Where are we going after effectiveness studies?

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MTN Annual Meeting
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Introduction

- 30 years into the HIV/AIDS epidemic, significant progress in prevention/treatment
- Number on ART in RLS increased over 10-fold, but
  - 2 new infections for every 1 person starting treatment
- Need for effective HIV prevention remains urgent!
- RCTs gold standard for informing HIV prevention and policies
- What has been happening in the HIV prevention research arena in the past 3 decades?

From questions to our 1st answers

- 39 RCTs between 1987 and 2010
- Only 7 with significant protective benefit
  - Male circumcision (**3**) – *Orange Farm, Kisumu, Rakai*
  - STI treatment (**1**) – *Mwanza STI treatment*
  - Vaccine (**1**) – RV144/*Thai vaccine*
  - Microbicides (**1**) – *CAPRISA 004*
  - PrEP (**1**) - *iPrEx*
- 2010 - first proof of concept

PrEP Timeline

PrEP Concept **2001**

Cambodia PrEP trial proposed with sex workers **2003**

Protests at Bangkok AIDS conference **2004**

West Africa phase II trial of tenofovir in sex workers **2005**

Safety of tenofovir reported at Toronto AIDS conference **2006**

Phase IIB & III trials start in IDUs, MSM & heterosexuals **2007-2009**

CAP 004 & iPrEx results **2010**

2011-2013: 2012: Possible FDA approval for Truvada as PrEP for HR MSM 2013 – VOICE, Partners and FEM-PrEP results

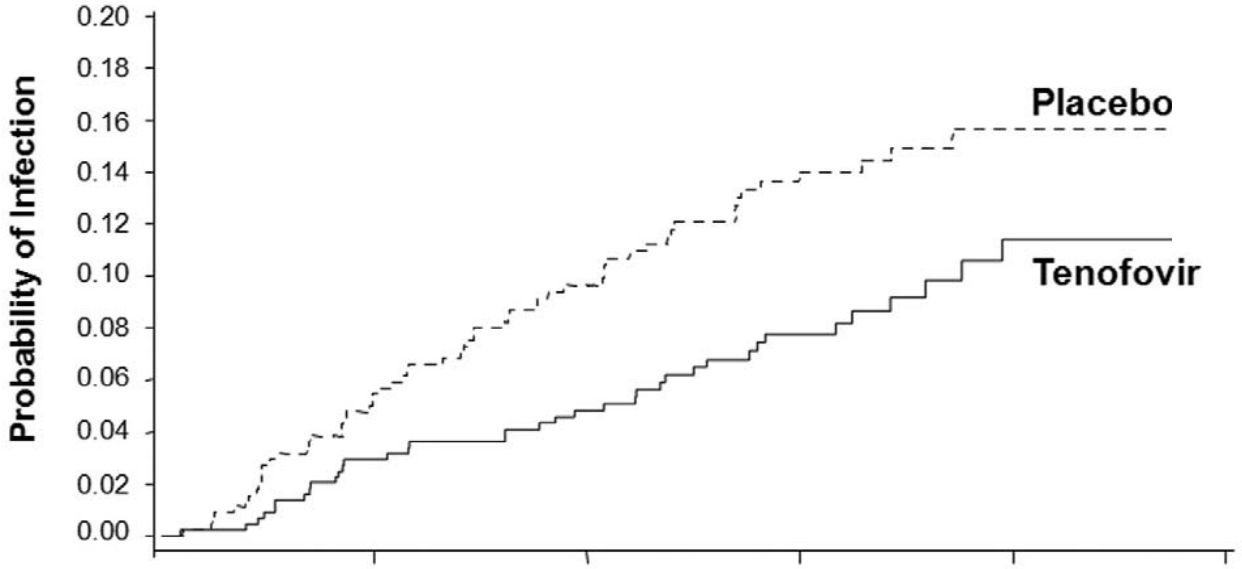
Next steps: FACTS 001, CAP 008 iPrEx OLE, MTN-018 Partners Open Label

Completed Trials

CAPRISA 004

- **Phase 2B trial:** safety and effectiveness of TFV gel for preventing HIV in women
- **889 women:** ≥18 years (mean age 23; mostly unmarried) from rural (69%) or urban (31%) communities in KwaZulu-Natal
- **Randomization:** to tenofovir gel (445) or placebo gel (444)
- **Coitally dependent:** gel within 12 hrs before & 12 hrs after sex, max. 2 applications/24 hrs (BAT-24)
- **Good safety profile:** ↑ mild, self-limiting diarrhea

HIV incidence in CAPRISA 004



Months of follow-up	6	12	18	24	30
Cumulative HIV endpoints	37	65	88	97	98
Cumulative women-years	432	833	1143	1305	1341
HIV incidence rates (Tenofovir vs Placebo)	6.0 vs 11.2	5.2 vs 10.5	5.3 vs 10.2	5.6 vs 10.2	5.6 vs 9.1
Effectiveness (*P*-value)	**47% (0.064)**	**50% (0.007)**	**47% (0.004)**	**40% (0.013)**	**39% (0.017)**

Abdool Karim Science 2010

The iPrEx Study

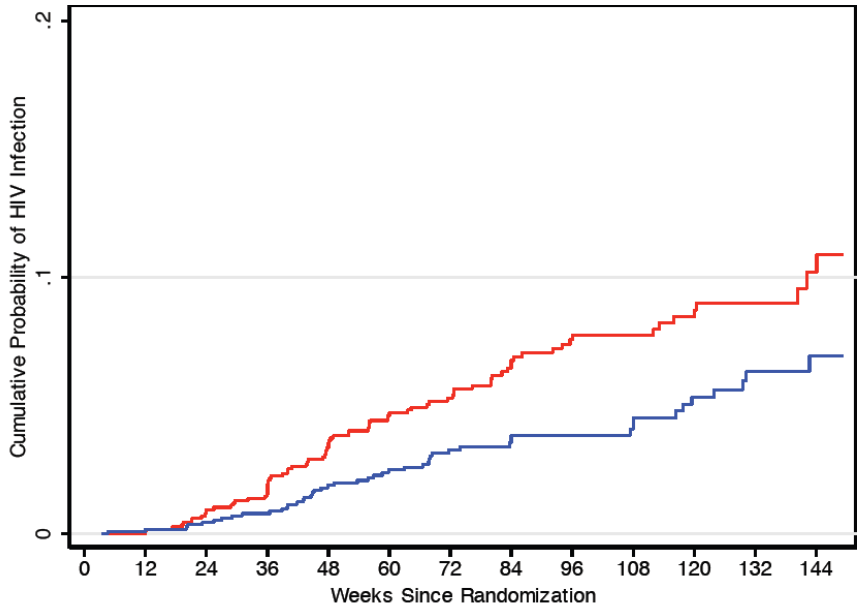
- **2499 MSM** randomized 1:1, daily oral FTC/TDF vs. placebo
- **Young high risk population**
  - 50% <25 yrs
  - Median 18 partners in 12 wks prior to enrollment
- **11 sites** (Brazil, Ecuador, Peru, South Africa, Thailand, US)
- Comprehensive HIV prevention package
- **Completed 2010; excellent safety profile**
  - ↑ nausea 1st month
  - Small decrease in bone mineral density

Updated iPrEx Efficacy

131 infections after randomization

48 on FTC/TDF

83 on placebo



Updated efficacy estimate (mITT):
42% reduction in HIV acquisition
(95% CI 18%-60%)

Data as of Nov 21 2010,
Grant *et al*, CROI 2011

Prevention in Pictures: 2010

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 30, 2010 VOL. 363 NO. 27

Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men

Robert M. Grant, M.D., M.P.H., Javier R. Lama, M.D., M.P.H., Peter L. Anderson, Pharm.D., Vanessa McMahan, B.S., Albert Y. Liu, M.D., M.P.H., Lorena Vargas, Pedro Goicochea, M.Sc., Martín Casapía, M.D., M.P.H., Juan Vicente Guanira-Carranza, M.D., M.P.H., Maria E. Ramirez-Cardich, M.D., Orlando Montoya-Herrera, M.Sc., Telmo Fernández, M.D., Valdilea G. Veloso, M.D., Ph.D., Susan P. Buchbinder, M.D., Suwat Chariyalertsak, M.D., Dr.P.H., Mauro Schechter, M.D., Ph.D., Linda-Gail Bekker, M.B., Ch.B., Ph.D., Kenneth H. Mayer, M.D., Esper Georges Kallás, M.D., Ph.D., K. Rivet Amico, Ph.D., Kathleen Mulligan, Ph.D., Lane R. Bushman, B.Chem., Robert J. Hance, A.A., Carmela Ganoza, M.D., Patricia Defechereux, Ph.D., Brian Postle, B.S., Furong Wang, M.D., J. Jeff McConnell, M.A., Jia-Hua Zheng, Ph.D., Jeanny Lee, B.S., James F. Rooney, M.D., Howard S. Jaffe, M.D., Ana I. Martinez, R.Ph., David N. Burns, M.D., M.P.H., and David V. Glidden, Ph.D., for the iPrEx Study Team*

Science

Science **329**, 1168 (2010)

Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women

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Trials in the Field

VOICE (MTN-003)

VOICE
VAGINAL + ORAL INTERVENTIONS TO CONTROL THE EPIDEMIC

- Phase 2B safety and effectiveness
  - daily use of oral tenofovir, oral Truvada and TFV gel vs. placebo tablet or placebo gel
- Endpoint-driven trial powered to detect 25-55% effectiveness
- 5,000 women at sites in Uganda, South Africa and Zimbabwe
  - 1800 w-y of safety data on tenofovir gel
- Able to assess which route women prefer
- Results expected Q1 2013

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microbicide trials network

Other Effectiveness Trials

- **Partners PrEP**
  - 4,700 HIV-serodiscordant couples
  - Phase 3, TDF or FTC/TDF use in HIV- partner
  - Fully enrolled, Kenya and Uganda
- **FEM-PrEP**
  - 3,900 high risk women, Phase 3, FTC/TDF use
  - Kenya, Malawi, South Africa, Tanzania, Zimbabwe
- **CDC 4370**
  - Phase 2/3 of daily TDF in IDU, Thailand
- **IPM 009A and 009B**
  - Planned Phase 3 DPV ring, sub-Saharan Africa

PARTNERS PrEP STUDY

FEM-PrEP

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

INTERNATIONAL PARTNERSHIP for MICROBICIDES

Planning for What's Next

Efficacy vs. Effectiveness

WHO/UNAIDS Consultation

- **Purpose**
  - Consensus plan to map next steps for regulatory approval of TFV gel following CAPRISA 004
- **Next steps defined**
  - Confirmatory Phase 2B/3 studies - BAT 24 strategy
  - Phase 3B/4, implementation science studies - assessing models for health service implementation
  - Phase 1 and 2 safety studies in adolescents, pregnancy, HBV

FACTS 001

- South African consortium of researchers formed following CAPRISA 004 results
- Planned Phase 3 study of BAT 24 regimen
- 3,150 HIV-negative, sexually active women, **16**-30 years old
- 7 sites in South Africa
- Safety and effectiveness of TFV gel for protection against both HIV and HSV-2
- 2000 w-y of safety data on TFV gel in a 24-month trial

CONRAD/FDA Meeting

- Normally, two well-controlled Phase 3 studies for standard regulatory approval
  - using drug formulation and dosing schedule requested for approval
- 3000 w-y safety needed for TFV gel NDA
- FDA to review TFV gel dossier under “fast-track”
- Pregnancy, adolescence, post-menopausal data a priority
- Both CAPRISA 004 and VOICE as pivotal trials despite different dosing strategies

Civil Society Consultation

- ***Next Steps for ARV-Based Prevention: A Civil Society Consultation on Follow-up Research***
- January 17-18, 2011, Johannesburg
- Forum to discuss challenges and opportunities
- Consultation to inform follow-up protocol to VOICE

CAPRISA 008

- Planned Phase 3B, two-arm, open-label randomized trial
  - **Control Arm**: CAPRISA clinics, monthly provision & monitoring, former CAPRISA 004 participants
  - **Intervention Arm:** Public sector family planning services, 2-3 monthly provision & monitoring, research naïve
- Feasibility and effectiveness of providing TFV gel in clinical setting
- 700 women (urban and rural)
- Study duration up to 30 months

Partners Follow-up Study

- Observational, open-label, prospective cohort
- Partners PrEP + additional naïve couples
- TDF or FTC/TDF decision pending results
- Uptake, adherence, retention, risk perception/ behaviors, monthly vs. quarterly HIV testing
- Ancillary: safety in pregnancy and BF
- Demonstrate deliverability in a non-clinical trial setting

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microbicide trials network

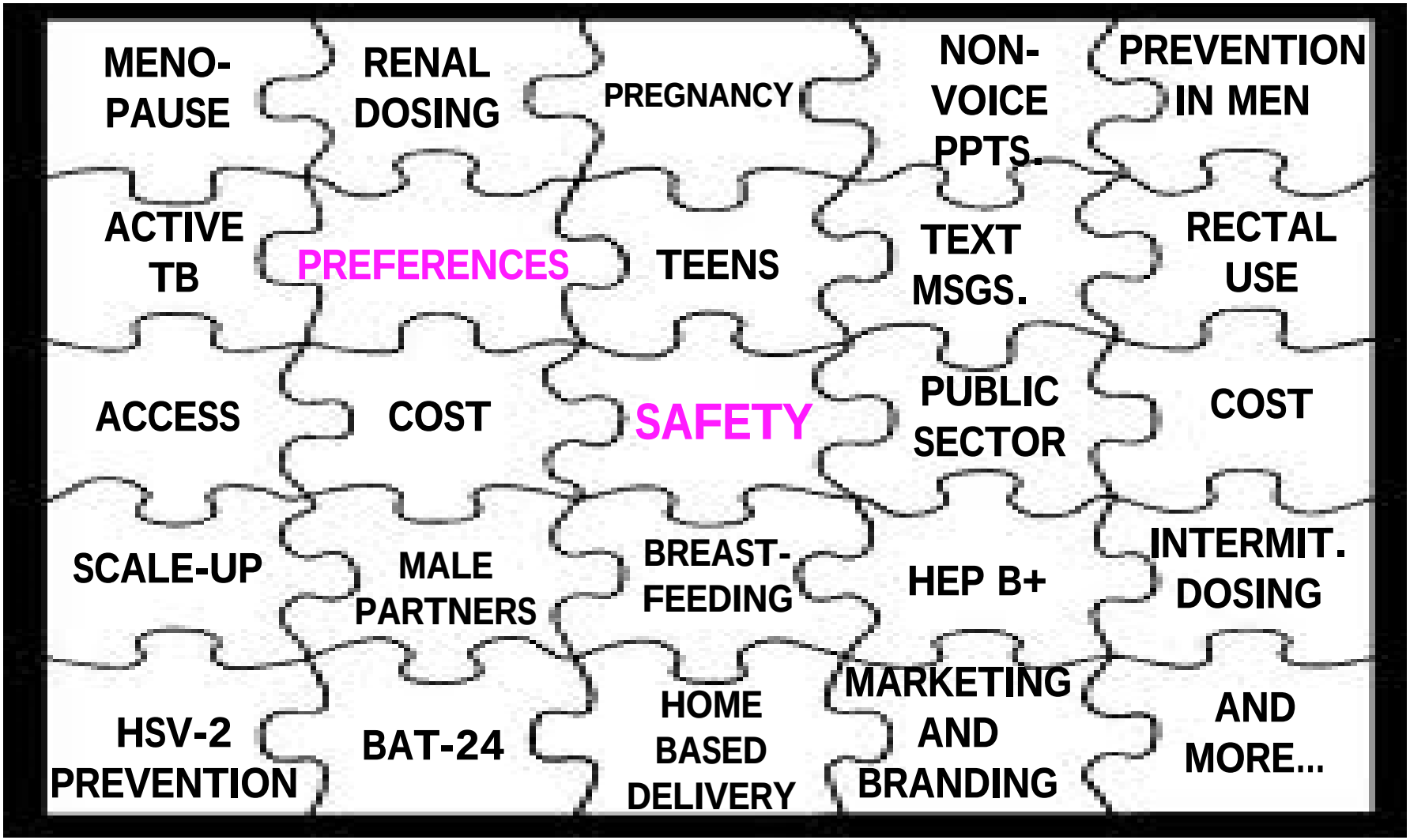
iPrEx OLE

- Intracellular drug almost never detected in iPrEx seroconverters – key finding r/t adherence
- Open label extension – roll over from active arm
  - **Can PrEP education increase adherence?**
  - Additional safety data on long-term PrEP use
- Information about PrEP efficacy might decrease perception of HIV risk
- Risk compensation/increased risk behavior
  - decreased use of condoms or more partners
- Information about PrEP safety and efficacy may increase pill use, drug exposure

Next steps after VOICE

- VOICE – necessarily intense monitoring
- Public sector – research-style regimen of labs/exams not sustainable
- Can we make safety monitoring more sustainable without compromising safety?
- How might women approach decisions about product use if more than one effective method of HIV prevention is available?

It’s a giant puzzle!



MTN-018 (CHOICE)

Committed to Having Options for Interventions to Control the Epidemic

CHOICE

- Phase 3B, open-label, multi-site, randomized
  - Monthly f/u vs.
  - Quarterly f/u
- Potential study products (pending VOICE results)
  - Tenofovir gel, Truvada tab and/or TDF tab
- Former VOICE sites
- HIV-, healthy population
  - ~ 4000 former VOICE participants
  - ~ 300 research-naïve participants
- Protocol version 0.4, PSRC first review 15 March

MTN microbicide trials network

Opportunities in CHOICE

- In context of monthly vs. quarterly visits
  - Understand product use, safety and risk behaviors in healthy HIV- women
  - Investigate validity of algorithm to identify acute seroconversion
- If both oral and topical products in CHOICE
  - Opportunity to let women choose
  - Product switching
- Pregnancy and BF substudies planned

CHOICE Timeline

Committed to Having Options for Interventions to Control the Epidemic

CHOICE

2010
- MTN EC approved concept
- Draft circulated, community consultation

2011
- Protocol consultation w/ advocates
- Protocol development & DAIDS approval

2012
- *Prepare for possible implementation*
- *Close f/u in VOICE, analyze results*

2013
- *Final IRB approvals*
- *Open for accrual*

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Food for thought

- Exciting time in HIV prevention research
- Many critical questions will remain after approval and registration of new products
- Public health impact driven more by coverage and use than by absolute level of effectiveness
- Phase 3B studies like CHOICE – key role in capacity to gain additional safety data for licensure and inform implementation

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Thank you


VOICE
VAGINAL + ORAL INTERVENTIONS
TO CONTROL THE EPIDEMIC


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CHOICE


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INTERNATIONAL
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FDA


fhi
THE SCIENCE OF
IMPROVING LIVES


GILEAD


CONRAD
Leaders in Reproductive Health and HIV Prevention


PARTNERS PrEP STUDY


GLOBAL
PrEX


CAPRISA


FACTS
Follow on Africa Consortium
for Tenofovir Studies


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