FEM-PrEP Trial Results

does this call for a different approach?

Khatija Ahmed
Setshaba Research Centre
27 October 2011

Setshaba - Location

- Soshanguve district is located
  - 30 minutes by car from Pretoria
- During the apartheid era, Soshanguve

(ethnic groups)

- Southern Sotho,
- Shangaan,
- Nguni,
- Venda

Setshaba Research Centre (SRC)

- Situated in Soshanguve Block H
- Founded and developed in 2003 by MEDUNSA and Population Council
- Involved in clinical trials since

Trials Conducted

- HIV prevention
- Social Science (related HIV)
- Vaccine
- Drug
  - Microbicide Carraguard trial- completed
  - FEM PrEP Clinical Trial-ongoing seroconvertors
  - FACTS - ongoing

HIV FROM 1980's.....

- 60 million infected- 25 million deaths
- 1990s- pandemic
- Emerging facts-
  - Not "gay" disease
  - ↑ infection and vulnerability in women (heterosexual trans)(biological/social/cultural)
  - Infections in babies
  - Association with STIs, etc

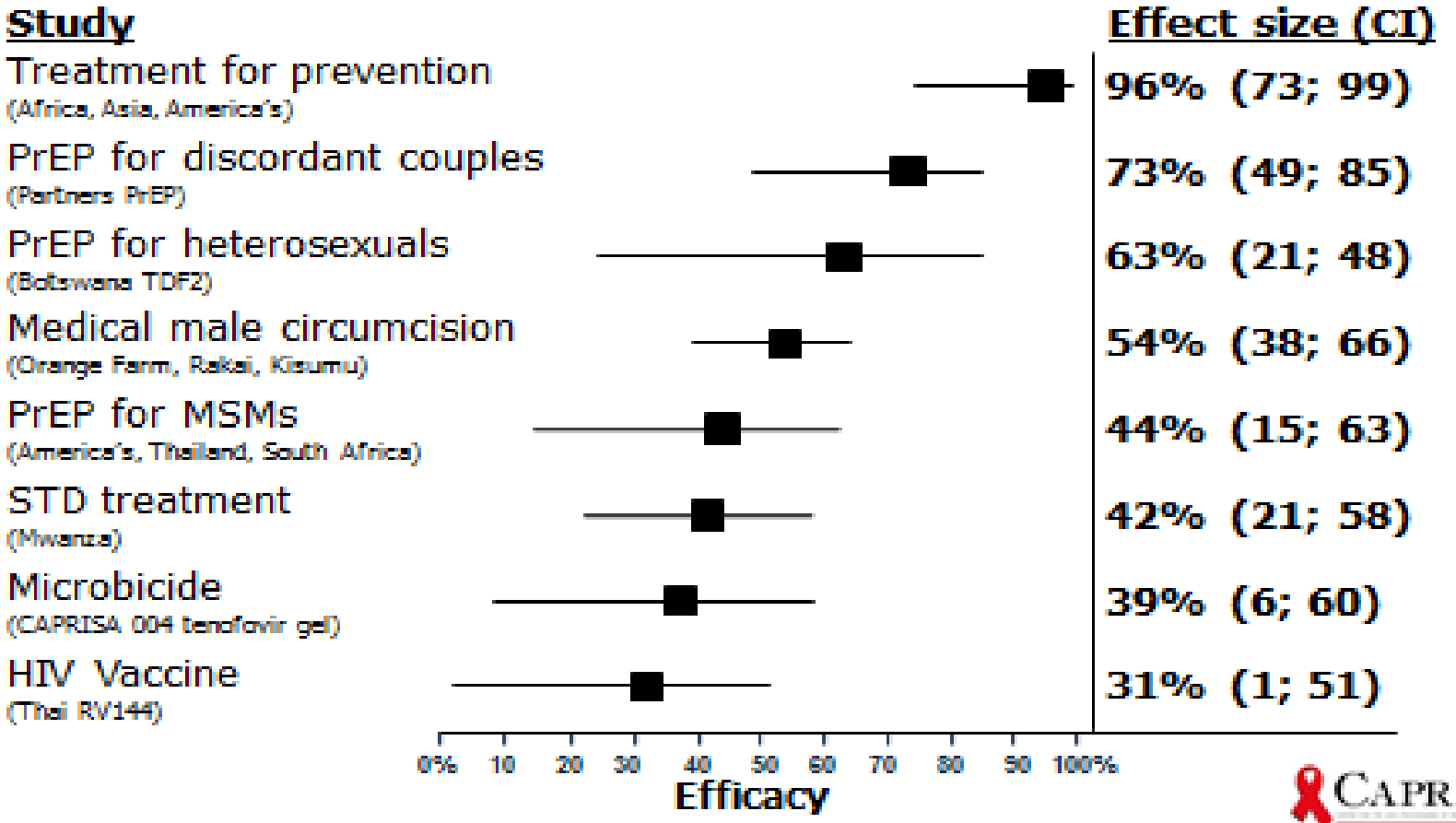
Pre 2010 - HIV Prevention

- Limitations in progress because:
  - Worldwide response – insufficient/slow
  - Social factors- inequalities, women abuse, drug use etc
  - Associated stigmatization and discrimination
  - Scepticism and denial
- Back to ABC.....
- Despite limitation in 25 years of research- progress in
  - Social science
  - Behavioural science
  - Medical science (Animal models, product development, PMTCT, circumcision, vaccine, microbicides, etc)
  - Product development
  - Many Clinical trials – wealth of information to move forward

2010/2011
BREAKING NEWS

- Vaccines
- Microbicides
- Oral PrEP
- Rx for prevention (T4P)

Clinical trial evidence for preventing sexual HIV transmission – July 2011



CAPRISA

Hot From the Press
VOICE Study

- VOICE : 5 arm study
  - 3 oral(Tenofovir, Truvada, Placebo)
  - 2 gel(Tenofovir once daily and Placebo)
- September 16, 2011, the VOICE DSMB reviewed study data (Sept. 9, 2009 - July 1, 2011)

VOICE Study

- DSMB-Not possible to show oral tenofovir tablets were any better than a placebo .
- Not apply to the women in the groups using either the tenofovir gel or oral Truvada® tablets, or the corresponding placebos

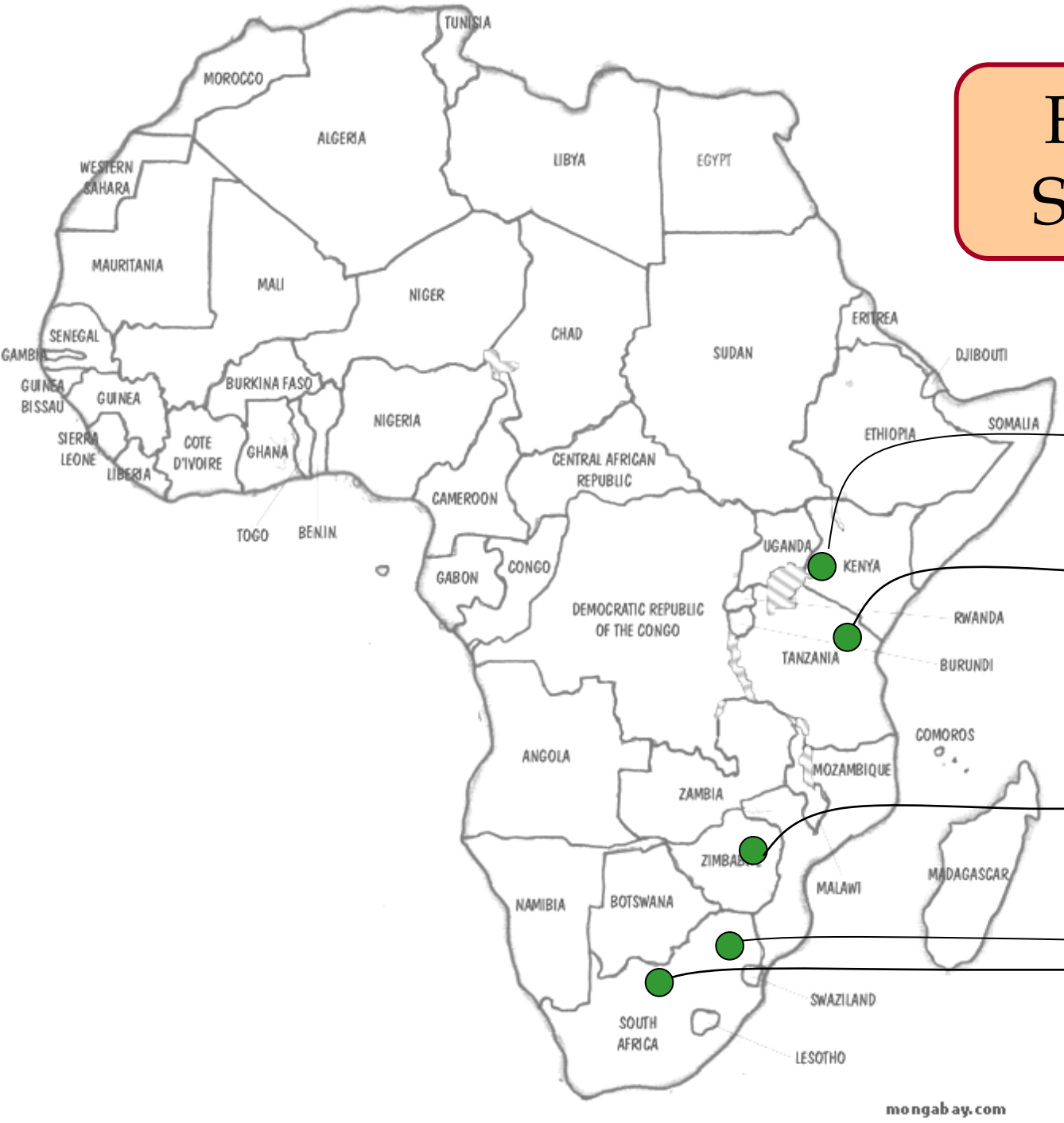
Why? (partners prep-62% efficacy)

Trial Results

FEM-PrEP

Pre-Exposure Prophylaxis for HIV

FEM PrEP Study Sites



Bondo, Kenya

Arusha, Tanzania

Zimbabwe

Pretoria, South Africa

Bloemfontein, South Africa

Clinical Trial Of Truvada

Phase III, randomized (1:1), placebo-controlled, blinded, multi-center trial of daily, oral tenofovir disoproxil fumarate - emtricitabine (TDF-FTC, Truvada)

- Sample size: ~3900 women
- Target: 72 HIV endpoints
- Women who are HIV-negative at higher risk of infection
- Follow-up for one year on study drug
- Seroconvertors followed for one year after diagnosis

FEM-PrEP Objectives

- Primary
  - safety
  - effectiveness
- Secondary
  - impact on infection (VL, CD4, ARV resistance)
  - adherence
  - risk compensation
  - pregnancies

Socio-Behavioral Research

- Preparatory and during study
  - Inform and support trial
  - Assess adherence and risk compensation
- Interviews with trial participants
  - HIV-negative participants: Adherence, retention, understanding of clinical trial, trial experiences and sexual behaviors, including risk compensation
  - Seroconvertors: access to care, coping, sexual behaviors and adherence
- Focus groups with community stakeholders
  - Community reactions to trial, concerns and rumors
  - Provide updates on trial progress
- Behavioral monitoring
  - Recruitment, adherence and informed consent

18 February 2011

Screened : 3752

Excluded
HIV 21%
Preg
Inclusion criteria not met

Mean age
24 years

Enrolled: 1951

Kenya: 739	Pretoria 764	Bloemfontein 432	Arusha 16

90 % retained in the study.

Self reported adherence to study product 95 %

Person-years of follow-up: 1100

Sex Acts : 3.7 acts in the seven days prior to enrollment, average of 3.6 acts during follow-up.

18 February 2011

HIV infection:
56
5% per year

Placebo
28

Truvada
28

Contraception:
66 % injectables
30 % oral contraceptives
9% pregnancy rate

Mild side effects

pregnancy rate 9% -
Higher among women in Truvada arm compared with placebo arm

IDMC

- Interim review of the trial data by the Independent Data Monitoring Committee (IDMC) found that FEM-PrEP would be

highly unlikely to be able to demonstrate the effectiveness of Truvada in preventing HIV infection in the study population, even if it continued to its originally planned conclusion

- The IDMC found that the trial was conducted to a high standard

Decision

- Trial was closed for the negative cohort in an orderly fashion
- Participants were informed of results
- Returned study product
- 3 month FU off product(last visit end august 2011)
- Analyses is ongoing (Nov)
- Cannot say for certain whether or not Truvada works to prevent HIV infection in women

Possible explanations

- Adherence too low to show effectiveness
- Biological (next slide)
- Product sharing
- Chance
- Combination of factors

Possible Biological Explanations

- Penetration of tenofovir and/or emtricitabine in female genital tract inadequate to provide protection
  - –Differential distribution to rectum and the female genital tract
- High drug levels required at site of HIV entry
  - –These levels may not be achieved in female genital tract with a single daily dose
- Contraceptive hormones
  - – May interfere with effectiveness of Truvada (TDF-FTC)
- Truvada side effects
  - – May have resulted in decreased adherence to study drug
- Inflammation?- causes & effect

Hypotheses for Pregnancy Finding

Higher preg rate in women using OCs and Truvada as compared to placebo

- Previously unknown interactions between Truvada (TDF-FTC) and contraceptive hormones
- Differential adherence to oral contraceptives between women on Truvada and women on placebo
- Possibly due to Truvada side effects
- Chance observation

Sample Testing to be Performed

- HIV endpoint (seroconverters)
  - Confirmation of HIV testing
  - Determination of time of infection
- ARV resistance (seroconverters)
- Tenofovir and emtricitabine levels
- Contraceptive hormone levels

Why Difference From Other Studies?

- **<u>Partners for PrEP-73%/TDF2-63%)</u>**
  - ? Difference in study populations related to sexual activity
  - ? other sexually transmitted infections
  - ? Adherence(discordant couples- Partners)
  - ?Inflammation that can affect HIV susceptibility
- FHI 360 /University of Washington /CDC - compare data from the three studies to better understand differences and similarities.

HIV Prevention

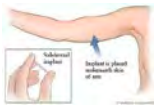
What we now know is that we

- Identify the driving factors that may have influenced FEM PrEP population

  (and VOICE)

Time for new strategies/tools?





Improving Adherence

Delivery tools

- Gels/vaginal ring
- Oral preps
- ? Injectables
- ? patches
- ? Implants
- MPPs

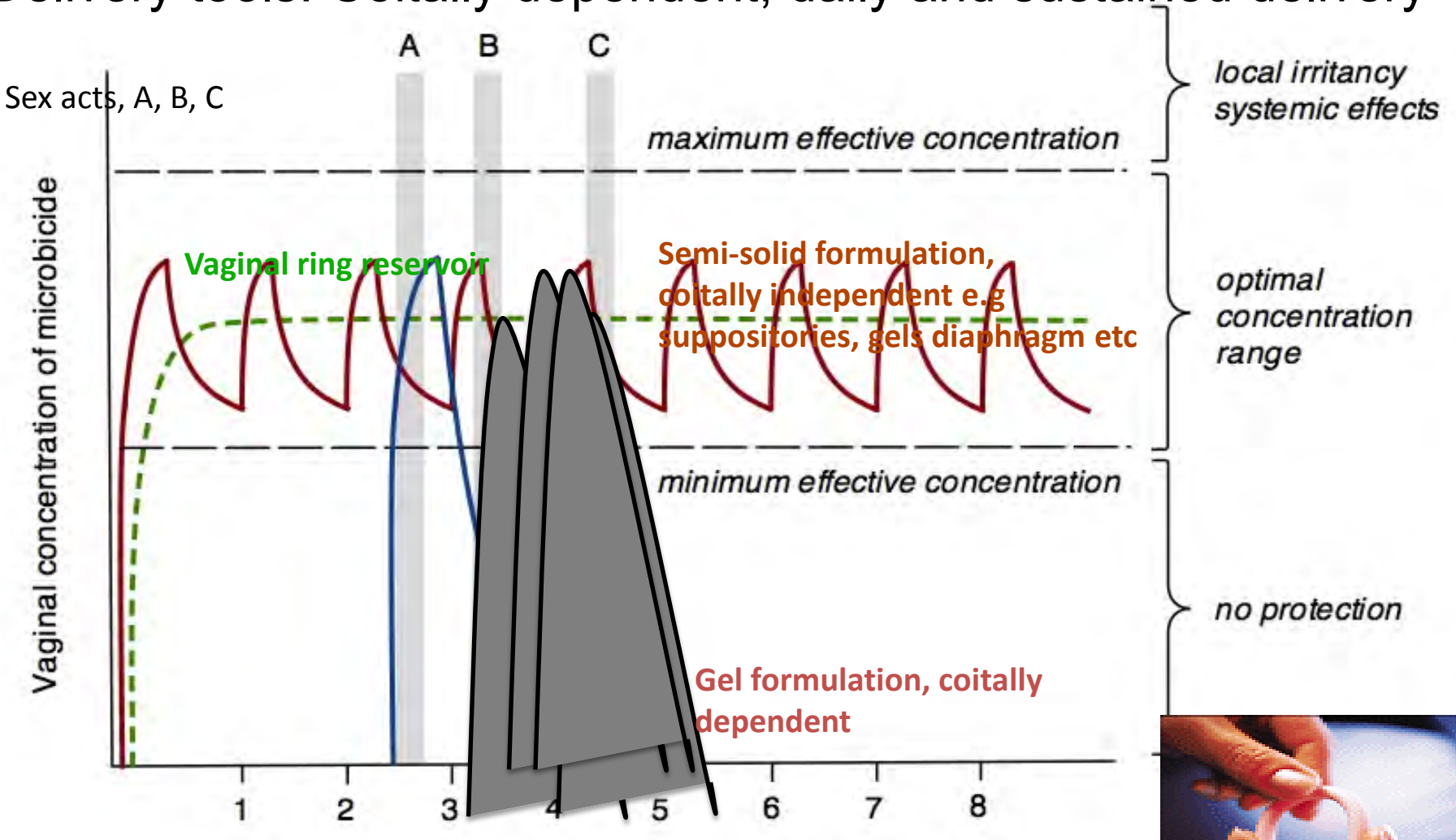
Measuring Adherence

- Self reported
- Pill/gel counts
- Dye test
- Wise bag
- Drug levels- blood/CVF
- Interviews

Explore methods of improving & measuring adherence

Improving Adherence

Delivery tools: Coitally dependent, daily and sustained delivery

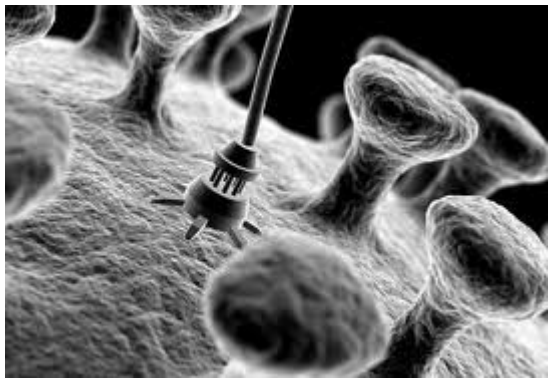


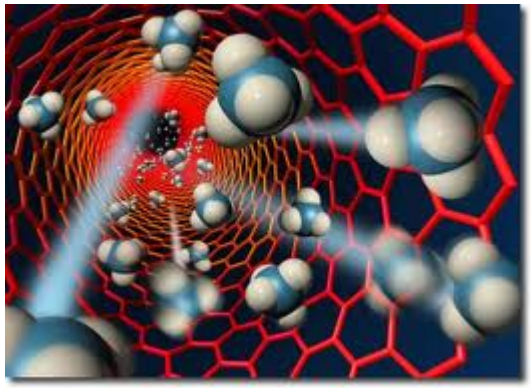
Adapted from Karl Malcolm - Queen's University Belfast

Nanotechnology

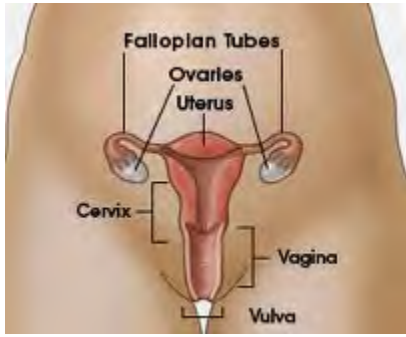
Mucus-penetrating nanoparticles (MPPs) for sustained microbicide delivery

- Novel approach to formulate microbicides potentially leading to uniform epithelial delivery.
- Delivery through vaginal mucus may be possible by controlling nanoparticle size and surface characteristics
- Co-delivery of microbicides and vaccines.





Biological factors



- Levels in genital tract not protective if taking oral product (? Partners for Prevention study showed levels- protective)
  - population -need higher drug levels?
  - More PK/PD studies- get the
    right dose/right drug/right place/right time
- Contraceptive hormones
  - need to explore levels and interactions
- Inflammation driving infection despite drug adherence
  - STIs, BV, HSV, allergy/Douching and other practices,
- Require greater adherence if inflammation present ?

Biological factors Inflammation

- Inflammation-driven infection despite drug adherence

<u>More needs to be done</u>

- Identify the causes of inflammation
  -STIs, BV, HSV, Douching and other practices
- Identify markers of inflammation(local and systemic)
- Prevent or decrease inflammation- ? Use of local anti-inflammatories?
  - Possibility for future-Addition of anti-inflammatory agents to HIV prevention product

CAP 004 sub study showed

HIV infected had higher levels of inflammation in the genital tract prior to HIV infection compared to women who remained uninfected

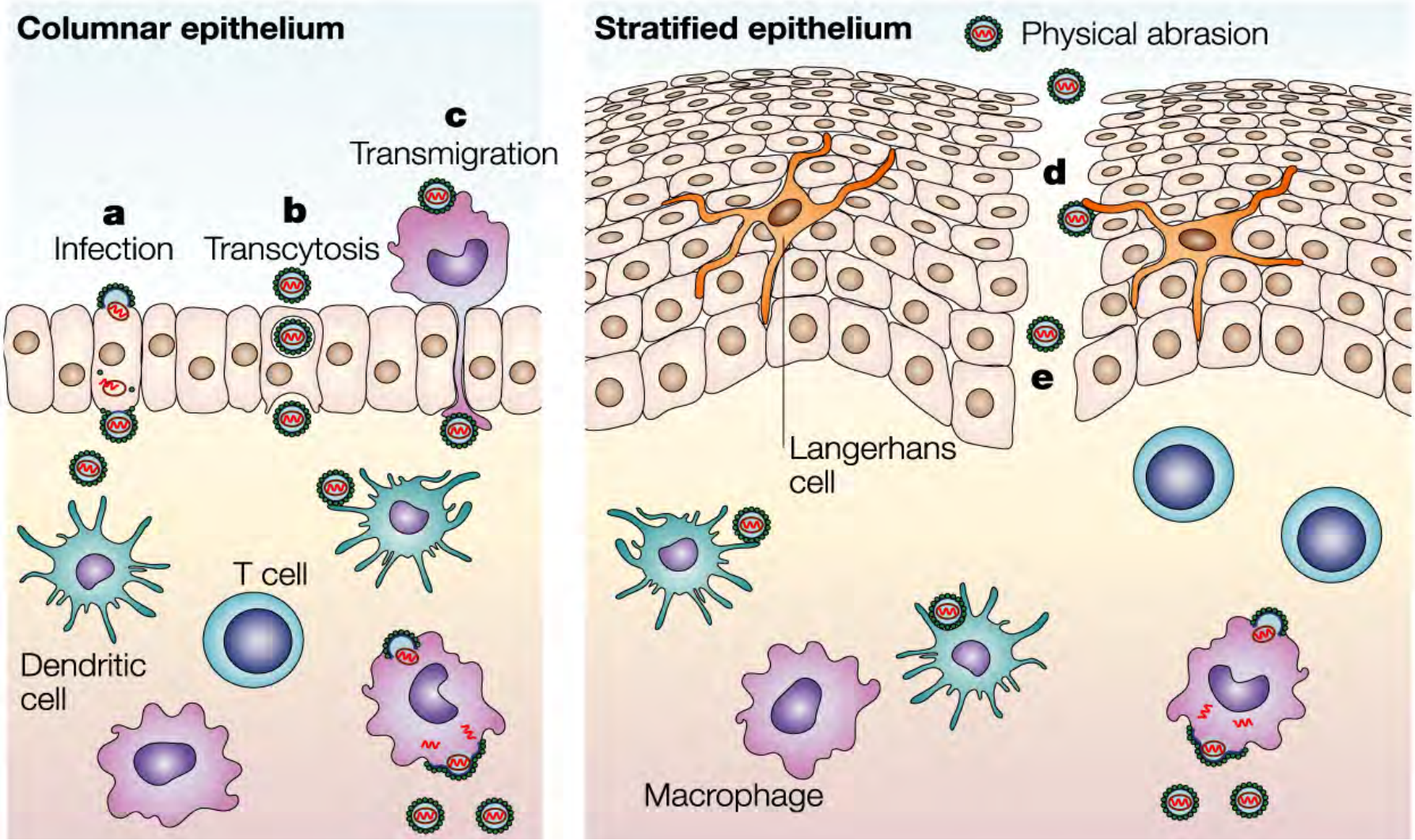
This suggests that high levels of genital tract inflammation may have facilitated breakthrough HIV infections in women using tenofovir gel

Future trials will need to add strategies to control genital tract inflammation

Mechanisms of sexual transmission

Robin Shattock

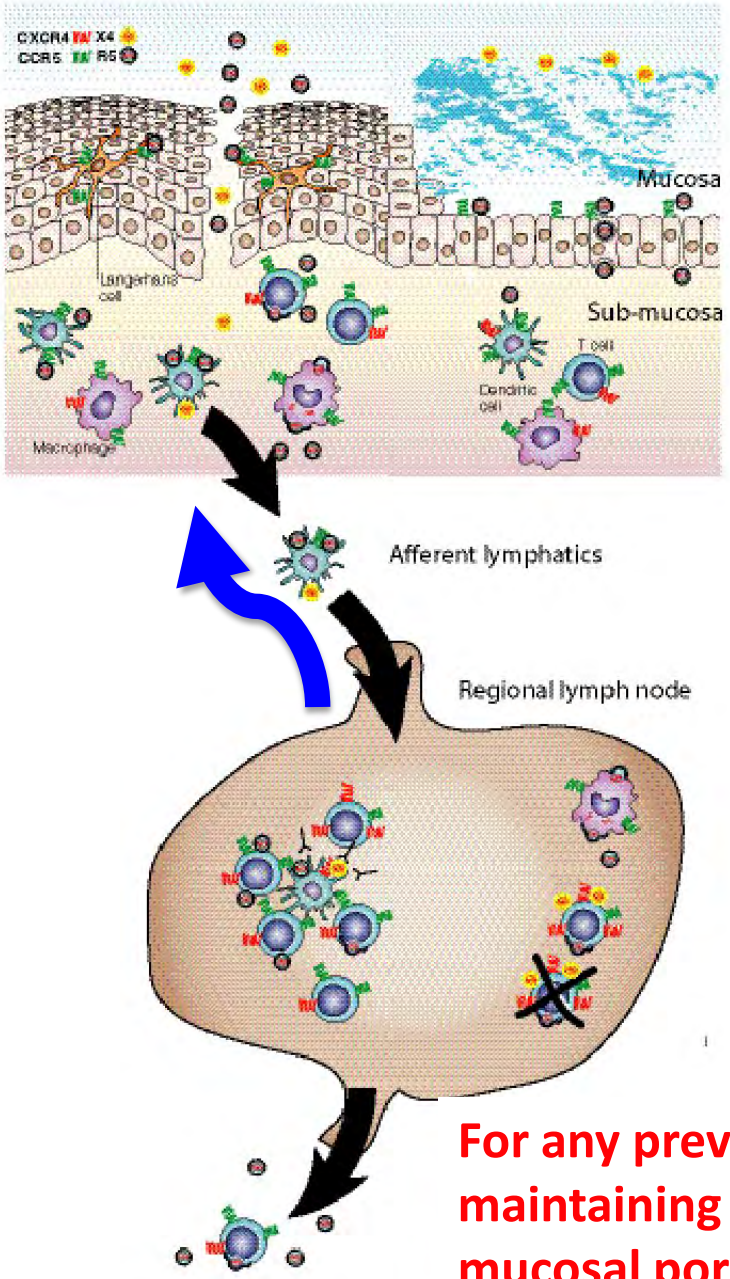
Centre for Infection, Division of Cellular & Molecular Medicine, St George's University of London, UK



Infection of macaques after vaginal exposure to cell-associated simian immunodeficiency virus. Sallé B, Le Grand R.J et al. Infect Dis. 2010 ;202(3):337-44.

Nature Reviews | Microbiology

The time to act is short !



Exposure: 30-60 mins

DC-T cell transfer 1-4 hours
(virological synapse)

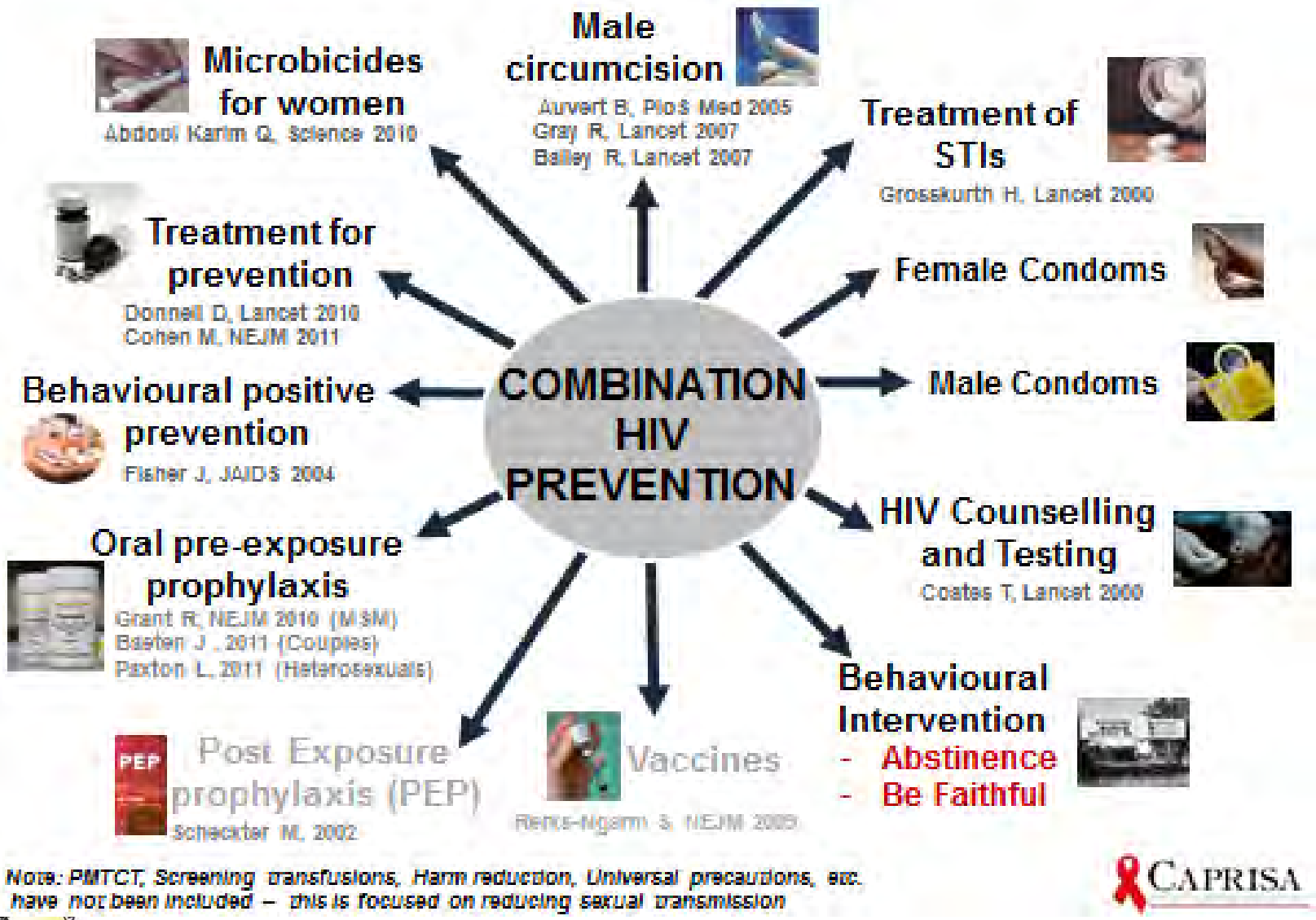
Localized infection: 16-72 hours

Dissemination to draining LN: 24-72 hours
(virological synapse)

For any prevention technology, success will depend on maintaining protective inhibitor concentrations at the mucosal portals of entry.

Combination of some or all factors

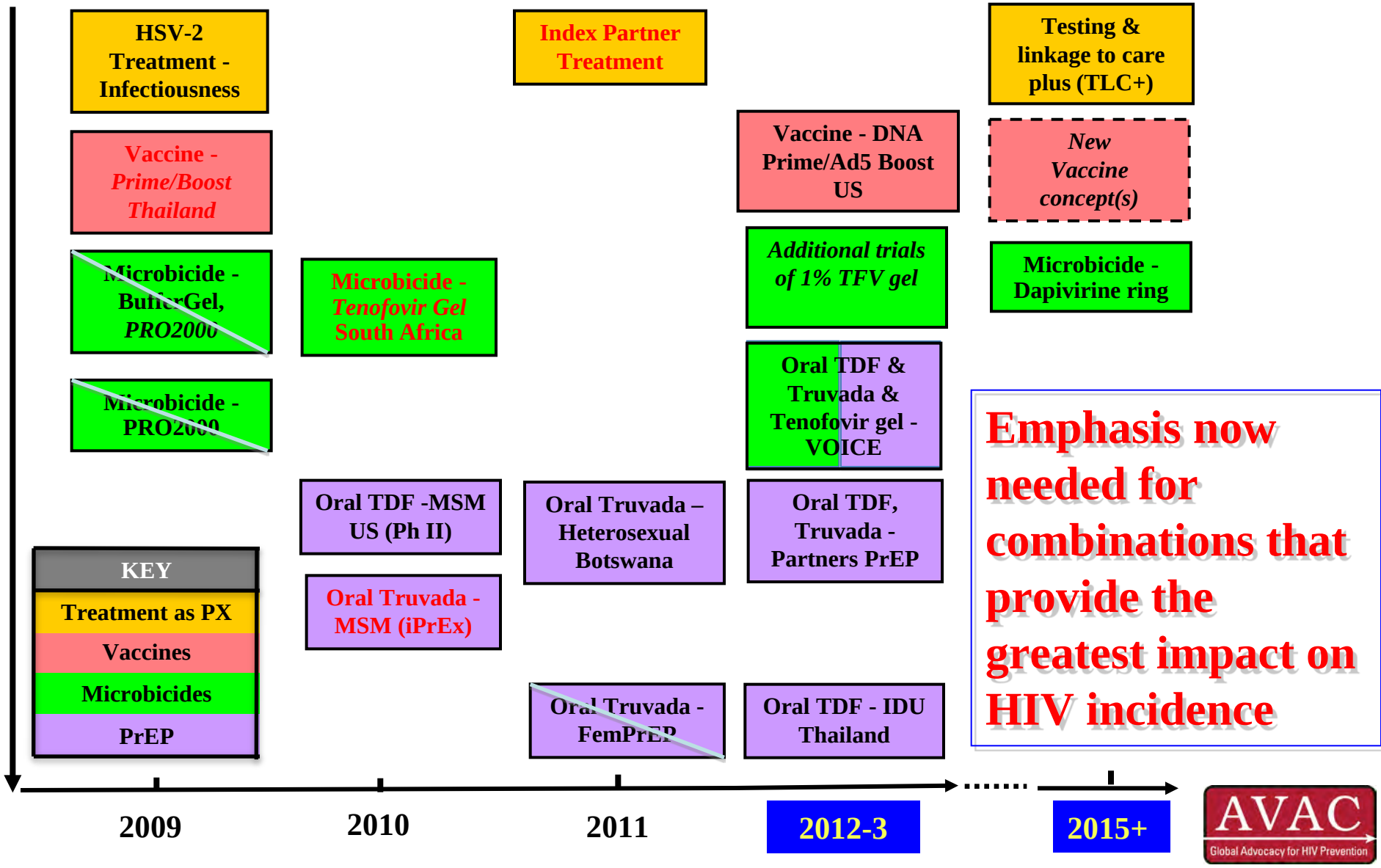
- Some adherence- sub optimal levels
- Biological -Increase inflammation/low drug levels
- Sharing
- Infection by Resistant isolates



Note: PMTCT, Screening transfusions, Harm reduction, Universal precautions, etc. have not been included – this is focused on reducing sexual transmission

CAPRISA

Current clinical prevention research is focused on efficacy trials of individual biomedical interventions



IAS 2011
6th IAS CONFERENCE ON HIV PATHOGENESIS, TREATMENT AND PREVENTION
17-20 JULY 2011 - ROME, ITALY
International AIDS Society
Stronger Together

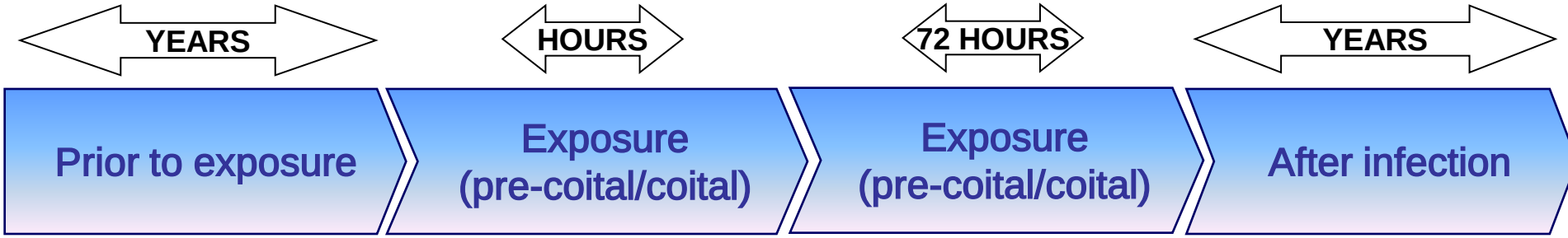
The Combined Approach to Preventing HIV Infection

Robin Shattock, Mitchell Warren,

Sheena McCormack, Catherine Hankins,

Imperial College London
EUROPRISE
UNAIDS
AVAC Global Advocacy for HIV Prevention
MRC Clinical Trials Unit

Opportunities for biomedical interventions



- Male circumcision
- Oral pre exposure prophylaxis (daily PrEP)
- Topical PrEP (daily gels or intra-vaginal rings (microbicides)
- Preventive Vaccines

- Oral pre exposure prophylaxis (intermittent PrEP)
- Coitally dependent topical PrEP (microbicides)

- Oral post exposure prophylaxis (PEP)

- Anti-retroviral therapy
- Immediate treatment of positive partners in discordant couples
- Treatment for prevention in all who test positive for HIV (T4P)

All have a behavioral and structural components

Robin Shattock

Time to consider a combination approach to biomedical interventions

Possible biomedical prevention combinations:

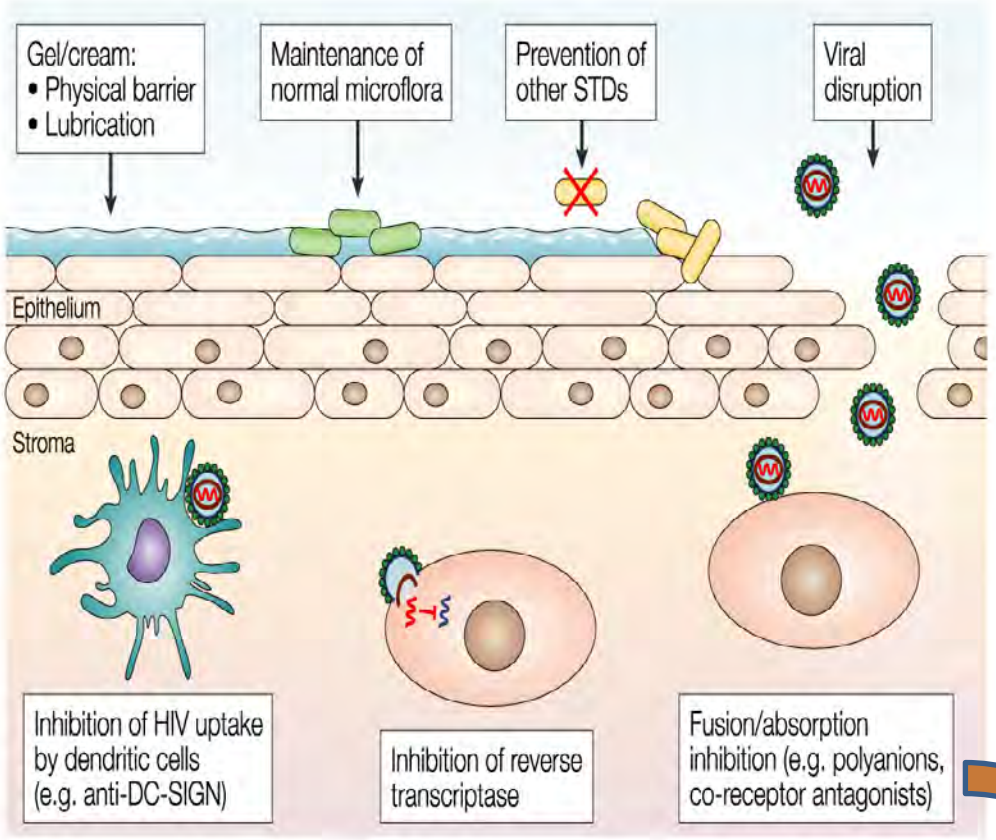
- Oral PREP and microbicides for intermittent dosing
  - optimal systemic and local drug levels (steady state and bolus)
- PrEP (oral, topical) for women combined with circumcision + oral PrEP for men
- T4P combined with ARV PrEP (microbicide or oral for women, oral for MSM) for the HIV-negative partner.
- Vaccines plus ARV PrEP – specific considerations

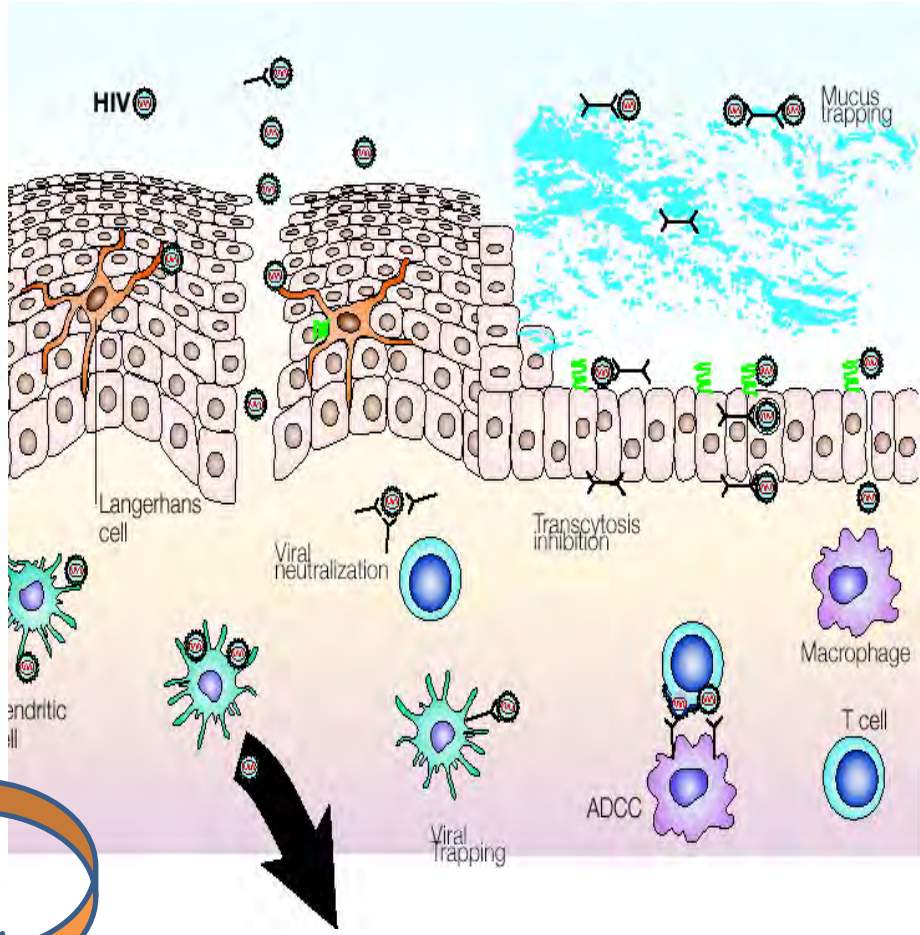
positive promotion of behavioural and structural interventions: providing a comprehensive package of prevention options

Robin Shattock

ARV protection

Immunological protection





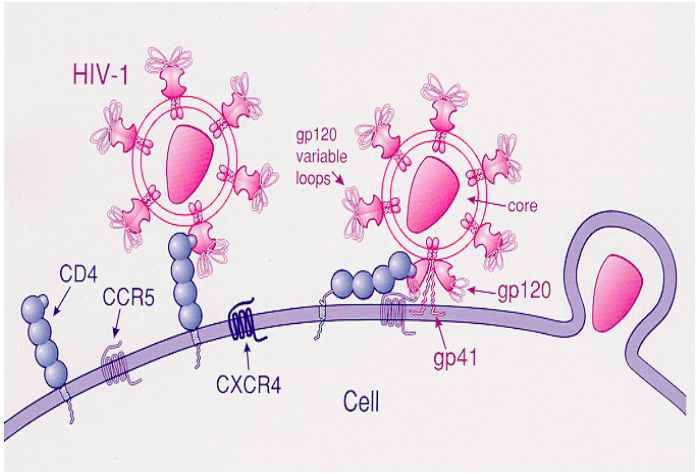
Can they be combined? **Are there potential benefits?**

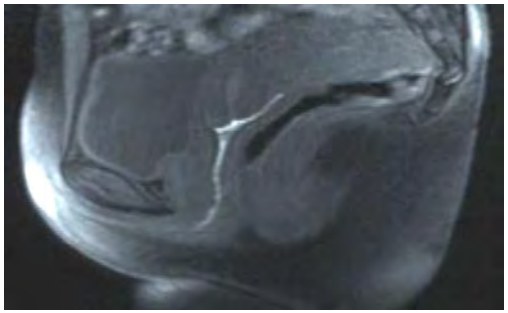
How might (VAXPrEP) deliver better protection?

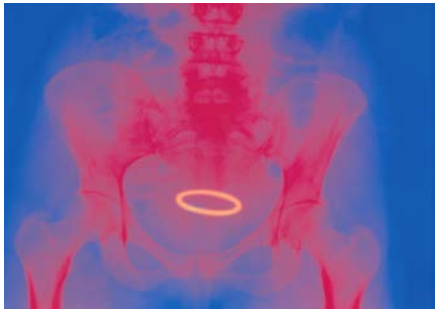
- Providing protection during the immunization period
- Reducing infectious challenge and primary foci of infection
- Boosting local immunity (virus/antigen)
- Coverage between potential re-vaccination campaigns as immunity wanes
- Providing immunological coverage of intermittent PrEP adherence, break through virus and resistance evolution
- And more….

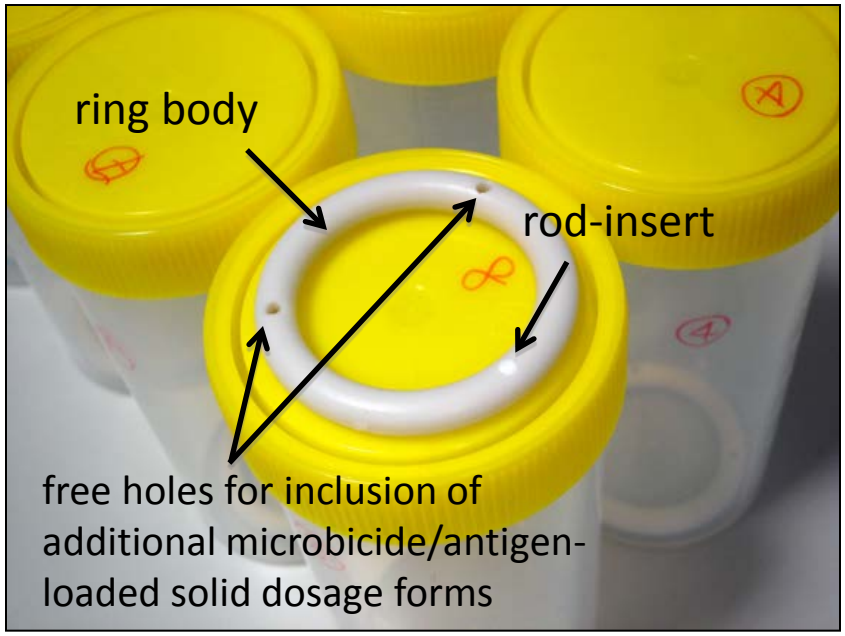
Can vaccine candidates be co-formulated with microbicides?

- Under investigation:
  - Stability analyses of gp140 in microbicide gels
  - Can mucosal vaccination boost localized immunity?



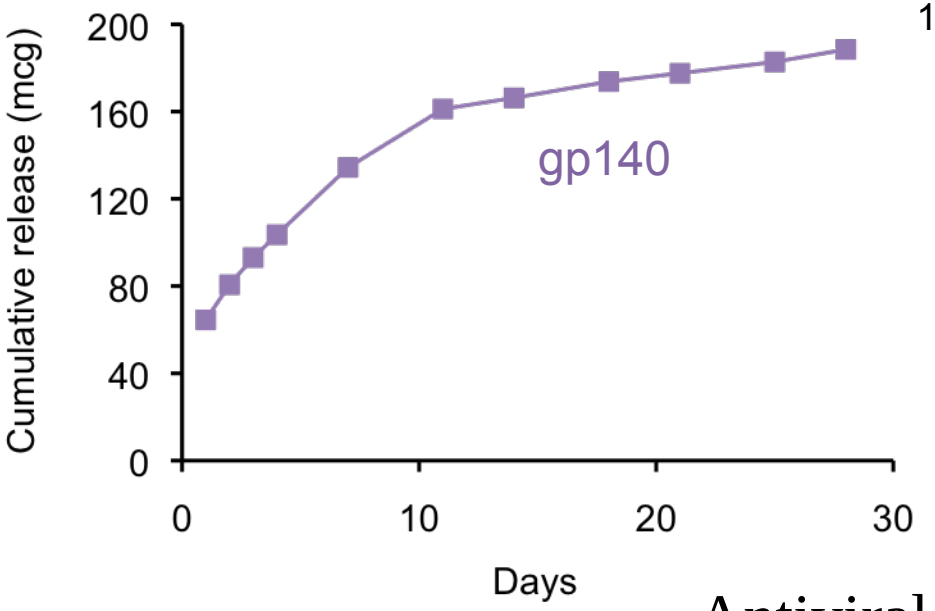


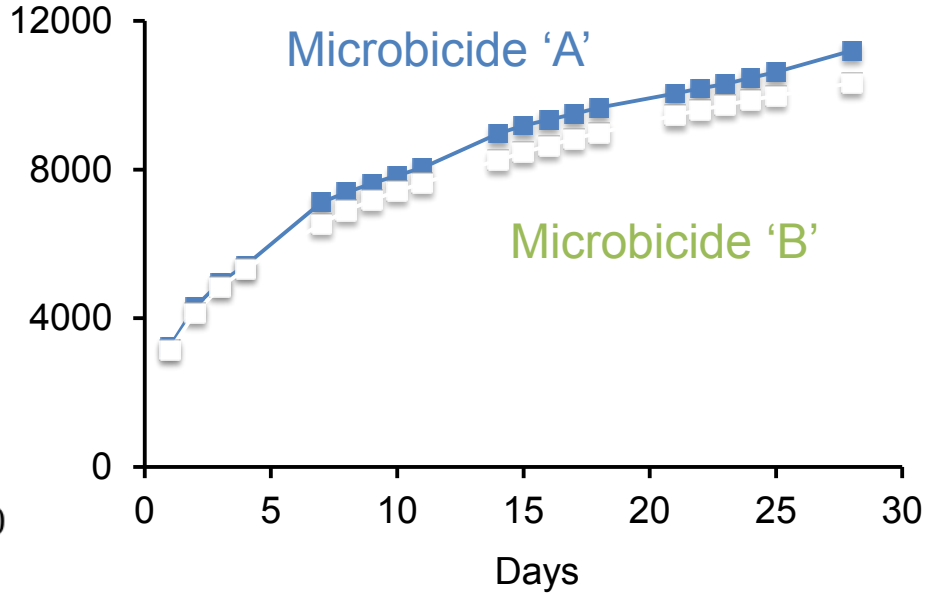




Vaginal ring device comprising single candidate antigen and two lead microbicide candidates

- gp140 in rod-insert
- Microbicide ‘A’ in ring body
- Microbicide ‘B’ in ring body





Antiviral Res. 2010 Dec;88 Suppl 1:S55-66

Can biomedical combinations be tested in clinical trials

Design 1: PrEP reduces risk of HIV acquisition (oral 44-73%, microbicide 39%) – assumes PrEP is available to all participants?

Two-arm study:

PrEP alone

Vaccine + PrEP (VAXPrEP)

- Requires 30 to 60 incident infections to assess the additional benefit of vaccination on risk of infection and setpoint viral load.
- Main challenge, PrEP as active control arm will reduce incidence and increase trial size
- Superiority of VAXPREP does not imply vaccine alone is efficacious
- Lack of superiority does not imply vaccine alone is ineffective (potential antagonism).

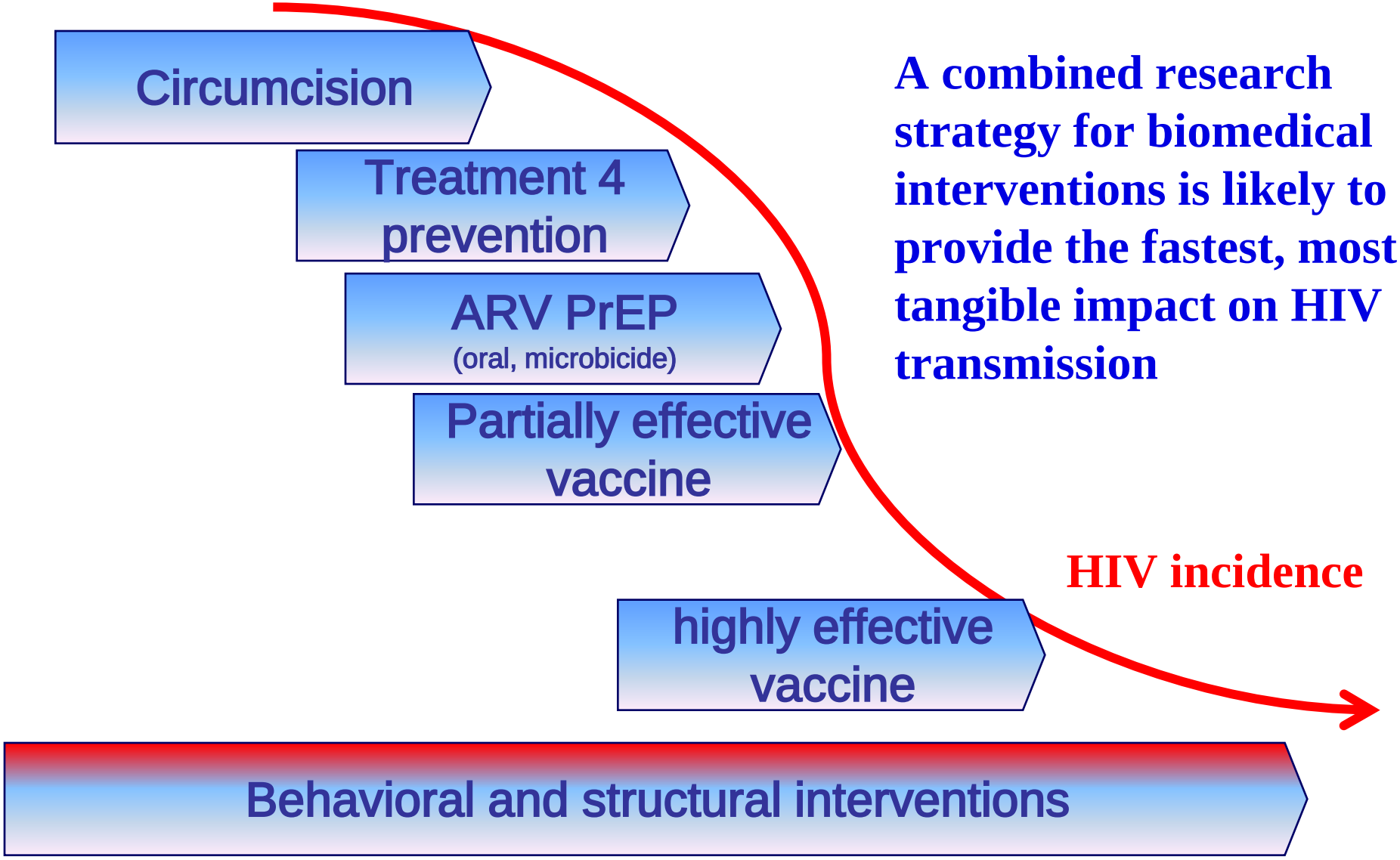
Excler JL, et al AIDS Res Hum Retroviruses. 2010 Dec 16.

Summary

- Can mucosal exposure to virus in the context of PrEP lead to immune response:
  - indicated in animals, yet to be tested in humans
- Can microbicide delivery technology be used for vaccination:
  - Yes
- Does vaginal vaccination modify mucosal immunity to HIV:
  - indicated in animals, yet to be tested in humans
- Can vaccine induced immunity be broadened through protected exposure to prevalent virus:
  - currently being tested in animals.
- Will VAXPrEp provide better protection than PrEP alone?:
  - currently being evaluated in animal models
- Can combination prevention be tested in human trials:
  - Yes

Pathway to reversing the epidemic

Seeing prevention research/funding as a continuum



A combined research strategy for biomedical interventions is likely to provide the fastest, most tangible impact on HIV transmission

Science. 2011;333:42-3

QUESTIONS?

Thank you