EDCTP Stakeholder Meeting on HIV/AIDS

Prevention: Microbicides and PrEP

-product portfolio

-questions and challenges

-potential role of EDCTP

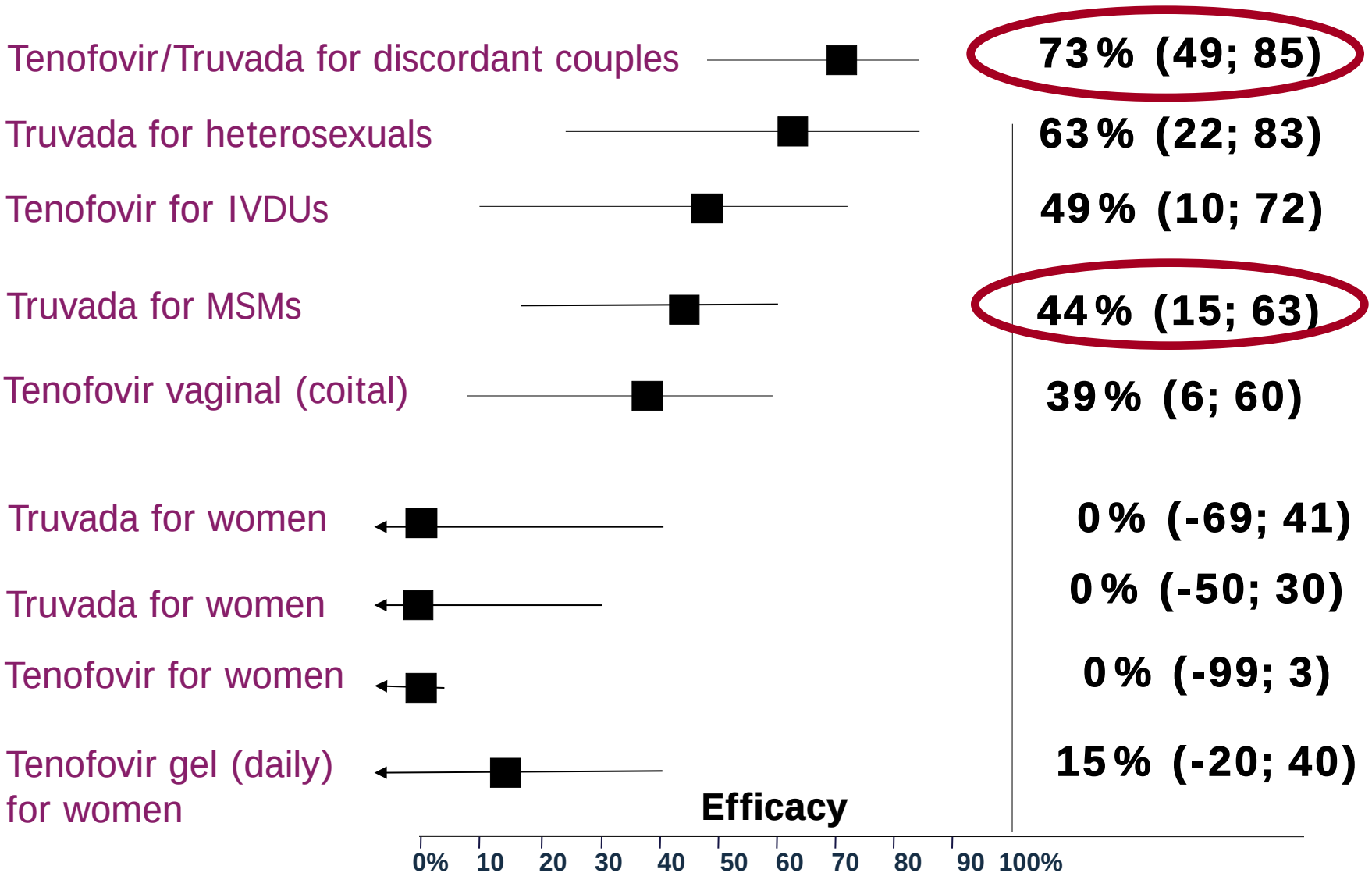
Sheena McCormack

Why do we need prevention?

- Successful treatment means numbers with HIV continue to expand exponentially

- Service providers are struggling to cope globally
  - **2 new infections** for every
  - **1 individual treated** in Sub-Saharan Africa

PrEP and Microbicide Studies



FDA approve Truvada

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

Ongoing PrEP and microbicide studies

- Numerous demonstration projects
  - Truvada
  - Maraviroc alone and in combination with tenofovir or with emtricitabine (FTC)

- iPerGay RCT assessing event driven Truvada compared to placebo
  - Two Truvada within 24 hours of sex
  - One as soon as possible afterwards and daily thereafter if sex continues until at least one day after the last act

Ongoing PrEP and microbicide studies

- One tenofovir vaginal gel study,dosing before and after sex, compared to placebo
  - FACTS 001: South Africa

- Two intra-vaginal ring studies of dapivirine compared to placebo
  - The Ring study: South Africa, Uganda
  - ASPIRE: Malawi, South Africa, Uganda, Zimbabwe

Oral and topical

- Topical advantages
  - More rapidly achieves high levels in genital tissues
  - Lower systemic levels suggests less toxicity
  - Potential to combine with contraception (rings)
  - Less obvious competition with treatment

- Oral advantages
  - Familiarity and decades of adherence experience
  - Levels of drug in the local lymph nodes could be important

Delivery Systems and products
In or soon to be in Clinical Trials (Phase I to III)

Vaginal gels
Tenofovir
FACTS 001

Dapivrine +/- Darunavir
CHAARM, IPM
MIV150/Zn/Carrageenan
Pop Council

Rectal Gels
Tenofovir
CHARM, MTN014, 017

Silicon Rings
Dapivirine
Aspire, The Ring

Maraviroc + Dapivirine
MTN 013/IPM 026

Maraviroc
IPM
Tenofovir
CONRAD

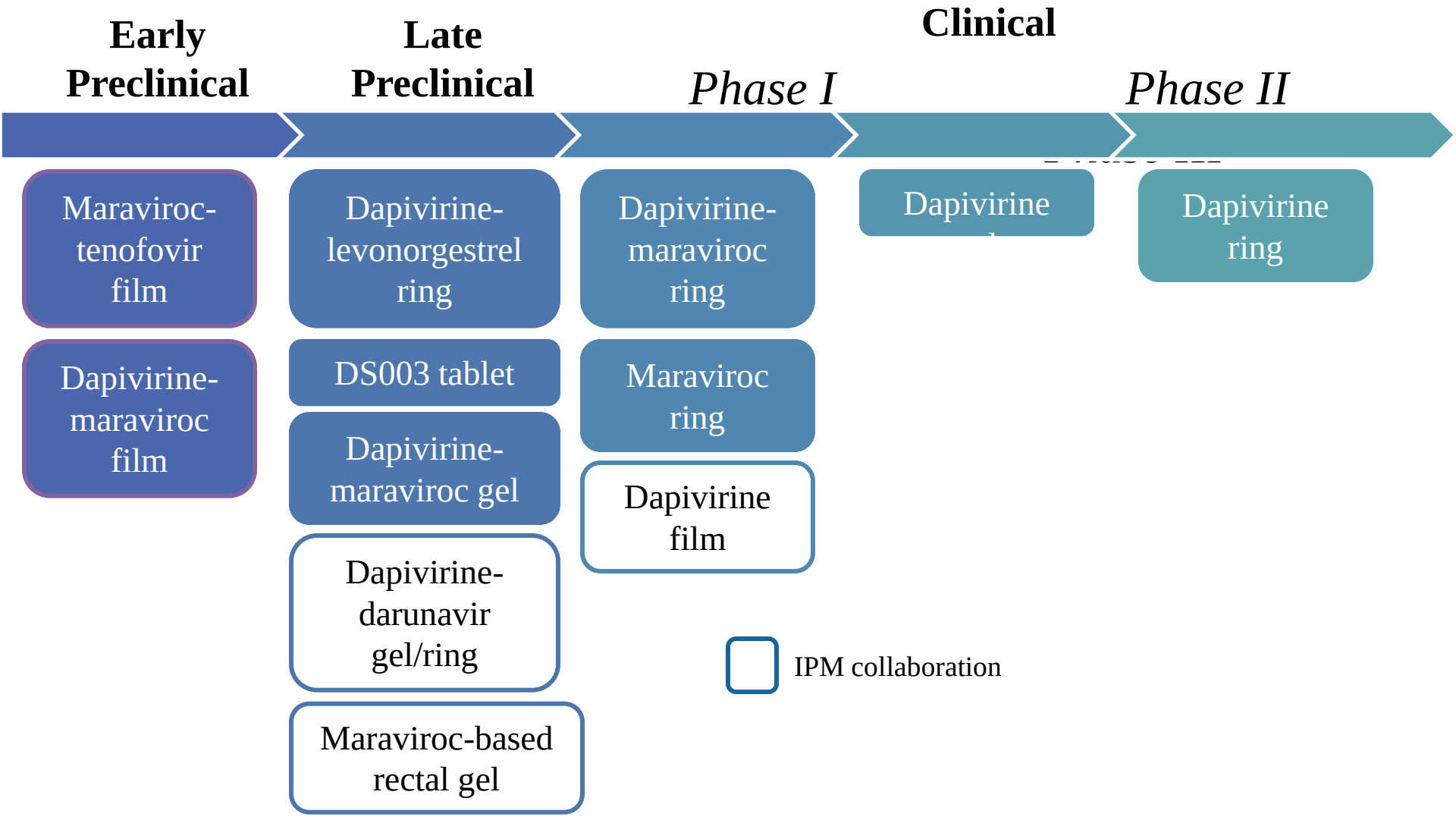
MIV150/Zn
Pop Council
Dapivirine/Darunavir

Oral
Truvada,
Maraviroc,
Maraviroc + FTC
Maraviroc + tenofovir
HPTN 069

Injectable
TMC278 LA
S/GSK '744
Phase I

Adapted from Jim Turpin's IRMA presentation

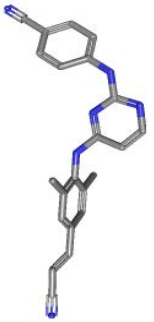
IPM Product Pipeline



DS003 (BMS 793)

- Potent gp120 binding entry inhibitor of HIV-1 infection
  - Licensed from Bristol-Myers Squibb in 2005
  - Targets the virus, not the host cell
    - Early PK assessments critical to formulation choice
  - New mechanism of action
    - Not currently employed in microbicide or treatment arena
  - Can be developed alone or in combination

Rilpivirine (TMC278) long-acting injectable



- NNRTI developed by Tibotec (Janssen) for treatment of HIV infection
  - Oral formulation approved
- Highly potent: EC_{50} <0.4 ng/mL 1^{o} HIV isolates
- LA formulation administered IM
  - 300 mg/mL; glass vials
  - Stable 2-8^{o}C for 36 months
- Phase I safety and PK
- Phase I pharmacodynamic endpoint to start soon
- Phase II in development with HPTN

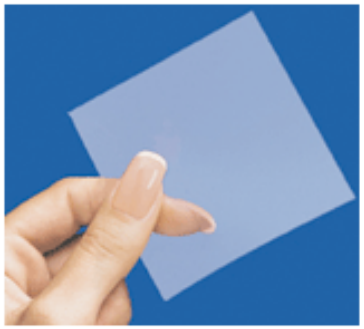
P. Williams, Janssen

S/GSK '744 long-acting injectable

- HIV-1 integrase inhibitor developed via joint venture between GSK/Shionogi/ViiV
- Evaluated clinically as an oral formulation, but not approved
- Phase I safety and PK (Spreen et al, IAC 2012)
  - IM or SC single dose of 100-800 mg
  - No adverse events of note
  - 800 mg IM sustained plasma levels above that required to produce >2.5 log reduction in viral load as monotherapy
- Macaque challenge: no detectable viraemia 3 weeks after the last of 2 rectal challenges with SHIV 162p3 in 8 males; 8 placebo controls were infected (Andrews et al, CROI 2013)

Next of Generation Delivery Systems In Development

Other gels
pH transition
Subliming Solid matrix



Vaginal Films
Tenofovir
Dapivirine-maraviroc
Tenofovir-marviroc

Pod Rings

Segmented Rings

Rings with other polymers

Quick Dissolve Tablets

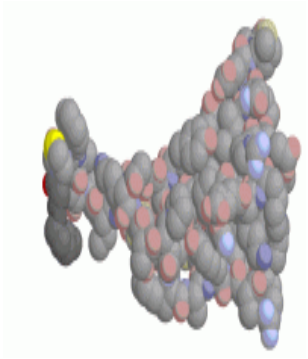
Devices +/- Gels

And in the distant future…

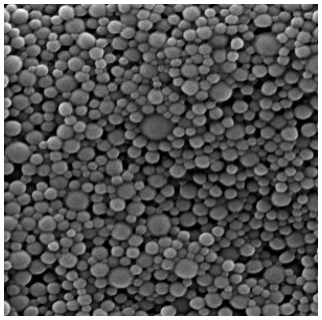
Nanotechnology for Prevention

Increasing Delivery Options

Drug

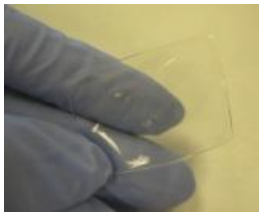


Drug in Nanoparticles



Drug-containing Nanoparticles in:

Vaginal Film



or

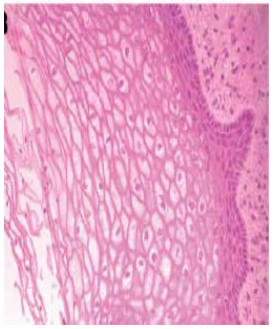
Vaginal Ring

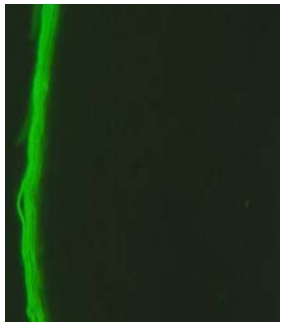
Normal Tissue

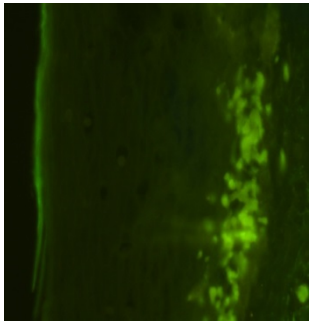
Drug alone

Drug in Nanoparticles

Vaginal Lumen







Ham, et al. Pharm. Res. 2009 26:502

Pictures courtesy of Lisa Rohan

Product portfolio - reality

Implementation studies

Now

- Daily oral Truvada
- Daily oral tenofovir

Maybe in 3-6 years time

- Before and after tenofovir vaginal gel
- Before and after oral Truvada
- Intravaginal ring releasing dapivirine

Product portfolio - reality

Large scale clinical trials

- Rectal tenofovir gel for gay men
- Other daily ARV regimens

Depending on FACTS and the dapivirine ring trials

- Single dose of vaginal gel
- Multi-purpose technologies: HIV and contraception

Small pharmacokinetic/pharmacodynamic studies

- Other formulations of tenofovir (vaginal tablets, rings)
- Long acting injectables

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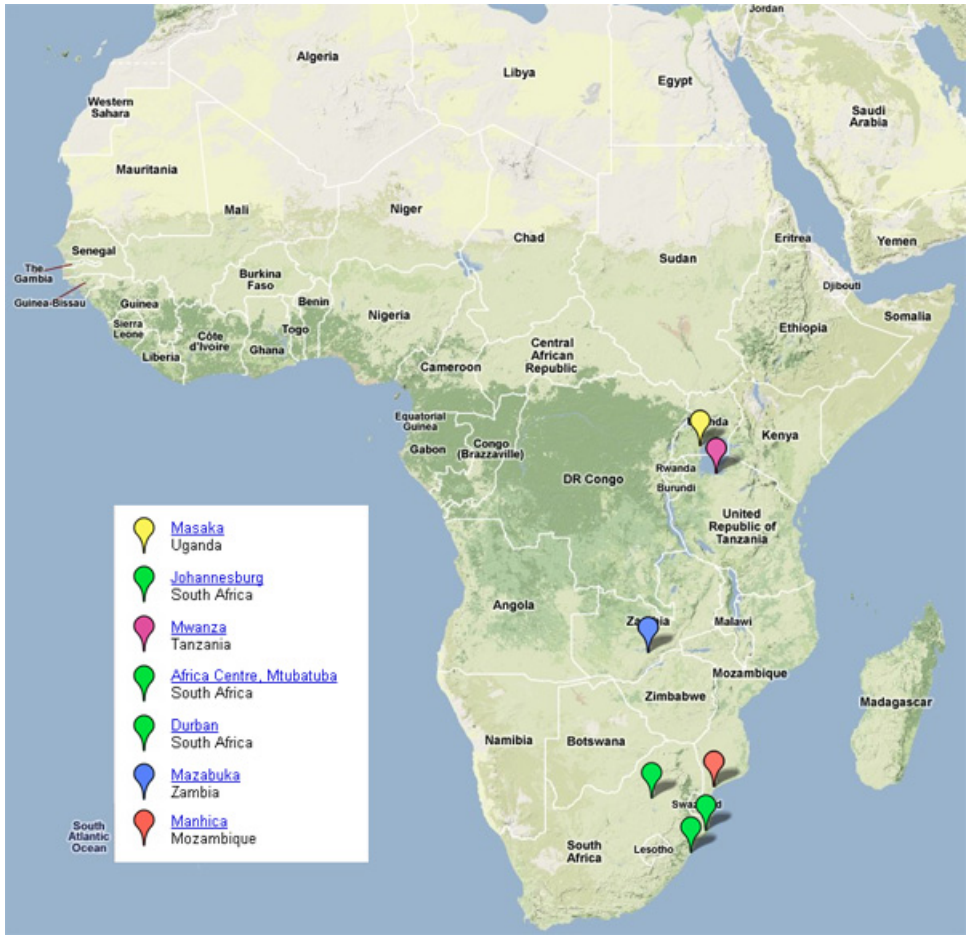
- product portfolio
- questions and challenges
- potential role of EDCTP

The biggest challenge?

- “In our discussions, the technical committee has not recommended the use of PrEP among HIV negative people. It’s morally unfit, not right and incorrect to put people who are HIV negative on treatment when we have not been able to enrol those who are HIV positive on it”

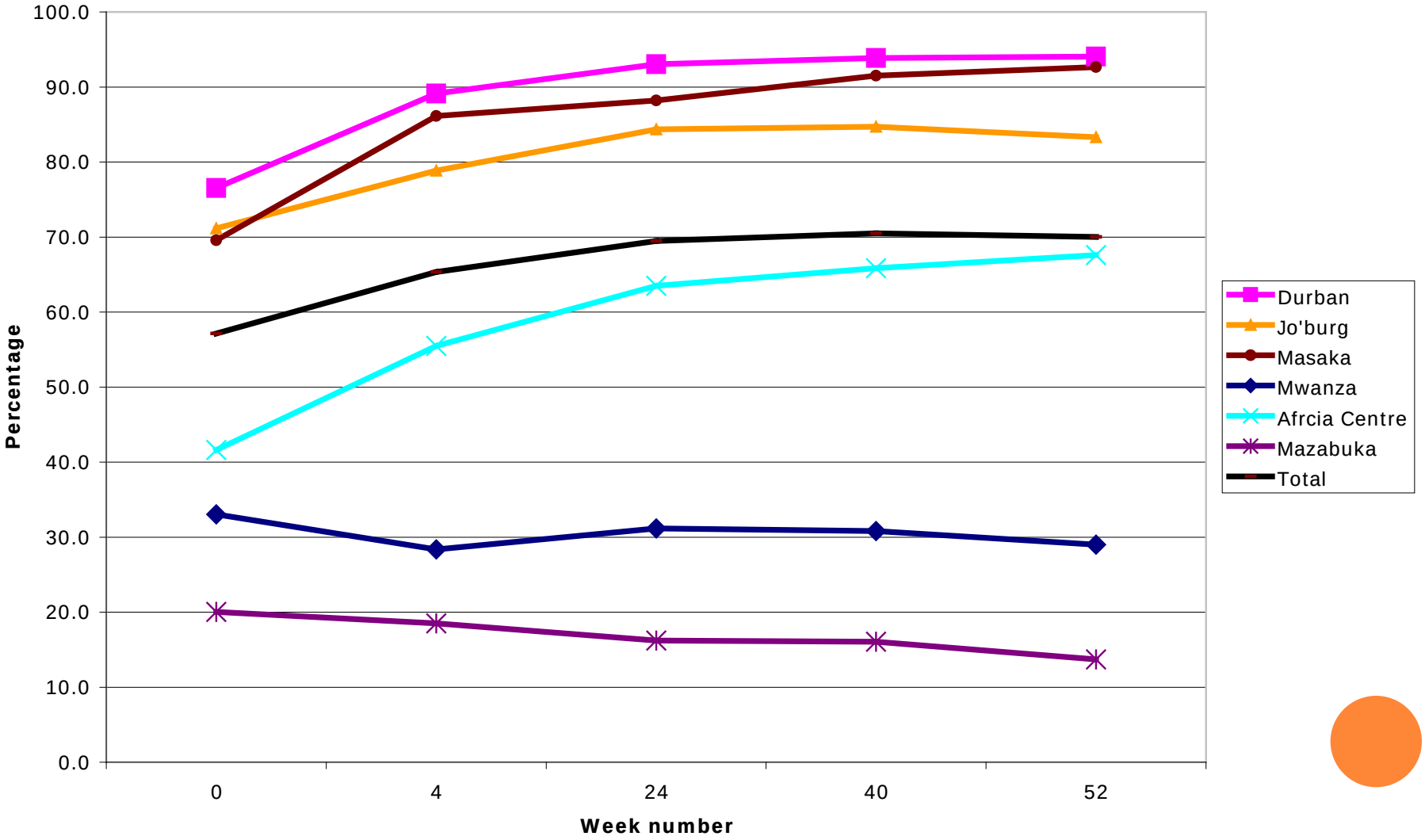
- “People will engage in reckless sex behaviour and rush to health facilities”

MDP 301 Clinical Research Centres



- Uganda:
  - Masaka
- Tanzania:
  - Mwanza
- Zambia:
  - Mazabuka
- South Africa:
  - Johannesburg
  - Mtubatuba
  - Durban

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



Two key areas

- Why didn’t women use the products they were given in FEMPREP and VOICE?
- How will we assess the efficacy/effectiveness of new products as effective ones are rolled out?
  - Single dose of tenofovir vaginal gel
  - Rectal tenofovir gel
  - Other daily oral ARV regimens
  - Multi-purpose technologies

The clinical trials and the real world

- The influence of placebo
  - Participants are not taking drug for themselves!

- The monthly visits, the attention of staff, and the information provided, including objective feedback on adherence are very different to real life

- So there is reason to believe adherence would go up in the real world, and reason to believe it would go down

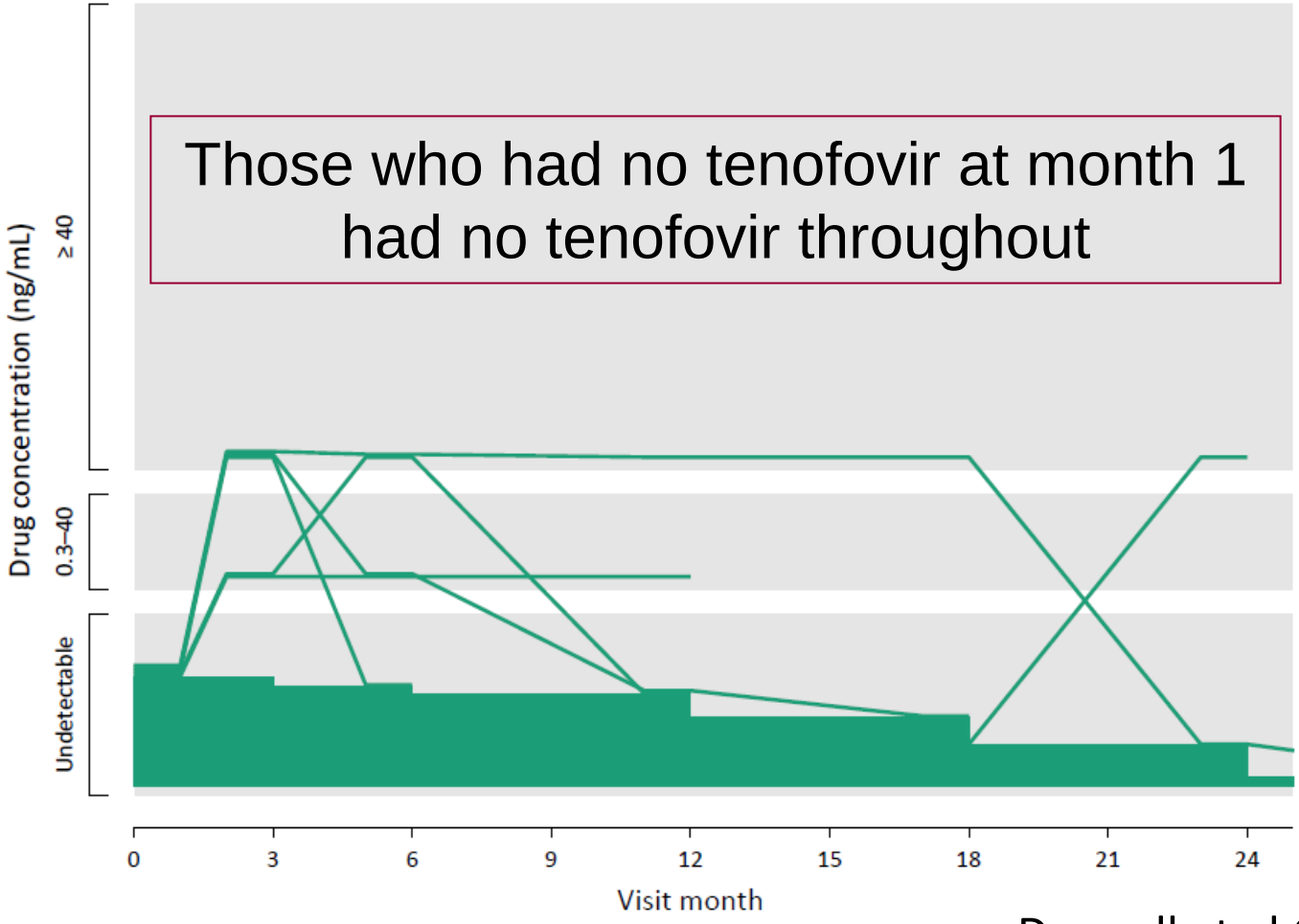
Adherence: how good is good enough?

	% of blood samples with tenofovir detected
Partners PrEP FTC/TDF arm	81%
TDF2	79%
BTS	67%
iPrEx	51%
FEM-PrEP & VOICE	<30%

	% 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

Adherence drives the trial result

Consistent adherence to daily drug = High level of protection



Donnell et al CROI 2012

Correlates of low adherence

- **Younger age** (Partners PrEP, VOICE)
- **Not partnered** (VOICE, FEM-PrEP)
- **Low perception of risk? Stigma?** (FEM-PrEP, others?)
- **Less sex** (Partners PrEP, iPrEx)
- **Alcohol use** (Partners PrEP)
- **Not attending appointments** (Partners PrEP, VOICE, others?)

Key questions for implementation studies

- Who needs extra help to reduce their risk of HIV? Do THEY recognise the need?
- Do they want what we have to address this need?
- Does that mean they will take it? And continue to take it with ‘real world’ support?
- Can we convince policy makers?
  - Controversy, stigma, threat to ART

Needs several disciplines working together, with open label product.

Needs personal stories, stronger community voices.

Key questions for implementation studies

- Common concern is whether people will drift away from condom use?
  - Cannot be assessed in placebo controlled trials as **placebo controls for behaviour**

Needs open label and a control group.

PROUD Pilot

MSM reporting unprotected sex
Willing to take a pill now or in 12M

↓

Randomize 500 HIV negative eligible MSM
(exclude if on treatment for hepB)

↙ ↘

Risk reduction includes Truvada **NOW**

Risk reduction includes Truvada **in 12M**

↓

Follow **3 monthly** for up to 24 months (+**1m** after start truvada)
Online **daily** diary and **monthly** questionnaires

Key questions for the pipeline

- Efficacy/effectiveness of daily oral ARV
  - Non-inferiority (huge and uncertain)
  - Open-label design like PROUD
  - Portfolio of evidence
    - HIV endpoints, but smaller N than Phase III
    - Pharmacodynamic endpoints

- Efficacy/effectiveness of rectal microbicides
  - Placebo-controlled, with daily Truvada offered to all/to those enrolled in countries where this is available

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Mobilising new expertise in clinical projects

- Behaviour, health seeking and society
  - Social scientists and anthropologists
  - Health psychologists
  - Social marketers, and commercial marketers
  - Health economists

- Capacity required for formulation and pharmacodynamic studies
  - Vaginal, cervical and rectal biopsies
  - Mucosal sampling
  - Specimen processing

Partnership

- To mobilise the partnerships with other donors required to fund large studies - if we need them
- To bring scientific groups from similar projects together to share their strategic vision
- EDCTP is unique, and it should dare to be different

Acknowledgements

- Jared Baeten
- Steve Becker
- Ian McGowan
- Joe Romano
- Gita Ramjee
- Jim Turpin
- Zeda Rosenberg
- MDP and PROUD teams and participants

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