

Overview of methodological challenges in HIV prevention trials

Sten H. Vermund, MD, PhD
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Interventions to Prevent HIV

Routes

- Sexual
- Blood
- Perinatal

-Reduce high risk behavior
-Rx STDs

Biological Facilitators

- Activated Immune Function
- Increased no. of target cells

HIV+



Newly HIV+



HIV-



-Rx of OIs
-PMTCT

-Treatment of HIV

-Block w/
physical or
chemical or
immunological
barriers
-Circumcision
-Blood/needle
safety



Prevention trials* differ markedly from *Therapeutic trials

- **Subjects are healthy**
 - Morbidity/mortality endpoints are elusive
 - Lower motivation to participate
- **Unexpected effects or events when trial takes years rather than months**
 - **Seroincidence may fall w/ baseline intervention**
- **Subjects entering treatment trials have infection**
 - High motivation to participate
- **Progression associated with VL/CD4 surrogates**
 - Outcome often within a short time frame

Six Methodological Challenges

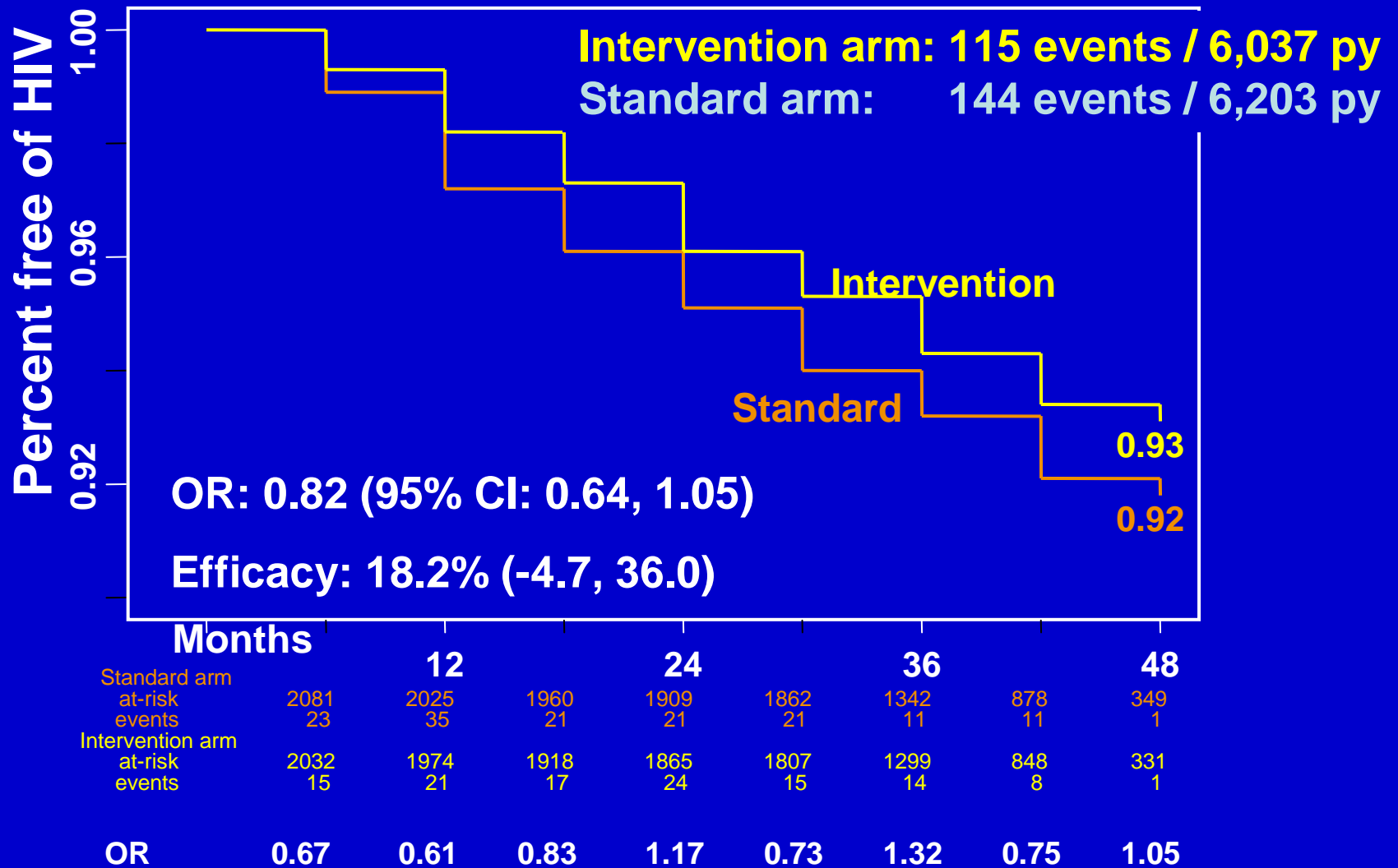
- 1. High sample sizes when HIV seroincidence is comparatively low**
- 2. Disinhibition dilutes prevention impact; efficacy \neq effectiveness**
- 3. Surrogate markers are unreliable**
- 4. Impact of the trial itself reduces transmission rates**
- 5. Need for confirmation**
- 6. Design challenges**

Two examples from the HPTN (HIV Prevention Trials Network)

–HPTN 015 Project EXPLORE to reduce HIV in MSM with intensive behavioral counseling

- n=4295 in six U.S. urban sites**
- Koblin B, et al. Effects of a behavioural intervention to reduce acquisition of HIV infection among men who have sex with men: the EXPLORE randomised controlled study. *Lancet* 2004;364:41-50.**

HIV Seroincidence = 2.1 (1.9, 2.4) per 100 py



Multivariable analysis of seroconversion risk: Drug use

Drug	N at baseline	No. of infections	Hazard ratio*	95% CI
Heavy alcohol**	419	41	1.9	1.2, 2.8
Amphetamines	527	67	1.9	1.4, 2.6
Alcohol/drugs before sex	2952	205	1.6	1.1, 2.3

* REF = no, light or moderate use of alcohol; no speed use; no use before sex

** 4+ drinks every day or 6+ drinks on a typical day

Example 2 from the HPTN (HIV Prevention Trials Network)

**–HPTN 024 in four African sites,
pregnant women: Treat
chorioamnionitis with antibiotics
to PMTCT of HIV**

- n=2098 HIV+ and 335 HIV-**

- Goldenberg RL et al. The HPTN 024 Study: the efficacy of antibiotics to prevent chorioamnionitis and preterm birth. *Am J Obstet Gynecol* 2006;194:650-61.**

PMTCT is an example of a “frequent” outcome

- **Nevirapine programs cut PMTCT rates in half such that 12% of exposed infants are expected to be infected**
- **Impact of a second intervention to reduce transmission an additional 25% represents a reduction of 12 to 9% (Δ of only 3%)**

Ongoing trials from current HPTN

- HPTN 037: IDU network intervention, US and Thailand
 - *N = 1124 in 3 sites (terminated early for futility)*
- HPTN 039: Acyclovir suppression of HSV-2, US, Peru, South Africa, Zambia, Zimbabwe
 - *N = 3250 in 8 sites (extended to 18 mo F/U)*
- HPTN 043: Project Accept, Community-based VCT; South Africa, Tanzania, Thailand, and Zimbabwe
 - *N = 192,860 persons in 48 communities, 4 countries*
- HPTN 052: ARV Rx in discordant couples; Brazil, India, Malawi, US, Zimbabwe
 - *N = 3500 (1750 couples) in 7 sites (pilot completed)*
- HPTN 058: Buprenorphine/naloxone to reduce HIV in IDUs; China Thailand, Vietnam
 - *N=1460 in 4 sites (March 2007 start)*

Infrastructure / Manpower

- **Note, too, that our studies typically involve some of the world's most resource-limited settings**
- **Need for laboratory, clinical, data, community, and manpower (usually heavily womanpower) investments**

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Challenge #2

- **Partially effective prevention modalities may include vaccines, microbicides, circumcision, ART in partner, etc.**
- **Disinhibition may overwhelm partial protective effects through increased risk behavior**
- **Modeling risk behavior and transmission pressure to adjust for prevention benefits in trials?**

Disinhibition

- **Substantial literature* suggests that potent antiretroviral therapy (ART) invites prevention complacency**
 - Feel better → Have more sex
 - Lower VL → Use fewer condoms
- **Concerns about user effectiveness of future prevention modalities, even in the face of trial-confirmed efficacy**

Example: DiClemente RJ, et al. Protease inhibitor combination therapy and decreased condom use among gay men. *South Med J* 2002;95:421-5.

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Challenge #3

- **Surrogate markers in therapeutic research → Viral load and CD4+ cells**
- **Surrogates in prevention research**
 - **Use of HIV as the outcome for trials focused on behavior change in seropositive persons requires a discordant couples/partners study or a trial with community as the unit of randomization. Correlation is a necessary but not sufficient condition for a surrogate to be valid.**
 - **Often used “surrogates” that cannot be validated without a couples/partners or community study.**
 - **Behavior change?**
 - **Viral load in positives?**
 - **STD incidence?**
 - **Reduced mixing in sexual or needle-sharing networks?**

Example of “Positive Prevention”

- 5-10 min. education from care provider* for HIV+ persons to reduce high risk behaviors
- Cannot use HIV as an outcome unless one had a discordant couples study
 - Even then, one would need ALL sexual partners
 - Hence, we rely on HIV self-reported behaviors with a biological marker of STI incidence (if funding permits); these may not correlate with HIV seroincidence

* Fisher JD et al. *JAIDS* 2006;41:44-52.

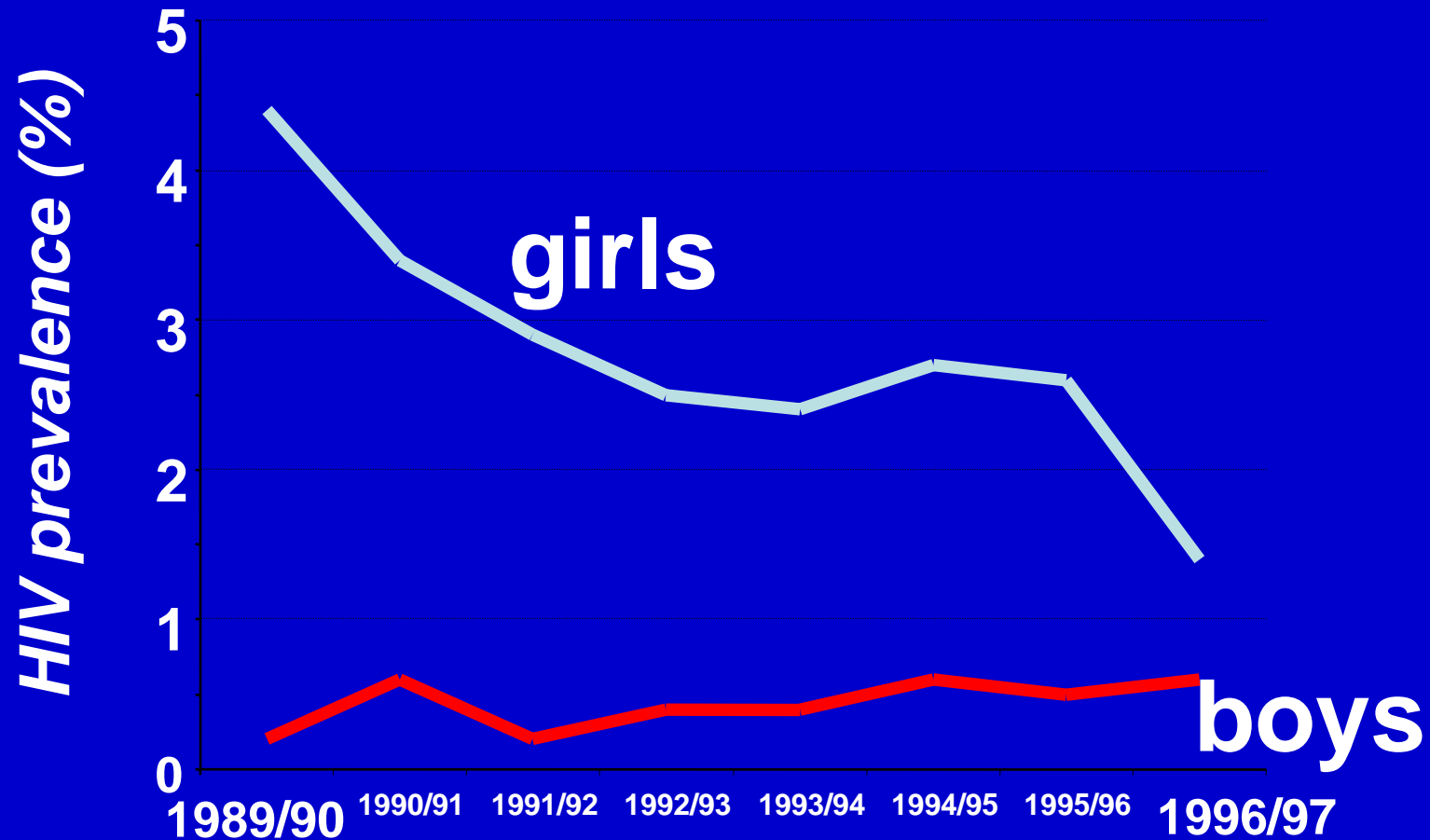
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Challenge #4

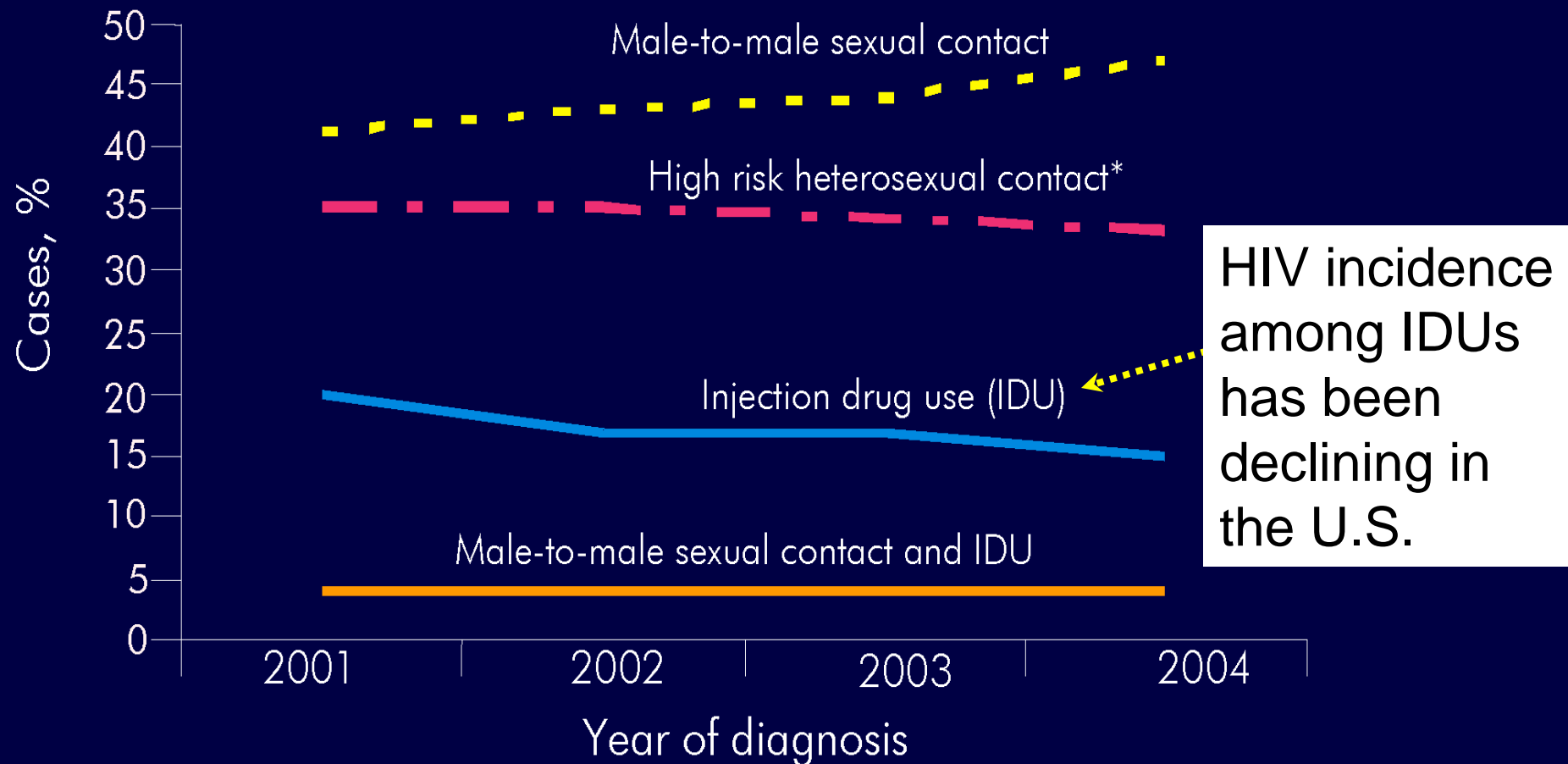
- **Good clinical practice demands that a reasonable standard of prevention be offered as the comparison to the intervention modality**
- **Good counseling, STD screening and treatment, and condom distribution (and, perhaps circumcision) does pretty well in reducing risk (halving risk in HPTN studies from expected)**
- **Then, see challenge #1, sample size!**

HIV prevalence rate among 13-19 year-olds Masaka, Uganda, 1989-97



Ref: Kamali et al. *AIDS* 2000, 14: 427-34

Proportion of HIV/AIDS Cases among Adults and Adolescents, by Transmission Category 2001–2004—35 Areas



Note. Data include persons with a diagnosis of HIV infection regardless of their AIDS status at diagnosis. Data from 35 areas with confidential name-based HIV infection reporting since at least 2000. Data have been adjusted for reporting delays and cases without risk factor information were proportionally redistributed.

* Heterosexual contact with a person known to have or at high risk for HIV infection.



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Challenge #5

- **Results in one venue may not apply in another**
 - Transmission dynamics may make some co-factors more or less important in given circumstances
- **Trials should be confirmed, but their complexity and high cost are a disincentive to do the right science**
 - (Congratulations to the circumcision teams and sponsors)
- **Example: Mwanza vs. Rakai control of STDs to prevent HIV**

Syndromic management of STDs Slowed HIV Transmission in an Emerging Epidemic

- **Mwanza (n=12,537)** suggested the benefits of syndromic management of bacterial STD control for HIV prevention under circumstances of an emerging epidemic with relatively low seroprevalence
- **Rakai (n=12,726)** suggested the lack of benefits of periodic mass antibiotic therapy for HIV prevention under circumstances of a mature epidemic with higher seroprevalence

REF: Grosskurth H, et al. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet* 1995;346:530-6.

Wawer MJ, et al. Control of sexually transmitted diseases for AIDS prevention in Uganda: a randomised community trial. Rakai Project Study Group. *Lancet* 1999;353:525-35.

STD control on one hand, circumcision on the other

- **After one positive trial in the circumcision arena, NIH continued the two extant trials**
 - Both trials confirmed the So. African trial, thus providing definitive guidance, three African venues
- **Mwanza was not replicated by Rakai**
 - The Rakai study was a different design all together, not likely to pick up symptomatic persons promptly but more likely to treat asymptomatic persons. Epidemic conditions differed. One study could not confirm or refute the other.

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Challenge #6

- **Design issues numerous**
 - Vehicle only vs. condom only as control for microbicides trials (MTN/HPTN035)
 - Incidence endpoints vs. viral load in breakthroughs for vaccine trials (PAVE-100)
 - Control group receiving detoxification in opiate agonist trial (HPTN 058)
 - Phase 2b vs. Phase 3
 - Need for equivalent of Phase 4 → Implementation Science, examples of post-circumcision and post-PMTCT research

Surgery to prevent HIV?

- **Acceptability and demand uncertain**
- **Disinhibition? Does not alter baseline gender inequities and violence**
- **Scaling up safely: Health manpower and surgery units for the world**
- **Like Hepatitis B vaccine, issue of emphasis on adults vs. infants**
- **Will we study circumcision as a component of multi-faceted prevention initiative?**
- **Will implementation science be done post-trial to assess the public health impact of this new tool in our prevention armamentarium?**

Example of implementation science: the PMTCT “cascade”

Refs (Stringer JS, Sinkala M, et al):
JAIDS 2000;24:369;
Am J Public Health 2002; 92: 365;
Lancet 2001;358:1611;
AIDS 2003; 17: 1377;
AIDS 2003; 17: 1659;
Lancet 2003; 362:667;
Lancet 2003;362:1850;
JAIDS 2004; 35: 60.
AIDS 2004; 18:939.
AIDS 2005; 19:1309.

Pregnant, HIV+ Women

i.e., women have access to ANC

Offered Intervention

i.e., have a VCT/ NVP program

Uptake Intervention

i.e., intervention is accepted

Adhere to Intervention

i.e., intervention is successful

Baby gets NVP soon after delivery

Family planning!!

In 2003, cord blood NVP indicated only 30% coverage

HIV Prevention Sciences

- **The HIV Prevention Trials Network (HPTN) evaluates novel or existing strategies in efficacy trials**
 - ART to prevent transmission
 - Control of STDs to reduce efficiency of transmission
 - Treatment and prevention of injection drug or stimulant use to reduce exposure
 - Behavioral change in at-risk populations
- **Other NIH-sponsored networks devoted to microbicides, PMTCT, vaccines, and prevention in adolescents**
- **Treatment and Cancer networks interested in prevention**

Questions, Debates?

sten.vermund@vanderbilt.edu

A few extra slides

For the IOM handout

How will we beat HIV/AIDS? - I

1. Avoid exposure, reduce “mixing” rates through behavior change

- “ABC”: abstinence for youth, ‘be faithful’ messages for sexually active, condom-use for highest risk, esp.
 - Self-esteem building, Negotiation skills, Change peer influences with opinion leaders, Condom social marketing
- Replacement feeding in place of breast feeding

2. Reduce risks via structural changes

- Political/social/religious/media leadership
- Reducing risk in target populations: e.g., sex workers, men working away from home, & drug users
- Blood/needle safety via blood banks
- Changing health care provider transfusion practices & re-use of equipment, including informal sectors
- Birth control by HIV-infected women wished to avoid pregnancy

How will we beat HIV/AIDS? - II

3. Reduce probability of transmission, given exposure

- STD control, Circumcision, Control of co-infections**
- Physical, chemical, and immunological barriers**
 - Male condoms, Diaphragms/Cervical caps/Female condoms, Microbicides, Vaccines**
- Killing the virus (reduce duration)**
 - Treatment/Cure to reduce infectiousness**
 - Pre-exposure Prophylaxis (PREP) or Post-exposure (PEP)**
 - ART in pregnancy/postnatal (PMTCT)**
- Exclusive breastfeeding**

We already have many tools

- **So why prevention research?**
 - Application of known modalities has been successful only in selected venues and in selected populations
 - Need adaptation and application of successful models in one context to others, e.g., adolescent risk reduction
 - New tools can help us prevent infections in a global context
- **Why clinical trials?**
 - Observational and clinical studies can point the way, but cannot confirm impact of interventions

Prevention modalities now available

- Bacterial STD control
 - Mwanza study, HPTN 039
 - Not all strategies or conditions are the same; huge array of possible approaches
- Intravenous drug use risk reduction
 - Needle exchange and expanded drug treatment
- Block mother to child transmission
 - With ART in mother and infant, Little success with breastfeeding
- Behavior change
 - HIVNET 015 in MSM, did NOT work if substance use or depression
- Condom promotion
 - Challenge of persistence of use and use by adolescents
 - See Holmes KK, et al. *Bull World Health Organ* 2004;82:454-61.
- Circumcision
 - Extent to which a surgical intervention in adults will be “rolled out” successfully is unknown
 - See Auvert B, et al. *PLoS Med* 2005;2(11):e298.

Prevention Research- Still unproven approaches

- New technologies Vaccines/Microbicides → Trials in progress
- PREP → Trials in progress for adults & for breastfed infants
- Female condoms → Never tested in trial, never will be
- Diaphragms and cervical caps → Trial in progress
- Control of non-bacterial STDs → HSV-2 trial in progress (HPTN039), no trial ever done for vaginosis/vaginitis
- Treat infected partner with antiretrovirals to prevent transmission → HPTN 052
- Control of co-infections (e.g., TB, malaria, helminthes, etc.) to downmodulate HIV and reduce viral load
- Penile hygiene, as a circumcision-like intervention
- Stimulant therapy (cocaine, methamphetamine) to reduce HIV
- Novel opiate agonists for risk reduction, such as buprenorphine/naloxone
- Positive prevention for risk reduction in HIV+ persons

HPTN Key Accomplishments

- **Two decades of international HIV prevention research experience**
- **Built enormous site capacity**
 - Clinical trials, laboratory, data
- **Interventions that enable rapid translation from research to policy and practice**
 - Already available and/or licensed modalities
- **Strong, multidisciplinary capacity**
 - ART, STD, Substance Abuse, Behavior with Ethics and Community consultations
- **Prevention continuum**
 - Uninfected → Acutely infected → Chronically infected
 - Synergy with other Networks