Professor Sheena McCormack

MRC Clinical Trials Unit at UCL, London

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Speaker Name	Statement
Date	April 2015

Research for policy

PROUD and

Self-testing (Pantheon)

FDA approve Truvada for PrEP

FDA NEWS RELEASE

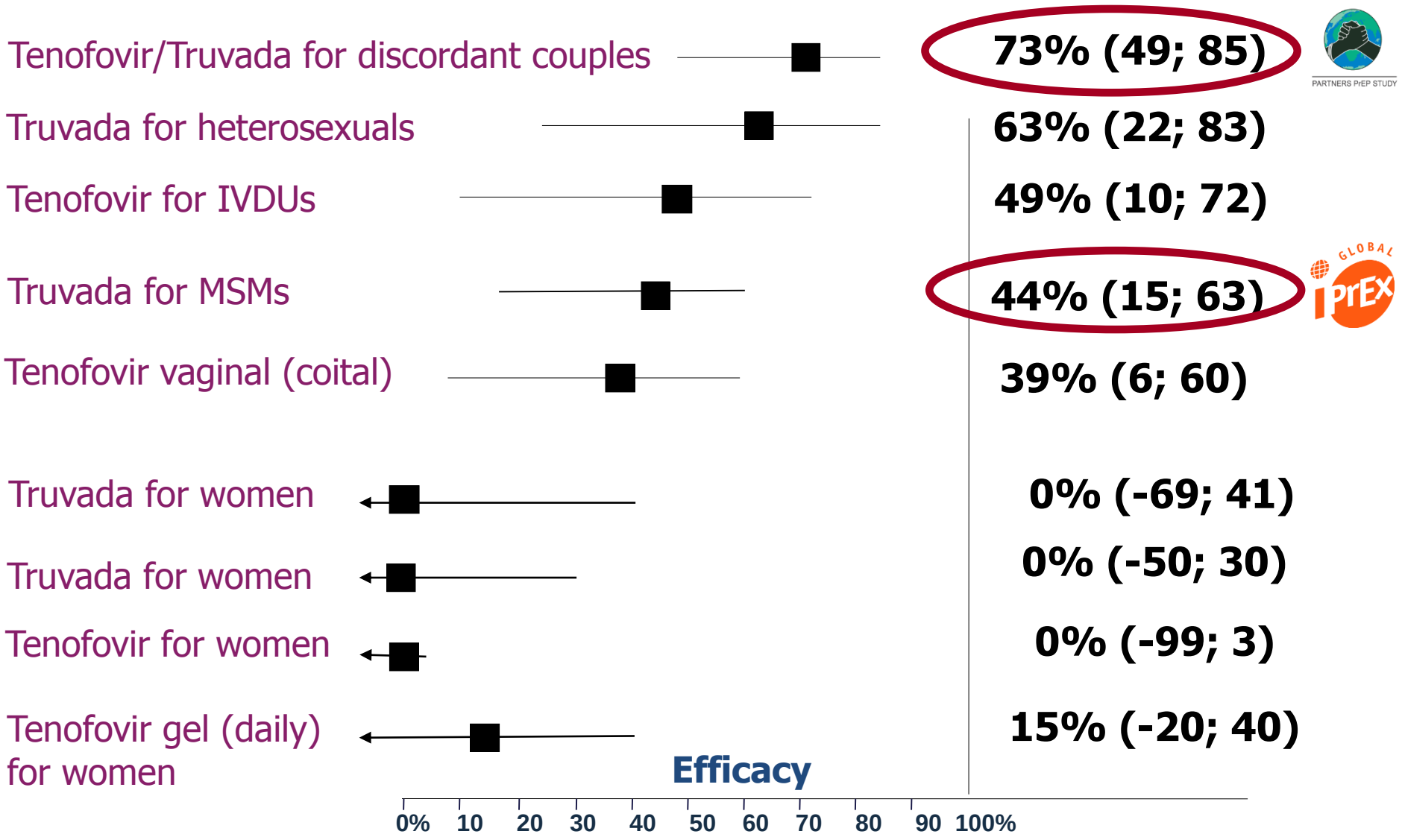
For Immediate Release: July 16, 2012
Media Inquiries: Erica Jefferson, 301-796-4988, erica.jefferson@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA approves first drug for reducing the risk of sexually acquired HIV infection

Evidence-based approach enhances existing prevention strategies

Today, the U.S. Food and Drug Administration approved Truvada (emtricitabine/tenofovir disoproxil fumarate), the first drug approved to reduce the risk of HIV infection in uninfected individuals who are at high risk of HIV infection and who may engage in sexual activity with HIV-infected partners

Several trials – but inconsistent



Why so different? Adherence…

	% of blood samples with tenofovir detected	HIV protection efficacy in randomized comparison	HIV protection estimate with high adherence
Partners PrEP FTC/TDF 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

Fully enrolled as of December 2009

Sites	11
Participants	2499

New England Journal of Medicine, online Nov 23, 2010

Why did we need more for policy?

- **PrEP may not work as well as iPrEx (44% reduction in HIV) in the real-world**

- **Why not?**
- Adherence less
  - trial schedules monthly
  - well resourced for adherence support

- Behaviour riskier
  - participants constantly reminded that they could be on placebo, and that effectiveness was unknown
  - well resourced for behaviour change interventions

PROUD Pilot

GMSM reporting UAI last/next 90days; 18+;
and willing to take a pill every day

↓

Randomize HIV negative MSM
(exclude if treatment for HBV/Truvada contra-indicated)

↓

Risk reduction includes Truvada **NOW**

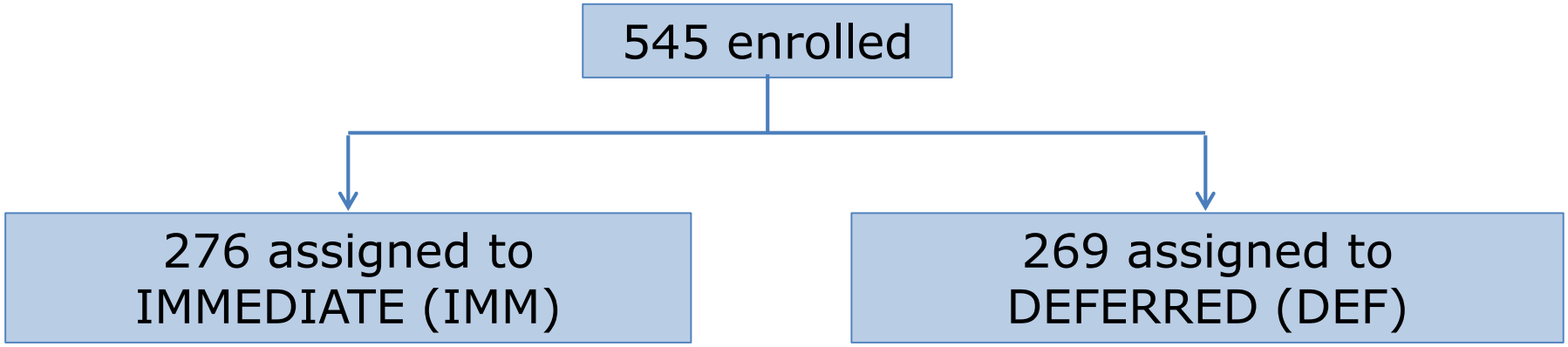
Risk reduction includes Truvada **AFTER 12M**

↓

Follow **3 monthly** for up to 24 months

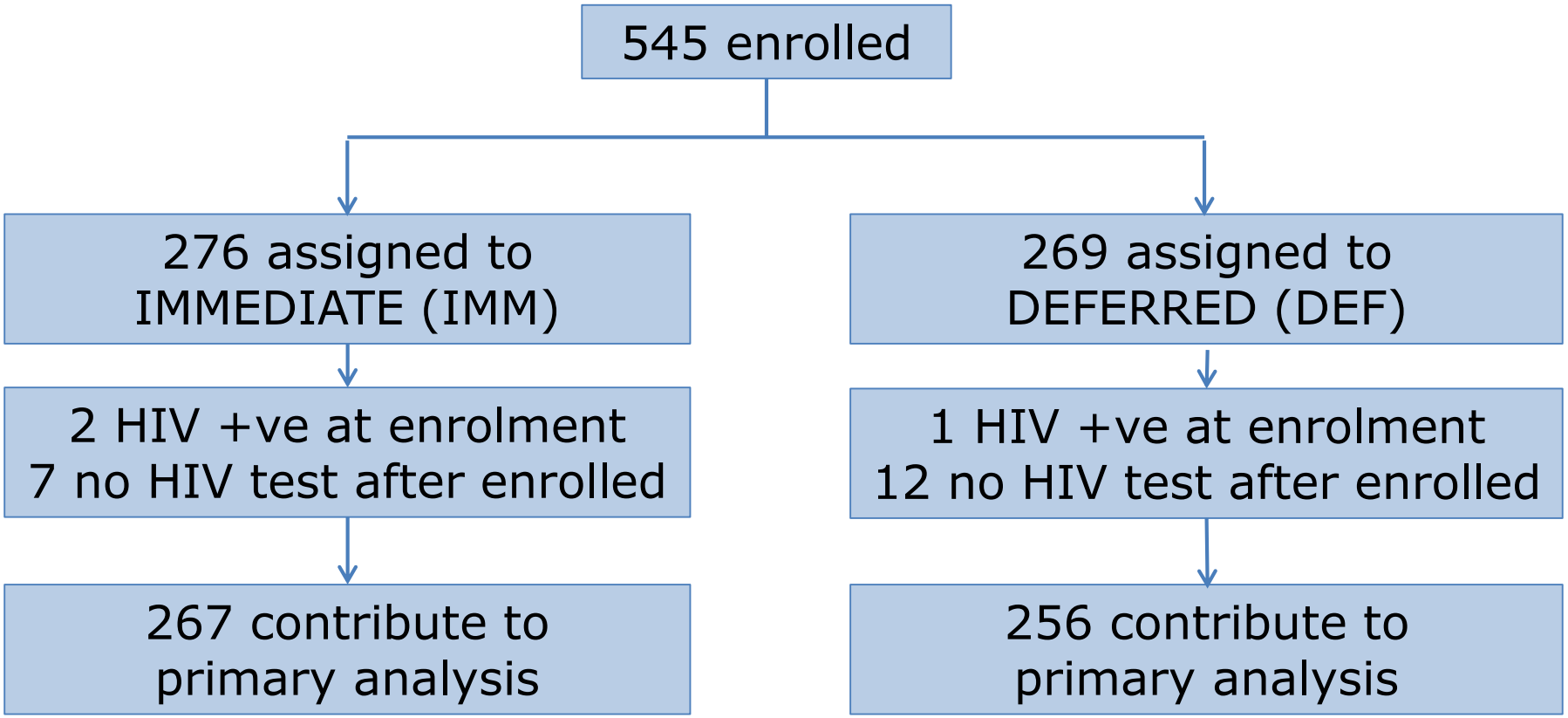
Main endpoints in Pilot: recruitment and retention
From April 2014: HIV infection in first 12 months

Participant randomization



April 2014 TSC review of baseline data:

- 35% had a rectal STI in the last 12 months
- 31% had accessed PEP in the the last 12 months
- 35% had used ChemSex drug in the last 3 months
- 25% had 20 or more condomless anal sex partners in the last 3 months

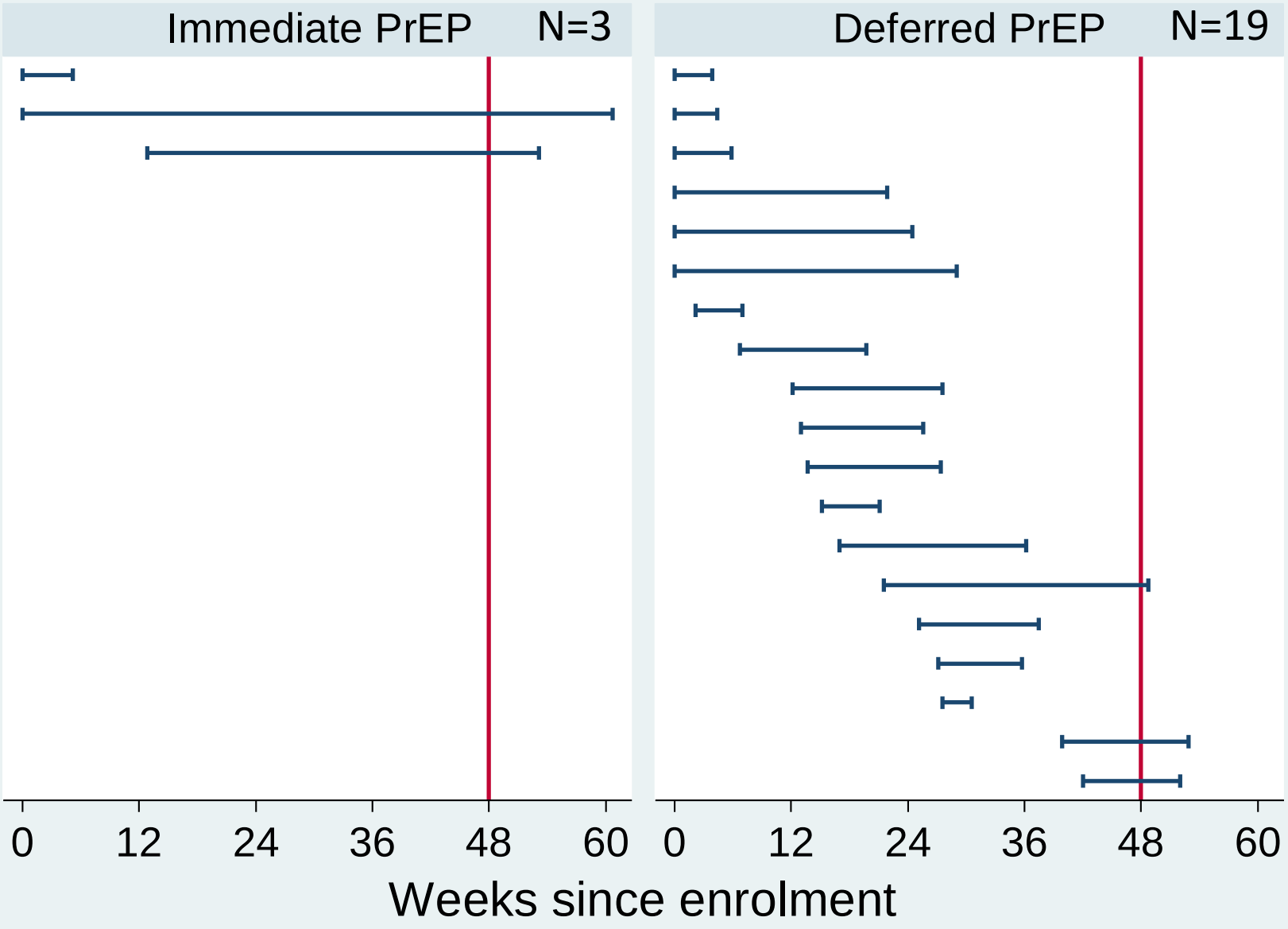


Calculation of person-years:

From enrolment to the first of the following:

- HIV test at m12, or
- HIV test at the time of access to PrEP, or
- diagnosis of HIV infection

Individual incident HIV infections



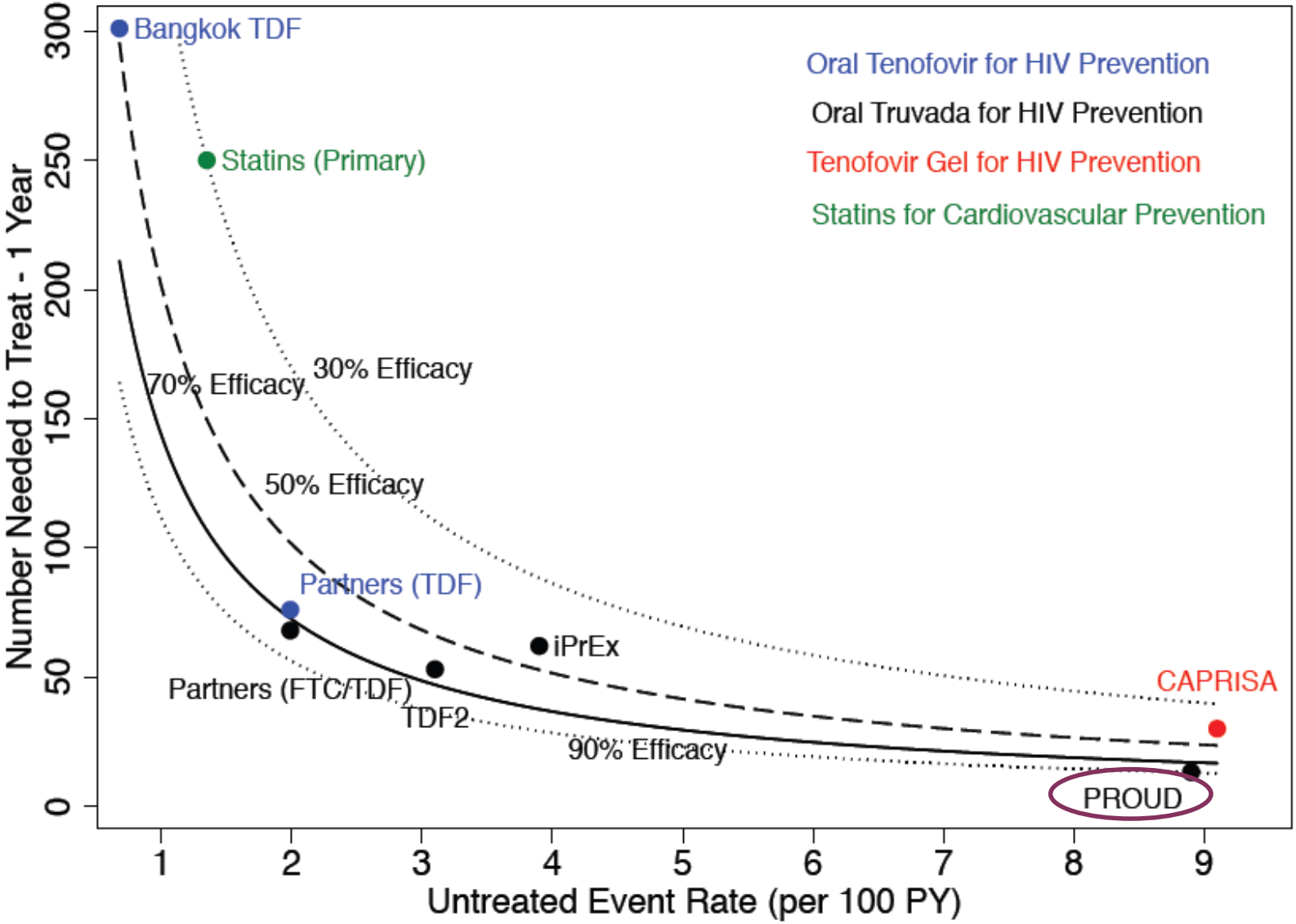
HIV Incidence

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)
Numbers Needed to Treat =13 (90% CI: 9 – 25)

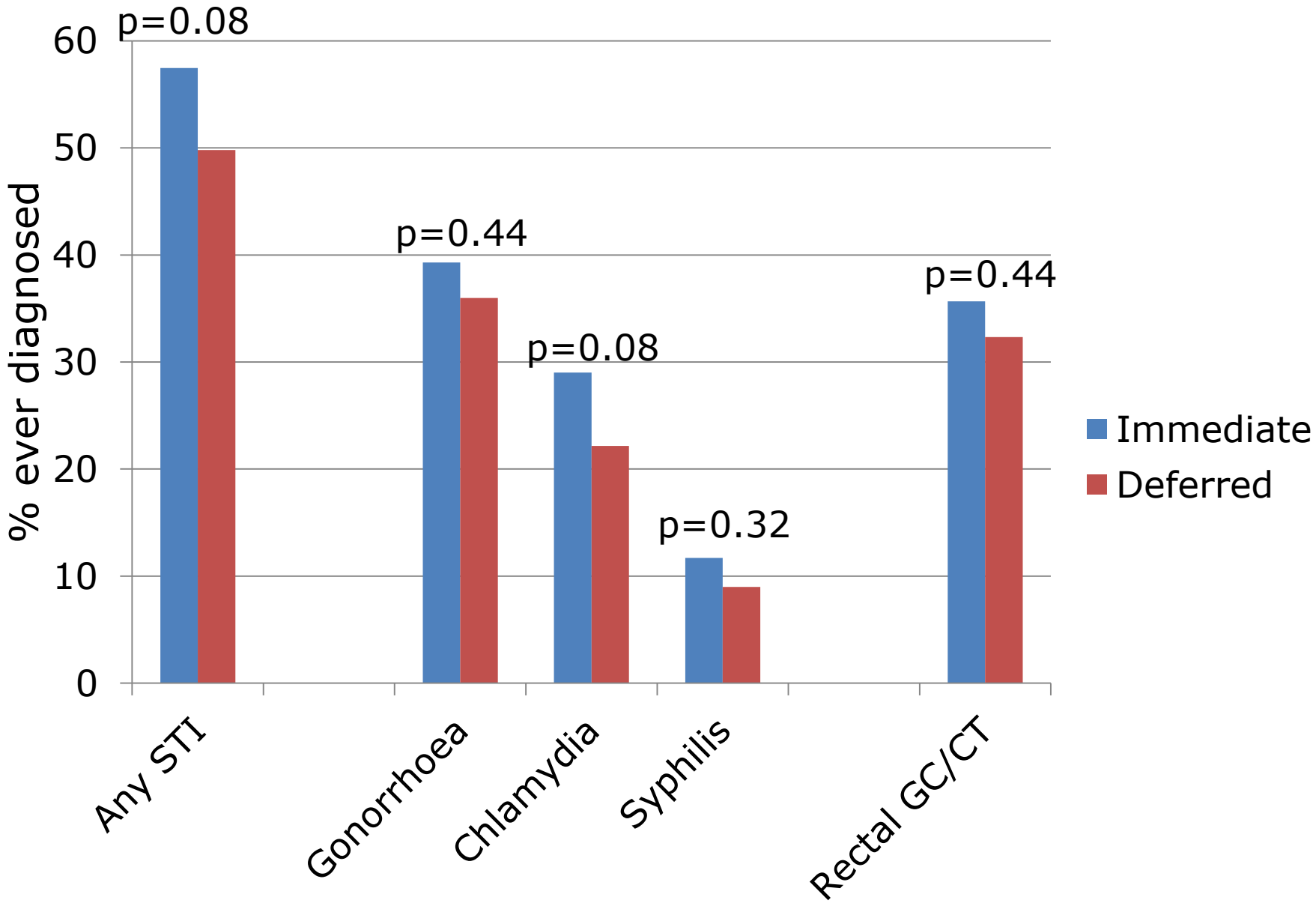
With thanks to Dave Glidden



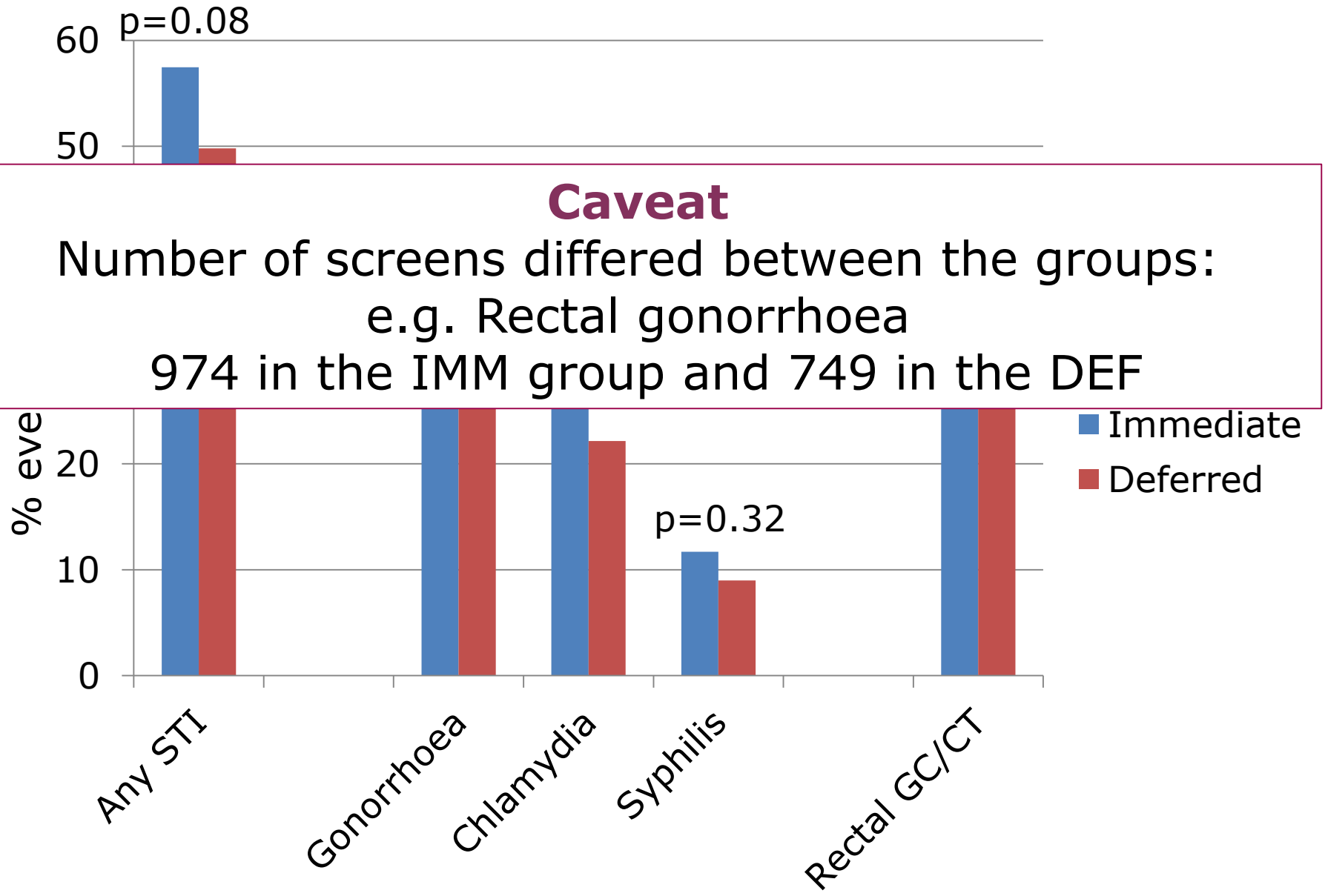
Results:

STI endpoints and risk behaviour

STIs


p=0.08
p=0.44
p=0.08
p=0.32
p=0.44
60
50
40
30
20
10
0
% ever diagnosed
Any STI
Gonorrhoea
Chlamydia
Syphilis
Rectal GC/CT
Immediate
Deferred

STIs



Caveat

Number of screens differed between the groups:
e.g. Rectal gonorrhoea
974 in the IMM group and 749 in the DEF

Reported sexual behaviour

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)
Participant receptive, no condom	3 (1-5)	2 (1-5)
Participant insertive, no condom	2.5 (1-6)	3 (1-7)

Anal sex partners in last 90 days **MONTH 12 (n=358)**	**Immediate** Median (IQR)	**Deferred** Median (IQR)
Total number of partners	10 (3-25)	8 (3-15)
Participant receptive, no condom	2 (1-7)	2 (1-5)
Participant insertive, no condom	3 (1-8)	2 (1-6)

Conclusions

- HIV incidence in the population was much higher than predicted - despite extensive use of PEP in the deferred period
- Our concerns about PrEP being less effective in the real world were unfounded
- Risk reduction strategies continued to include condoms
- There was no difference in STIs
- Clinics adapted routine practice to incorporate PrEP

Acknowledgements (1)

Study participants

MRC CTU at UCL

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HIV & STI Dept, PHE

Monica Desai, Sarika Desai, Noel Gill, Anthony Nardone, GUMCAD team, HIV team

Clinics

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Acknowledgements (2)

Trial Steering Committee

Independent members: Mike Adler (Co-Chair), Gus Cairns (Co-Chair), Dan Clutterbuck, Rob Cookson, Claire Foreman, Stephen Nicholson, Tariq Sadiq, Matthew Williams

Investigator members: Brian Gazzard, Noel Gill, Anne Johnson, Sheena McCormack, Andrew Phillips

Gilead: Matt Bosse, Rich Clarke, Jim Rooney, Murad Ruf

University of Liverpool: Saye Khoo

Independent Data Monitoring Committee: Anton Pozniak, Simon Collins, Fiona Lampe

Community Engagement Group

Community: Yusef Azad (NAT), Gus Cairns (NAM), Rob Cookson (LGF), Tom Doyle (Mesmac), Justin Harbottle (THT), Marion Wadibia (NAZ), Matthew Hodson (GMFA), Cary James (THT), Roger Pebody (NAM)

Clinics: Anthony Bains, Alan McOwan (Lead),

MRC CTU at UCL: Sheena McCormack, Mitzy Gafos, Annabelle South

Social Science Advisory Group

Interviewers: Caroline Rae, Gill Bell, Michael Rayment, Sonali Wayal, Will Nutland, Mitzy Gafos

Advisors: Ingrid Young, Ford Hickson, Lisa McDaid, Marsha Rosengarten, Nicolas Lorente, Agata Pacho, Elizabeth Poliquin, Anthony Nardone, Catherine Dodds, Adam Bourne, David Dolling, Sheena McCormack, Rob Horne

A comprehensive assessment of the cost-effectiveness of HIV prevention and testing strategies, including HIV self-testing, among men who have sex with men (MSM) in the UK

PANTHEON

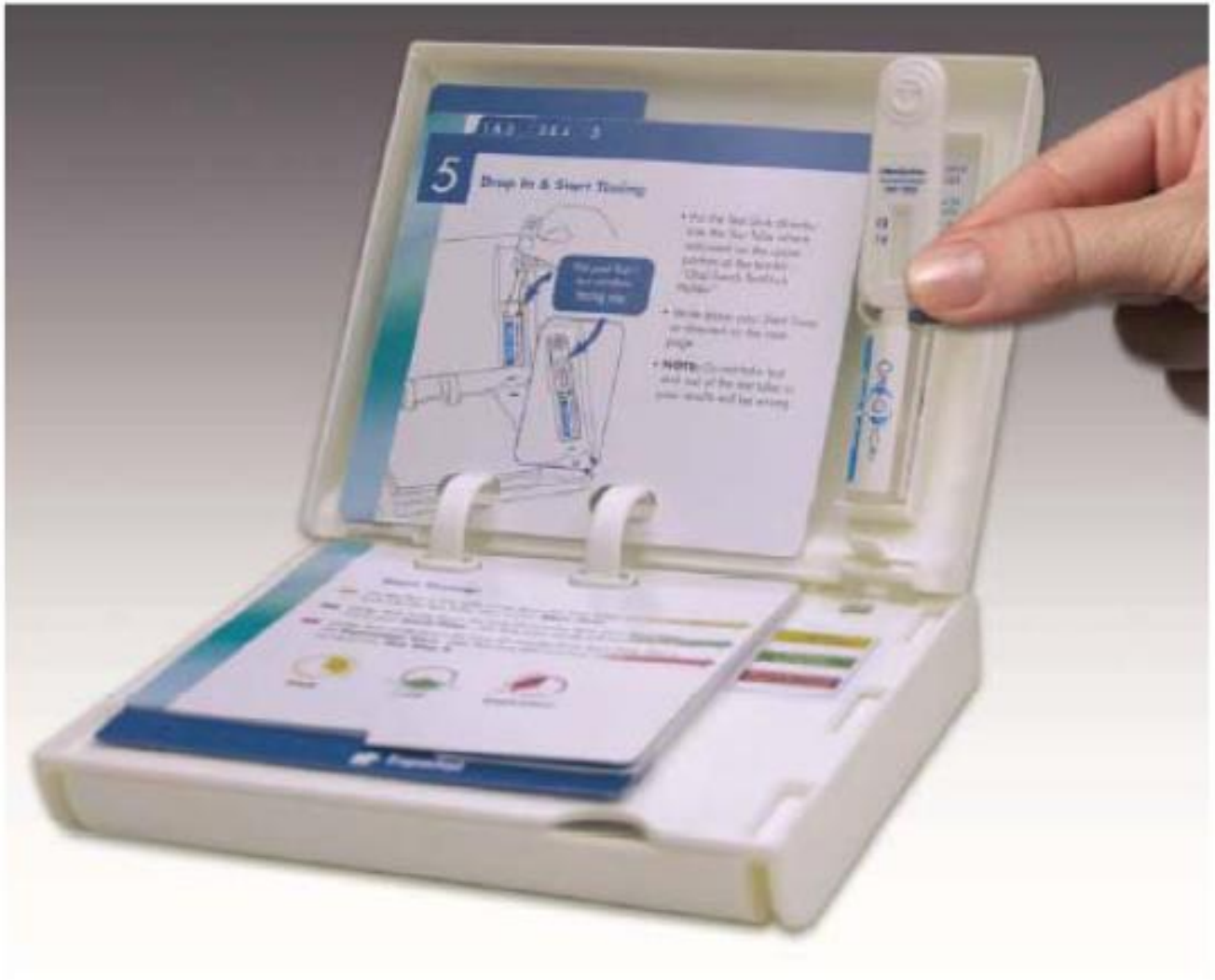
(Prevention ANd Testing for HIV: Economics and Outcomes of Novel Approaches)

- **UCL:** Alison Rodger (PI), Andrew Phillips (co-PI), Fiona Lampe, Fiona Burns, Sheena McCormack, David Dunn, Graham Hart, Anne Johnson, Richard Gilson, Lorraine Sherr, Susan Michie
- **LSHTM**: Tim Rhodes, Alec Miners, Peter Weatherburn
- **PHE**: Kevin Fenton, Tony Nardone, Valerie Delpech
- **Chelsea and Westminster Hospital**: Alan McOwan, David Asboe, Nneka Nwokolo, Brian Gazzard
- **Terence Higgins Trust**: Michael Brady
- **City University**: Jonathan Elford
- **Brighton University Hospitals**: Martin Fisher
- **iBase**: Simon Collins

Background

- 25% of HIV positive MSM unaware of their infection
- 60-80% of new HIV infections among MSM originate from undiagnosed men
- Reducing the interval between HIV infection and diagnosis would reduce the number of sexual partners undiagnosed infected men have sex with
- Became legal to buy HIV **self-testing kits** in UK in April 2014
- No kits currently kite-marked in UK

Figure 2: Running the OraQuick® In-Home HIV Test



Potential disadvantages of self-test

- Most rapid tests are third generation (less sensitive, require longer interval after potential HIV exposure)
- Immediate counselling not available in event of a reactive result
- No certainty of linkage into care
- Lost opportunity to test for other STIs
- Lost opportunity for risk-reduction counselling

Studies to date on self-testing

- Have mainly assessed acceptability and ease of use
- Some ongoing studies (USA, Australia) where primary outcome is frequency of use of self-testing kits
- Does not address the key question: **will HIV self-testing increase rate of HIV diagnoses?**
- Difficult question to answer: how to evaluate and collect information on test done in privacy of own home?

Research Questions

The main ***RESEARCH QUESTIONS*** in the application:

- Does provision of free HIV self-testing increase rates of diagnosis in MSM?
- Which HIV prevention initiatives for reducing HIV incidence are most cost-effective?

Workstreams

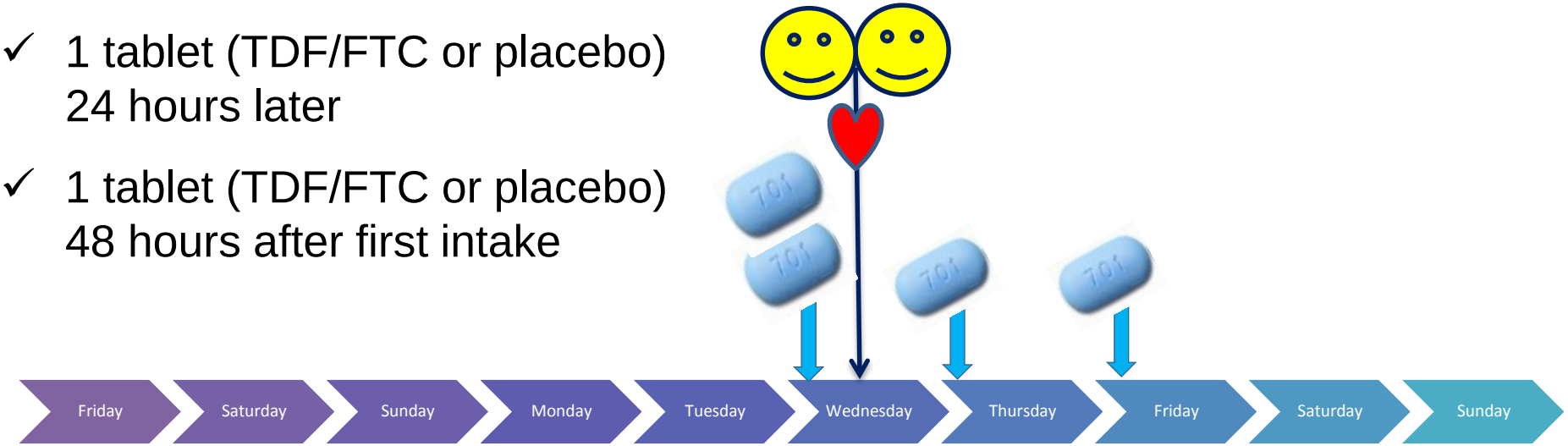
1. Feasibility studies	To increase understanding of accessibility and feasibility of HIV self-sampling and self-testing among MSM, while collating evidence about ideal intervention designs
2. Internet-based randomised controlled trial	To assess whether free availability of HIV self-testing leads to earlier diagnosis of HIV infection compared with standard of care
3. Modelling and economic evaluation	To assess the cost-effectiveness of strategies for preventing HIV in MSM, including free self-testing

Back to PrEP and policy

ipergay
ANRS
Intervention Préventive
de l'Exposition aux Risques
avec et pour les Gays

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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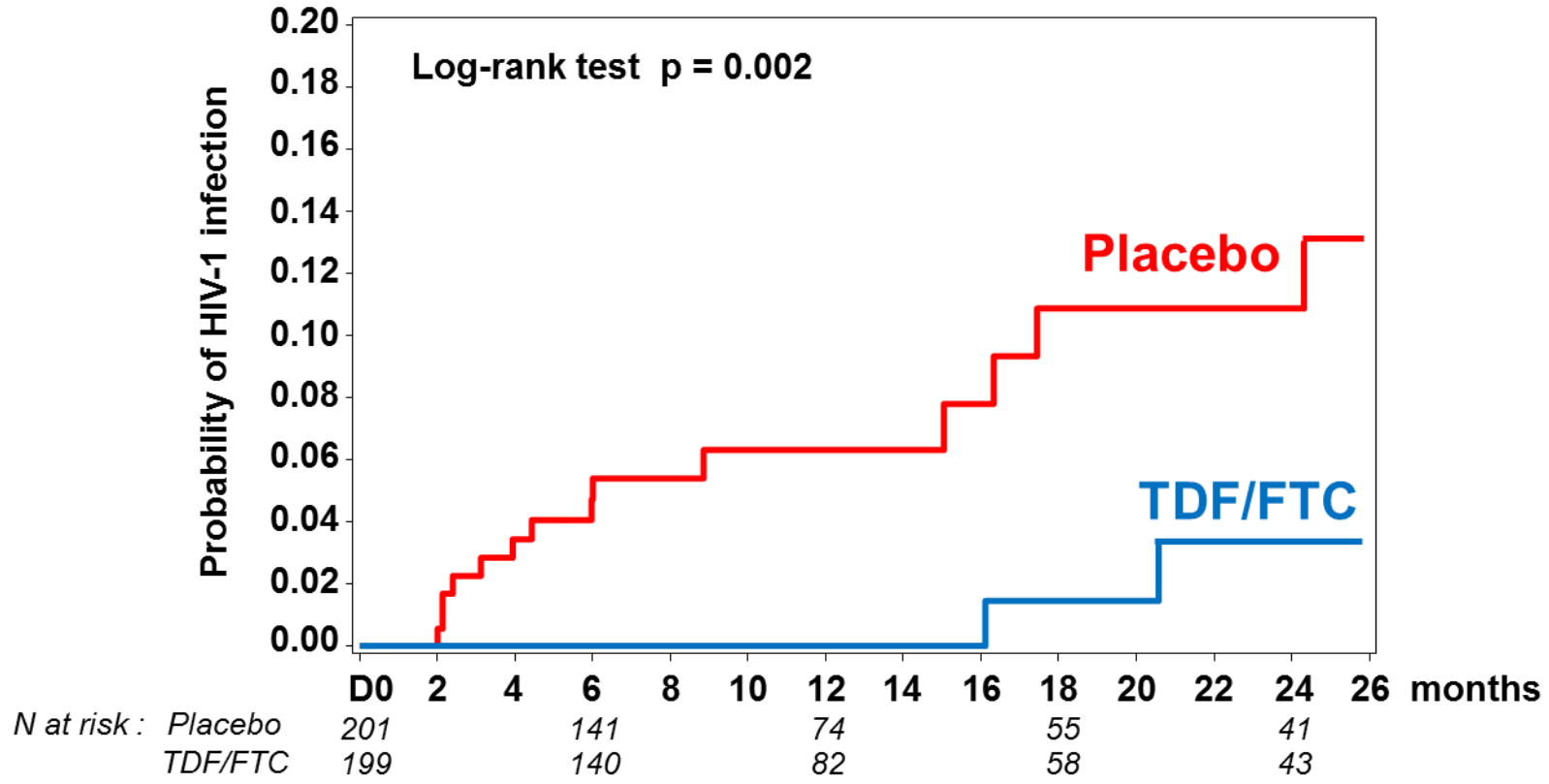
Intervention Préventive de l'Exposition aux Risques avec et pour les Gays

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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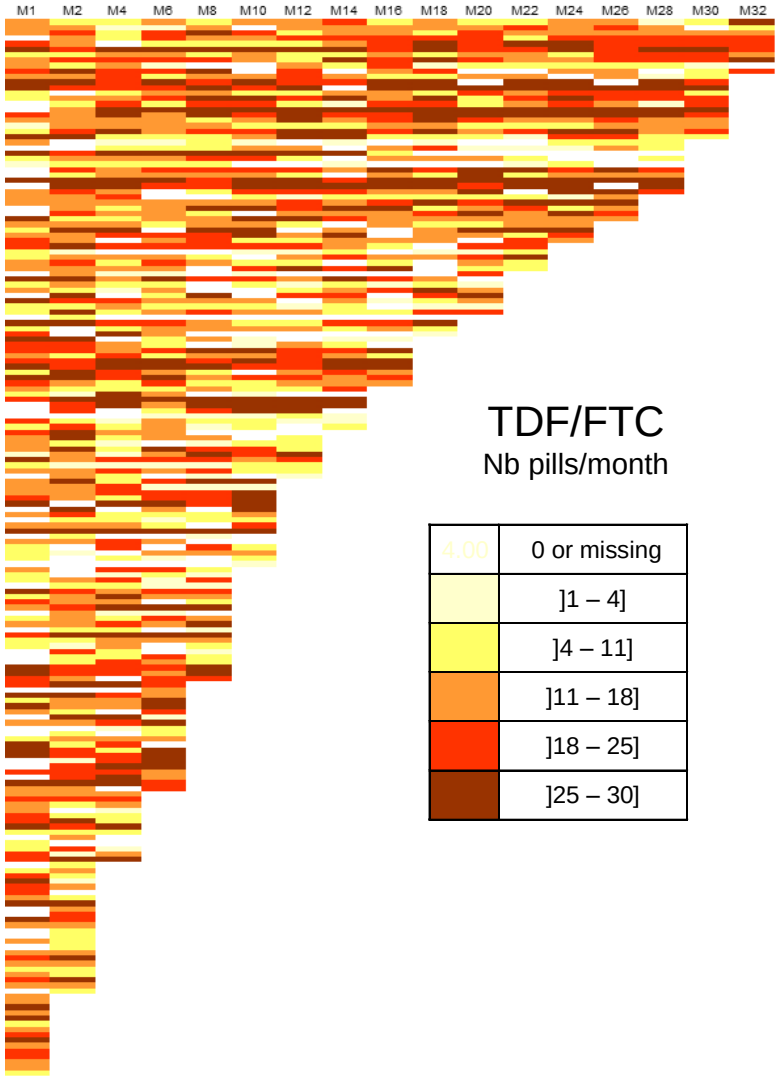
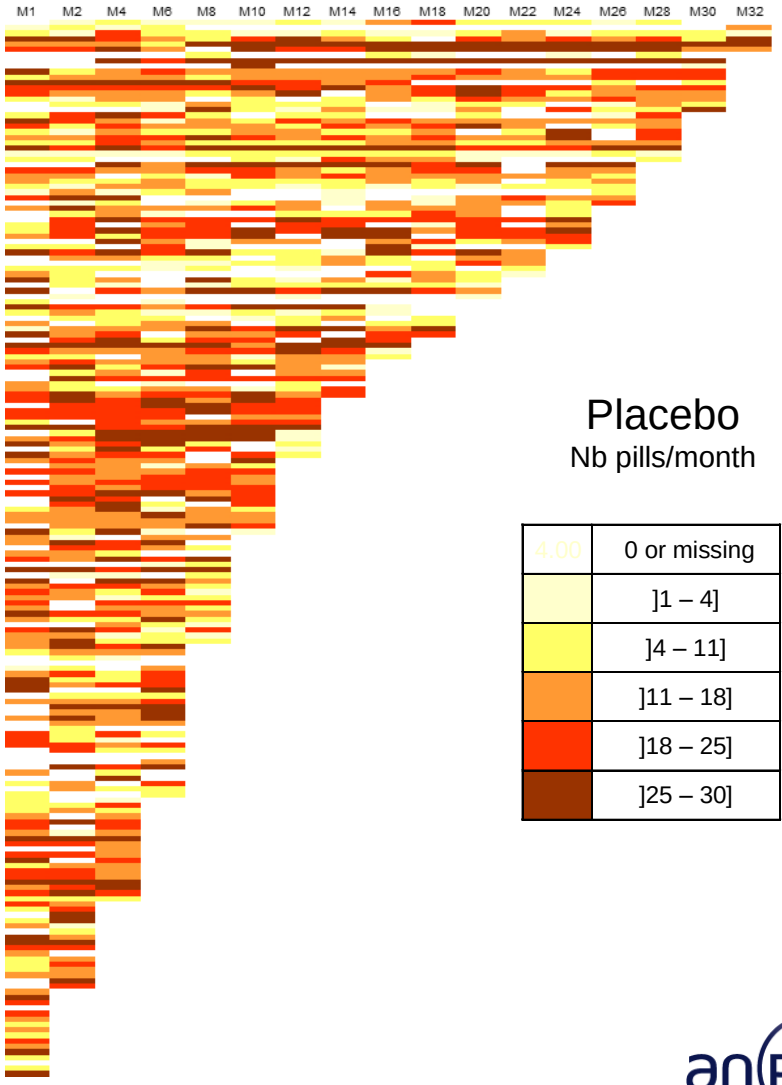
Adherence by Pill Count



TDF/FTC
Nb pills/month

4.00	0 or missing
	]1 – 4]
	]4 – 11]
	]11 – 18]
	]18 – 25]
	]25 – 30]



Placebo
Nb pills/month

4.00	0 or missing
	]1 – 4]
	]4 – 11]
	]11 – 18]
	]18 – 25]
	]25 – 30]

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Conclusions (edited)

- Incidence of HIV-1 infection in the placebo arm was higher than expected

- "On Demand" oral PrEP with TDF/FTC was highly effective - as good as the daily regimen followed in PROUD

Policy activities from April 2014

- PrEP policy sub-group of National HIV Clinical Reference Group established September 2014 – includes Local Authority representation
- PICO agreed and evidence review completed for published trials, reviewed December 2014
- Cost-effectiveness x2 underway and Clinical pathway drafted – reviewed 30 March 2015
- On target to complete the decision processes for implementation in April 2016
  - Clinical Priorities Advisory Group
  - 'Affordability'

Professional activities

- Position statement revised following PROUD, iPerGay, FACTS001 and Partners PrEP

- Writing group comments
  - Not strong enough
  - Should we comment on support for those who buy PrEP online?
  - Need to comment on eligibility
  - Need to include a comment on regimen

Which regimen?

- Advantages of iPerGay regimen
  - Less pills (less toxicity, less cost)
  - No resistance with this regimen (may be a fluke)
  - Easier to interrupt/stop when not at risk
  - Facilitates discussion about risk, whereas no need for detailed discussion with daily dosing

- Concerns
  - Less evidence overall
  - Cannot predict condomless sex
  - GI toxicity could be exacerbated by stopping and starting

For discussion or further study?

- Regimen?
- Eligibility? What about women and heterosexual men?
- Even less safety monitoring? Could PrEP be dispensed outside a clinical environment?
- Alternative drugs?
- Other sources of PrEP?

British HIV Association

BHIVA

21st Annual Conference of the British HIV Association (BHIVA)

#BHIVA2015

21–24 April 2015

The Brighton Centre, Brighton, UK