MRC Clinical Trials Unit

Microbicides –

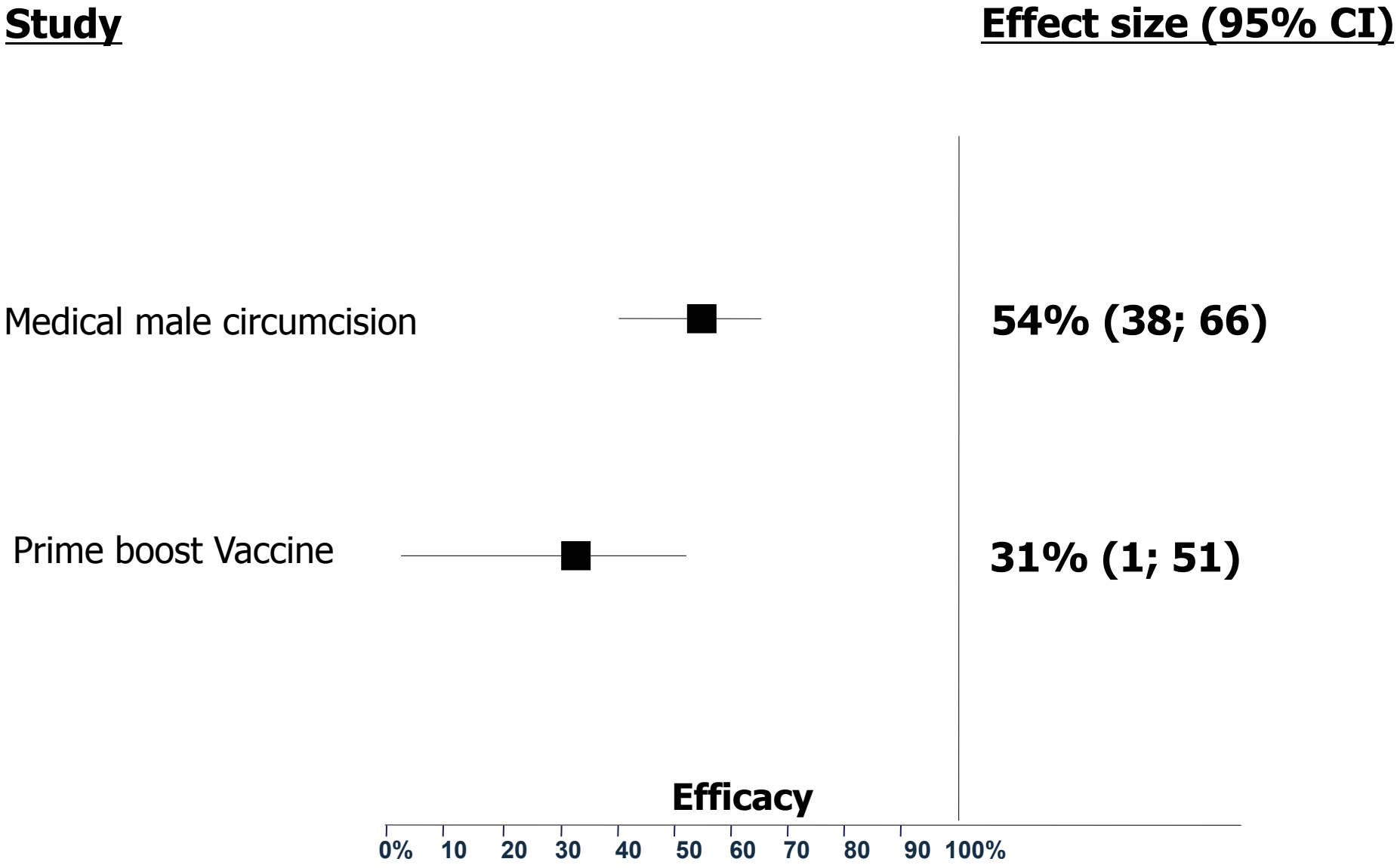
an overview

Sheena McCormack

What are microbicides?

- Microbicides are ***experimental, candidate products*** which would be used vaginally or rectally to reduce the risk of HIV infection

Reducing the risk of HIV: context

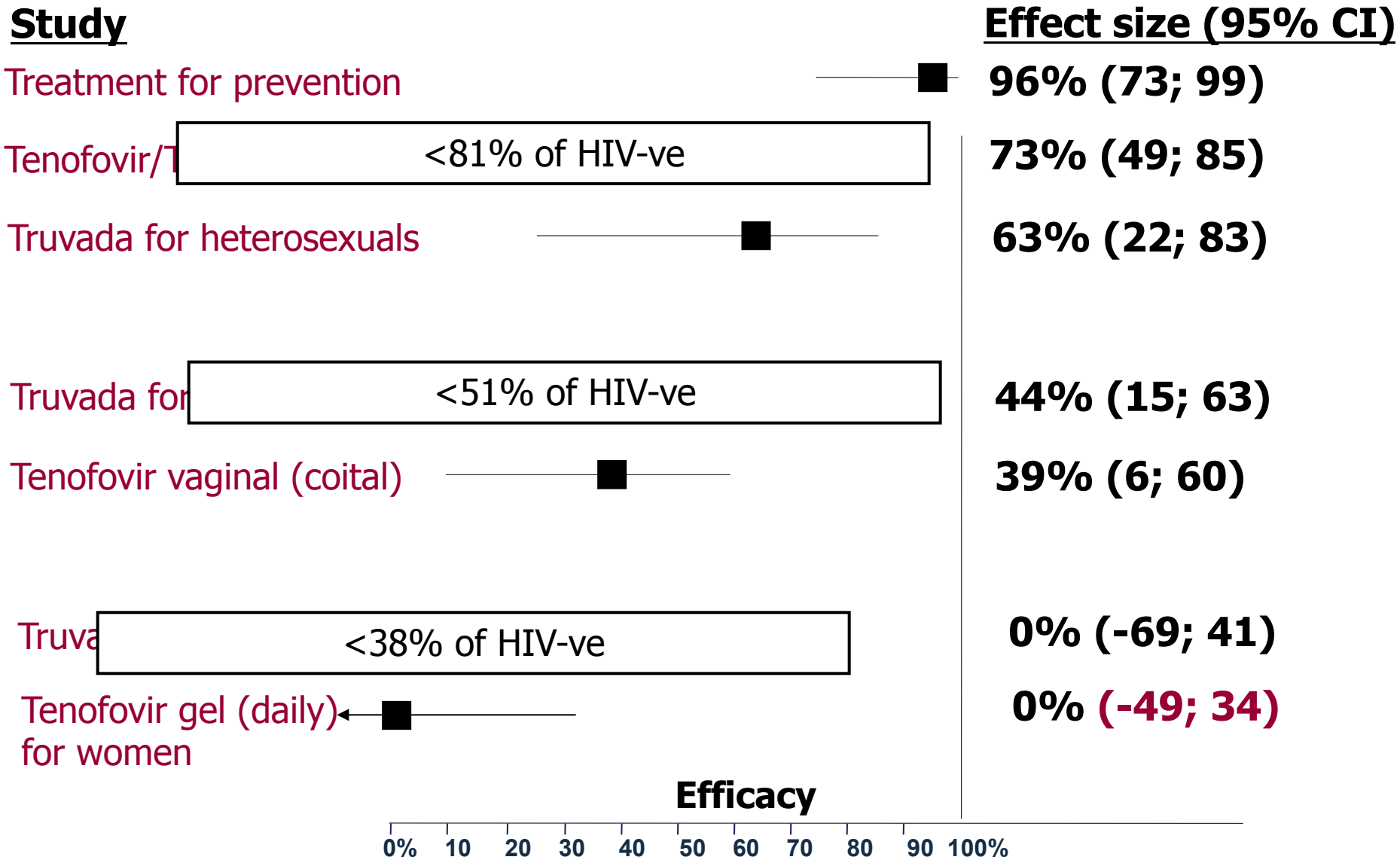


CAPRISA 004 – Science 19 July 2010

39% effectiveness (95% CI: 6-60%)(p=0.017)

- Mostly general population in rural KZN with smaller urban KZN population which included CSW early on in enrolment
- Incidence in the control group was 10%; reported condom use 80%
- Tenofovir 1% vaginal gel
- Dosing was BAT24: up to 12hrs **B**efore sex, **A**fter sex up to 12 hrs and no more than **T**wo in **24** hrs

Reducing the risk of HIV: antiretrovirals



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

So why bother with microbicides?

- Giving drug topically delivers drug
  - ***where it is needed*** in genital tissue
  - closer to ***when it is needed*** as the absorption is local
  - at a much ***higher level*** (10-100x) than a tablet

Ongoing microbicide studies

- VOICE: stopped gel groups for futility and will report at CROI
- FACTS 001: tenofovir vaginal gel (CAPRISA dosing of before and after sex) compared to placebo
- The Ring Study and ASPIRE: two dapivirine intra-vaginal ring studies compared to placebo

FDA Guidance

- Tenofovir vaginal gel
  - FDA previously indicated VOICE could support CAPRISA
  - And more recently, that FACTS 001 can
- Trial design should be placebo-controlled as no licensed microbicide
  - HEC placebo acceptable

Combination products

- Two antiretrovirals eg dapivirine and maraviroc in an intra-vaginal ring (IPM/MTN) or gel (CHAARM)
- Antiretroviral and hormonal contraception eg tenofovir and levonorgesterol (CONRAD, Pop Council)

Rectal microbicides

- Initial focus was on formulation to ensure it is safe for rectal use (thinner cell layer compared to the vagina)
- MTN017 open label, cross-over, safety and acceptability of oral Truvada and rectal tenofovir reduced glycerin gel
- Recommend the Rectal Revolution video (MTN, IRMA and Pop Council)

Summary

- CAPRISA provided proof of concept for microbicides, and for intermittent event driven use
- Confirmation is needed for licensure, and trials are ongoing
- The benefit of achieving high levels of drug in the genital tissue with topical application is clear

CHAARM
Combined Highly Active Anti-Retroviral Microbicides

1st Jan 2010 – 31st Dec 2014
European Union Funding €12M

31 participating institutions

Coordinators: Charles Kelly (King's College London)
Robin Shattock (Imperial College)

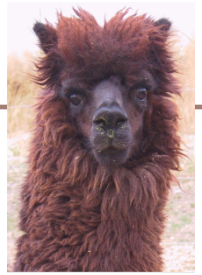
CHAARM
Combined Highly Active Anti-Retroviral Microbicides

Aims:

1. To develop new microbicides
   Biologics: peptides, small proteins
   Drugs: new reverse transcriptase inhibitors

2. To develop combination anti-retroviral drug-based microbicides to include protease inhibitors: Dapivirine + Darunavir - pre-clinical, phase I clinical trial

CHAARM
Combined Highly Active Anti-Retroviral Microbicides



New microbicides (i):

1. Fragment of a llama antibody (VHH) with broad spectrum neutralising activity
   (University College London, University of Utrecht)

2. Peptides that block HIV binding to CD4 or CCR5 (CEA, France; University of Geneva; Mintaka Foundation; San Raffaele Institute)

3. New NNRTI active against Dapivirine-resistant virus (University of Antwerp)

CHAARM
Combined Highly Active Anti-Retroviral Microbicides

New microbicides (ii):

1. Formulation studies– gel and ring
   (University of Leuven, Queen's University Belfast)

2. Pharmacokinetic studies in non-human primates (CEA, France)

3. Challenge studies in non-human primates
   CD4 peptide mimic 5/6 protected
   (CEA, France)

CHAARM
Combined Highly Active Anti-Retroviral Microbicides

ARV combination: Dapivirine + Darunavir

(Janssen Infectious Diseases - Diagnostics BVBA; International Partnership for Microbicides)

- gel and ring formulations (Particle Sciences Inc; Queen's University Belfast)
- pharmacokinetic studies in non-human primates (CEA, France)
- phase I (safety) clinical trial planned 2013/2014. Vaginal tolerance (out to tender) (University of York)

CHAARM
Combined Highly Active Anti-Retroviral Microbicides

Biomarker studies (Institute for Tropical Medicine, Antwerp; University of Liverpool, St Georges University of London)

- The ideal microbicide:
  - decreases the risk of HIV infection while preserving the integrity of the cervicovaginal epithelium.
- Traditional approach has failed to predict the safety for initially promising, potent and safe antiviral compounds.

➔ Needed: baseline ranges of biomarkers related to the vaginal environment in potential candidates for microbicide trials

CHAARM
Combined Highly Active Anti-Retroviral Microbicides

Biomarker studies

To define the effect of the microbicide on:

- Vaginal Microbial Flora
- Mucosal Immunology
- Cell or tissue associated factors
- Influence of hormonal status and genital hygiene practice

In collaboration with EDCTP and IPM-funded projects, samples collected from African and Belgian women.

Microbiological, multiplex and proteomic analyses in progress

CHAARM
Combined Highly Active Anti-Retroviral Microbicides

Key Points

- Novel NNRTI and VHH identified for formulation and NHP challenge (pipeline)

- Dapivirine + Darunavir clinical grade gel formulation established

- Phase I trial of Dapivirine + Darunavir scheduled (development)

INTERNATIONAL PARTNERSHIP FOR MICROBICIDES

Update on IPM's pipeline: Dapivirine Ring and Beyond

Jeremy Nuttall

Senior Director, Preclinical Sciences & Product Development

AVAC Webinar

26 February 2013

Developing HIV Prevention *Products for* ***Women*** *worldwide*

IPM's Mission

- Non-profit product development partnership (PDP)
- Offices in the United States, South Africa, Europe
- IPM's mission is to develop new HIV prevention technologies and make them available to women in developing countries

IPM's Current Pipeline Scope

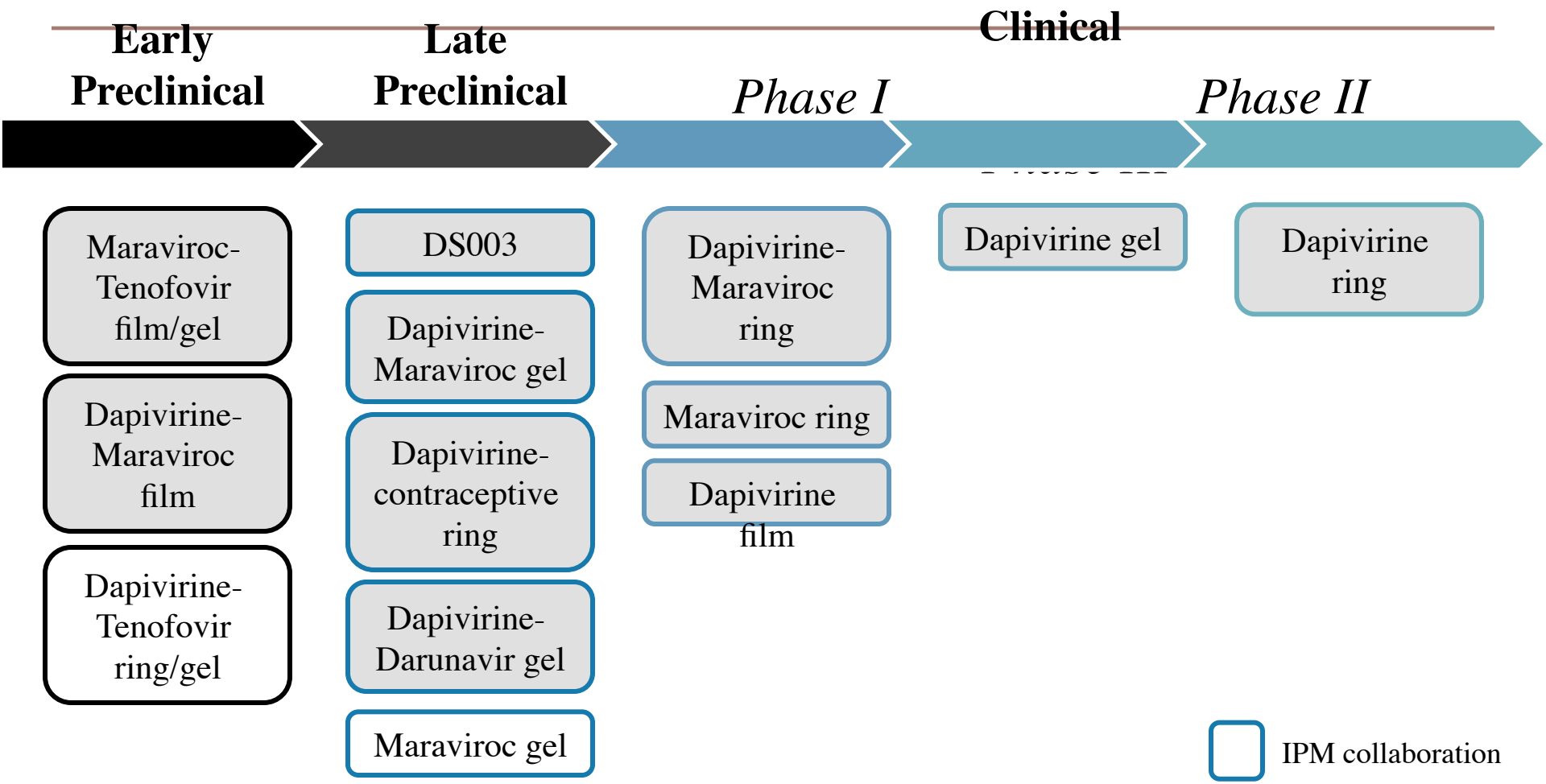
- **Microbicides**
  - Single ARVs
    - Various mechanisms of action
    - Formulated in numerous dosage forms for topical use
  - Combination ARVs
- **Dual-purpose products**
  - HIV prevention
  - Unintended pregnancy and/or STIs
- **Novel Formulations and/or Delivery Mechanisms**

IPM Active Compound Portfolio

Compound	License	Year	Type/ Stage	Development Status
Dapivirine	Janssen R&D Ireland (previously Tibotec)	2004	NNRTI	Phase 3 clinical (ring) Phase 1/2 clinical (gel)
DS001 (L167) **DS004 (L872)** **DS005 (L882)**	Merck Bristol-Myers Squibb GILEAD	2005	CCR5 blockers	Early preclinical
DS003 (BMS793)	BMS	2005	gp120 binder	Preclinical
Tenofovir ***(CONRAD & IPM)***	Gilead ViiV Healthcare MERCK	2006	NRTI	Proof-of-concept (CAPRISA) Phase 3 clinical (FACTS)
Maraviroc	ViiV (from Pfizer)	2008	CCR5 blocker	Phase 1 clinical (ring) Preclinical (film, gel) ***Alone and in combinations***

Non exclusive, royalty-free licenses to develop compounds as microbicides in developing countries

IPM Product Pipeline



Dapivirine Ring Licensure Program

IPM 027
The Ring Study

- **Long-term safety and efficacy study**
- 1650 participants, ongoing (2012-2015) in Africa
- 1100 participants on Ring-004

MTN-020
ASPIRE

- **Safety and effectiveness study**
- 3476 participants, planned (2012-2014) in Africa
- ~1738 participants on Ring-004

Additional planned safety studies

- Drug-Drug interactions
- Condom compatibility: Male and Female
- Safety in Adolescents and Post-menopausal women

INTERNATIONAL PARTNERSHIP FOR MICROBICIDES

MTN microbicide trials network

National Institute of Allergy and Infectious Diseases
Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases.

Dapivirine-Maraviroc Ring

- Phase I pharmacokinetic & safety ring trial
  - 3 research centers in the United States
- Study design:
  - 4 arms: dapivirine-maraviroc ring, dapivirine ring, maraviroc ring, and placebo ring
  - N = 48 women (12 women in each arm)
  - 28 days on product + 24 days of follow-up
- Study start date: Nov 2011
- Last patient out: Jul 2012

First-in-human combination microbicide product

Dapivirine–Contraceptive Ring

- Advance multi-purpose prevention technology
  - Need exists for both HIV prevention and contraception in Sub-Saharan Africa
- USAID award of $2M for preclinical development (through GMP manufacture) of dapivirine-contraceptive ring for 60 days use
- Numerous hormones evaluated
  - Levonorgestrel selected
- Two polymers under evaluation
  - Silicone
  - Ethylene vinyl acetate (EVA)

Film Projects

- Collaboration with Magee Women's Research Institute on existing NIH U19 on combinations:
  - Dapivirine film being evaluated in Phase I trial (FAME 02) comparing PK and safety with dapivirine gel (n = 60)
  - Work initiated on DS003 film formulation Q4 2012

Rectal Gel

- Combination tenofovir-maraviroc and maraviroc alone rectal gels in development at Magee
- IPM providing regulatory support
- Prototypes developed containing 1% TFV and 0.1% maraviroc in stability testing
- Gels tested in macaques for PK and now being tested for efficacy
- Targeting 2 Phase I trials in 2013

IPM Donors

This list includes all donors who have contributed to IPM since its founding in 2002

INTERNATIONAL PARTNERSHIP FOR MICROBICIDES

Thank you!

IPM@10

A decade of progress advancing HIV PREVENTION FOR WOMEN

AVAC & NAM: European HIV Prevention Webinars – Microbicides

Community Advocacy for Microbicides in Europe

- Questions and Observations

Harriet Langanke, Germany
GSSG – Gemeinnützige Stiftung Sexualität und Gesundheit, Köln
Charitable Foundation Sexuality and Health, Cologne

February, 25th, 2013

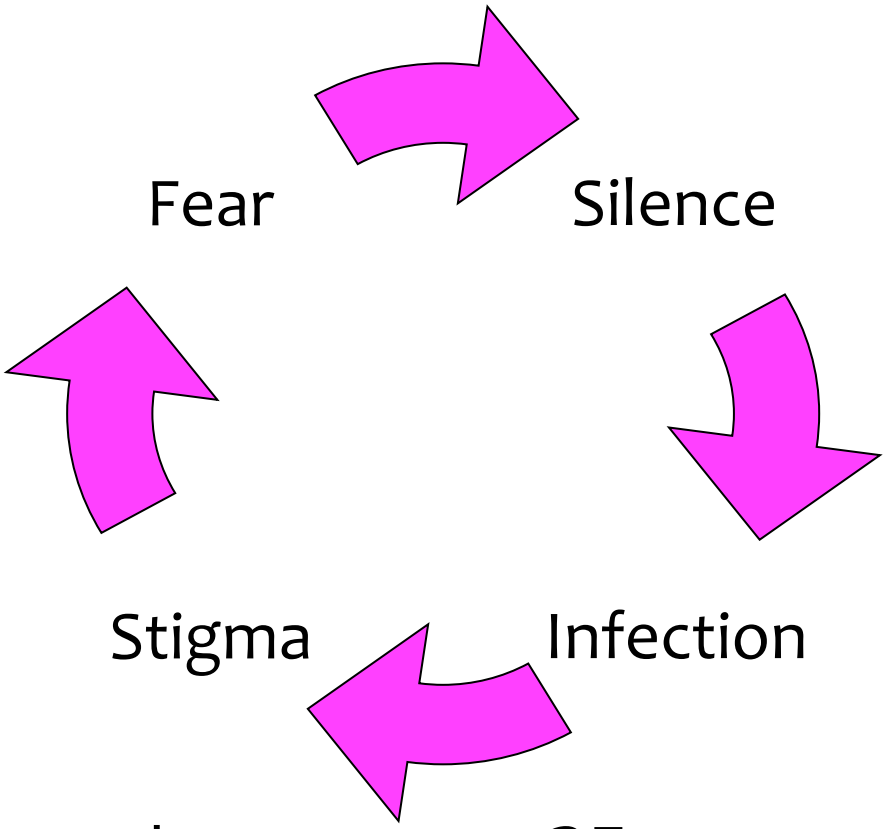
Community Advocacy 1

- PLWH →
  - allies in prevention
  - know their status

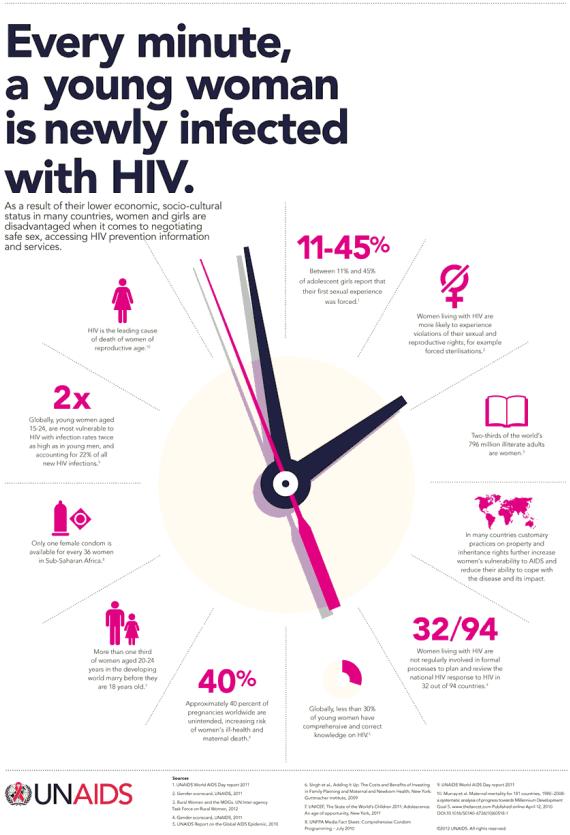
PLWH → responsibility is to be shared (NOT solely with the PLWH)

Community Advocacy 2

Breaking the Silence,
Fighting Vicious Circles



Why Women?



- empower women (living with and without HIV+ diagnosis) to negotiate safer sex and safer use

Female Condoms

Photo: Intellex

- male condoms need
  - a man ‘s willingness
  - a man ‘s ability
- BUT:
  - female condoms are hardly available
- further barriers:
  - obstacle to romantic issues
  - bad reputation
    - expensive, noisy, unavailable…

Acceptance of Female Condom

A small field test with two German sex workers communities in 2010 conducted by GSSG reported diverging results:

- Cologne 2010:
  - A group of 25 female sex workers tried but did not show any further interest in using the FC
- Frankfurt 2010:
  - A group of 30 female sex workers, most IDUs, tried and appreciated the FC as a welcome alternative

Microbicides

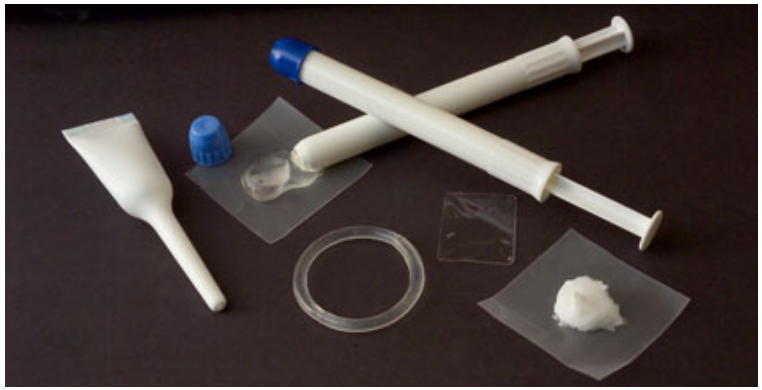


Photo: GCM

- "Could really be something"
- "Too far out on the horizon"

Good idea for those already comfortable with diaphragms etc.

PrEP

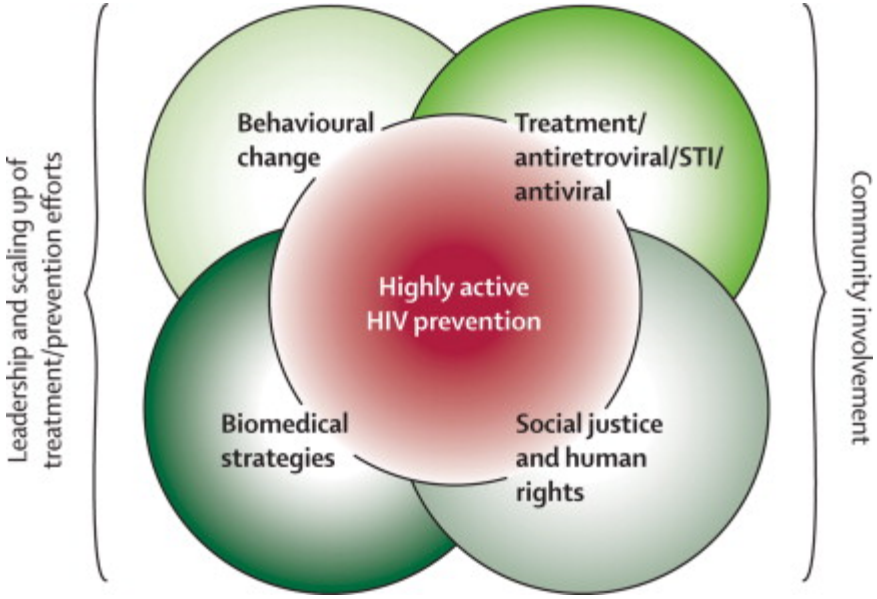
- uncommon for "sex only"
- quite common in planning for pregnancy in serodifferent couples
  - "to be on the very safe side"

Treatment as Prevention

- the “Swiss Statement” has been practiced way before it was published
  - enormous relief for many PLWH
  - “this statement is even better than Swiss chocolate”
- STI and genital health play a crucial role
  - which is not always understood

Combination Prevention

- a silver bullet for everyone and every situation?
- combining classic and modern strategies – individually and structural!



Graphic: The Lancet, Vol. 372, 2008 (!)

Questions?

- Harriet Langanke

  - GSSG – Gemeinnützige Stiftung
    Sexualität und Gesundheit
    Odenwaldstraße 72
    D – 51105 Köln
  - +49 – 221 – 340 80 40
    harriet.langanke@stiftung-gssg.org
  - www.stiftung-gssg.org

Photos on slides 4, 5, 9 and 10 © GSSG, photographed by PLWH;