Controlling the epidemic

Clinical considerations – design, set-up and conduct

Sheena McCormack

A tale of two epidemics

1. Sub-Saharan Africa
   - Heterosexual women

2. UK
   - gay and other MSM

- Starting with PrEP…

Concerns common to both

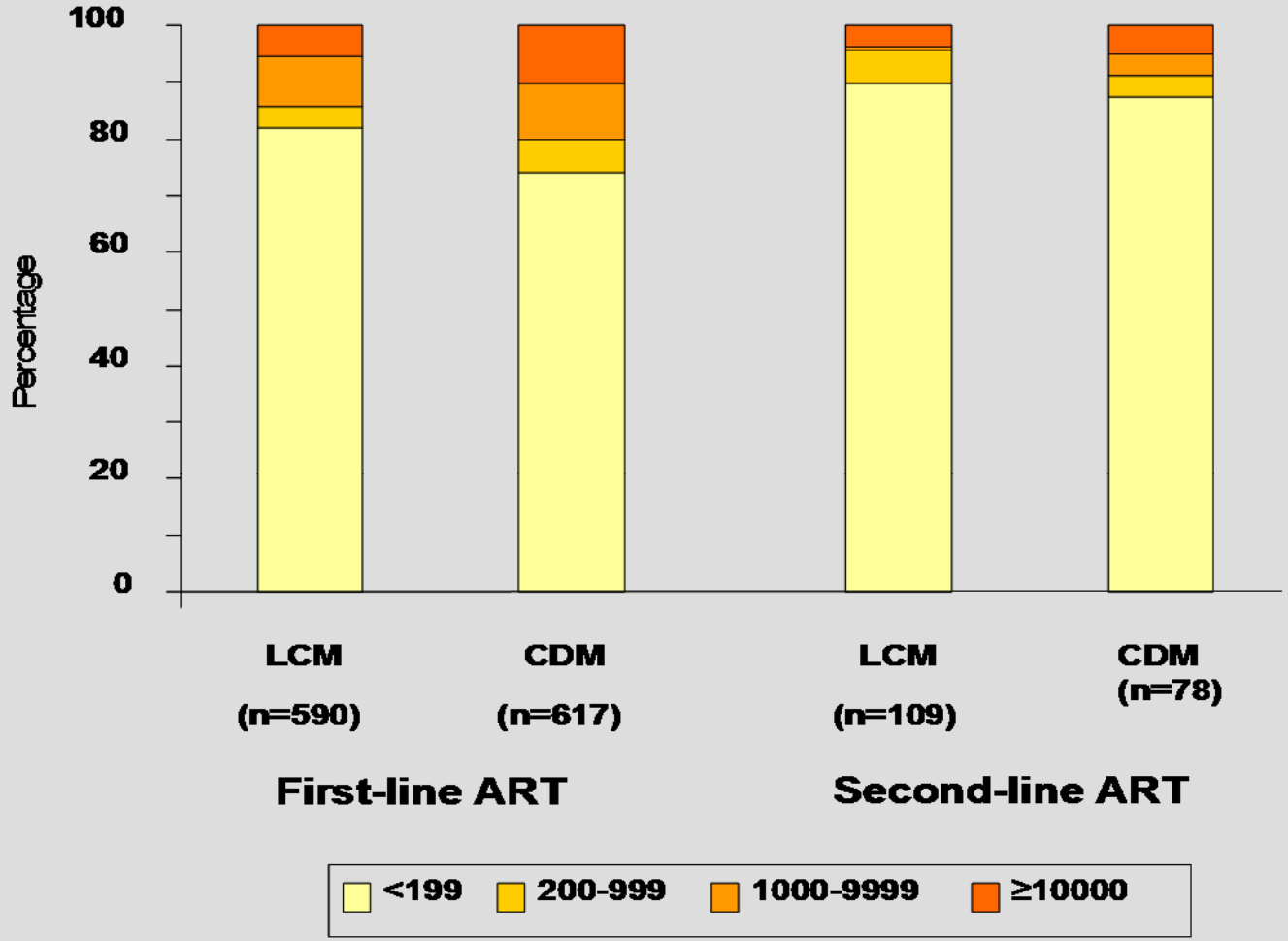
- Who will pay for it?
- Will people drift away from condom use?
  - Cannot be assessed in placebo controlled trials as placebo controls for behaviour
- Is there a danger of exploitation?
- How will PrEP be delivered [safely]?
  - Toxicity
  - Resistance

Tenofovir gel, truvada tablets

- Safety
  - Generally very reassured by data in positive individuals and in trials to date
  - Serious adverse reactions only

- Resistance
  - Resistance more likely to come from treated population and reassured by DART in which viral load and resistance were not done in real time
  - Least concern with coital regimens which have limited systemic absorption

VL at 5y in DART, by monitoring strategy



N.B. 149 values of <400 c/ml imputed as <199 c/ml

C Kityo, D Dunn, R Kasirye et al CROI 2011

For delivery – know your service setting

- Understand and build on successes in HIV prevention
  - Zambia ART coverage
  - Kenya MMC
- Forge partnerships between research, service and community
- Seek out champions in leadership positions
- Remember these are drugs, so we need clinicians, but we are not giving them to patients

Back to design - feasibility

- Critical questions about efficacy of intermittent and coital regimens to answer
  - To improve acceptability by offering a choice that suits sexual lifestyle…which changes with time
  - Bonus being this will reduce the cost
- Need to demonstrate safe to reduce HIV, pregnancy and lab monitoring
  - Also to improve acceptability
  - Also bonus of reducing cost

Epidemic 1 – heterosexual women

- Feasibility and cost-saving
  - We know women like using gel – multiple trials
  - Simplify dosing to a ***single dose pre-sex*** - simplifies training and social marketing, and halves cost
  - Reduce procedures especially HIV and pregnancy testing and stop routine laboratory monitoring
  - Demonstrate ***safe to continue in pregnancy***
  - Demonstrate ease of transition to service providers

Epidemic 1 – heterosexual women

- Design
  - Single dose of tenofovir 1% vaginal gel prior to sex
  - ***Placebo control, as we don't know it's effective***
  - 6m HIV testing
  - Pregnancy testing if indicated and continue dosing in pregnancy – it's ***much worse to catch HIV in pregnancy***
  - 18m trial endpoint then transition dispensing to service providers with second randomisation(s)

- Set-up and Conduct
  - Experienced network (no time for set-up if use placebo) with characterised incidence
  - Mozambique, Tanzania and Zambia in general population; Uganda sero-discordant couples

Pregnancy rates & Outcomes among women on triple-drug antiretroviral therapy in the DART trial IAS 2009

60% tenofovir based regimen

206 live births and 26 stillbirths

Any congenital abnormality reported	**7 (3.0%)**
▪ Congenital talipes (club foot)	3 (2TDF, 1NVP)
▪ Congenital hydrocephalus	1 (died) (TDF)
▪ Cardiac (PDA and ASD)	1 (NVP)
▪ Undescended testes	1 (NVP)
▪ Skin tag on neck	1 (TDF)

Rates similar to previously reported:

3.0/100 (2.4-3.7) HIV-infected women with first trimester ART in the Antiretroviral Pregnancy Register

2.7/100 live births in the CDC birth defects register

174/206 infants are enrolled into the separate infant follow up study.

Of 137/174 (79%) for whom test results are available, none are HIV infected

P Munderi; H Wilkes; D Tumukunde et al

Epidemic 2 – gay/other MSM in UK

- Feasibility
  - Uptake and adherence – ***will anyone want it***? Have to offer more than daily
  - Procedures need to mimic routine care
  - Concern regarding condom drift could be a barrier to funding – ***have behavioural and other interventions been given a proper chance***?

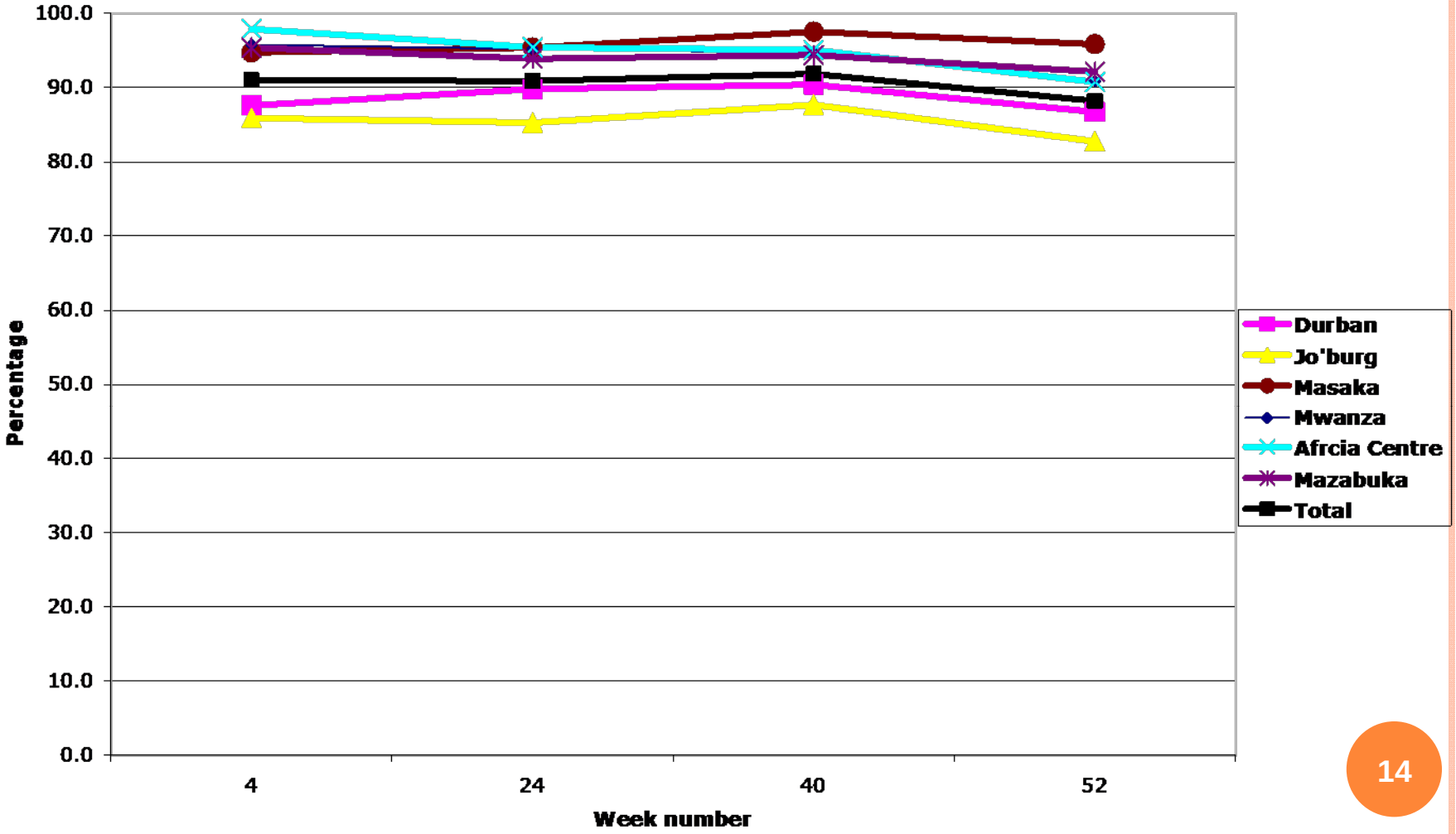
Epidemic 2 – gay/other MSM UK

- Design
  - Truvada orally daily or ‘before and after’ coital
  - Open label randomisation to immediate offer vs deferred offer after 12m
  - 3m STI/HIV testing and behavioural interventions for all
- Set- up and Conduct
  - 10+ clinics in UK that see large numbers of MSM
  - Pilot phase essential as we know little about longitudinal behaviour patterns

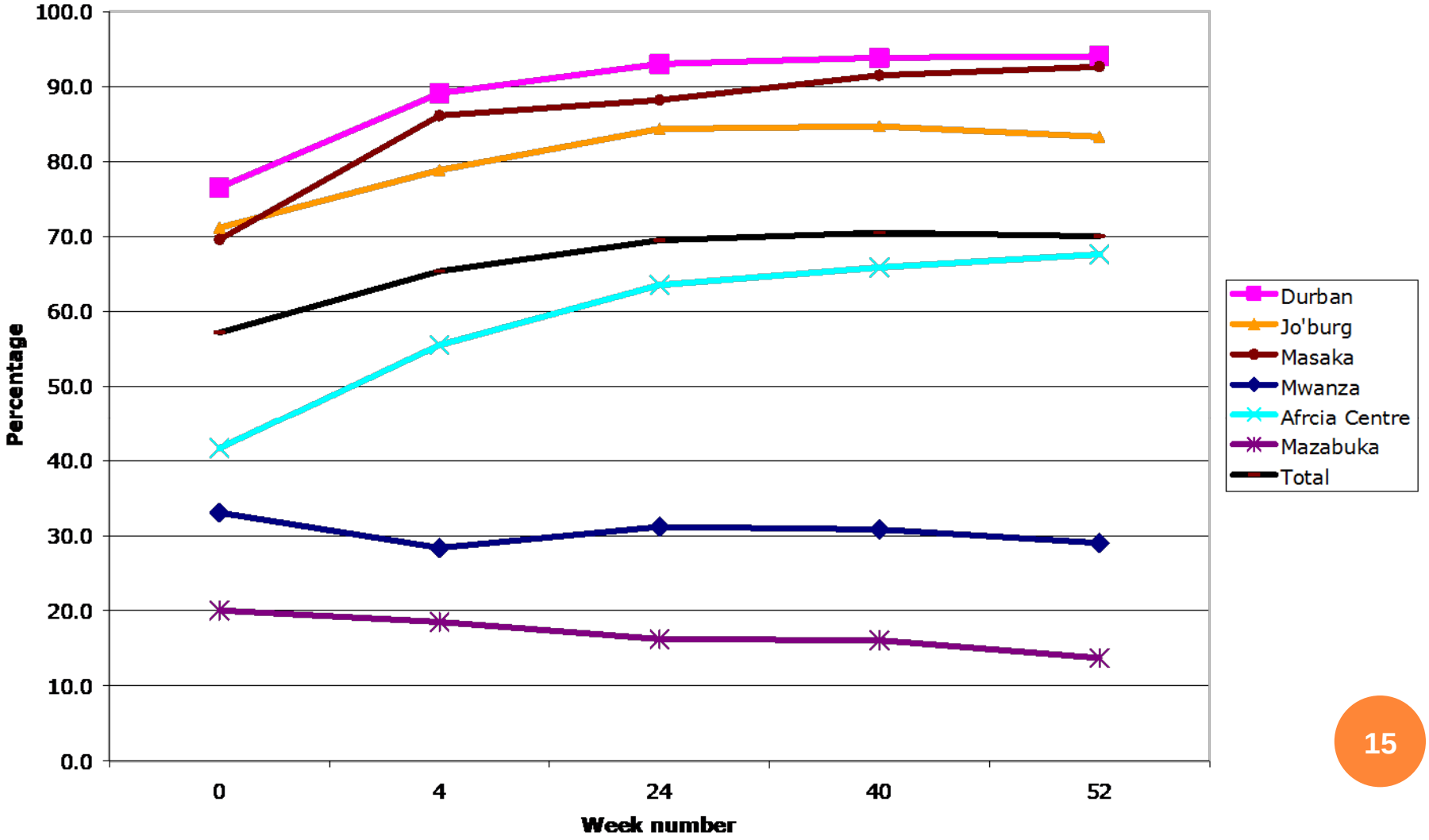
Condom drift

- Condom drift
  - Can only be assessed in an open-label design when participants know they are taking an effective alternative
- Exploitation
  - Also needs open-label design
  - Needs to be carefully solicited through qualitative research

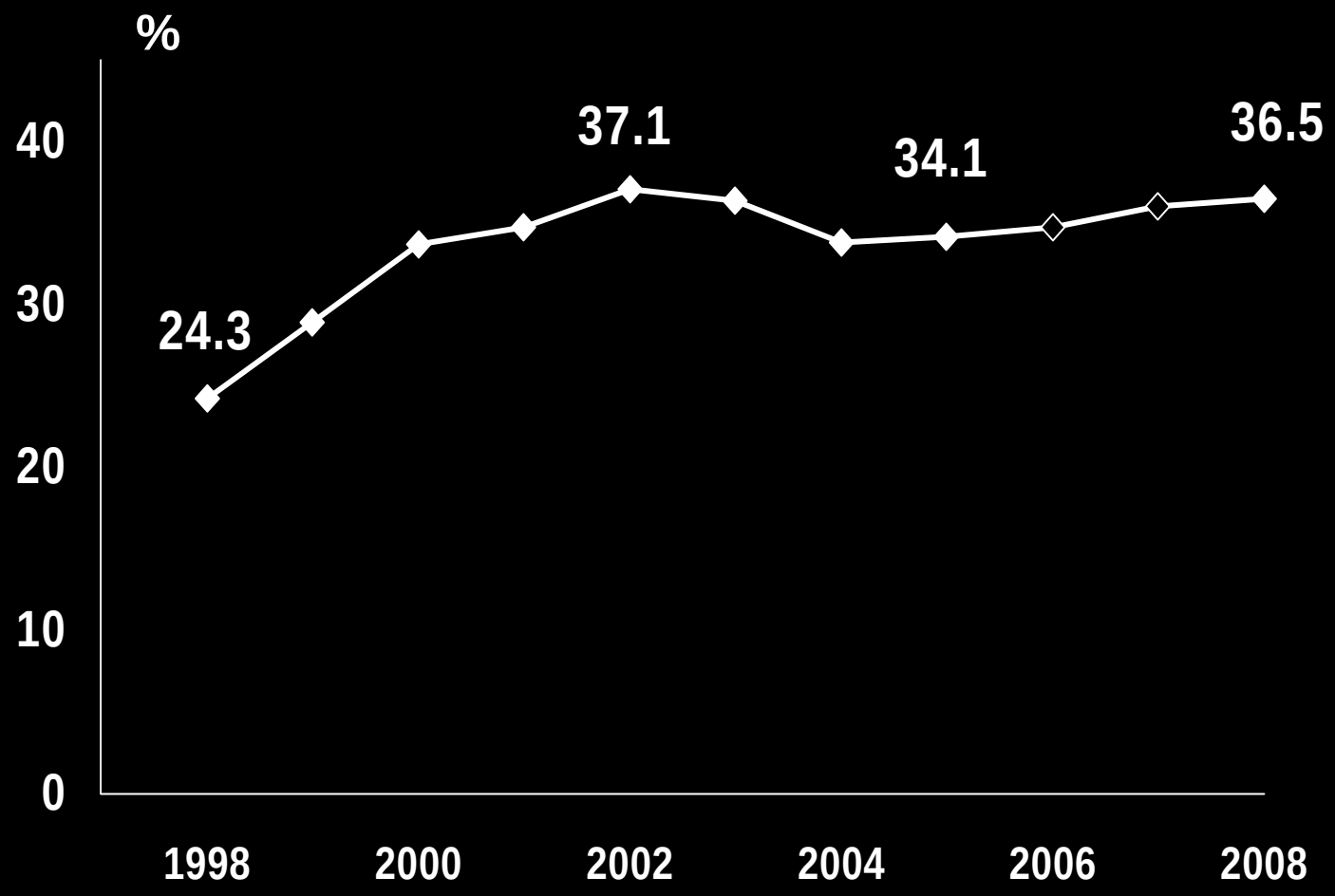
Gel use at last sex act with/without Condom by Centre over Time



Condom use at last sex act with/without Gel by Centre over Time



Unprotected anal intercourse 1998 – 2008 UK gym surveys MSM



Issues for the trials

- Tenofovir gel vs placebo
  - For how long will placebo be acceptable?
  - May have to do open-label
- Truvada open label
  - Will participants share drug?
  - Negative result difficult to interpret without ANRS placebo controlled data for coital regimen

A tale of two epidemics

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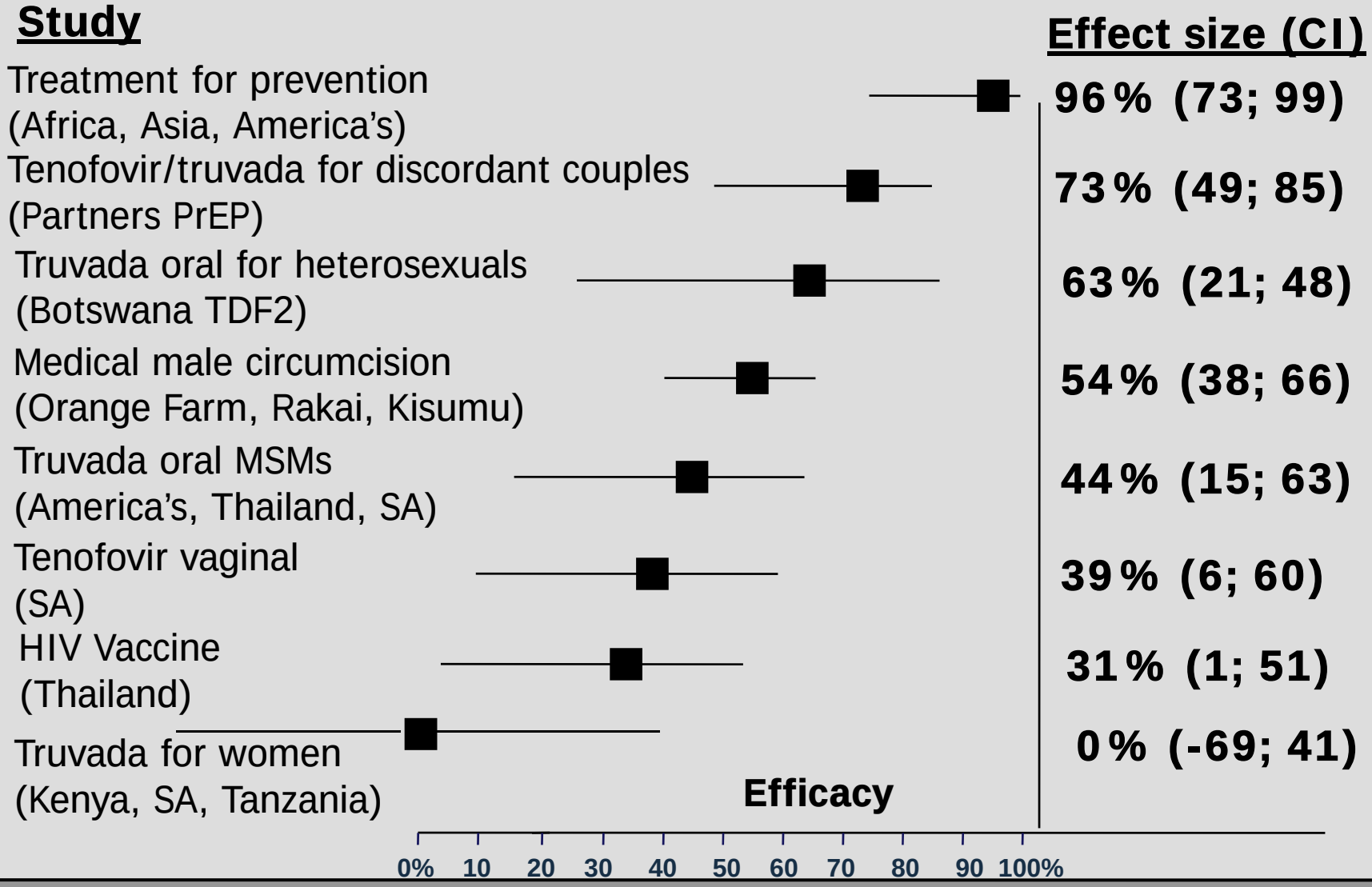
- But it’s not just PrEP…

Clinical trial evidence for preventing sexual HIV transmission – 14 July 2011



Modified from Slim Karim 6th Transmission Workshop, 2011

Epidemic 1 – heterosexual SSA

- Design
  - Incidence high enough to support cluster-randomised designs
  - Control clusters receive standard of care
  - Intervention clusters receive combination prevention – could have the toolkit and the garage
  - Incidence through structured x-sectional surveys
- Conduct
  - Clusters well defined and characterised
  - Communities engaged, government and ministry support essential
  - Large number of field staff needed

Concluding thoughts

1. Testing at the centre of all initiatives

2. The science has delivered, but successful implementation is all about behaviour

3. Know your epidemic, know your service setting, forge those partnerships and find the champions!

Acknowledgements

- Slim for the trial evidence slide

- MDP partners for prioritising questions and generating ideas for design and conduct in SSA for women

- UK PrEP Working Group for prioritising and generating ideas for design and conduct in UK for MSM