

HIV Prevention Trials Network

“State of the Network” - 2009

Sten Vermund, MD, PhD

Vanderbilt University Institute for Global Health
P.I., HPTN Coordinating and Operations Center at FHI

Thanks: Quarraisha Abdool Karim, Katie Allen, Kathy Hinson, Nirupama Sista

HPTN-IMPAACT Annual Meetings, May 4-8, 2009, Maryland



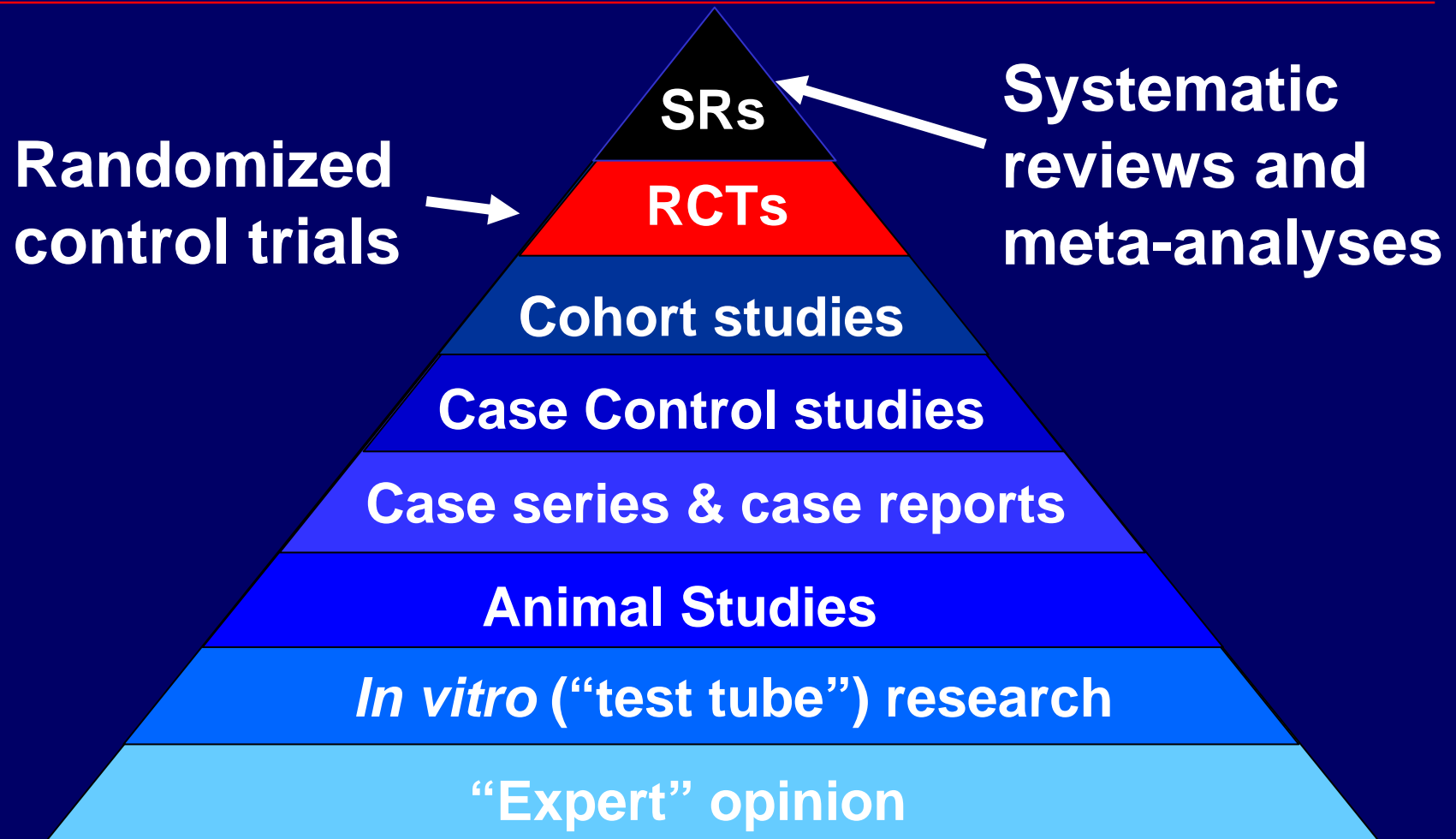
Introduction to the HPTN

- *Our Vision:* Discovery of effective HIV prevention strategies that can be applied immediately
- *Our Theme:* **Prevention NOW!**

Our strategy to prevent sexual and parenteral HIV infection

- Evaluate biomedical and behavioral interventions
- Optimize combinations of interventions
 - Evaluate application of proven &/or efficacy of unknown
- Target populations at highest risk geographically
 - In 4 regions: US, South America, Africa, Asia
- Address the full continuum of infection
 - Uninfected at high risk → Recently HIV infected → Established HIV infection

Our Approach: RCTs



HTPN Overview

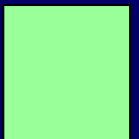
- Preventing HIV infections in 2009
- HPTN's recent contributions to prevention science
- Challenges to prevention of HIV

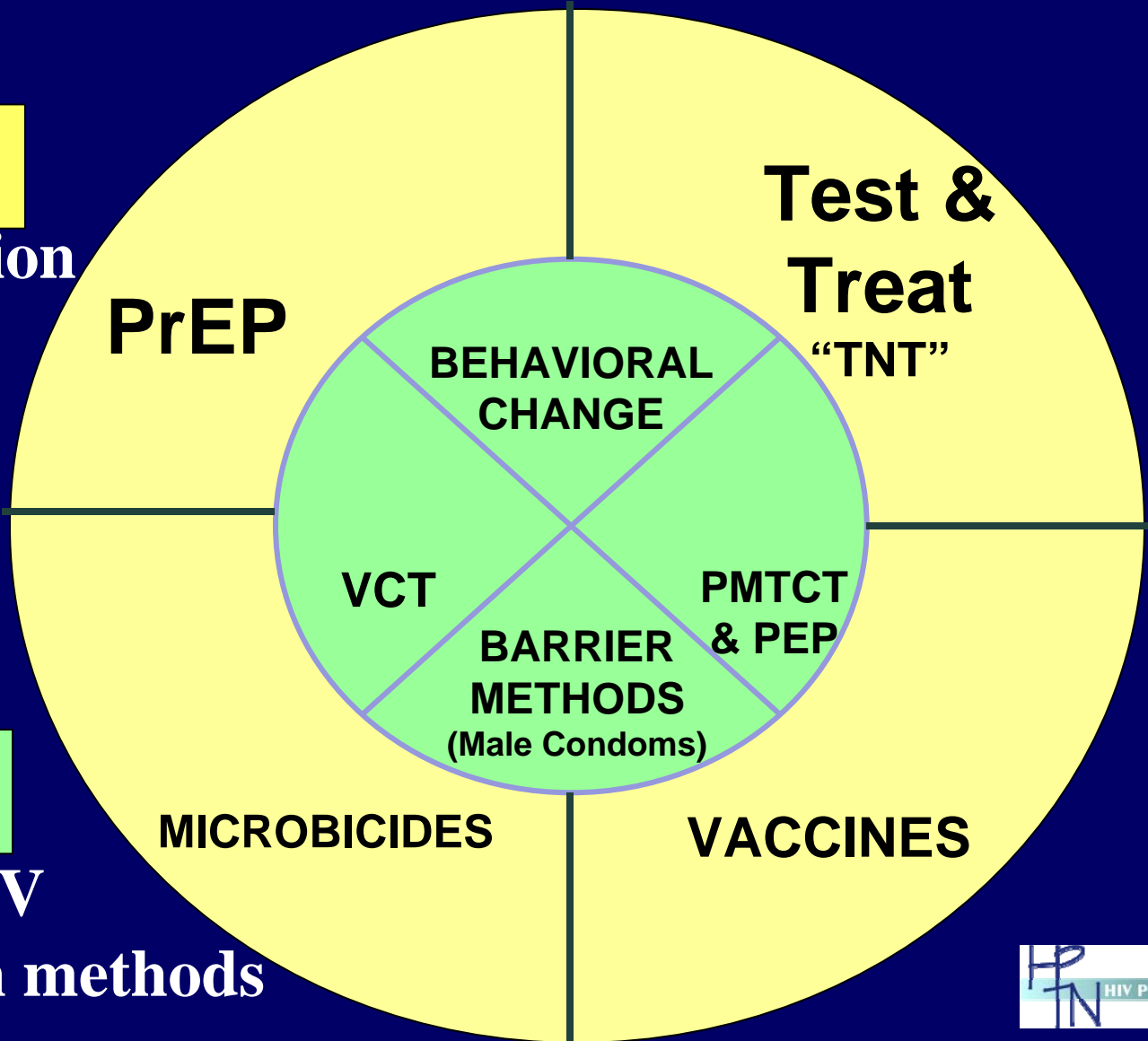
Preventing sexual and parenteral transmission

- Adult male circumcision effective (3 of 3 RCTs)
- Promise of Pro 2000 gel 0.5% (1st microbicide)
 - Safe & 30% reduced HIV incidence (**HPTN 035**)
- STD control effective (1 of 5 RCTs)
- “ABCC” behavior modification successes
 - ABc in Uganda
 - aBC in Thailand (100% condom use)
- Needle exchange and opiate agonists

Prevention Strategies - 2009

Under investigation 

 Proven HIV prevention methods



HPTN Trial Achievements

- Past: 037, 039 trials completed in 2007-'08
 - 037: IDU network intervention-- US & Thailand
 - 039: Suppress HSV-2 to reduce HIV-- MSM in No. & So. America, high risk women in Africa
- Present: 043, 052, 058 trials in 2009-'10

Examples of HPTN Publications

- Diverse and compelling published findings in past year:
 - Celum C et al. Effect of aciclovir on HIV-1 acquisition in HSV-2 sero+ women and MSM: : a randomised, double-blind, placebo-controlled trial. *Lancet* 2008
 - Kapiga S et al. Risk factors for incidence of STI among women in South Africa, Tanzania, and Zambia: HPTN 055. *Sex Transm Dis* 2009
 - Khumalo-Sakutukwa G et al. Project Accept (HPTN 043): a community-based intervention to reduce HIV incidence in populations at risk for HIV in ... Africa & Thailand. *JAIDS* 2008
 - Laeyendecker O et al. The effect of viral suppression on cross-sectional incidence testing in the Johns Hopkins Hospital emergency department. *JAIDS* 2008

More HPTN publication examples

- Latkin CA *et al.* The efficacy of a network intervention to reduce HIV risk behaviors among drug users and risk partners in Chiang Mai and Philadelphia. *Soc Sci Med* 2009
- MacQueen KM *et al.* Partnering for Care in HIV Prevention Trials. *J Empirical Res Human Res Ethics* 2008
- Morin SF *et al.* Building community partnerships: case studies of CABs at research sites in Peru, Zimbabwe, & Thailand. *Clin Trials* 2008.
- Mayer KH, Pizer HF, *editors.* *HIV Prevention: A Comprehensive Approach.* Academic Press; 2008.

What's next for HPTN prevention science in 2009?

- Future: 4 trials to be launched in next months
 - HPTN 061 (BROTHERS) and 064 (ISIS)
 - HPTN 063 (+ prevention) and 062 (risk reduction in acute infection)
 - Capsules approved for Concept development
 - HARP, PrEP x3, TNT

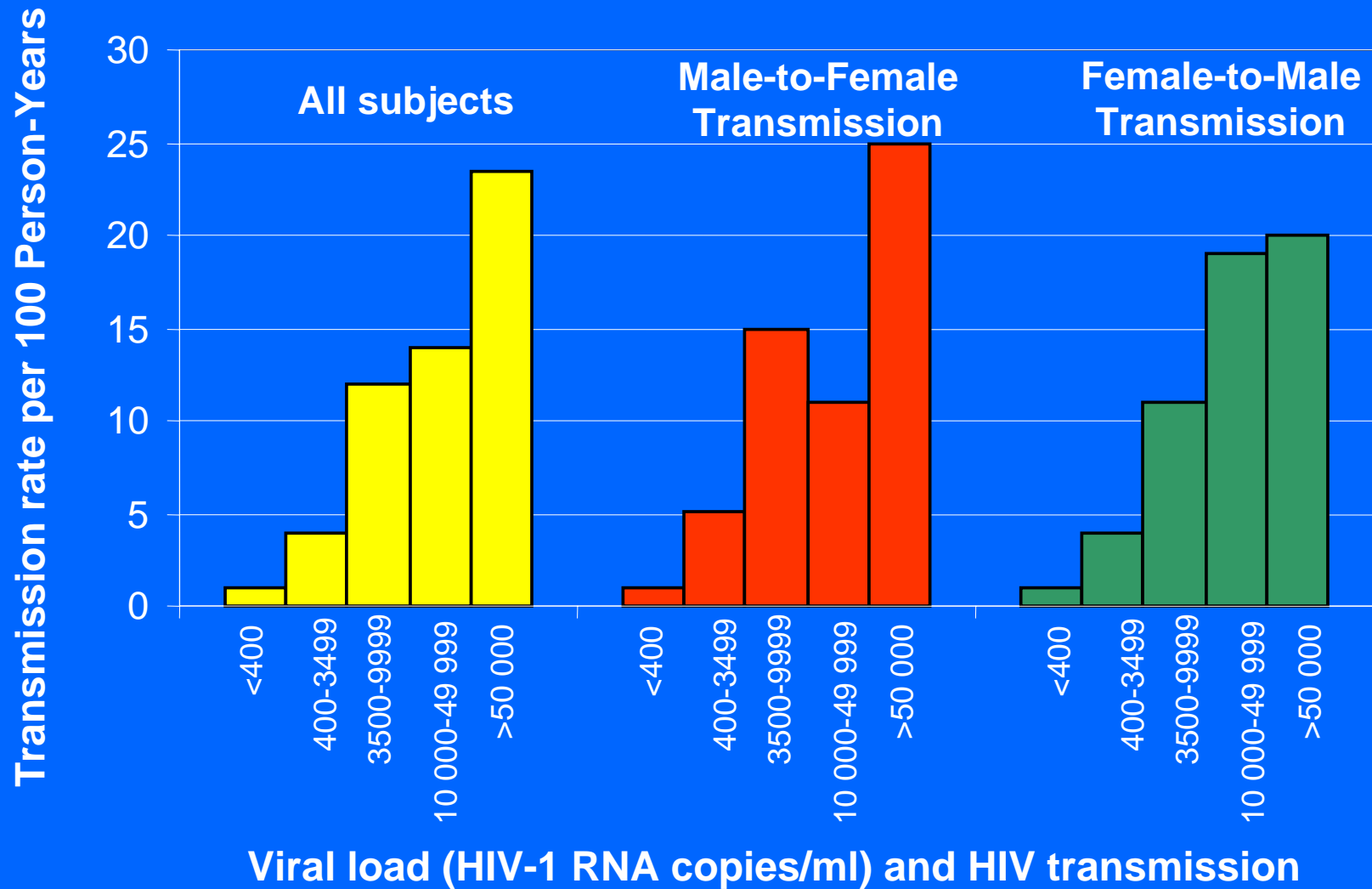
What are these acronyms?

- **HARP:** highly active antiretroviral therapy
 - Use of multiple prevention strategies together
- **PrEP:** pre-exposure prophylaxis with ART
 - ART to seronegative persons at high risk
- **TNT:** test and treat
 - Expanded testing and peer health navigation
 - Early therapy, adherence, positive prevention
 - Links to mental health and substance abuse programs

ART for Prevention: Key Research Questions

1. Does expanded HIV testing reduce HIV transmission in a given community?
2. Does an HIV+ person who is treated early or has a behavioral intervention transmit less to an HIV-sexual partner?
3. Should HIV therapy be started earlier than current SOC?
4. Do behavioral interventions in HIV positive individuals prevent transmission?
5. Can we better engage hard-to-reach populations?
6. Can combined testing expansion and bridging to good HIV/AIDS care reduce HIV incidence?

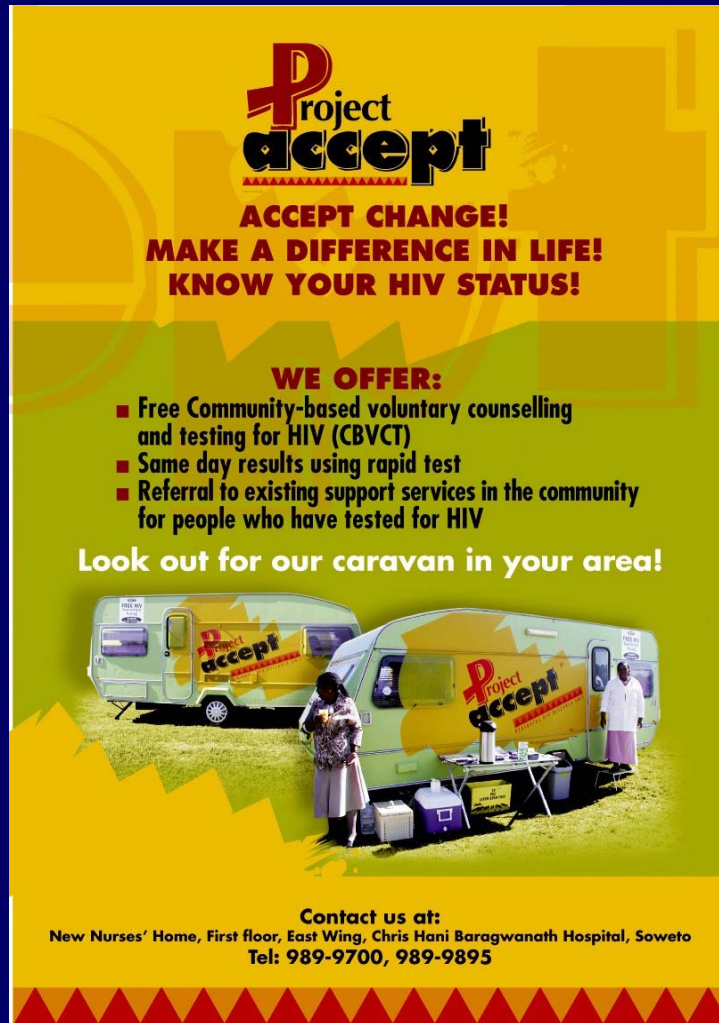
Correlation Between Viral Load and HIV Transmission: Rationale for HPTN 052



REF: Quinn T. *N Engl J Med* 2000; Fideli U. *AIDS Res Hum Retrovir* 2001.



1. Does expanded HIV testing reduce HIV transmission in a given community? HPTN 043




Project accept
ACCEPT CHANGE!
MAKE A DIFFERENCE IN LIFE!
KNOW YOUR HIV STATUS!

WE OFFER:

- Free Community-based voluntary counselling and testing for HIV (CBVCT)
- Same day results using rapid test
- Referral to existing support services in the community for people who have tested for HIV

Look out for our caravan in your area!



Contact us at:
New Nurses' Home, First floor, East Wing, Chris Hani Baragwanath Hospital, Soweto
Tel: 989-9700, 989-9895

A Phase III RCT of
Community Mobilization,
Mobile Testing, Same-
Day Results, and
Post-Test Support for
HIV in sub-Saharan
Africa and Thailand
(HPTN 043)



HPTN 043: Project Accept

Reinforcing Components of the Intervention

COMMUNITY
MOBILIZATION

MOBILE VCT

POST TEST
SUPPORT
SERVICES



HPTN 043: Project Accept Community RCT similar to TNT

- 48 Communities Randomized
 - 36 in rural Africa (Zimbabwe, Tanzania, & So.Afr.)
 - 8 in urban South Africa
 - 14 in northern Thailand
- Massive community mobilization
 - >12,000 persons in pilot studies in 2006
 - >56,000 samples for seroincidence estimates in the full intervention



HPTN 043

- Targeted # of study participants: 250,000
- Accrued to date: 184,760
- Projected end of accrual: March 2010
- Projected end of follow up: June 2011

2. Does an HIV+ person who is treated early transmit less to an HIV- sexual partner? HPTN 052

- RCT of ART to prevent the sexual transmission of HIV in serodiscordant couples (12 sites, Africa/Asia)
 - Randomize persons with 350-550 CD4+ T lymphocytes to early treatment vs. SOC
 - 1000 couples of 1750 recruited to date
 - Accrual will be completed in 2010, f/u to 2015
- Assess seroconversions in primary sexual partners

HPTN 052

Thailand, South Africa, Botswana, Kenya, Malawi, Brazil, India

HIV-infected subjects with CD4+ cells 350-550/ μ L

Randomization



ZDV+3TC+EFV

Immediate ART
350-550cells/ μ L

Deferred ART
CD4 <250 cells/ μ L

Endpoints: i) HIV Transmission to partners
ii) OIs and clinical events
iii) ART toxicity

3: Should HIV therapy be started earlier than current SOC? HPTN 052

- Observational data suggest benefits of early ART
 - Kitihata MM. NA-ACCORD/IeDEA. *N Engl J Med* 2009
 - Reynolds S. Rakai, Uganda. CROI 2009, Abst.52a
 - Sullivan P. Rwanda and Zambia. CROI 2009, Abst.52bLB
 - HOWEVER: Unmeasured confounders likely with persons who want therapy and whose care providers agreed → **RCT needed**
- Original secondary endpoint of HPTN 052 now a co-primary endpoint (ACTG 5245)
- New initiative from INSIGHT (START)

HPTN 052

- 1000 of 1750 discordant couples enrolled
- Excellent retention
- Concomitant consideration of the benefits of earlier ART and HIV transmission prevention
 - “Treatment as prevention”
 - “early ART”
 - ...*HPTN 052 will confirm or refute*

4. Do behavioral interventions in HIV positive individuals prevent transmission?

- Intervention in HIV positive individuals: Positive Prevention (HPTN 063)
- Identification and intervention in acutely infected individuals to reduce risky behaviors (HPTN 062)

Positive Prevention (HPTN 063)

- Preparing for international prevention trials involving HIV+ individuals in care
- Protocol approved by DAIDS PSRC.
- Sites: Zambia, Brazil, Thailand
- Projected open date – August 2009
- Targeted number of participants - 800
- Projected end of follow up – 3rd Q 2011

Acute HIV Infection (HPTN 062)

- Feasibility and Acceptability of an Individual-Level Behavioral Intervention for Individuals with Acute and Early HIV-Infection
- Protocol approved by DAIDS PSRC.
- Sites: Malawi and South Africa
- Projected start of accrual- July 2009
- Targeted number of participants – 48
- Projected end of follow up – January 2011

5. Can we better engage hard-to-reach populations? HPTN 061 & HPTN 064



BROTHERS: Community-Based, Multi-component HIV Prevention Intervention for Black MSM



**ISIS
HIV Seroincidence Study in Women**

HPTN Feasibility Studies

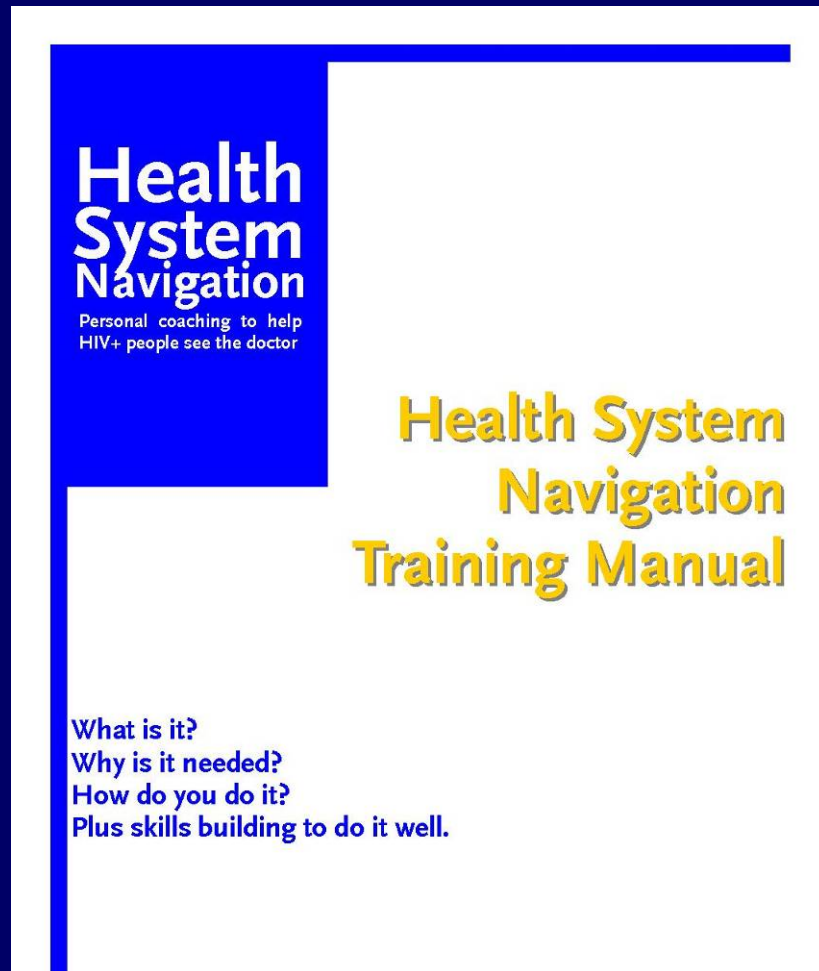
BROTHERS (061)

- Feasibility of ...
 - recruitment of Black MSM
 - recruitment of their sexual/social networks
 - HIV testing of index cases and network members
- Impact of peer navigation for prevention and care

ISIS (064)

- Accurate estimate of HIV incidence in US women at highest risk
- Feasibility of ...
 - follow-up of cohort of highest risk women
 - US prevention study with HIV seroconversion as the primary outcome

HIV System Navigation (HSN): An Emerging Model to Improve HIV Care Access



- Near Peers
- Structured training as per HRSA evaluation
- Finding at-risk persons for testing
- Engagement in testing, bridging to care, adherence to care, retention in care

BROTHERS (HPTN 061)

- Protocol approved by DAIDS PSRC
- Projected open date: June 2009
- Targeted number of participants : 2536
- Projected end of follow up: June 2011
- Sites in Boston, New York City, Washington DC, Atlanta, San Francisco, Los Angeles

ISIS (HPTN 064)

- Protocol approved by DAIDS PSRC
- NC and NJ sites activated in April 2009
- Targeted number of participants : 2400
- Projected end of follow up: April 2011
- Sites in New York City x2, Newark x2, Baltimore, Washington DC, North Carolina x2, Atlanta x2

ART for Prevention: Key Research Questions

1. Does expanded HIV testing reduce HIV transmission in a given community? **HPTN 043**
2. Does an HIV+ person who is treated early or has a behavioral intervention transmit less to an HIV- sexual partner? **HPTN 052**
3. Should HIV therapy be started earlier than current SOC? **HPTN 052/ACTG 5245 & INSIGHT START**
4. Do behavioral interventions in HIV positive individuals prevent transmission? **HPTN 063 & HPTN 062**
5. Can we better engage hard-to-reach populations? **HPTN 061 (BROTHERS) & HPTN 064 (ISIS)**
6. Can combined testing expansion and bridging to good HIV/AIDS care reduce HIV incidence? **TNT, HARP, PrEP**

Test and Treat (TNT) Hypothesis

Test



Adoption of safer behaviors by HIV+ persons

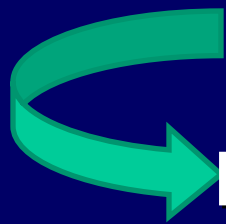
Treat with ART

+

Adherence



Maintain viral suppression



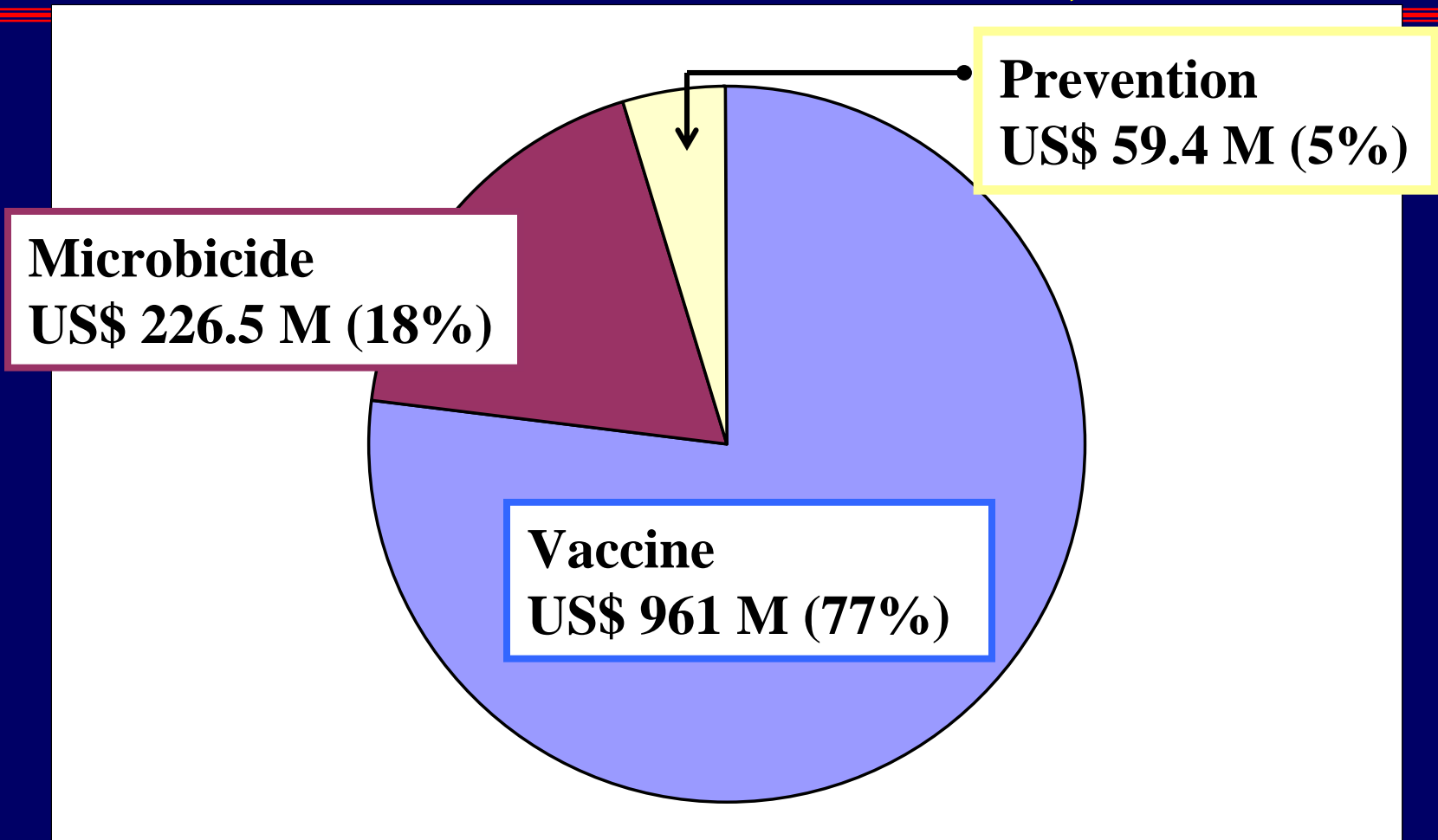
Decrease in HIV Transmission



HPTN Challenges - I

- Too few HIV prevention RCTs; in 28 years...
 - Mwanza STD control
 - 3 RCTs of male circumcision
 - Pro 2000 Gel (0.5%) microbicide promising
- Measuring HIV endpoints at a pop. level
- Current NIH-Network-CTU funding system
- Ensuring a scientific portfolio that includes strategies, not just technologies
- Funding for international trial investments

Total Global Investment Allocated for HIV Prevention R&D, 2007



Source: HIV Vaccines & Microbicides Resource Tracking Working Group, 2008

AIDS Vaccine Advocacy Coalition (AVAC); Alliance for Microbicide Devel. (AMD)
Int'l AIDS Vaccine Initiative (IAVI); Joint UN Prog. on HIV/AIDS (UNAIDS)

HPTN Challenges - II

- Populations at highest risk
- Reinvestment needed for CTUs
- Application of combination prevention
- Implementation Science: Scaling up what works
- Individual level interventions → dyad, network, population, & structural levels
- Highest level of evidence – RCTs with HIV endpoints

HIV Prevention Trials Network

- Thank you for your contributions to the HPTN/IMPAACT joint annual meeting
- We welcome your feedback
- We are very proud of the networks' contributions to HIV research, our...
 - ...Sites, Labs, Data centers, Operations centers, Community and Ethics partners, and Government colleagues

HPTN-IMPAACT Annual Meetings, May 4-8, 2009





Ongoing HPTN Achievements - IV

- Substantial Protocol Team Meetings and Training
- Pivotal workshops on PrEP, TNT, Adherence
- CORE site visits, training
- Lab –testing, QA/QC, repository
- SCHARP - CRFs, data cleaned, analyses
- Quality of science/site performance - high accrual rates, retention rates and QC rates
- Regional activities (Africa, Asia, So. & No. America)
- Community Program achievements
- Ethics Guidance

State of HIV Prevention

- Heterogeneous epidemic
 - Regional variability in disease burden, dominant routes of transmission and populations at risk
 - Therefore, critical to know your local epidemic and to customize responses accordingly
- Global response most energetic with treatment
 - Ambivalent response to prevention
 - Constrained by “sexual politics”

HPTN Trials Completed in 2009

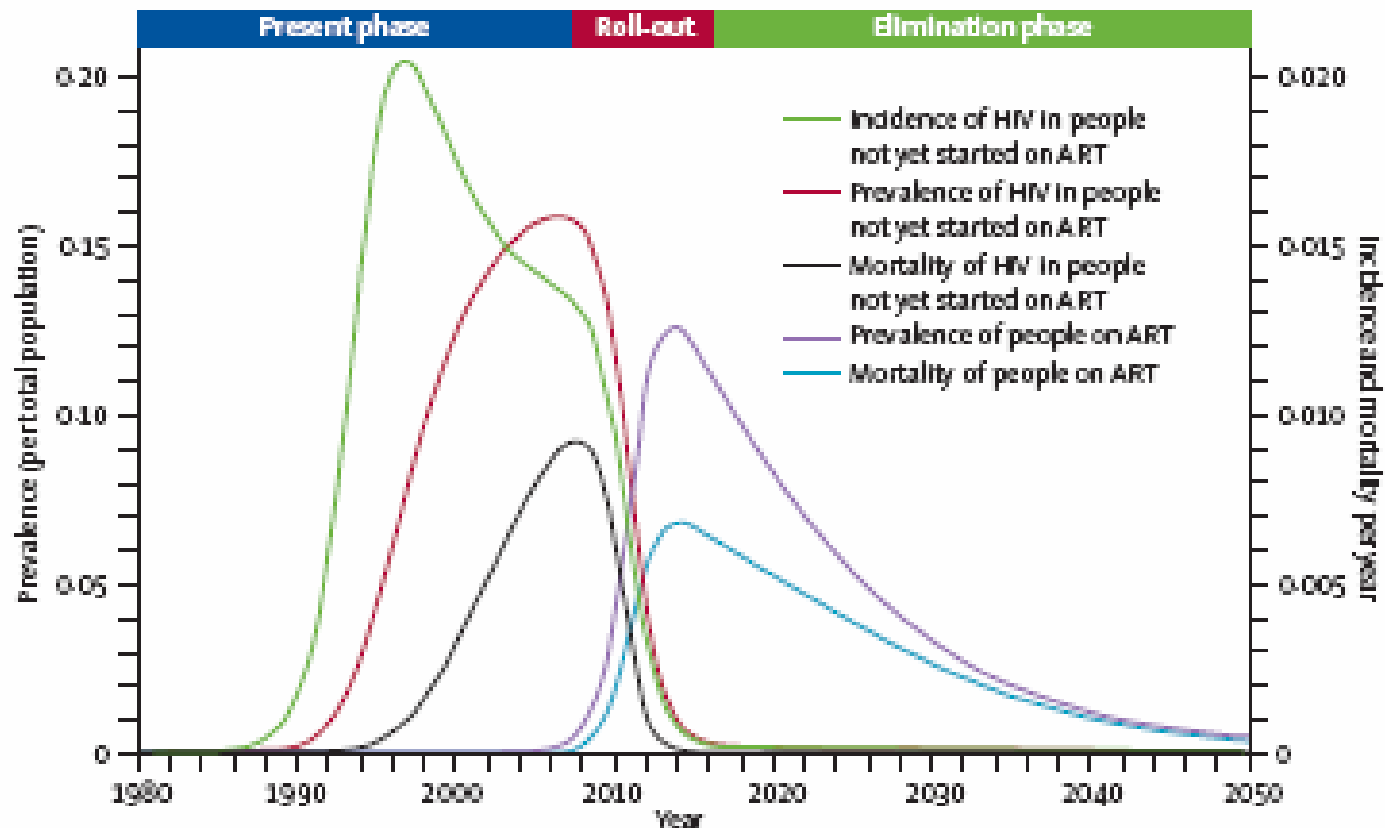
- HPTN 035: **Pro 2000 gel (0.5%)** was 30% effective at decreasing HIV incidence
- HPTN 039: Demonstrated that **HSV-2 suppression** did not prevent HIV infection
- HPTN 037: Showed the **feasibility of network-level** interventions for IDUs

Test & Treat (TNT)

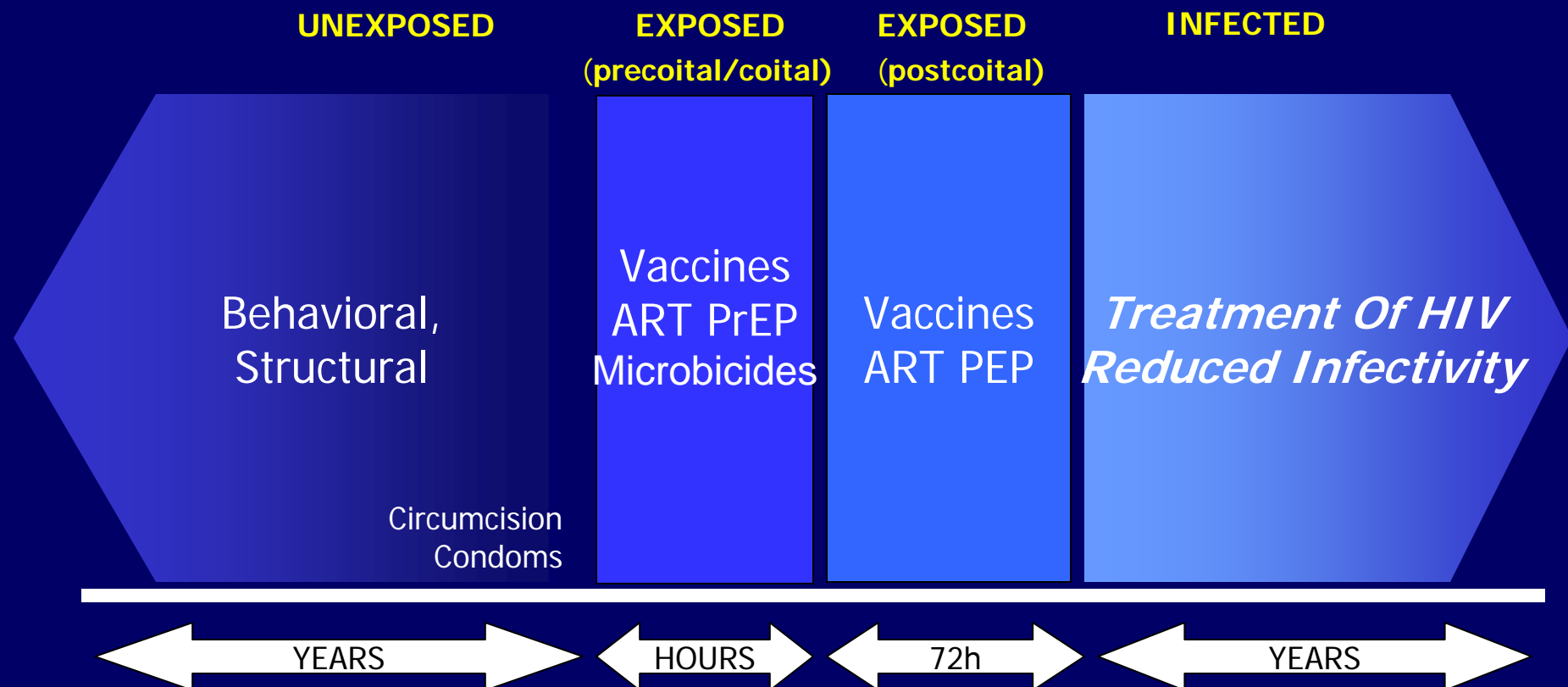
Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model

Reuben M Granich, Charles F Gilks, Christopher Dye, Kevin M De Cock, Brian G Williams

Lancet 2009; 373:48-57



Four Prevention Opportunities



REF: Cohen MS et al, *JCI* 2008

Combination Prevention

- Combining Treatment and Prevention
 - One will not succeed without the other
 - Treatment as prevention (TNT)
 - Implementation of known prevention strategies (HARP)
 - Commitment, strategic focus, & evidence-base
- Prioritize countries & populations at greatest risk
- Multi-Level Interventions - Individual, Dyadic, Community and Structural

HIV Treatment as Prevention has strong biological plausibility

Retrospective Studies

Musicco et al. Archives Int Med 1994

Castilla et al. JAIDS 2005

Observational Studies

Kayitenkore et al. IAS, 2006

Bunnell et al. AIDS 2006

Reynolds et al. CROI 2009 Abstract 52a

Sullivan et al. CROI 2009 Abstract 52b

Ecological Analysis

Katz et al. Am J. Public Health 2002

Duker et al. AIDS 2002

Porco et al. AIDS 2004

Fang et al. JID 2004

Montaner et al. Lancet 2006

ISIS (HPTN 064) Sites

- Emory University, Atlanta, GA (x2)
- Johns Hopkins Adult AIDS, Baltimore, MD
- University of North Carolina-Chapel Hill, NC (x2)
- Columbia University, New York, NY (x2)
- New Jersey Medical School Adult Clinical Trials Center, Newark, NJ (x2)
- George Washington University School of Public Health and Health Services, Washington DC

BROTHERS (HPTN 061) Sites

- Emory University: Atlanta and Decatur, GA
- San Francisco CA Vaccine and Prevention CRS
- New York Blood Center (NYBC)/Union Square and Harlem Hospital Center/Columbia U. in New York NY
- University of California at Los Angeles (UCLA) CA
- Fenway Community Health in Boston, MA
- George Washington University in Washington, DC