On Demand PrEP with Oral TDF/FTC in MSM Results of the ANRS Ipergay Trial

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Disclosures

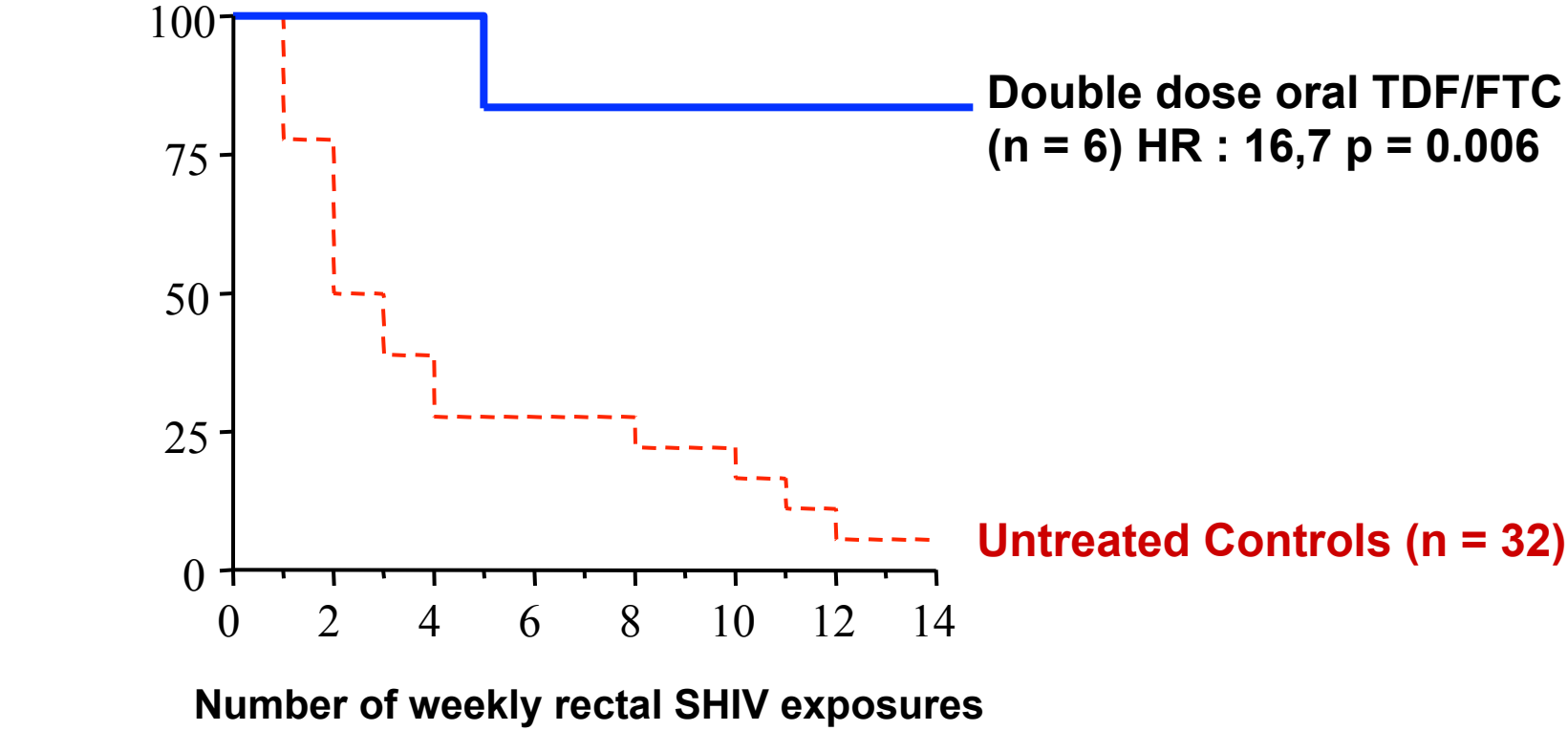
- Advisory Boards: BMS, Gilead, GSK
  Janssen, Merck, ViiV

- Research Grants: Merck and Gilead

Background

- High number of new HIV infections among MSM in France and Canada
- Conflicting results from PrEP trials with oral daily TDF/FTC: Adherence « Achilles' heel » of PrEP
- More convenient dosing regimen: « On demand »
- Could improve adherence, safety and cost-effectiveness and make PrEP more attractive
- Supported by animal models

Effect of a Double Dose of oral TDF/FTC (-2h, + 24h)



Garcia-Lerma et al. Science Trans Med 2010, 14,14ra4

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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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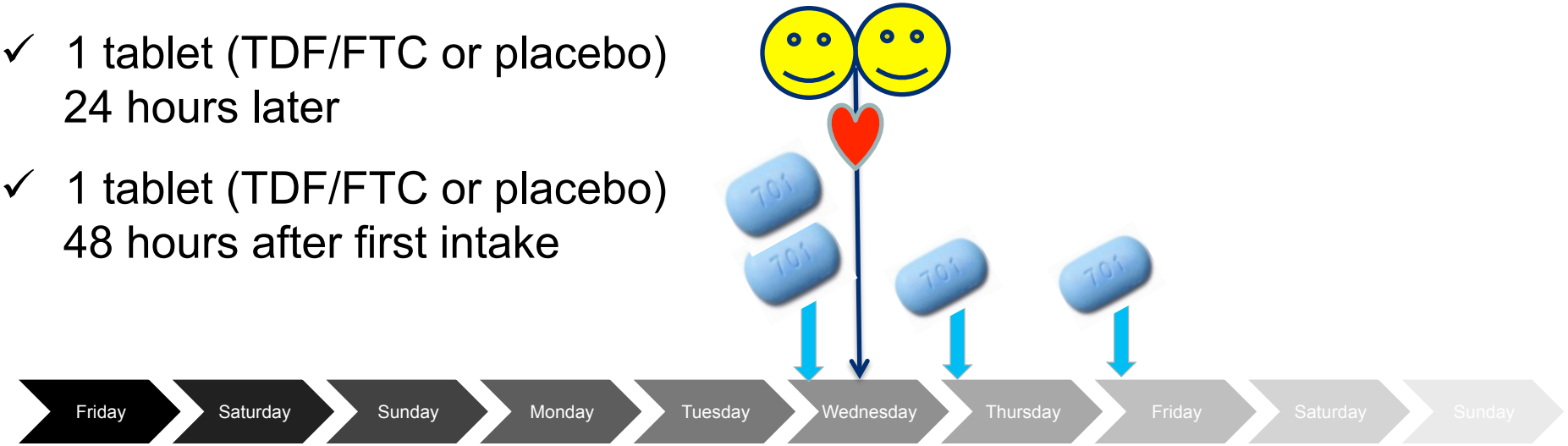
Ipergay : Event-Driven iPrEP

- ✓ 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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Study Endpoints

Primary Efficacy Endpoint: HIV-1 infection

- HIV seroconversion using a 4th generation assay combining Ab/Ag detection on serum or detection of HIV-1 RNA in plasma (stored plasma samples used to date time of infection)

Secondary end-points

- Safety and tolerability
- Adherence (pill count, plasma drug levels, computer assisted self-interviews (CASIs)
- Sexual behavior (condom use, number of sexual acts, number of partners)
- Sexually transmitted infections

⇨ October 23, 2014 (7th meeting) the DSMB recommended the discontinuation of the placebo arm and that on demand PrEP be offered to all participants

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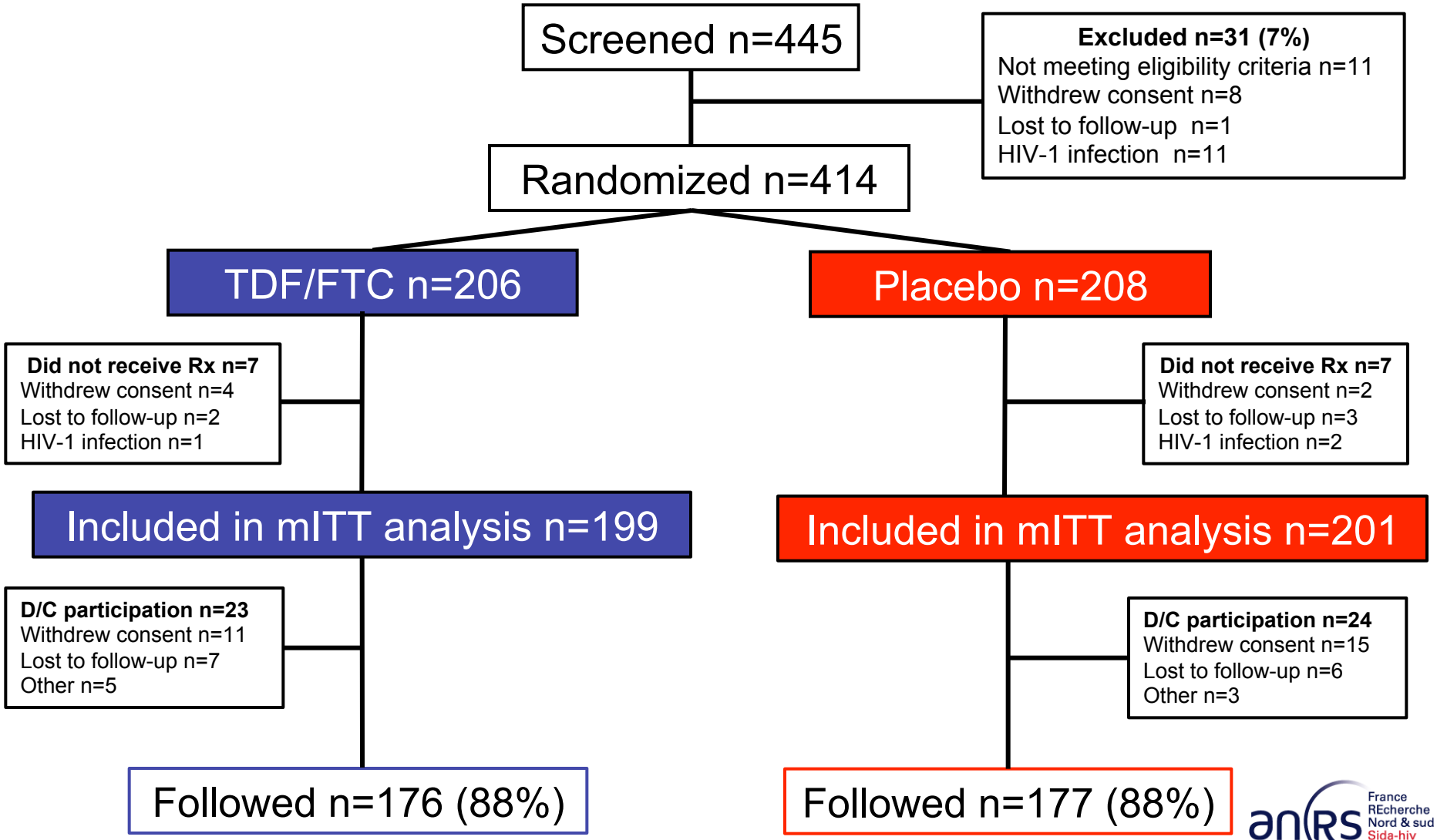
Study Flow-Chart



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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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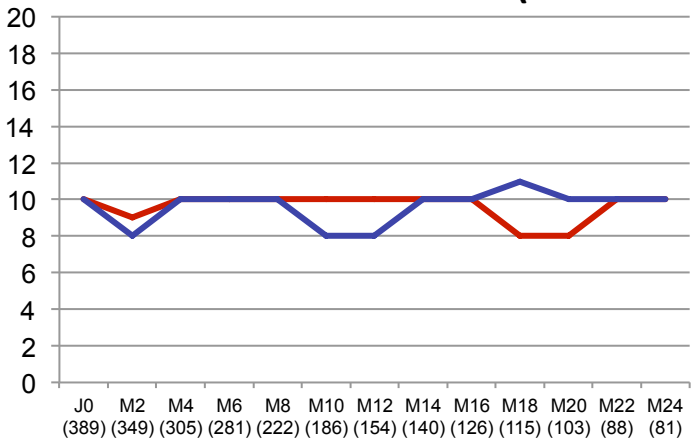
Sexual Behavior

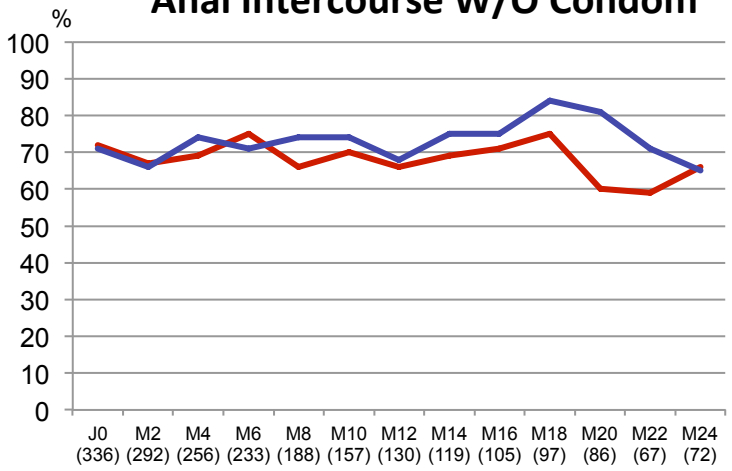
Median Nb of Sexual Acts (last 4 weeks)



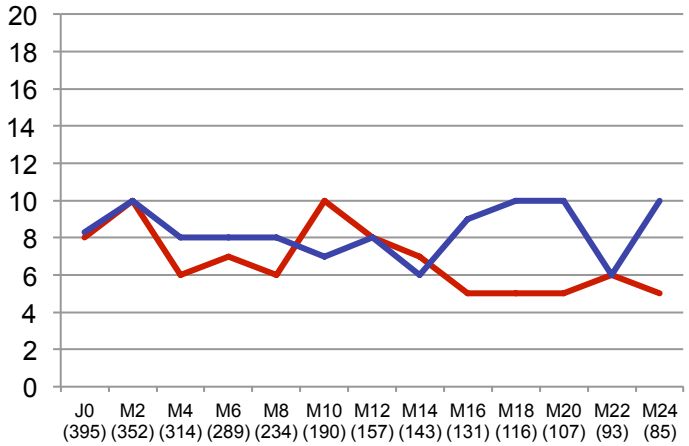
TDF/FTC

Placebo

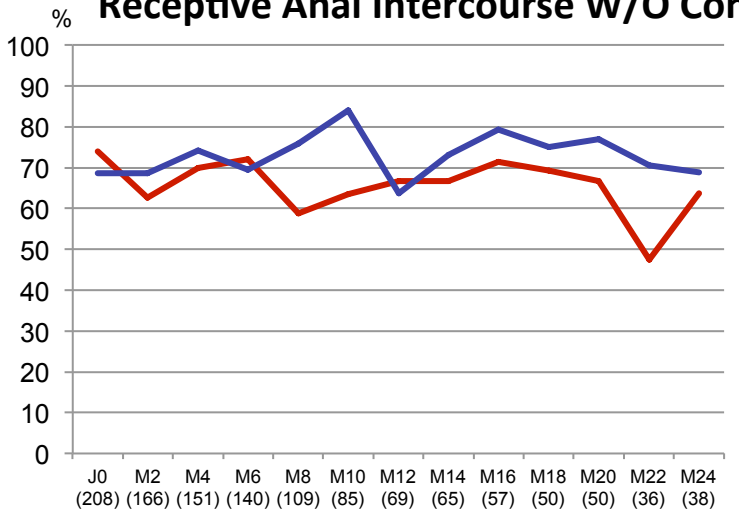
Anal Intercourse W/O Condom



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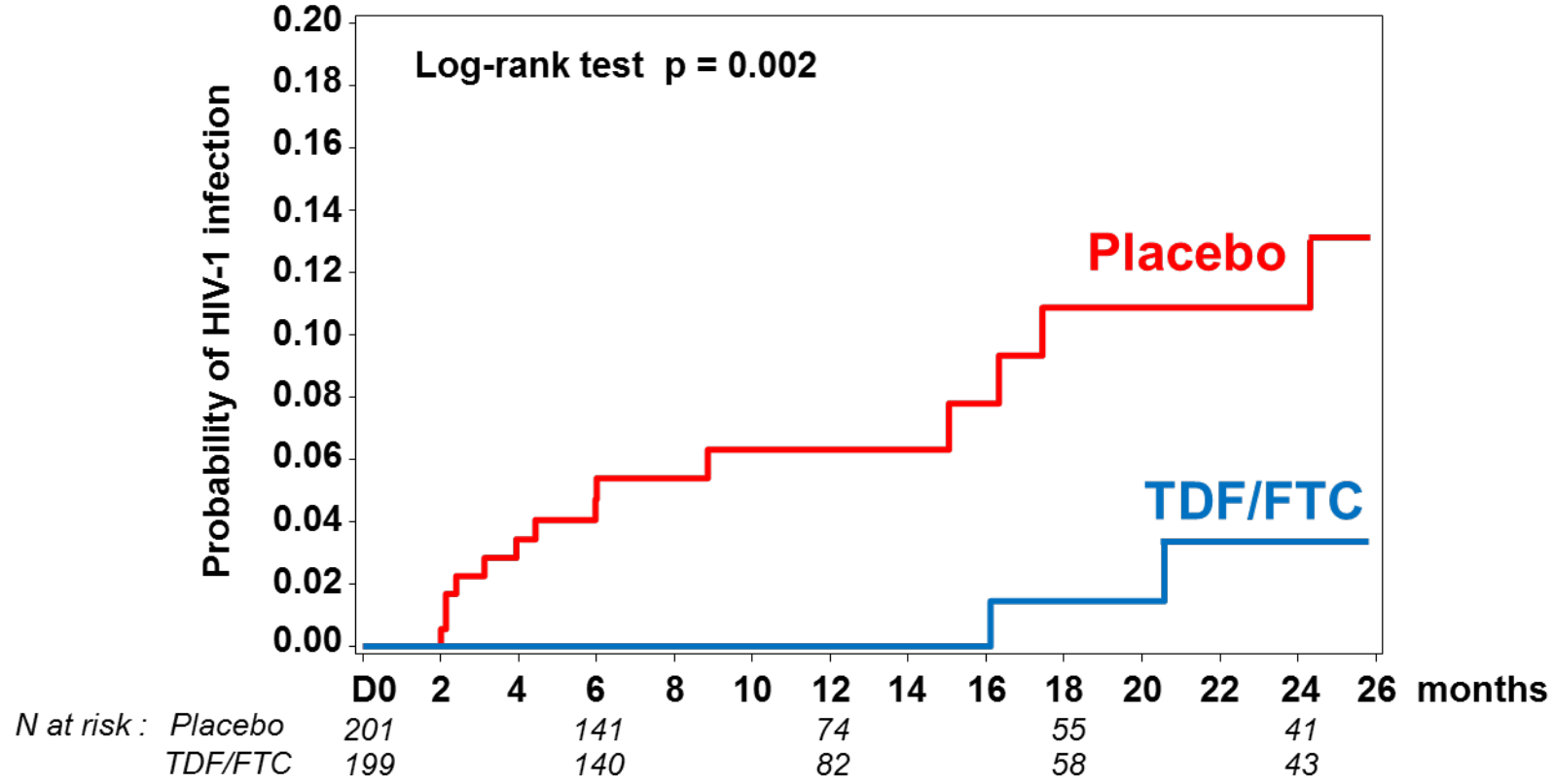
KM Estimates of Time to HIV-1 Infection (mITT Population)



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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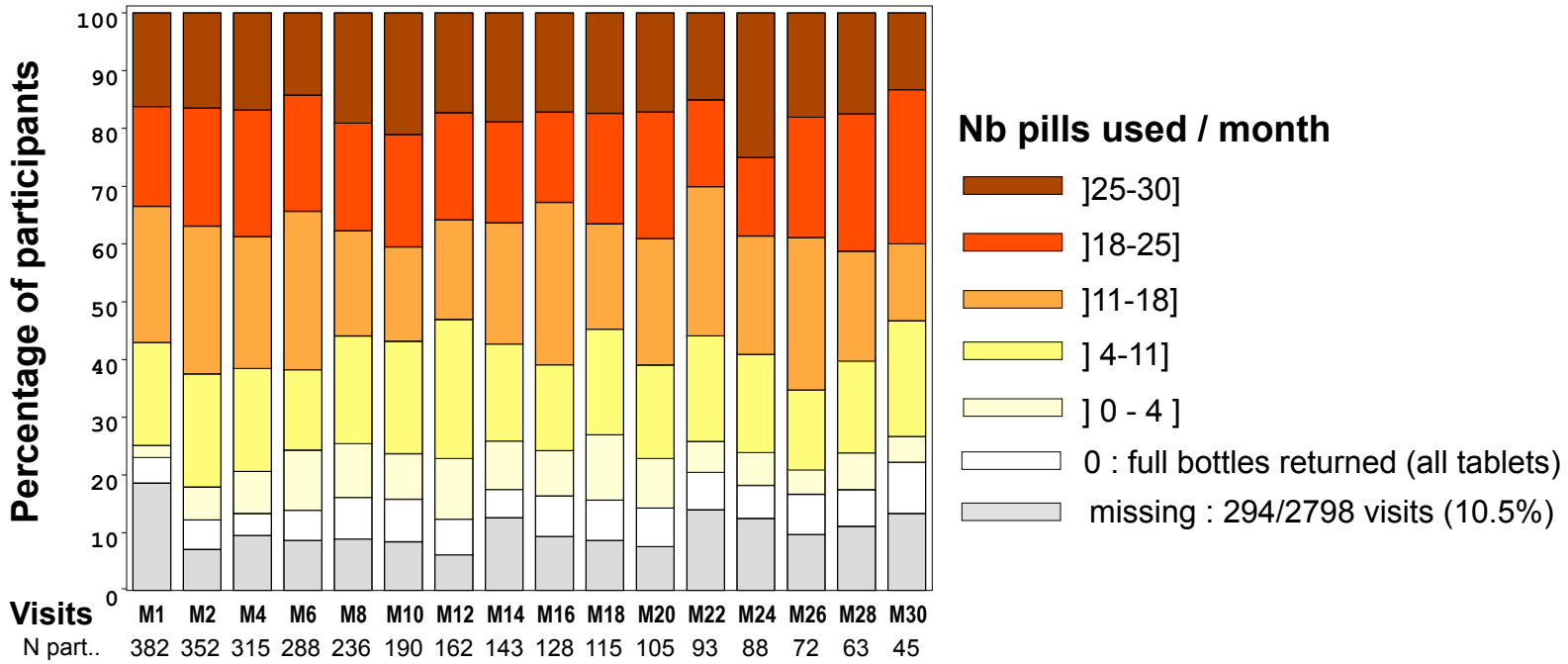
Adherence by Pill Count



- **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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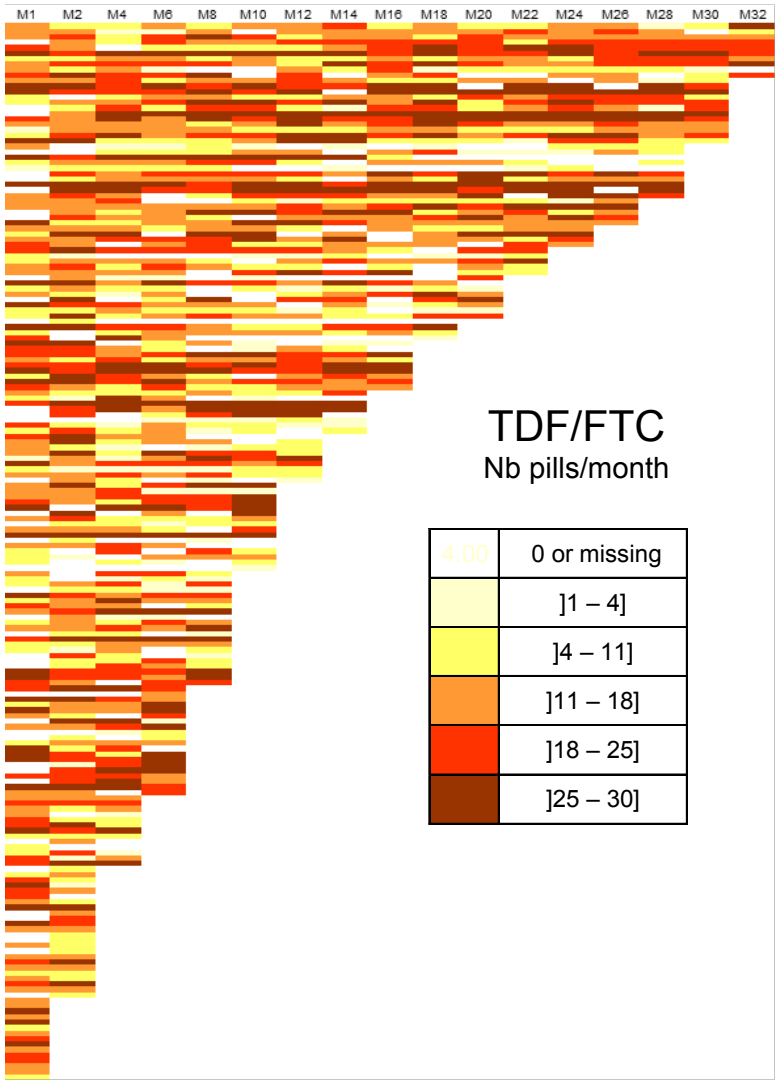
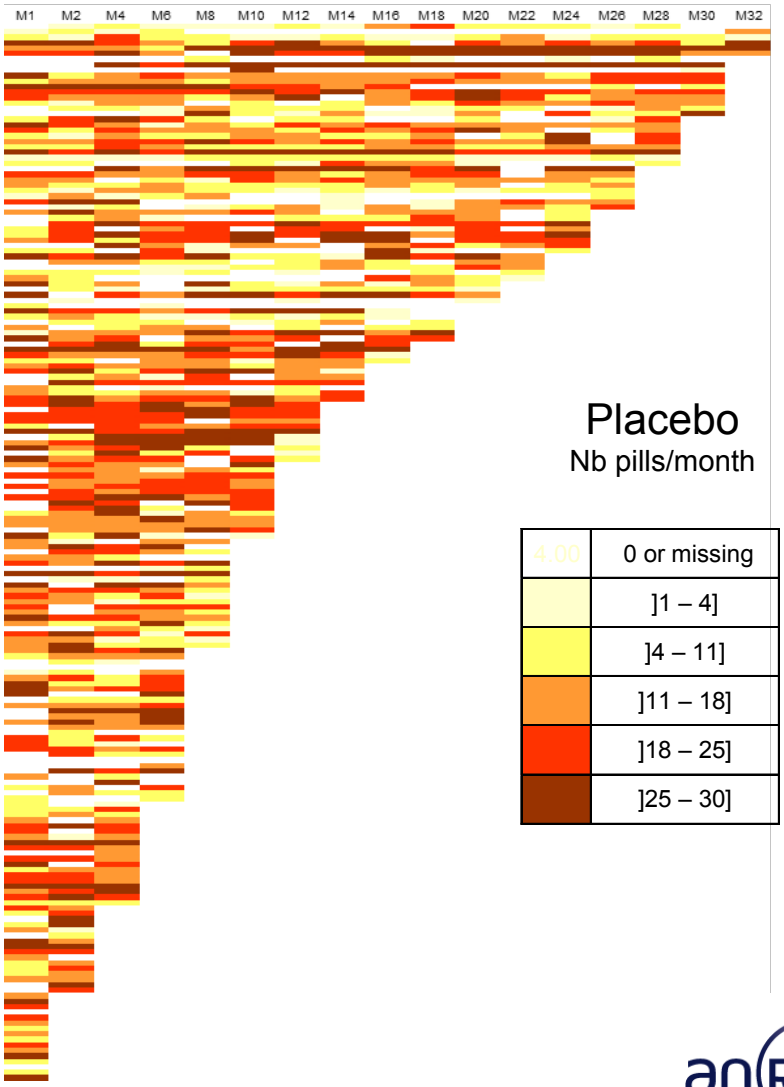
Adherence by Pill Count





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Adherence Assessed by CASIs

PrEP use during the last sexual intercourse

1212 sexual intercourses assessed in 319 participants

% PrEP Use (min-max)	TDF/FTC n = 649 acts	Placebo n = 563 acts	Total % (min-max)
Correct use*	45 (36-57)	40 (22-49)	43 (35-51)
Suboptimal use	27 (14-35)	31 (18-44)	29 (20-38)
No PrEP	27 (15-37)	29 (24-44)	28 (20-38)

* According to the protocol, or at least one pill before and one pill after sex

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Adverse Events

Nb of Participants (%)	TDF/FTC n=199	Placebo n=201	P value
Any AE	184 (92)	178 (89)	0.18
Any Serious AE	18 (9)	16 (8)	0.70
Any Grade 3 or 4 AE	17 (9)	14 (7)	0.56
Treatment D/C due to AE	1*	0	
Drug-Related GI AEs	25 (13)	11 (6)	0.013
Nausea/vomiting	15	2	
Abdominal pain	11	4	
Diarrhea	7	5	

* deep veinous thrombosis with suspected DDI with dabigatran

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Lab Abnormalities

Nb of Participants (%)	TDF/FTC n=199	Placebo n=201	P value
Grade 1 Creatinine	28 (14%)*	15 (7%)	0.042
Proteinuria ≥ 2+	10 (5%)	9 (5%)	0.83
Glycosuria ≥ 2+	1 (1%)	0 (0%)	1.00
All Grades ALAT	33 (17%)	26 (13%)	0.37
Grade 3 or 4 ALAT	1 (1%)**	4 (4%)***	0.36

* 2 Participants in the TDF/FTC arm had a transient creatinine clairance < 60 ml/mn
** Acute HCV infection
*** Acute HCV infection in 3 and syphilis in one

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Conclusions

- In this population of high risk MSM, incidence of HIV-1 infection in the placebo arm was higher than expected
- "On Demand" oral PrEP with TDF/FTC was very effective with a 86% (95% CI: 40-99) reduction in HIV-incidence
- Adherence to PrEP was good supporting the acceptability of "on demand" PrEP
- Safety of "on demand" TDF/FTC was overall similar to placebo except for gastrointestinal AEs
- No evidence of risk compensation
- On demand PrEP: attractive alternative to daily PrEP in high risk MSM who do not use condoms consistently

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- The Community Advisory Board
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Public Health England

PROUD

MRC Clinical Trials Unit

Pragmatic Open-Label Randomised Trial of Pre-Exposure Prophylaxis: the PROUD study

http://www.proud.mrc.ac.uk/

Disclaimers

- Gilead Sciences plc provided drug free of charge, and distributed it to participating clinics
- Gilead Sciences plc provided funds for the additional diagnostics including the pharmacokinetic sub-study

Sexual health service in England

- ~220 sexual health clinics, linked through professional guidelines
- Accessed by 110,000 HIV negative gay men per year
- Diagnoses made and services provided reported to Public Health England

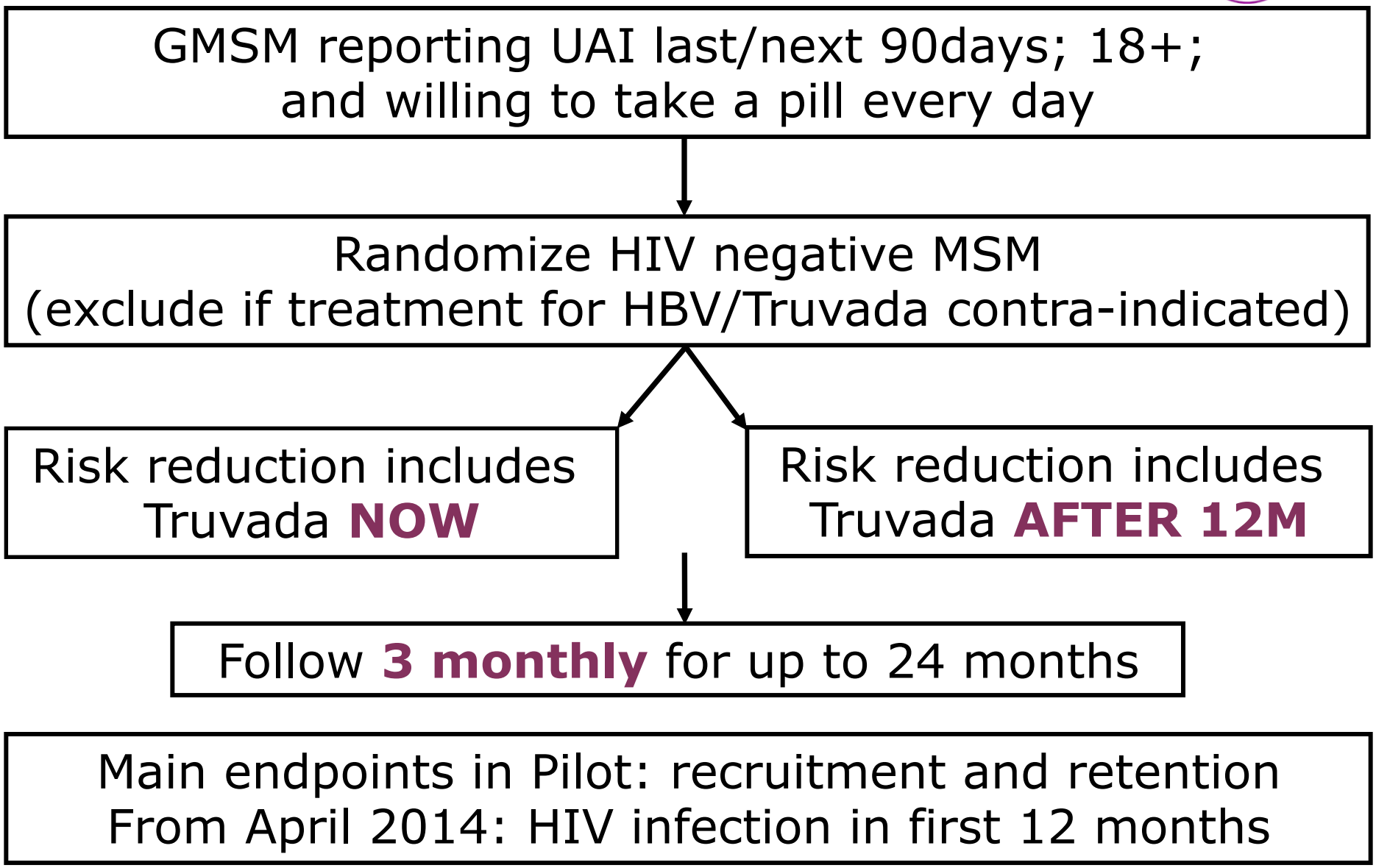
Rationale

- **To determine whether PrEP worked as well as iPrEx in this setting (44% reduction in HIV)**

- **Why might effectiveness be less in real world?**
- 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

Designed to mimic real-world

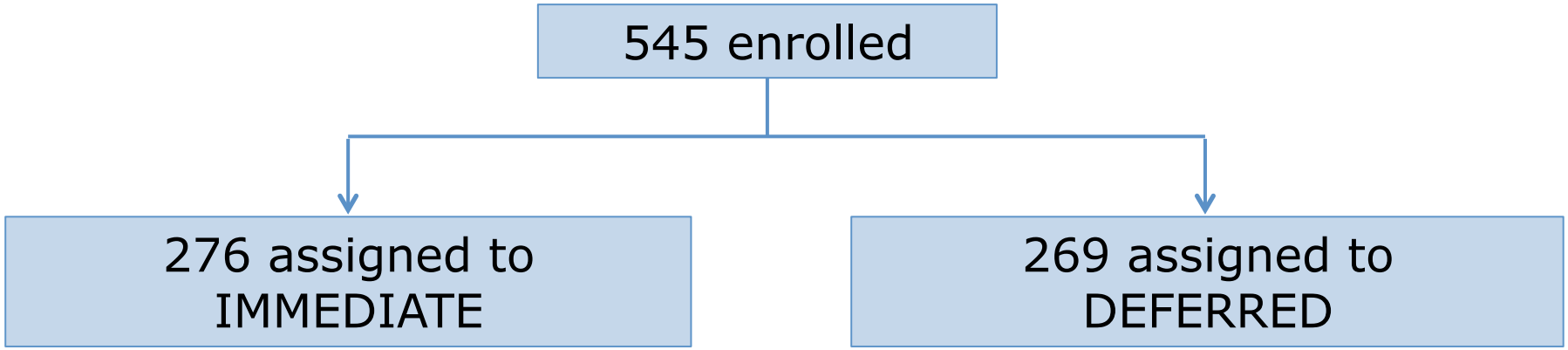
- Eligibility: routine clinic data and p24Ag/Ab serology at enrolment (no PCR)
- Safety: serum creatinine when starting and annually; additional tests if 1+ protein on dipstick
- STIs: (mainly) quarterly HIV, syphilis, HCV, gonorrhoea and chlamydia according to routine clinic
- Behaviour change interventions according to routine clinic (sexual risk, adherence, addiction)

- **Study procedures: web-randomisation, data entry, participant-completed questionnaires**

Results:

Population, Prescribing, Tolerability

Participant randomization



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

Prescriptions of PrEP and PEP

Immediate	Deferred
• 14 (5%) **never started PrEP**	• Anecdotally, **rare use of PrEP**
• 156 (56%) prescribed sufficient drug for 100% daily dosing	
• Overall, drug prescribed covered 86% of days in follow-up	
• 13 (5%) prescribed **PEP** (total 15 prescriptions)	• 83 (31%) prescribed **PEP** (total 174 prescriptions)

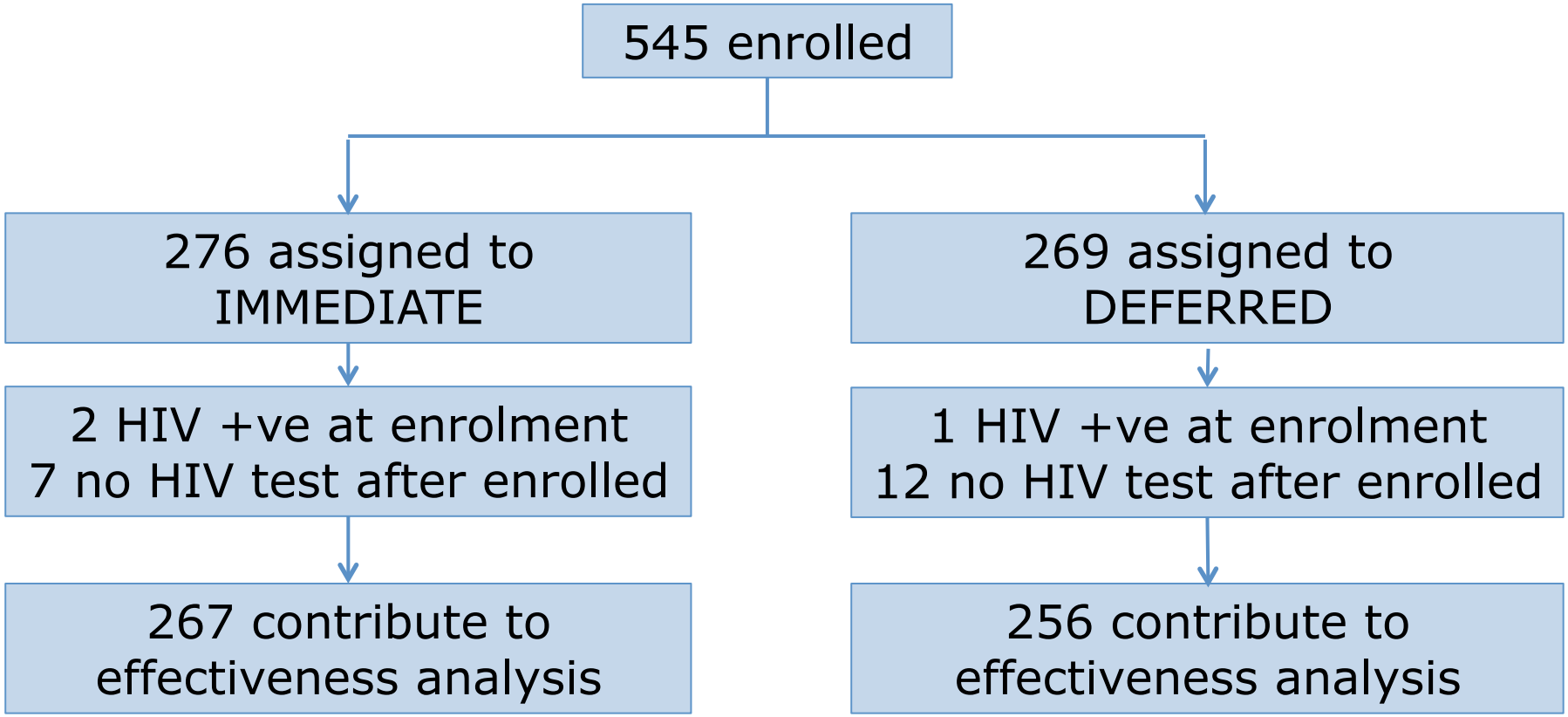
PrEP interruptions for medical event

- **PrEP interrupted** by 28 participants (**both groups**) but only **13** had events considered related to drug:
  - nausea alone or with diarrhoea/abdominal pain/aches and fatigue (n=5)
  - decline in creatinine clearance (n=2)
  - headache (n=2)
  - joint pain, with fatigue in one case (n=2)
  - sleep disturbance (n=1)
  - flu-like illness (n=1)

- **PrEP re-started** by 11 of 13 participants above

Results:

HIV endpoint



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

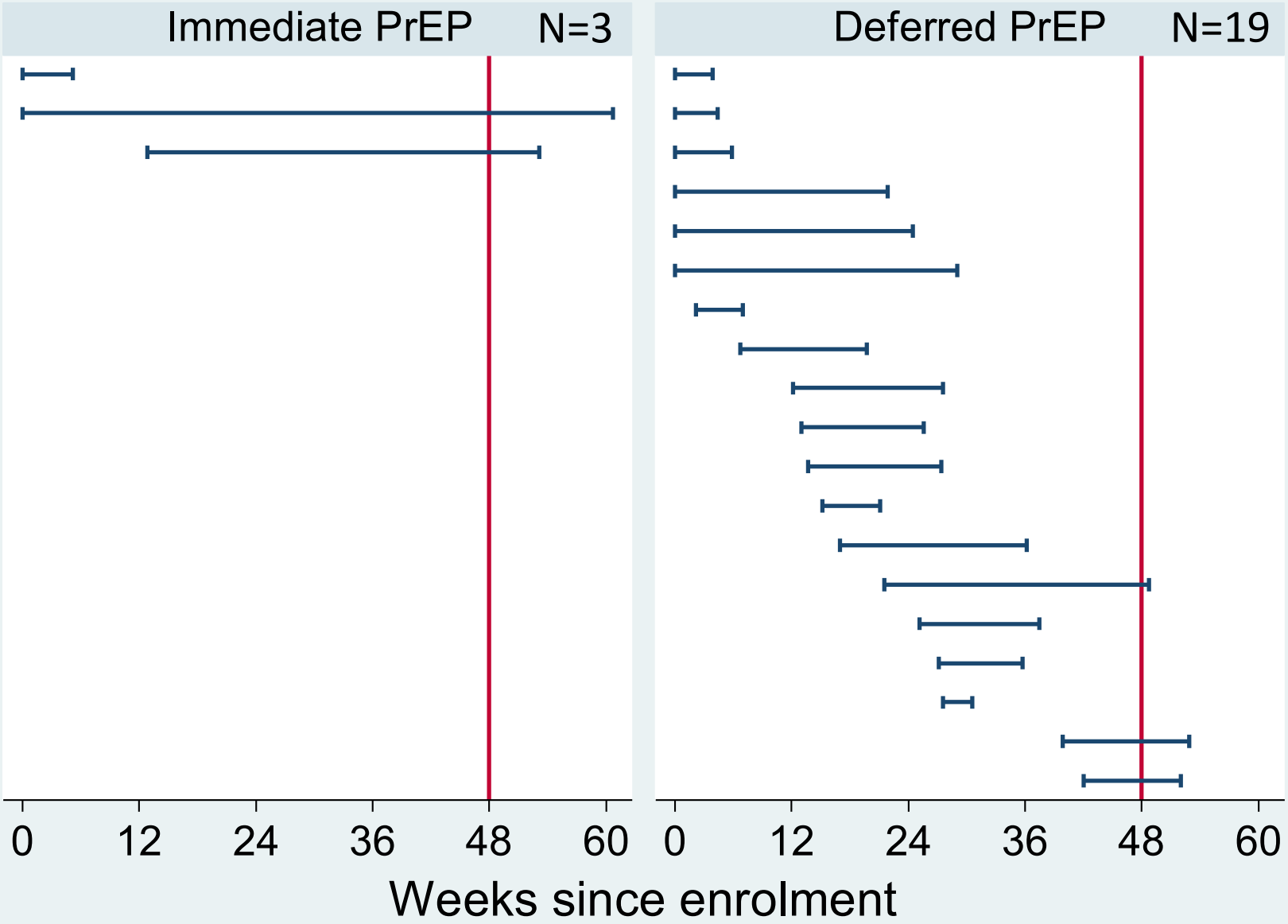
Completeness of follow-up for HIV

- **Expected** person-years calculated assuming they had precisely followed protocol schedule

Observed/expected follow-up:

- Immediate: 239/261 person years (92%)
- Deferred: 214/242 person years (88%)

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

Drug Resistance

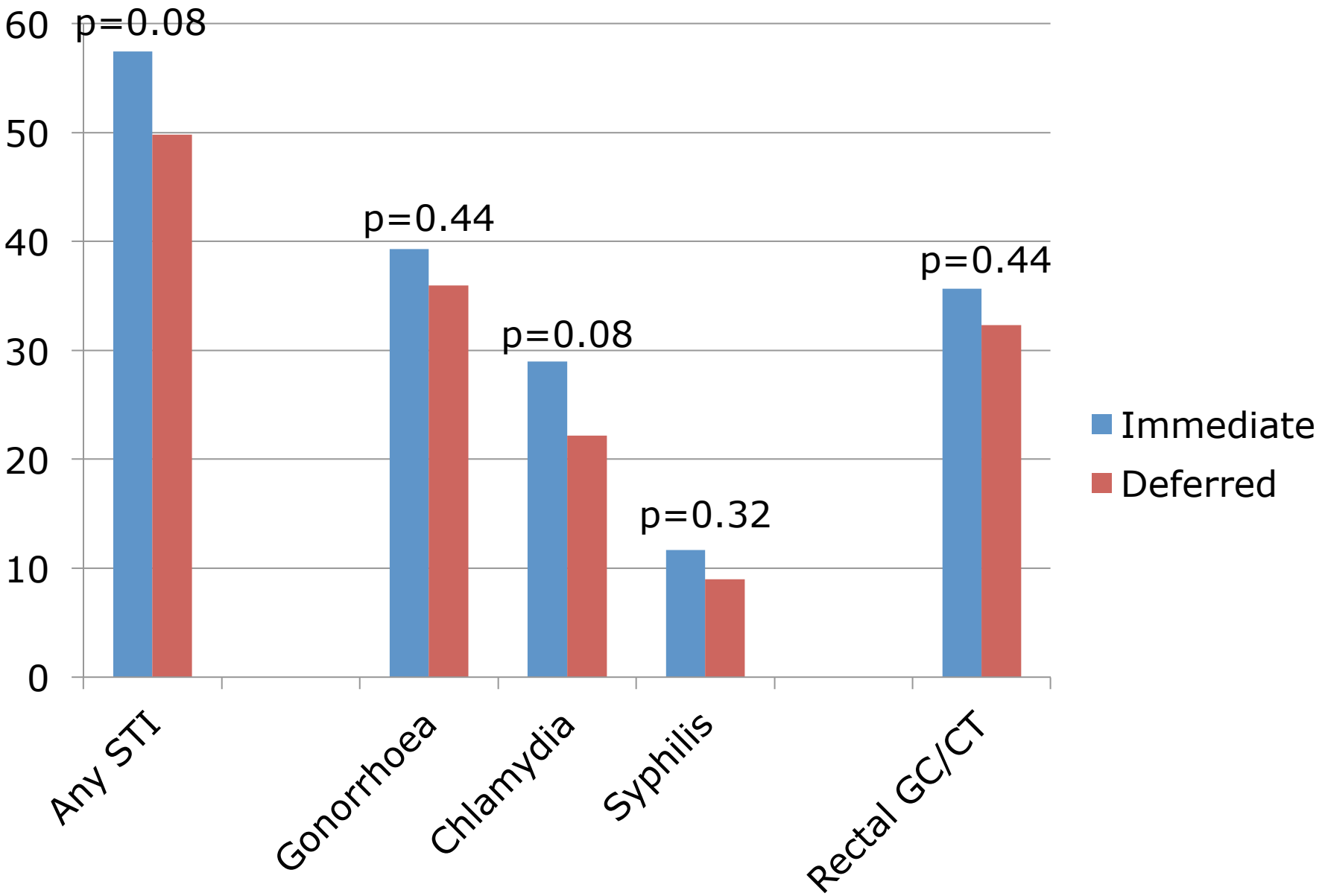
- **3** of **6** individuals who were seroconverting around baseline (immediate group) or month 12 (deferred group) developed **M184V/I** mutations (as a mixture with wild type)

- **K65R** was not detected

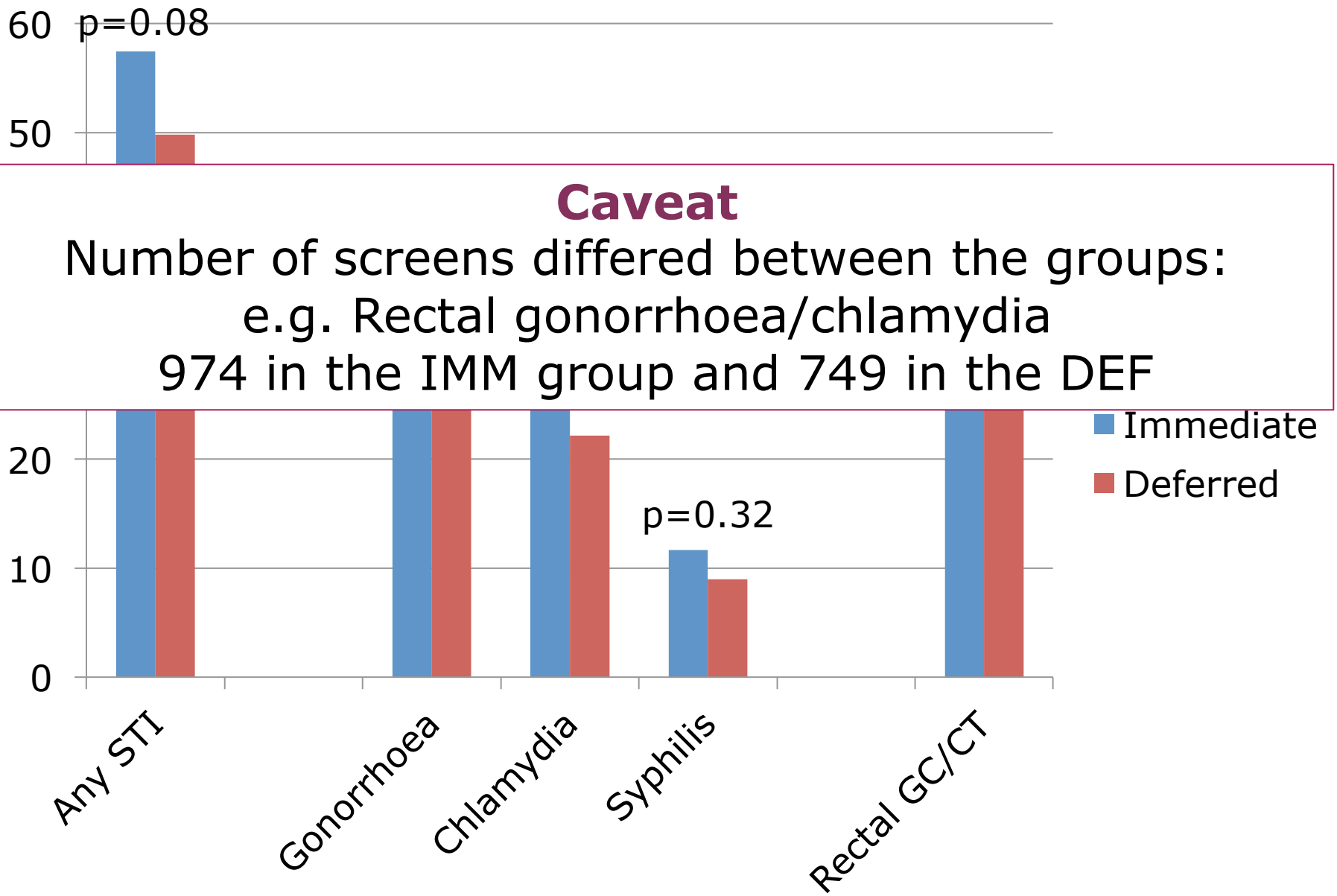
Results:

STI endpoints

STIs


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

STIs



Caveat

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

Results:

Sexual behaviour

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)

Conclusions

- HIV incidence in the population who came forward to access PrEP was much higher than predicted based on all MSM attending sexual health clinics
- Despite extensive use of PEP in the deferred period
- Our concerns about PrEP being less effective in the real world were unfounded

- MSM incorporated PrEP into existing risk reduction strategies which continued to include condom use
- There was no difference in STIs, which were common in both groups

- Clinics were able to adapt routine practice to incorporate PrEP

Acknowledgements (1)

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