15th Annual Conference of the
National HIV Nurses Association (NHIVNA)

National HIV Nurses Association

Yvonne Gilleece

Royal Sussex County Hospital, Brighton

27-28 June 2013- The International Convention Centre, Birmingham

Decision making and dilemma: the challenges of supporting discordant couples in practice

Yvonne Gilleece

Brighton & Sussex University Hospitals NHS Trust

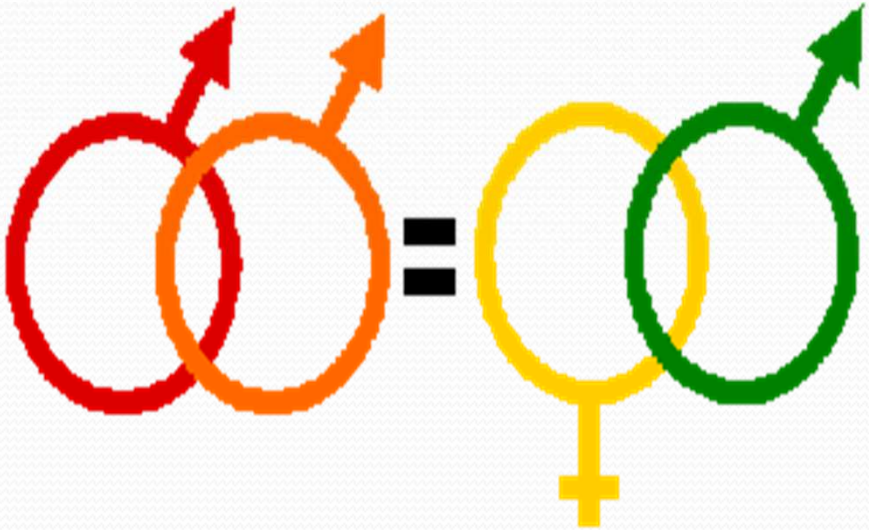
Introduction

- Definitions
- Prevention of HIV transmission
- Conception

Definitions

HIV serodiscordant couples

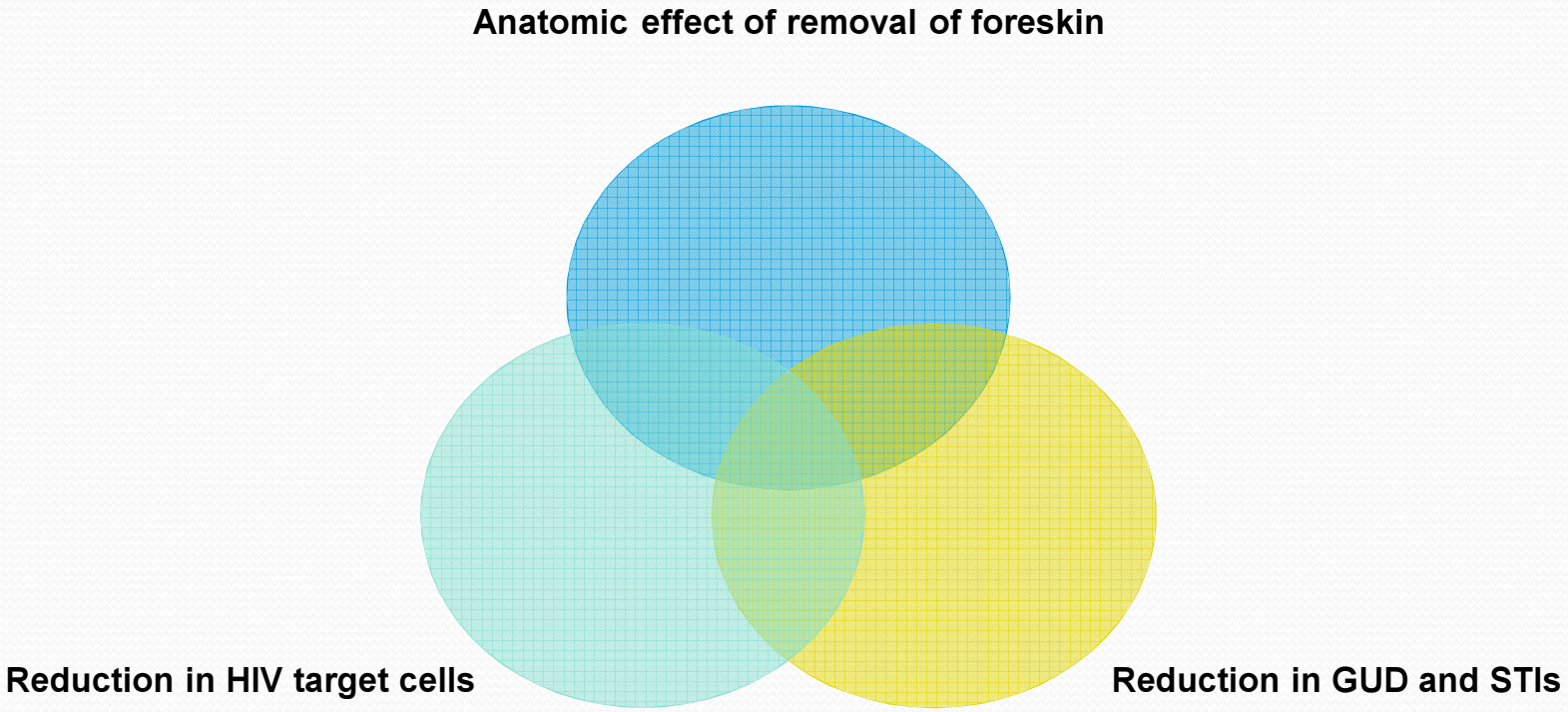
Heterosexual or same sex (MSM) couples where one partner is HIV positive and the other is HIV negative



Prevention of HIV Transmission

- Condoms
- Male circumcision
- PEPSE
- PrEP
  - Oral
  - Gel
- Antiretrovirals for the HIV positive partner

Theory of how male circumcision reduces HIV acquisition



During trial effectiveness 58%
Post-trial effectiveness ~ 67%
Reduce female infection by 42%

How do we know PEPSE is effective?

How do we know PEPSE is effective?

① **Large randomised control trial showing 81% efficacy**

15%

② **Small randomised control trial showing 81% efficacy**

14%

③ **Cohort data showing 81% efficacy**

37%

④ **None of the above**

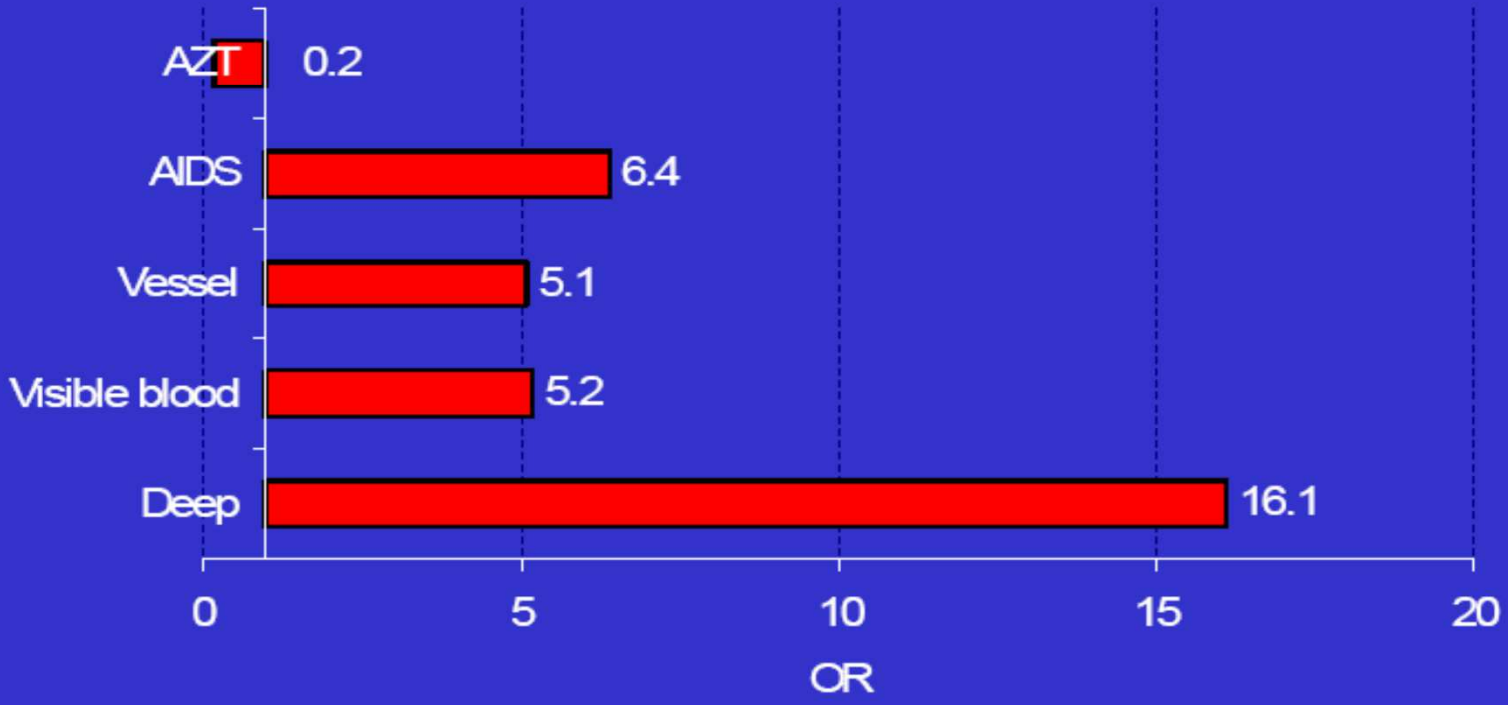
34%

Q

PEPSE

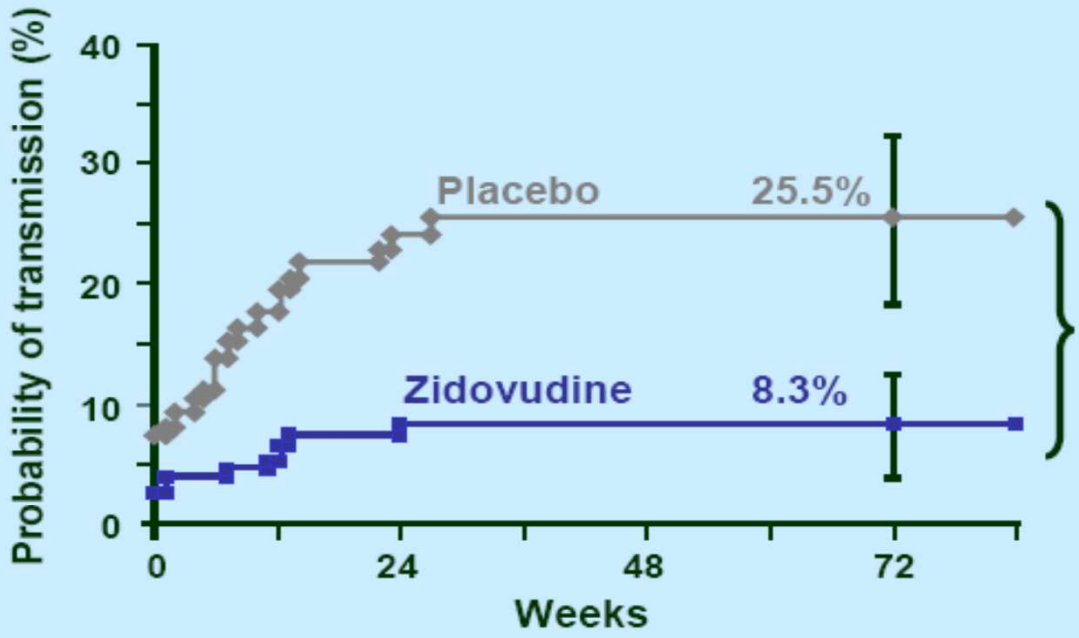
Risk Group	Efficacy of Protection	Strength of Evidence
HIV negative man having IVI with a woman	Not established	LOW: Estimate from occupational exposure is 81% (48-94%) reduction
HIV negative woman having RVI with a man	Not established	LOW: Single observational study in sexual assault 0/182 with PEPSE 4/145
HIV negative man having IAI with a man or woman	Not established	LOW: quality of single observational study was weak 18 10/11 seroconvertors did not use PEPSE, but no population benefit compared to historical control
HIV negative man having RAI	Not established	LOW: quality of single observational study was weak 18 10/11 seroconvertors did not use PEPSE, but no population benefit compared to historical control

Evidence for Occupational PEP: humans



Cardo DM et al. N. Engl. J Med 1997; 337:1485

PACTG 076 Study



Placebo (n)	183	84	42	37
Zidovudine (n)	180	105	51	43

Connor EM *et al. NEJM* 1994;331:1173–1180

PEPSE:
Evidence of effectiveness

- Animal studies
  - Macaques: 100% protection if within 36 hours

- Uncontrolled studies:
  - Sao Paolo (gay men): 0.6% PEP users seroconverted vs 4.2% non-PEP ($p<0.05$)
  - Rio (sexual assault): 0% versus 2.7% ($p<0.05$)

Table 4 Situations when post-exposure prophylaxis (PEP) is considered (IV, grade C)

	Source HIV status			
	HIV-positive		Unknown from high prevalence group/area*	Unknown from low prevalence group/area
	Viral load detectable	Viral load undetectable		
Receptive anal sex	Recommend	Recommend	Recommend	Not recommended
Insertive anal sex	Recommend	Not recommended	Consider†	Not recommended
Receptive vaginal sex	Recommend	Not recommended	Consider†	Not recommended
Insertive vaginal sex	Recommend	Not recommended	Consider†	Not recommended
Fellatio with ejaculation‡	Consider	Not recommended	Not recommended	Not recommended
Fellatio without ejaculation‡	Not recommended	Not recommended	Not recommended	Not recommended
Splash of semen into eye	Consider	Not recommended	Not recommended	Not recommended
Cunnilingus	Not recommended	Not recommended	Not recommended	Not recommended
Sharing of injecting equipment	Recommended	Not recommended	Consider	Not recommended
Human bite§	Not recommended	Not recommended	Not recommended	Not recommended
Needlestick from a discarded needle in the community			Not recommended	Not recommended

*High prevalence groups within this recommendation are those where there is a significant likelihood of the source individual being HIV-positive. Within the UK at present, this is likely to be men who have sex with men and individuals who have immigrated to the UK from areas of high HIV prevalence (particularly sub-Saharan Africa)

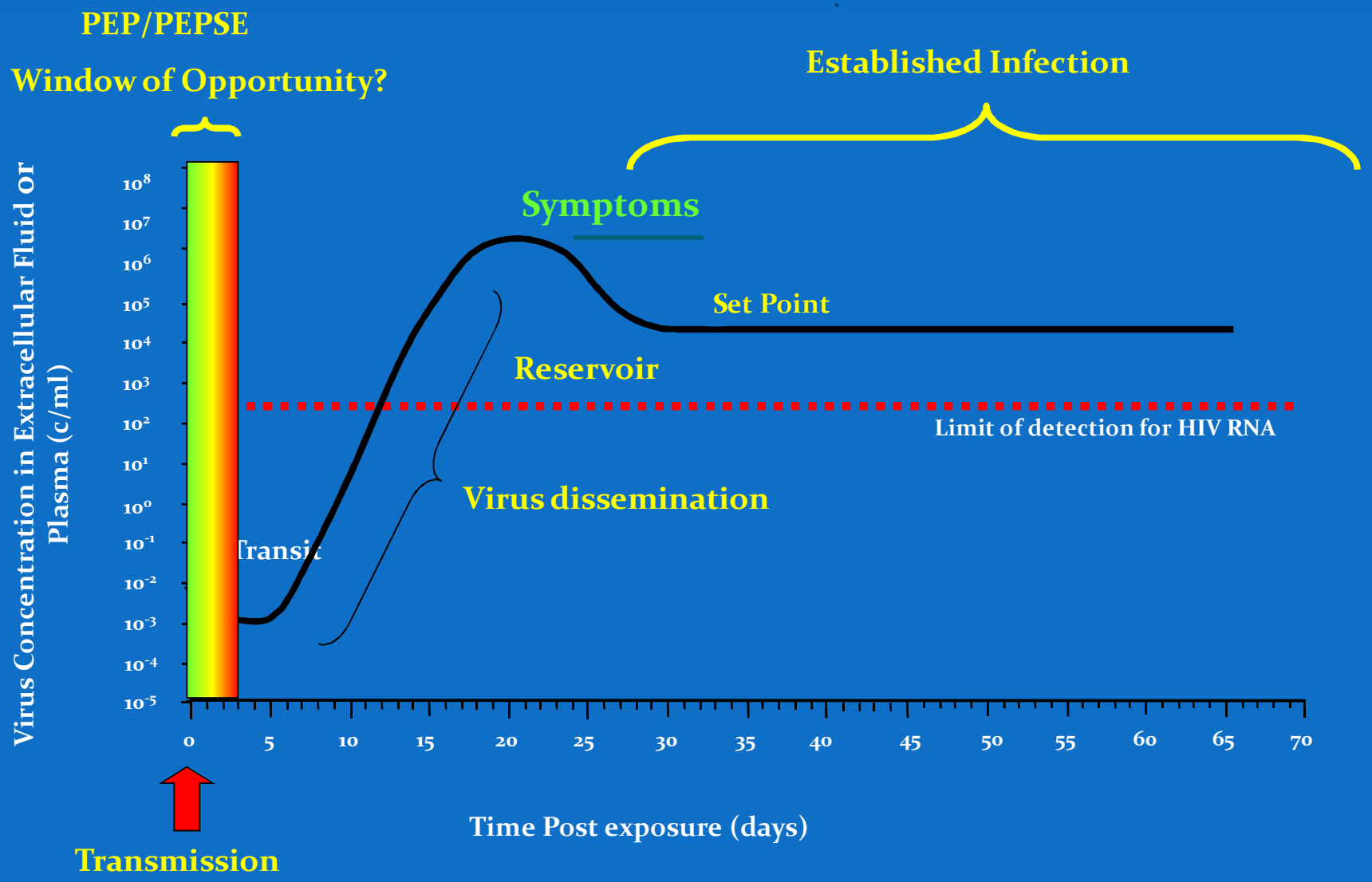
†More detailed knowledge of local prevalence of HIV within communities may change these recommendations from *consider* to *recommended* in areas of particularly high HIV prevalence

‡PEP is not recommended for individuals receiving fellatio i.e. inserting their penis into another's oral cavity

§A bite is assumed to constitute breakage of the skin with passage of blood

Pre Exposure Prophylaxis for the HIV uninfected partner

HIV-1 Acquisition and Acute Infection



Slide courtesy of Myron Cohen Personal communication

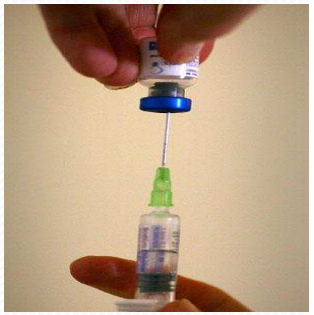
PrEP Delivery Platforms:
Long-acting topical & systemic delivery

Pill

Gel with applicator

Vaginal film

Vaginal ring (sustained delivery)



Injectable (long-acting)

- ✓ Ideal: long acting, safe, effective, low cost and user-friendly
- ✓ Maximize choice & optimize effectiveness
- ✓ Potential for combination ARVs to increase effectiveness
- ✓ Potential to combine ring or injections with contraception

Pre Exposure Prophylaxis is

① **95% effective in all randomised control trials so far**

3%

② **80% effective in some trials if adherance is over 95%**

58%

③ **Now standard of care in the UK**

7%

④ **Should only be given in the UK as part of a trial**

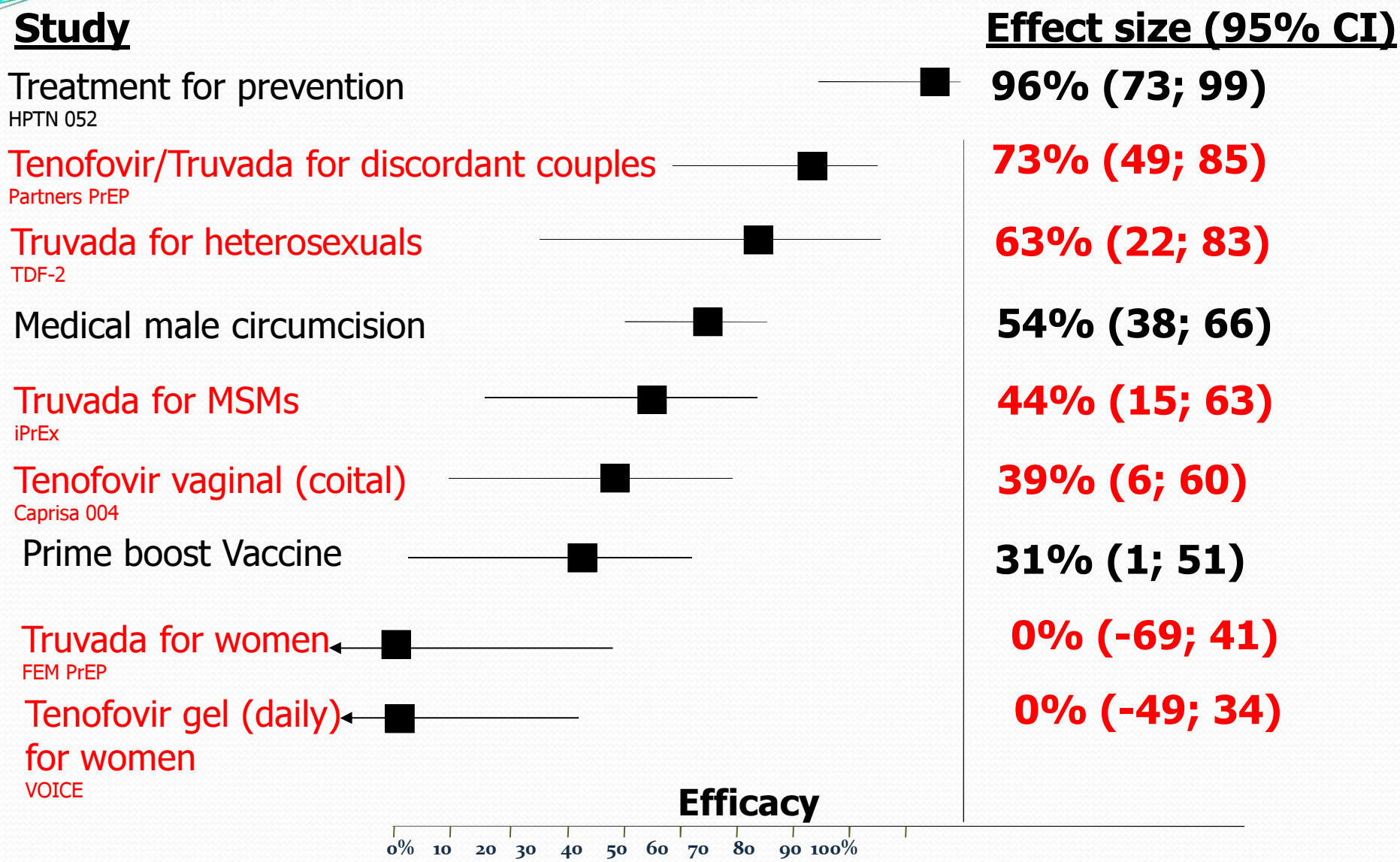
25%

⑤ **Other**

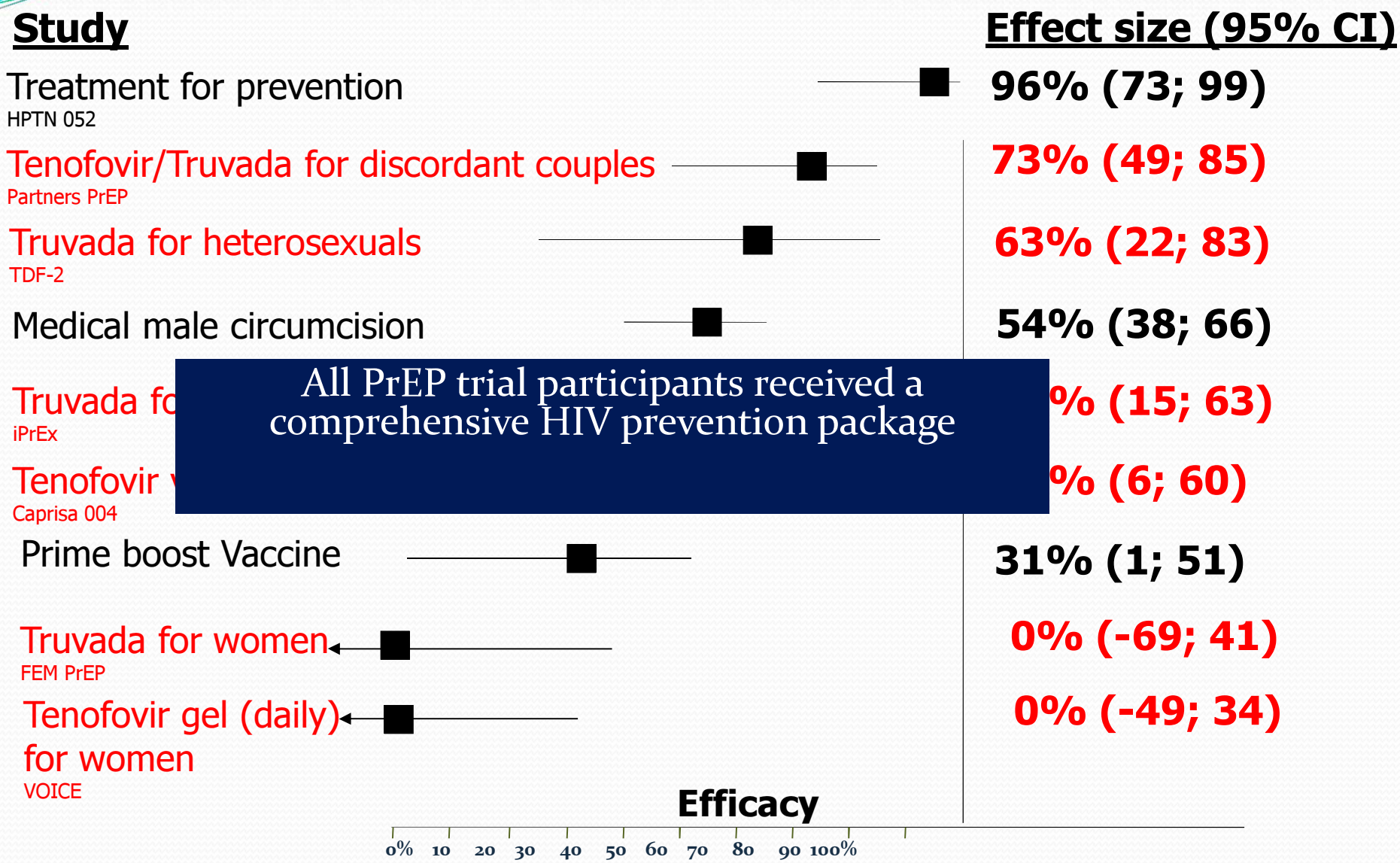
7%

Q

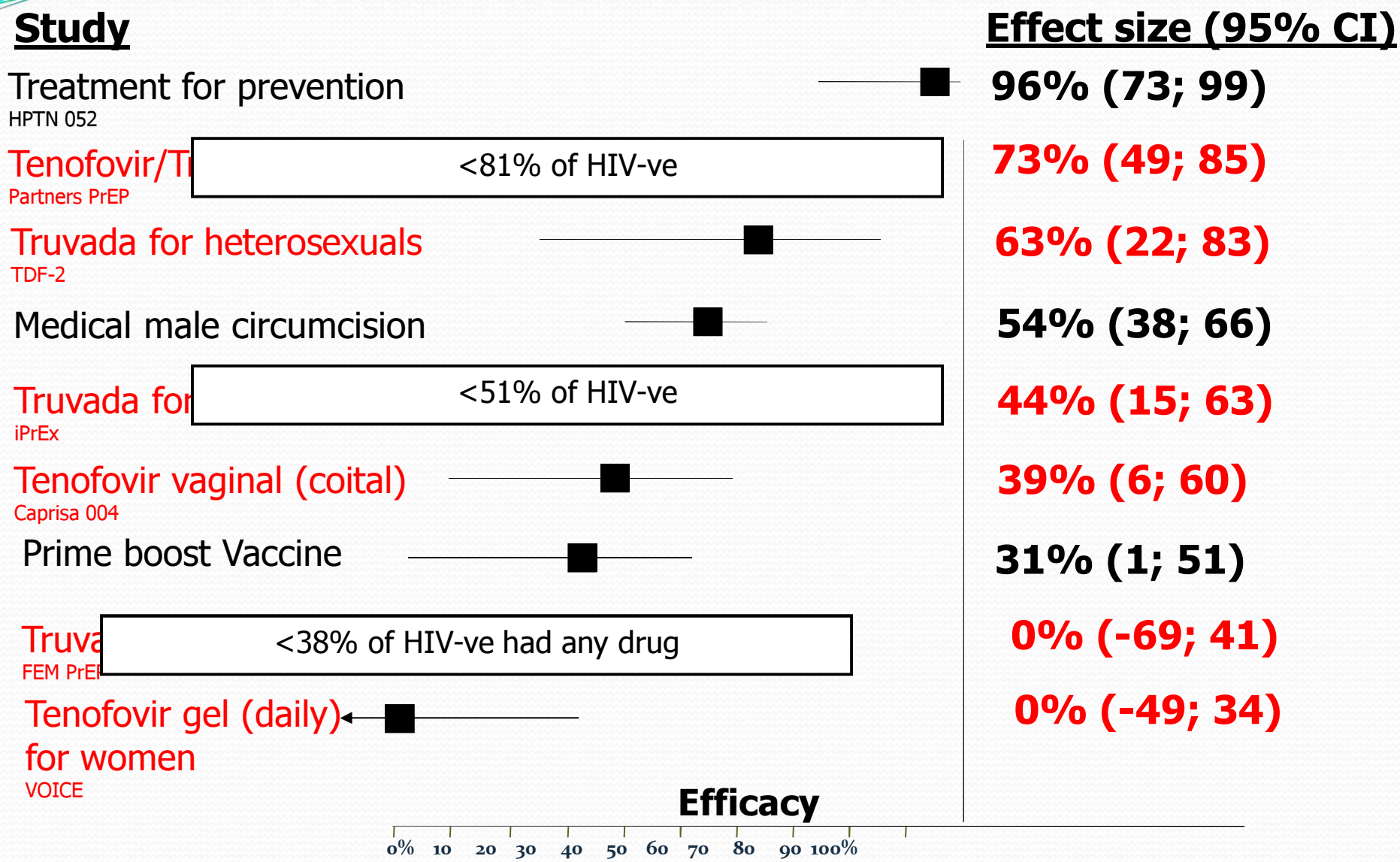
Recent Prevention Trials



Recent Prevention Trials



Recent Prevention Trials - Adherence



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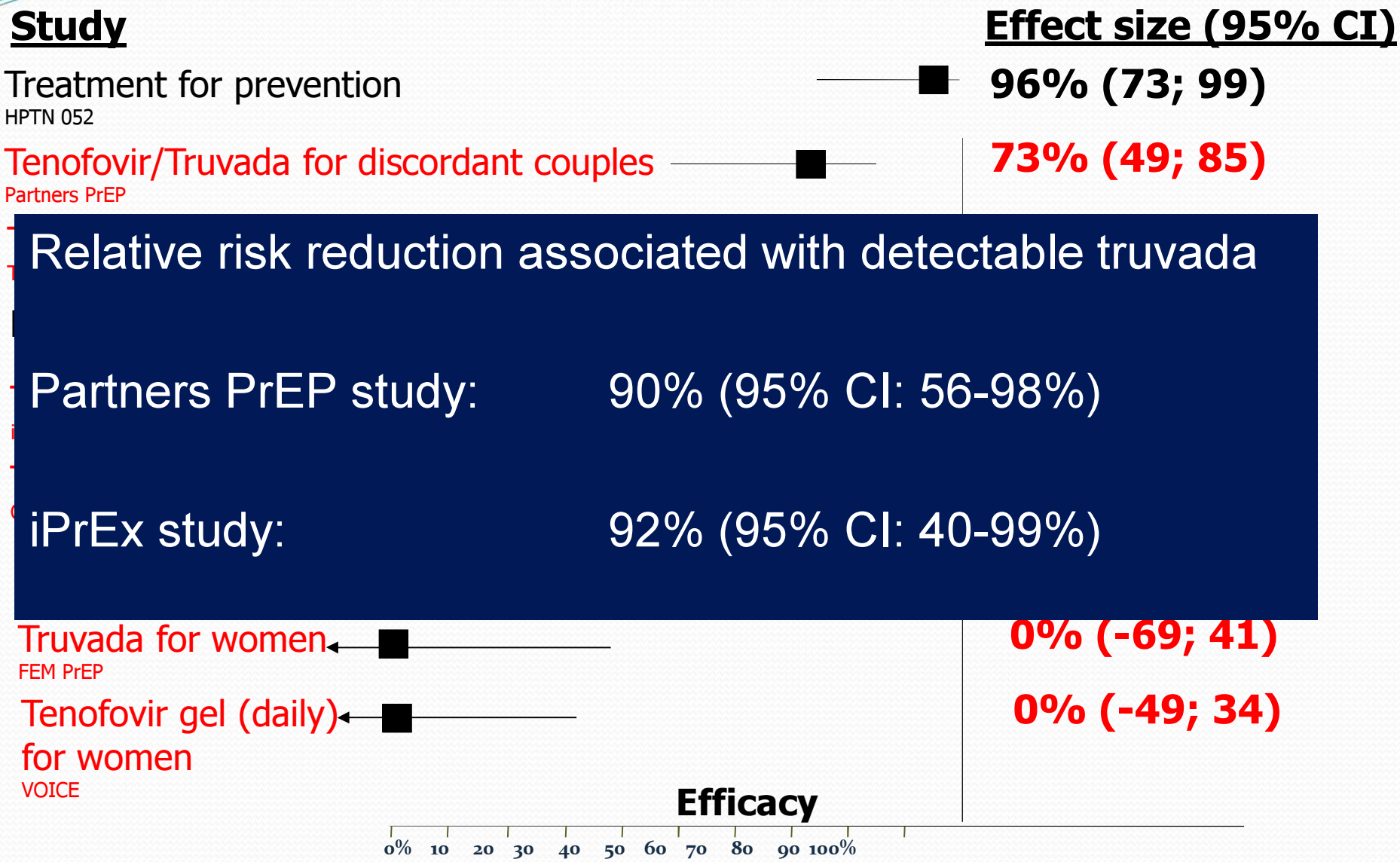
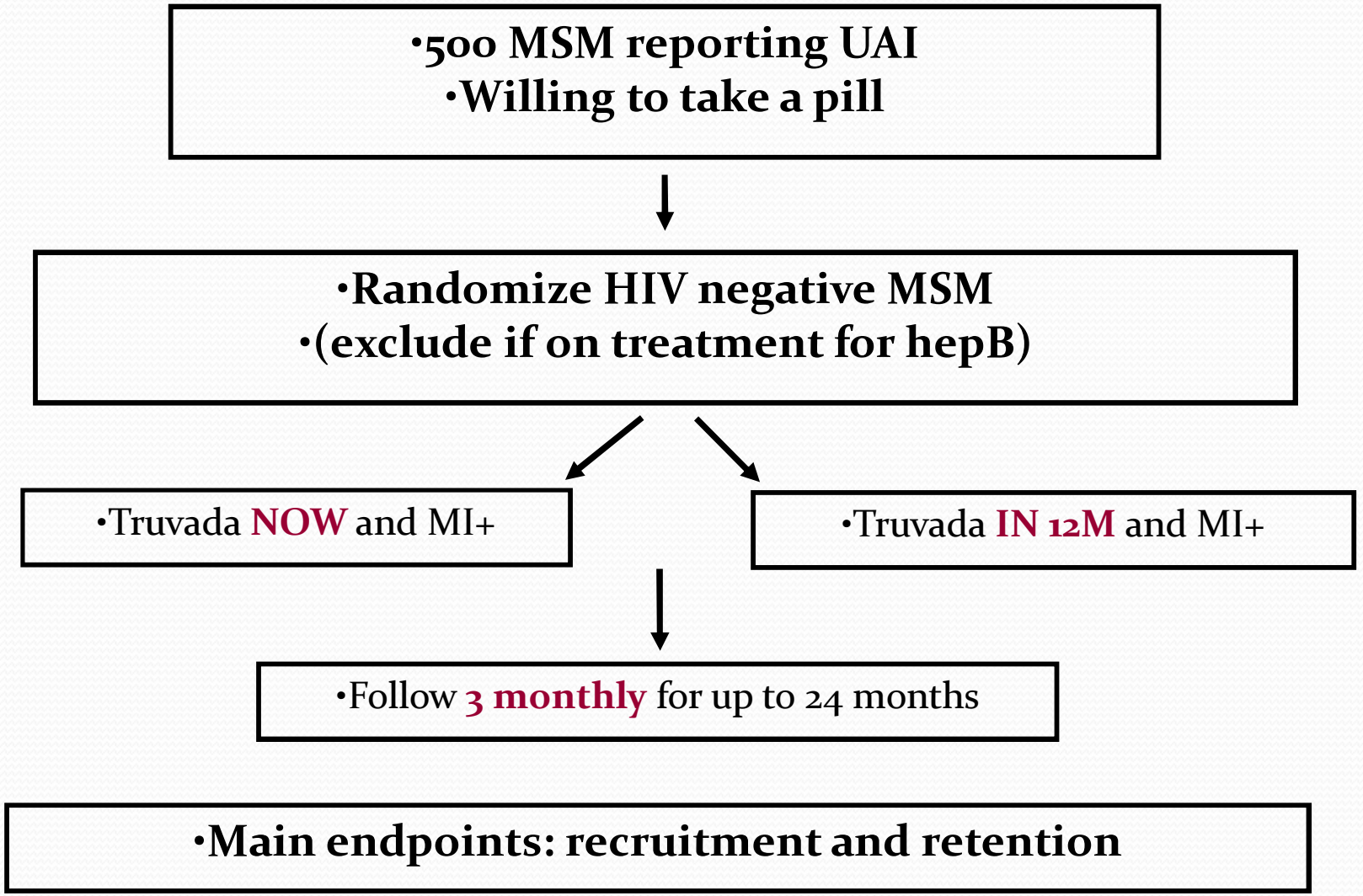


PROUD

Pre-exposure ***O***ption for preventing HIV in the ***U***K: an open-label randomisation to immediate or ***D***eferred inclusion of Truvada as part of a comprehensive HIV prevention package

•PROUD Pilot


•500 MSM reporting UAI
•Willing to take a pill
•Randomize HIV negative MSM
•(exclude if on treatment for hepB)
•Truvada NOW and MI+
•Truvada IN 12M and MI+
•Follow 3 monthly for up to 24 months
•Main endpoints: recruitment and retention

Reminder of concerns around PrEP

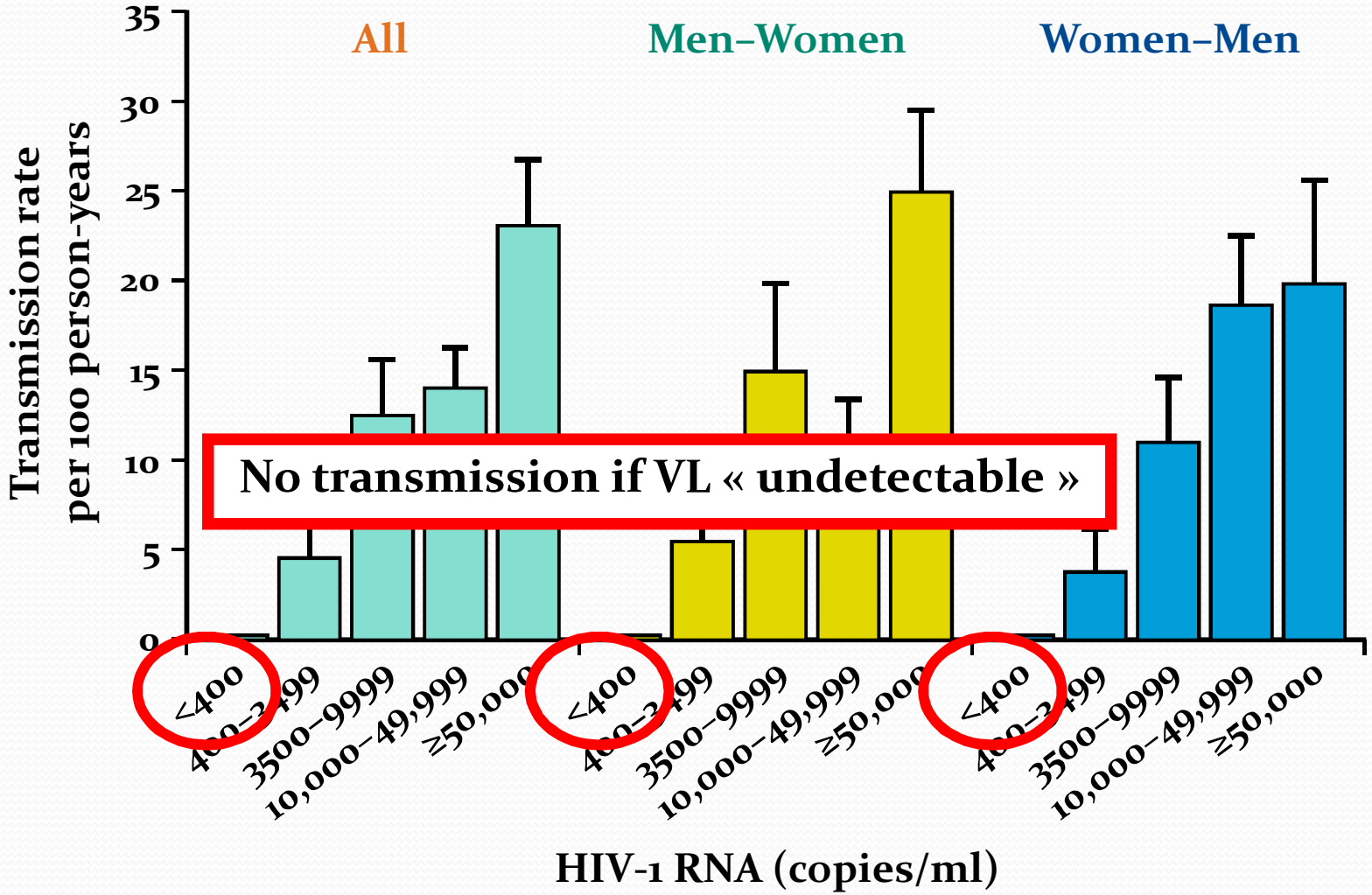
- Cost (including delivery costs) precludes universal access
- Viral resistance
- Toxicity
- Possibility that biological efficacy of PrEP could be negated by behavioural changes:
  - replacement of condom use by less effective pharmacological prevention methods
  - increase in risky behaviour by alteration of individuals' perceptions of their HIV risk
- These concerns are widely shared: gay community, regulatory authorities, commissioners, clinicians, research community

Treatment as Prevention

ARVs for HIV positive partner

Risk Group	Efficacy of protection	Strength of evidence
HIV negative man having IVI with HIV positive woman	92 - 96% if monogamous	HIGH: 96% (95% CI 82-99%) effect based on 28/39 seroconversions that were genetically linked (HPTN052)13 and metanalysis of cohort studies. At least 7/11 remaining were not linked
HIV negative woman having RVI with HIV positive male	92- 96% if monogamous	HIGH: 96% (95% CI 82-99%) effect based on 28/39 seroconversions that were genetically linked (HPTN052) and meta-analysis of cohort studies. At least 7/11 remaining in 052 were not linked
HIV negative man having IAI with an HIV positive man or woman	92 - 96%	MODERATE: for MSM-HIGH for heterosexuals: one RCT (HPTN052) with 3% MSM couples, and meta-analysis of heterosexual cohorts, so anal sex with men infrequent. However, many ARV concentrate in the rectal tissue, so viral shedding should be controlled
HIV negative man having RAI	92 – 96%	MODERATE: one RCT (HPTN052) with 3% MSM couples, and meta-analysis of heterosexual cohorts, so anal sex with men infrequent. However, viral shedding in ejaculate should be controlled by ART

RAKAI study:
Transmission risk as a function of viral load



Thai Study: no transmissions <1049; Tovanabutra *JAIDS* 2002

Quinn *et al, N England J Med* 2000;342:921–9

Meta analysis of HIV transmission according to viral load and ART

Study	Location	Risk Group Index Case	VLLLD	Total analysed	Index case on ART	HIV transmission on ART	HIV transmission not on ART	Overall HIV transmission rate (p100py)
Bunnell	Uganda	Het	Not stated	62	62	1	NA	0.5 (0.01,3.0)
Castilla	Spain	Het, IDU	50	393	60	0	5	0.3 (0.1,0.8)
Melo	Brazil	Het, IDU	50	93	41	0	6	5.7 (2.1,12.3)
Reynolds	Uganda	Het	400	205	20	0	34	8.1 (5.6,11.3)
Sullivan	Rwanda, Zambia	Het	No VL data	2993	Not stated	4	171	3.1 (2.7,3.6)
Fideli	Zambia	Het	400	317	0	NA	129	7.1 (5.9,8.3)
Mehendale	India	Not stated	Not stated	242	0	NA	1	1.5 (0.001,8.1)
Operskalski	USA	Blood transfusion	400	16	0	NA	3	14.1 (2.9,41.4)
Quinn	Uganda	Het	400	415	0	NA	90	11.6 (9.3,14.2)
Ragni	USA	Blood products	400	39	0	NA	5	1.3 (0.4,3.0)
Tovanabutra	Thailand	Not stated	50	310	0	NA	12	5.3 (2.8,9.3)

Attia S, Egger M, Muller M, et al. AIDS 2009,23:1397-1404

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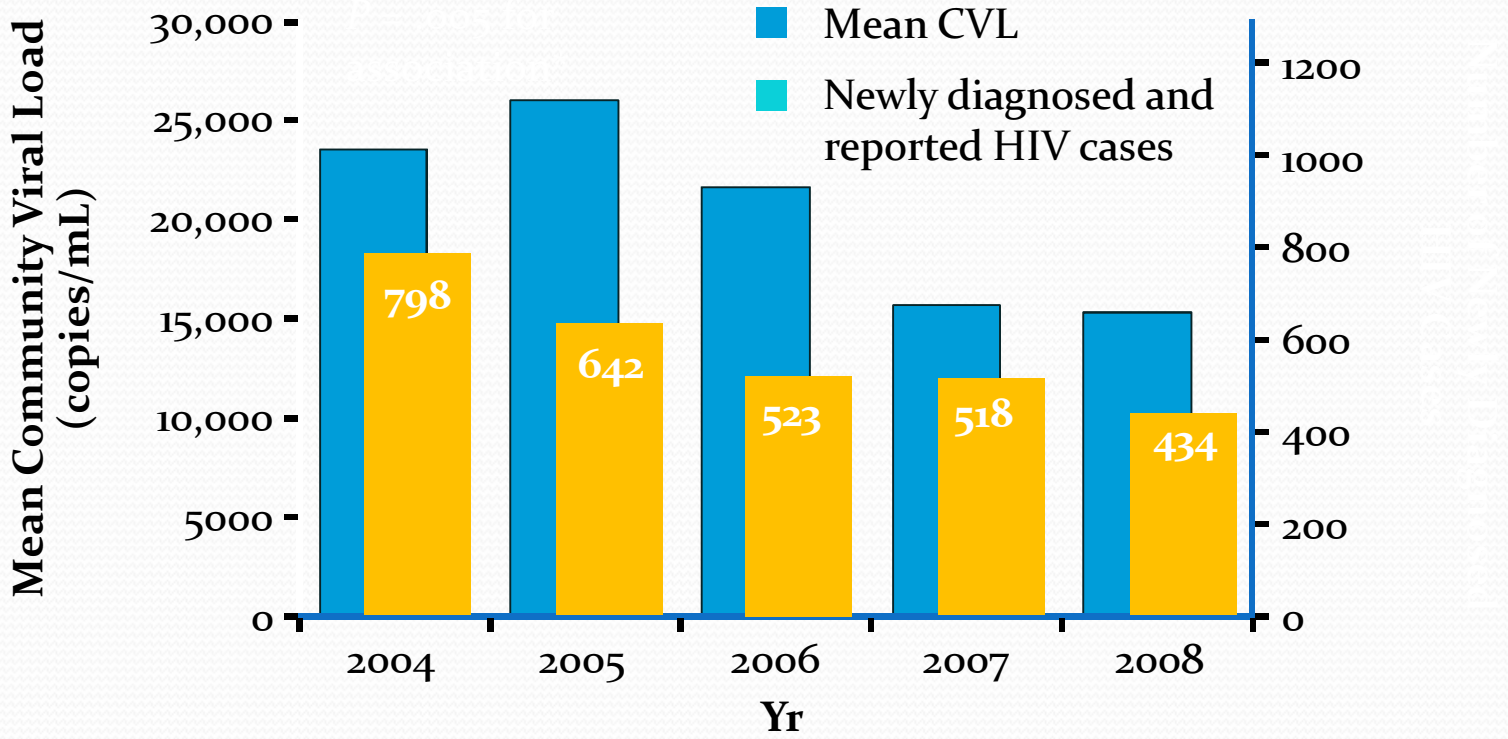
92% reduction in transmission with ARVS

Attia S, Egger M, Muller M, et al. AIDS 2009,23:1397-1404

Community Viral Load Mirrors Reduced Rate of New HIV Cases in San Francisco

- Retrospective analysis of relationship between community viral load (mean of summed individual HIV-1 RNA results per yr) and new HIV diagnoses



*Data insufficient to prove significant association with reduced HIV incidence.

Das-Douglas M, et al. CROI 2010. Abstract 33. Reproduced with permission.

Partners in Prevention Study

Donnell, Lancet, 2010

	Follow-up during which HIV-1 infected partner had not initiated ART			Follow-up after HIV-1 infected partner initiated ART			Unadjusted incidence rate ratio (95% CI; p value)*	Adjusted incidence rate ratio (95% CI; p value)*
	Number of HIV-1 transmissions	Length of follow-up (person-years)	HIV-1 incidence per 100 person-years (95% CI)	Number of HIV-1 transmissions	Length of follow-up (person-years)	HIV-1 incidence per 100 person-years (95% CI)		
Overall	102	4558	2·24 (1·84–2·72)	1	273	0·37 (0·09–2·04)	0·17 (0·00–0·94; p=0·04)	0·08 (0·00–0·57; p=0·004)
By CD4 cell count†								
<200 cells per μL	8	91	8·79 (4·40–17·58)	0	132	0·00 (0·00–2·80)	0·00 (0·00–0·40; p=0·002)	0·00 (0·00–0·38; p=0·001)
200–349 cells per μL	41	1467	2·79 (2·06–3·80)	1	90	1·11 (0·27–6·19)	0·40 (0·01–2·34; p=0·58)	0·65 (0·02–4·00; p=1·0)‡
350–499 cells per μL	24	1408	1·70 (1·14–2·54)	0	30	0·00 (0·00–12·30)	0·00 (0·00–8·16; p=1·0)	0·0 (0·0–15·3; p=1·0)‡
≥500 cells per μL	29	1592	1·82 (1·27–2·62)	0	21	0·00 (0·00–17·57)	0·00 (0·00–10·29; p=1·0)	0·0 (0·0–15·0; p=1·0)‡

*All analyses adjusted for time since study enrolment and, for the overall analysis, CD4 cell count (as ≥200 cells per μL vs <200 cells per μL). †For follow-up before ART initiation, CD4 cell count was lowest previous value; for follow-up after ART initiation, CD4 cell count at the time of ART initiation was used. ‡Adjusted incidence rate ratio for combined CD4 cell count strata of 200 cells per μL or more was 0·55 (95% CI 0·01–3·24; p=0·9).

Table 3: **Antiretroviral therapy (ART) use and risk of HIV-1 transmission**

92% reduction in HIV transmission with ART

Partners in Prevention Study

Donnell, Lancet, 2010

	Follow-up during which HIV-1 infected partner had not initiated ART			Follow-up after HIV-1 infected partner initiated ART			Unadjusted incidence rate ratio (95% CI; p value)*	Adjusted incidence rate ratio (95% CI; p value)*
	Number of HIV-1 transmissions	Length of follow-up (person-years)	HIV-1 incidence per 100 person-years (95% CI)	Number of HIV-1 transmissions	Length of follow-up (person-years)	HIV-1 incidence per 100 person-years (95% CI)		
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Table 3: Antiretroviral therapy (ART) use and risk of HIV-1 transmission

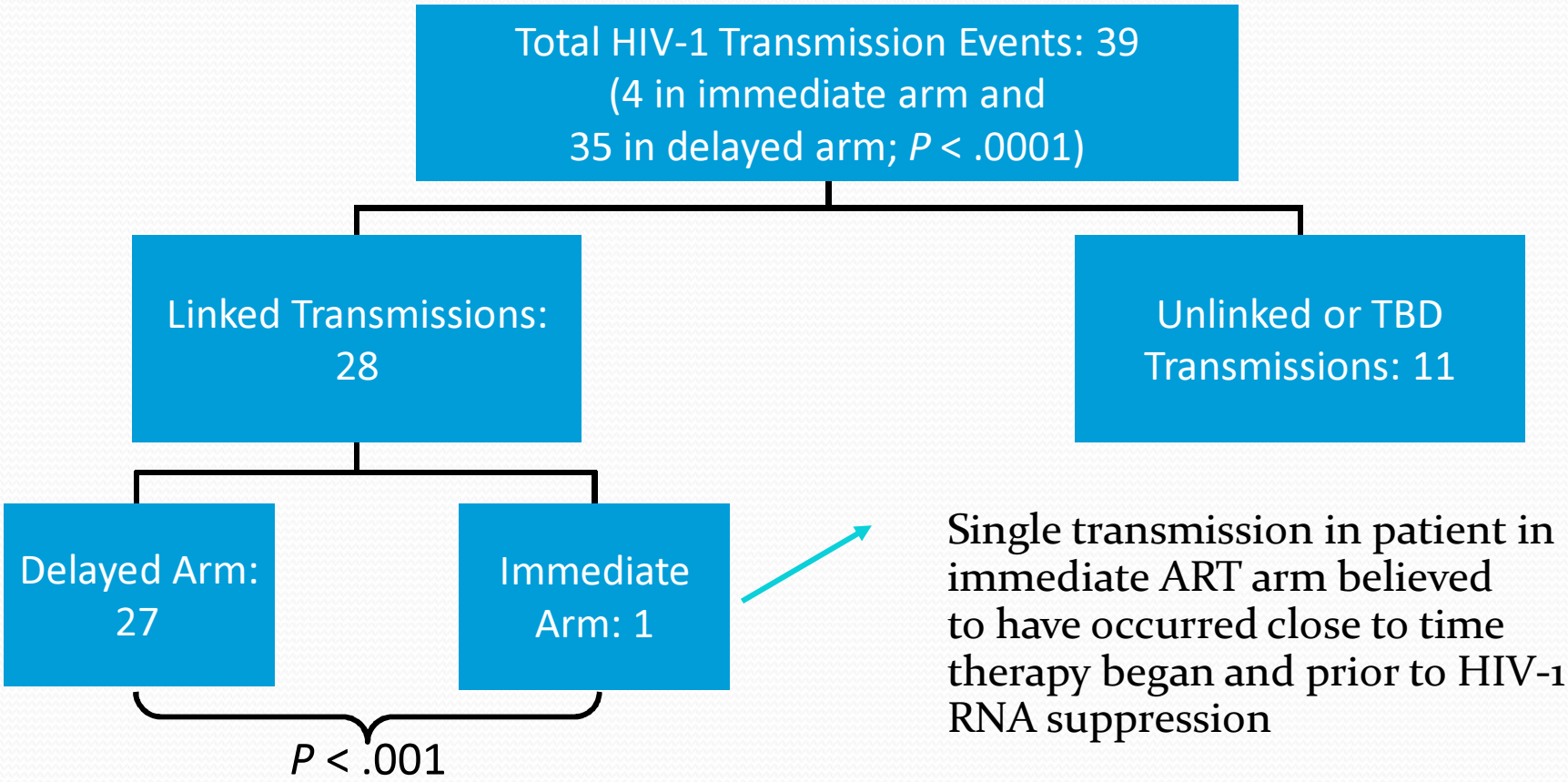
Number of MSM contributing to data: 0

92% reduction in HIV transmission with ART

HPTN 052: Immediate vs Delayed Treatment

HIV Transmission Reduced by 96% in Serodiscordant Couples

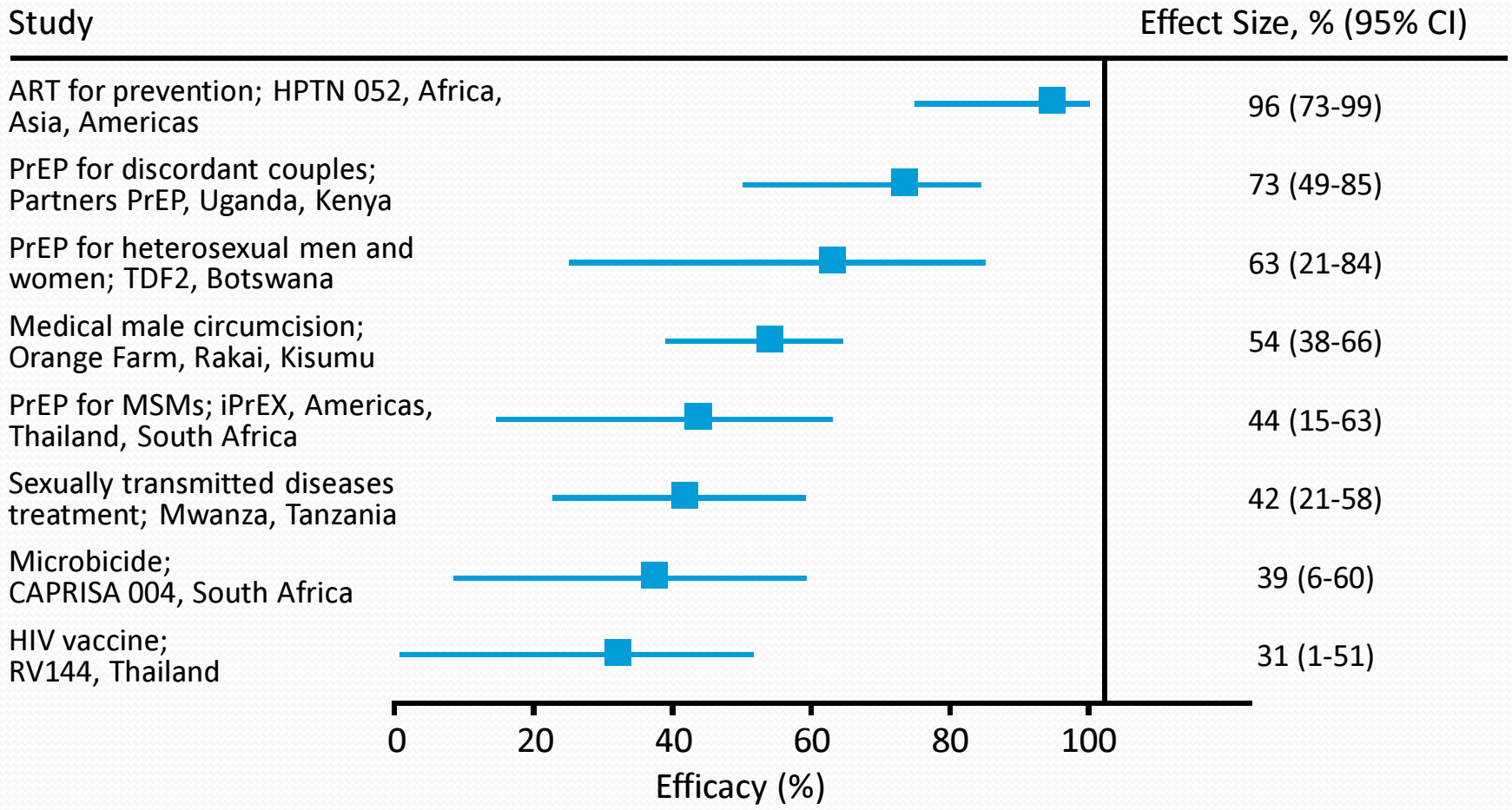
n=1763



Single transmission in patient in immediate ART arm believed to have occurred close to time therapy began and prior to HIV-1 RNA suppression

Cohen MS, et al. IAS 2011. Abstract MOAX0102.
Cohen MS, et al. N Engl J Med. 2011;[Epub ahead of print].

Efficacy of HIV Prevention Strategies From Randomized Clinical Trials



Abdool Karim SS, et al. Lancet. 2011;[Epub ahead of print].

The PARTNER study (Partners of people on ART: a New Evaluation of the Risks) is an NIHR funded, observational multi-centre study, taking place in 75 European sites from 2010 to 2014 (Phase 1) and 2014-2017 (Phase 2)

- Recruits serodifferent partnerships (+ve partner on ART) who had condomless (CL) penetrative sex in the past 4 weeks in order to study:
- (i) the risk of HIV transmission to partners, in partnerships that do not use condoms consistently and the HIV positive partner is on therapy with a viral load < 50 copies/mL
- (ii) why some partnerships do not use condoms, the proportion who begin to adopt consistent condom use, and factors associated with this

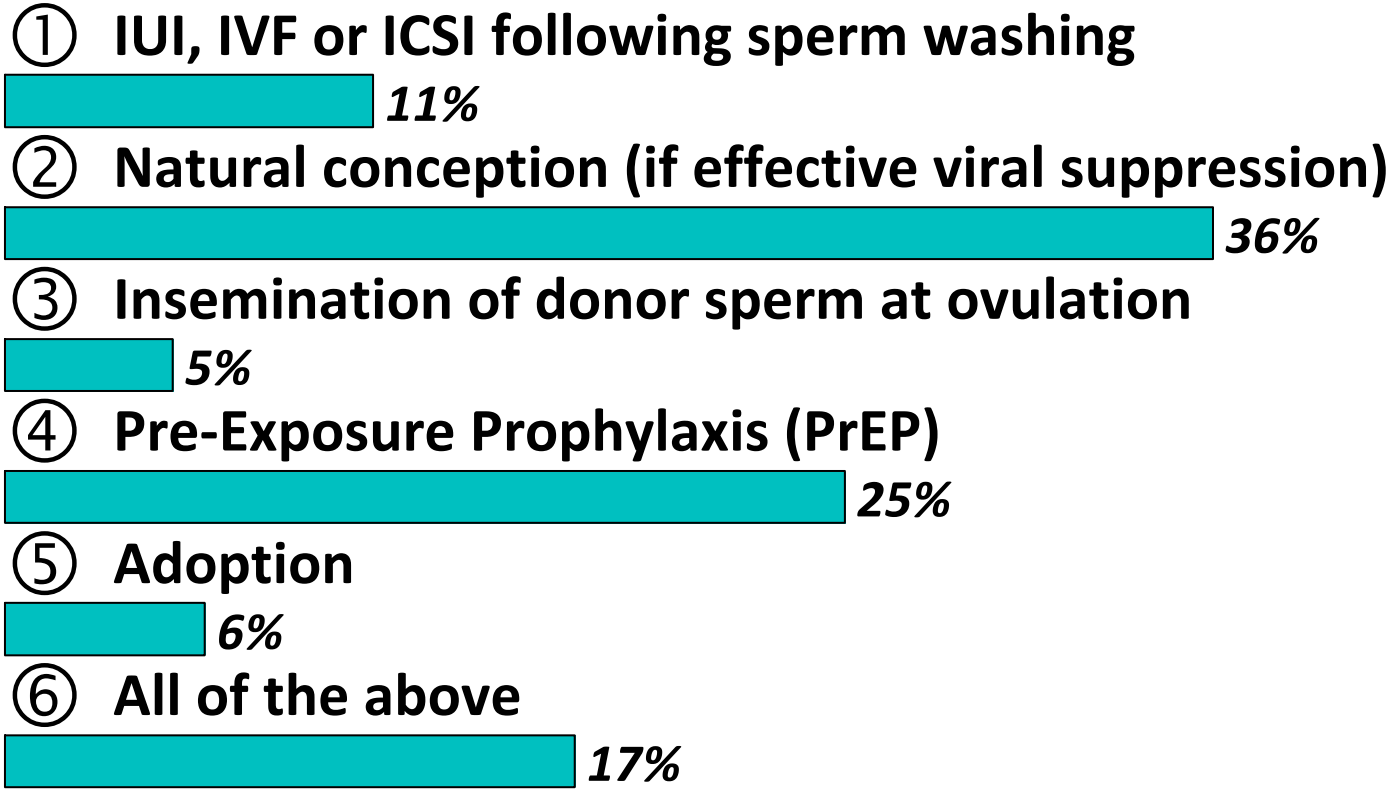
- 4-6 monthly self completed confidential risk behaviour questionnaire and collection of clinical data including HIV results

Courtesy of Alison Rodger, RFH on behalf of the PARTNET study BHIVA 2013

Conception

Male HIV+, CD4 540 cells/mm3, HIV VL <40
Female HIV-

What methods of conception would you recommend?



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Female HIV+, CD4 653 cells/mm3, HIV VL 1356 c/ml, ARV naive
Male HIV-

What method of conception would you recommend?

① **Insemination of partner's sperm at ovulation (whether or not on ARVs / detectable viral load)**

81%

② **Natural conception**

8%

③ **Assisted reproduction in case of fertility disorders**

7%

④ **Adoption**

2%

⑤ **All of the above**

2%

Q

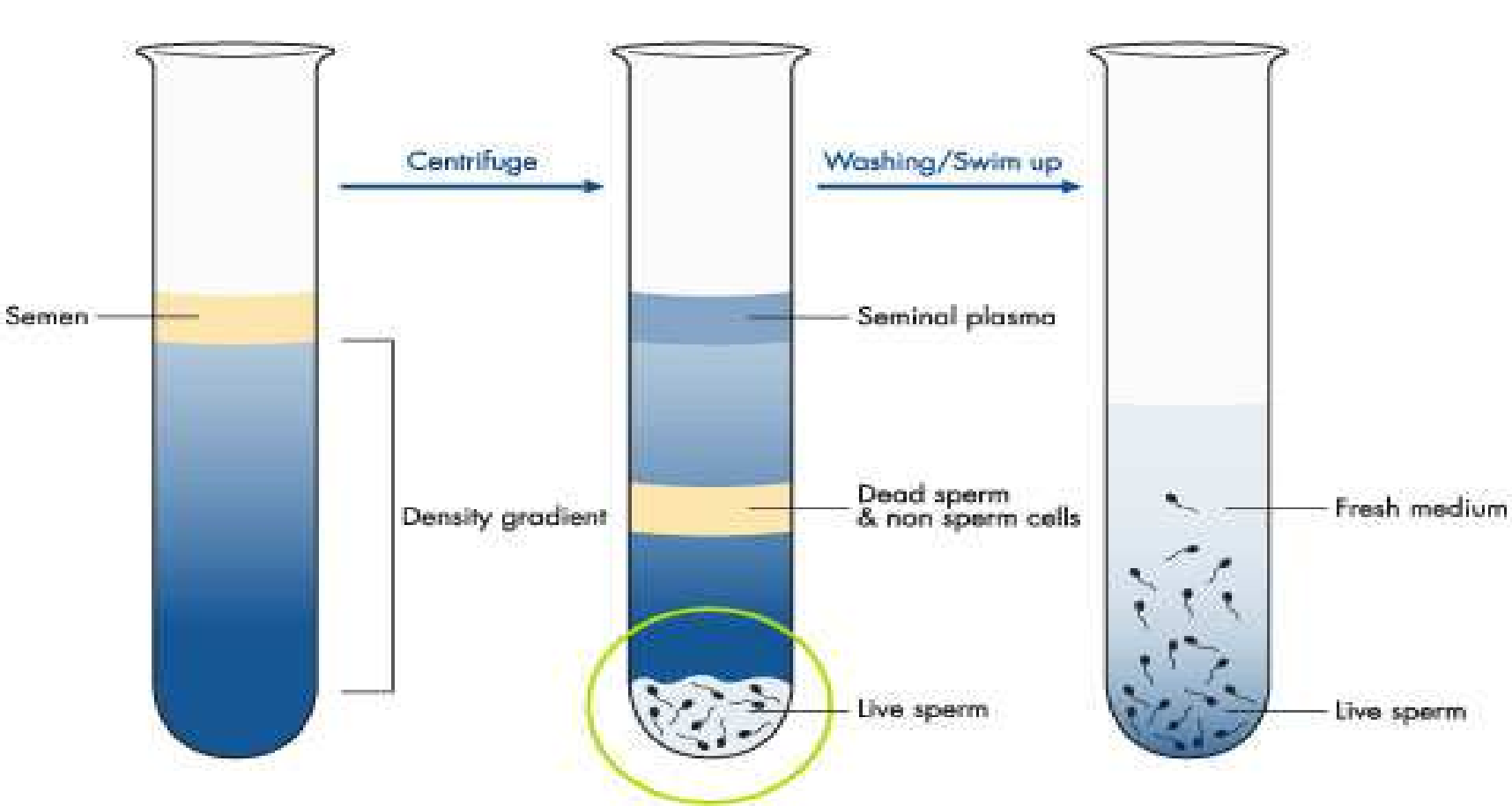
HIV +ve: Reproductive options

HIV+ woman & HIV- man
• Insemination of partner's sperm at ovulation (whether or not on ARVs / detectable viral load) • Natural conception (if effective viral suppression) • Assisted reproduction in case of fertility disorders • Adoption

HIV+ man & HIV- woman
• IUI, IVF or ICSI following sperm washing • Natural conception (if effective viral suppression) • Insemination of donor sperm at ovulation • Pre-Exposure Prophylaxis (PrEP) • Adoption

Slide Courtesy Y Gilleece and S Taylor Nov 2011

Spermwashing



There is a large evidence base for the safety and efficacy of sperm washing [1-4]
No HIV transmissions

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Assisted reproductive techniques

- Intrauterine insemination (IUI) 14% LVB
  - Normal fertility investigations
  - Sperm is introduced directly into the uterus after spermwashing by inserting an injectable device through the cervical os
- Intracytoplasmic sperm Injection (ICSI)
  - semen sample is not “normal”
  - Low number of sperm in the ejaculate(**Oligozoospermia**)
  - Poor progression or movement of the sperm (**Athenzoospermia**)
  - High numbers of abnormally formed sperm (**Teratzoospemia**)
- In vitro fertilisation (IVF) 35% LVB
  - Tubal infertility
  - Oligospermia
  - Unexplained subfertility

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However…

- Usually, more than one reproductive procedure is needed to attain pregnancy which increases the final cost of ART [1]
- In general, the substantial expenses per procedure make these methods not affordable
  - At PCT level
  - At an individual level
- Technical constraints also limit where spermwashing can be performed, usually London based
  - separate laboratory facilities are required to avoid cross-contamination to uninfected patients [2,3]

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1. Gilling-Smith et al., 2006 . 2. Englert et al., 2001. 3.Gilling-Smith et al., 2001

Natural Pregnancy

- Increasing number of requests in both HIV concordant couples and HIV discordant couples (HIV + male)
- Many reasons
  - Cost
  - Failure of ART
    - Up to 30% of couples drop out before starting insemination
    - 30% may not complete ART
      - Drop-out
      - Failure
    - After ART completed but failed – natural attempts reported to be as high as 50% in one cohort[1]
  - Swiss statement
  - PrEP
  - Treatment as Prevention

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1. Vernazza et al, 2006 .

Combined antiretroviral treatment and heterosexual transmission of HIV-1: cross sectional and prospective cohort study

	ARVs Baseline n=149 Follow-up n= 144	No ARVs Baseline n=476 Follow-up n=341
Baseline HIV seroprevalence in non-index partner*	n=0 (0%)	n=44 (9.2%)
No. of UPSI sex acts	7,000	11,000
Natural pregnancies	47	50
No. of seroconversions	0	5
Per sex act	0-0.00001	0.004 (95% CI 0.0001-0.0010)

Brighton and Sussex University Hospitals NHS Trust

Published 14 May 2010, doi:10.1136/bmj.c2205
Cite this as: *BMJ 2010;340:c2205*

ARC

ANTI-RETROVIRALS FOR CONCEPTION DATABASE

DISCUSSION

Advice only
Sperm washing
PrEP-C
Adoption

Rationale of using ARVs to decrease infectiousness
Swiss Statement
Current data

No blame
Worst case scenario

Timed ovulation

Consent

FEMALE INVESTIGATIONS

HIV tests 1-3 monthly

Day 2-3 FSH/LH/Oestradiol
Day 21 Progesterone
TFTs
Prolactin
Transvaginal ultrasound pelvis
Hysterosalpingogram

STI screen inc syphilis and hepatitis serology

Follicular Tracking

MALE INVESTIGATIONS

Semen analysis

Seminal viral load

STI screen
syphilis and hepatitis serology

OUTCOME

All results reviewed

Recommendations

Sperm Washing

PrEP-C + TOI

Follicular Tracking

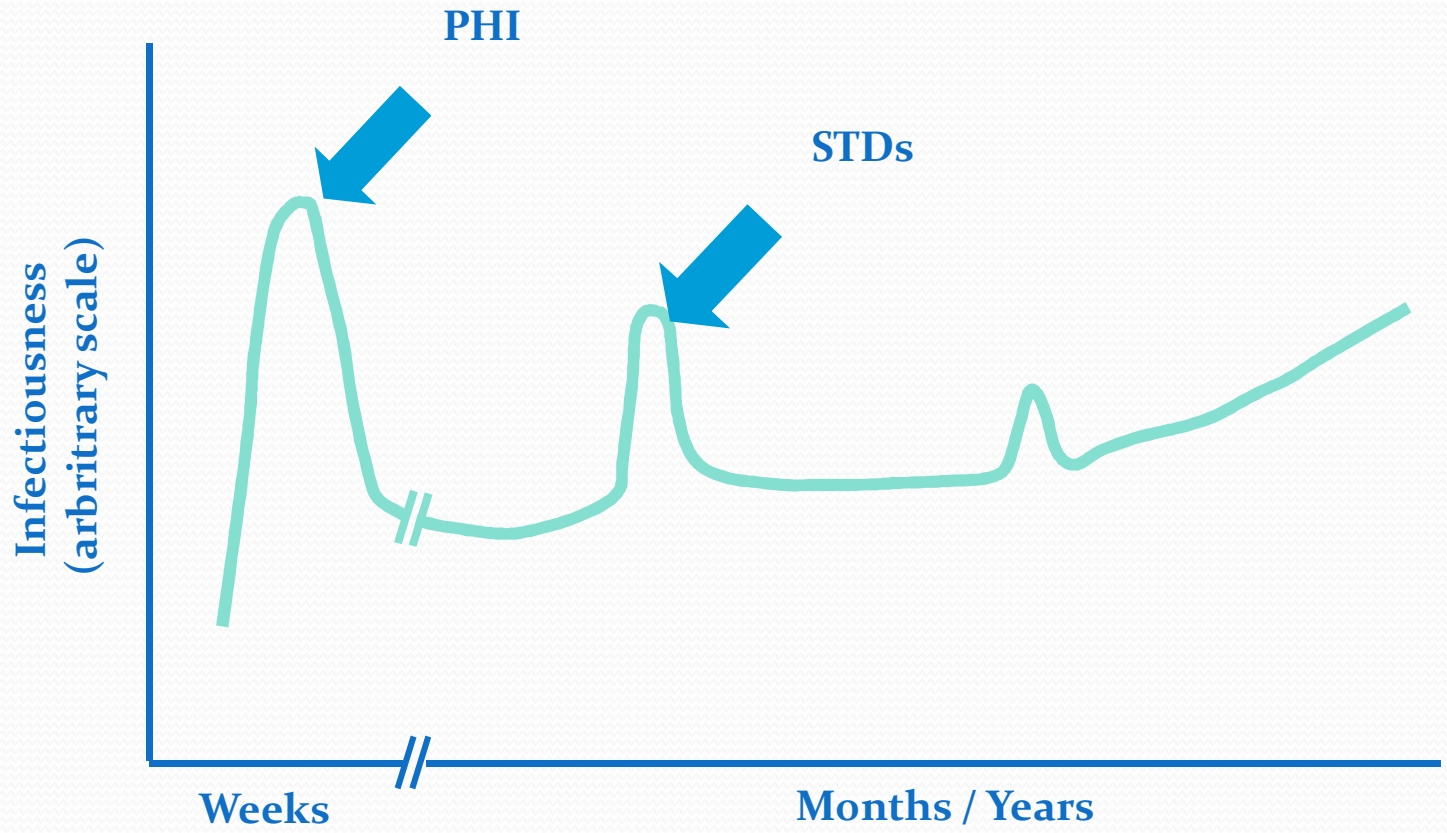
Ovarian stimulation

IVF

Slide Courtesy of Y Gilleece and S Taylor adapted from BHIVA 2010

What about control of STIs?

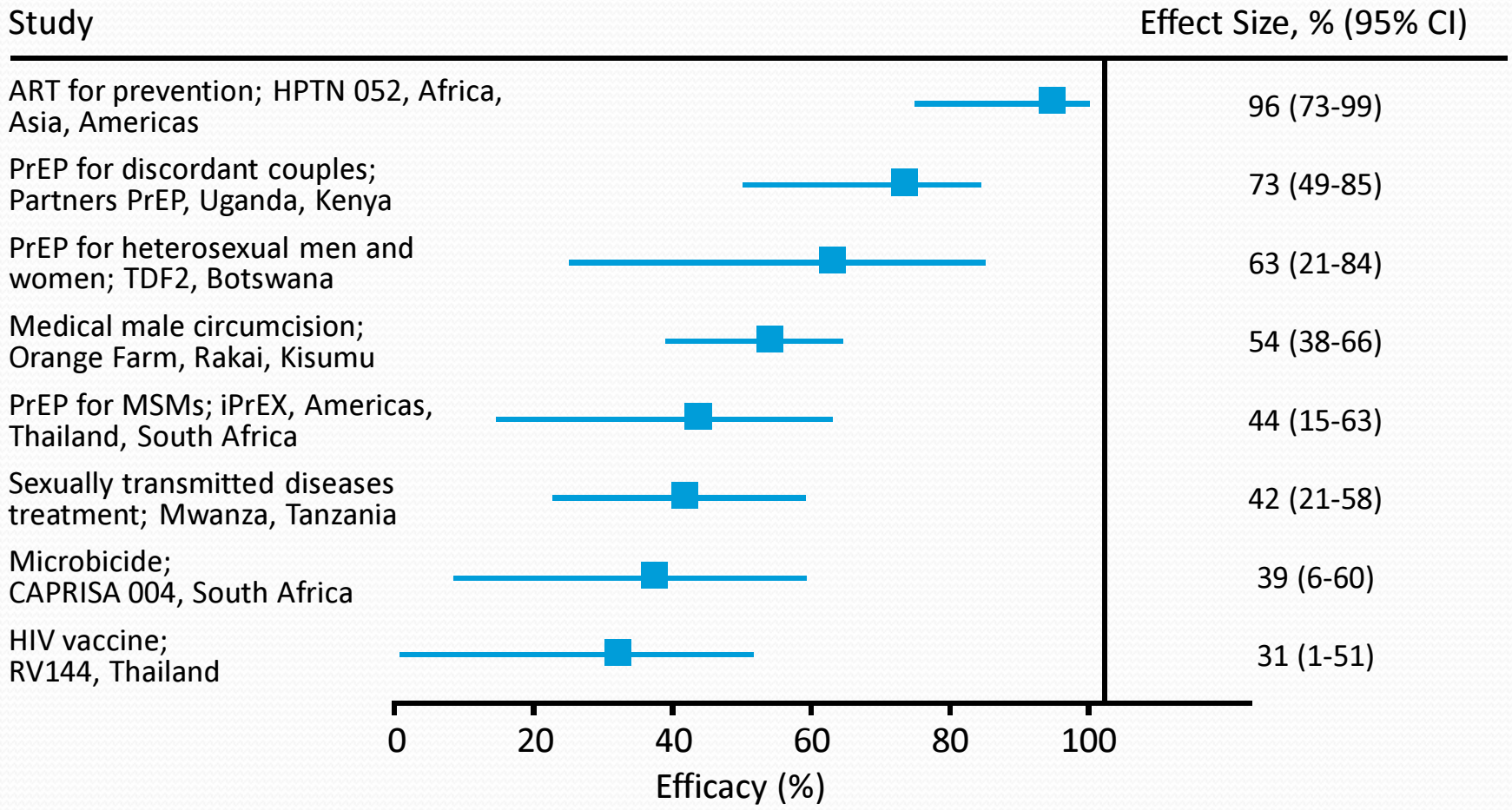
HIV-transmission risk over time



Brighton and Sussex University Hospitals NHS Trust

Vernazza, *AIDS* 1999;13:155–166 (adapted)

Efficacy of HIV Prevention Strategies From Randomized Clinical Trials



Abdool Karim SS, et al. Lancet. 2011;[Epub ahead of print].

What should you recommend?

PrEP is only part of the solution for HIV Prevention

- We now have good data about ARVs reducing transmission risk
- Pros and cons for PrEP which remains trial based in the UK currently
- Risk reduction counseling (individual and couple)
- Free condoms and condom counseling
- Contraception counseling and provision
- Screening and treatment for STIs
- Counseling & referral for other HIV prevention interventions (e.g. male circumcision), per national policies

An evidence based individualised discussion with your patient is key!

Acknowledgments

- Steve Taylor
- Alison Rodger