIV-positive or unknown status
    - Rectal bacterial STI (CT, NG or TP)
    - Methamphetamine use
  - Medium risk - consider prescribing daily PrEP if the client acknowledges any of the following in the last 3 months:
    - >1 episode of AI when proper condom use was not achieved (e.g. condom slipped off or broke)
    - if client is uncircumcised and reports >1 UIAI where the serostatus of the partner was unknown or was HIV-pos with detectable VL.

Estimated number of MSM eligible for PrEP in Australia

- Number of HIV-negative, sexually active gay men: approx. 89,000
- Number of men eligible for PrEP under high-risk criteria: approx. 8,300 (6,500 - 13,000)
- Number of men potentially willing to take PrEP as it becomes available and accessible: approx. 3,500 - 6,500

Risk compensation in VicPrEP

- Currently 115 MSM enrolled
- Condom use dropped at 3 months on PrEP vs. baseline: “never used condom” increased from 10.8% to 27.1%
- Adherence: 53.9% reported missing any PrEP dose in 3 months (median 1, mean 2.04).

Potential impact of PrEP on HIV epidemic in Australia

- Nationally:
  - observed: 758 HIV diagnosis among MSM in 2014
  - expected: 332 infections among 8,300 high-risk MSM over 12 months
- Assumption: HIV incidence = 4.0 per 100 PY if no PrEP
- Estimated impact if PrEP is available:
  - scenario 1: PrEP intake = 100% among high-risk MSM, PrEP efficacy = 100% among these men; 332 infections prevented in 12 months (44% reduction in new diagnosis)
  - scenario 2 as above but PrEP efficacy = 86%; 285 infections prevented (38% reduction)

New Zealand: Auckland Sexual Health PrEP Demonstration Project

- ART still not available for all those living with HIV
  - Pharmac criteria for funding still have a CD4 threshold
- No application lodged by Gilead for TRUVADA® to be available as PrEP
- Auckland Sexual Health Service along with a range of collaborating NGOs and colleagues from other DHBs are working to establish a PrEP Demonstration Project.

New Zealand: Auckland Sexual Health PrEP Demonstration Project

- Collaborators:
  - The New Zealand AIDS Foundation
  - Body Positive
  - Gay Men's Sexual Health Group University of Auckland
  - Tauranga Sexual Health Service
  - The NZ Sexual Health Society has also been consulted in the process.

New Zealand: Auckland Sexual Health PrEP Demonstration Project

- A desire to have access to PrEP has been expressed by some MSM in New Zealand
- Some prescribers have been approached by individual MSM seeking support to import TRUVADA® for use as PrEP
- Anecdotal reports of people finding ways to access TRUVADA® for PrEP via informal channels – e.g. buying from HIV positive people, sharing medications, acquiring TRUVADA® via PEP
- No clinical guidelines for the management of PrEP in NZ
- The project is not funded and is being progressed by the collaborating agencies using their existing resources.

New Zealand: Auckland Sexual Health PrEP Demonstration Project

- Aims of the project:
  - gain experience in use of PrEP for those at high risk of HIV in the New Zealand setting
  - provide a way for those who are at risk and highly motivated to access PrEP under clinical supervision.
  - assess demand for PrEP amongst those who are at high risk
  - monitor adherence and barriers to adherence
  - develop clinical protocols for the management of PrEP in the NZ context
  - monitor impacts on condom use, risk taking behaviour, other STIs and HIV infections
  - provide information that may assist in assessing the cost benefit of funding PrEP as a targeted intervention for those at high risk
  - expected duration 12 - 18 months.

New Zealand: Auckland Sexual Health PrEP Demonstration Project

- Progress to date:
  - approval gained from ADHB to prescribe TRUVADA® for PrEP purposes
  - work underway on project protocol for access criteria, schedule of events, clinical protocol etc.
  - work underway on retrospective analysis of clients of Auckland Sexual Health Service to provide a comparison to project participants (i.e. in lieu of a control group)
  - initial approach to Gilead for assistance with providing TRUVADA® for project
  - preparatory work for ADHB ethics application.

New Zealand: Auckland Sexual Health PrEP Demonstration Project

- Challenges/funding:
  - there is no public funding to provide TRUVADA® for the project
    - if the medication is not donated by the manufacturer the project will depend on clients who can self-fund and be of very limited scope
  - monitoring of adherence is critical to understanding and managing PrEP use in the real world setting
    - therapeutic drug monitoring is not available in New Zealand and would be an expensive component of the project.

The future of PrEP

- Oral Maraviroc (CCR5 inhibitor; ?fewer long-term side effects than TDF)
- Long-acting injectables (Cabotegravir, Rilpivirine)
- Topical delivery systems (Dapivirine vaginal ring; multi-purpose vaginal rings for contraception, HIV, and STI prevention).