

Biomedical Interventions to Prevent HIV Infection

What works, what doesn't, and
where do we go next?

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How do we develop and test the efficacy of a preventive intervention?

Basic science and animal experiments

Observational Epidemiologic studies

Randomized Controlled Trials (RCTS)

“Gold standard of proof” of efficacy in medicine

Program implementation to assess effectiveness

Randomized Controlled Trials (RCTs) for HIV Prevention

- Volunteers are randomly assigned to receive:
 - the HIV prevention intervention being tested, or
 - a control treatment (e.g., placebo or standard care)
- Compare new HIV infections in the intervention arm to those in the control arm
- Large scale, rigorous, costly and difficult studies
- **Pivotal studies for policy and practice**

Outline of Biomedical HIV Prevention Studies

- **RCTs of Adult HIV Prevention**
 - Control of Sexually Transmitted Infections (STIs)
 - Female controlled methods: Microbicides and diaphragm
 - HIV vaccines
 - Male circumcision
- **RCTs of Prevention of Mother-to-Child HIV Transmission**
 - At time of birth
 - During breast feeding
- **HAART for HIV prevention**
 - Ongoing RCT

Sexually Transmitted Infection (STI) Control for HIV Prevention in Populations

- Bacterial and viral STIs are associated with HIV infection
- **Is this association causal?**
 - Do STIs increase the risk of getting HIV?
 - Do people with STIs acquire HIV because the same high risk sexual behaviors spread both infections?
- **Needed randomized trials to assess efficacy**

Results of STI Control for HIV Prevention Trials

- 5/6 trials of bacterial STI control showed no reduction in HIV acquisition
- 2/2 trials of herpes suppression showed no reduction of HIV acquisition
- CDC and WHO still recommend STI control for HIV prevention at a population-level, and many programs promote it.
- Is it time to change policy?

Microbicide and Diaphragm Trials

- Female-controlled HIV prevention strategies are urgently needed
- **Microbicides are inserted into the vagina to kill or disrupt HIV**
 - Surfactants (detergents).
 - Buffering and HIV binding agents.
 - Microbicides with antiretroviral drugs.
- **Diaphragm provides a physical barrier by covering the cervix.**

Results of Microbicide & Diaphragm RCTs

- **Surfactant Microbicides 8 RCTs:**

- **Nonoxynol-9 (spermicide):**

- (Wilkinson, *Lancet Inf Dis*, 2002)

- Cellulose Sulphate:**

- (Van Damme L, 4TH IAS 2007 WESS301)

- SAVVY gel:**

- (Feldlum PLoS 2008, Peterson PLoS 2008)

No reduction of HIV acquisition, some showed increased risk, all found vaginal irritation and ulceration

- **Diaphragm:**

- **No effect on HIV acquisition** (Padian Lancet 2007)

Why did the microbicide trials fail?

Nature 2007; Gray Lancet, 2007; Lugakos NEJM 2008;358:1543

In retrospect there may have been gaps in:

Planning of trials

- e.g., use High risk populations:
 - Frequent intercourse → multiple use
 - Poor compliance
 - Vaginal irritation with frequent use may increase HIV risk
- Need improved screening for:
 - Safety (e.g., vaginal irritation)
 - Effectiveness in the presence of seminal fluid (Patel JID 2007)

HIV Vaccines evaluated in large-scale RCTs

- **Goals**
- **Prevent initial infection**
 - Neutralizing antibody vaccines
- **Reduce HIV viral load and disease progression**
 - Stimulate cellular immunity to HIV to reduce viral replication and prevent disease progression

HIV vaccine trial results to date

- **Neutralizing vaccines (VAXGen)**
 - 2 trials, US and Thailand (Flynn JID 2006, Pitisuttithum JID 2005)
 - **No effect on HIV acquisition or HIV viral load**
- **Cellular immunity vaccine (Merck Adeno-5 trivalent HIV vaccine)**
 - Adeno virus vector (Ad5) to deliver vaccine containing synthetic fragments of HIV genes
 - 2 trials: STEP multicenter RCT and Phumbili RCT in South Africa. (S Buchbinder CROI 2008)
 - **No effect on HIV**
 - **Trend towards higher risk of HIV in the vaccinated group**
 - **Significant increased risk in uncircumcised men with prior adeno-5 virus immunity.** What does this mean??
 - . Phumbili trial stopped

Why have HIV vaccine trials failed?

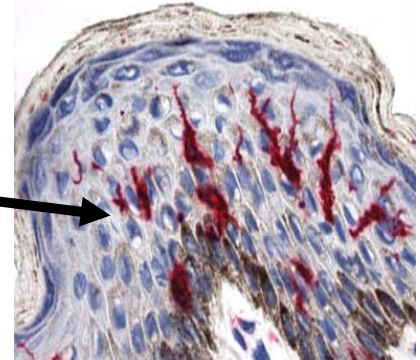
- We do not know how or whether the immune system can prevent HIV acquisition or reduce disease progression, so screening of candidate vaccines is problematic (Excler AIDS 2007)
- HIV is rapidly disseminated in body, infects and destroys immune cells
 - HIV is incorporated into the cell's genome and cannot be eliminated
 - Vaccines that induce an immune cell response may actually increase the number of target cells for HIV (e.g., Adeno 5) (Sodora AIDS 2008)

Male Circumcision for HIV Prevention

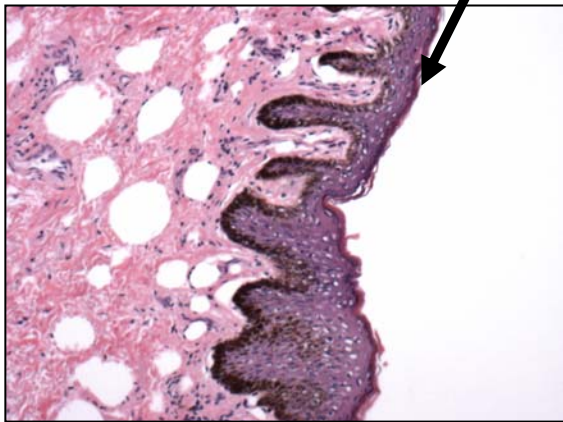
- Three randomized trials:
 - Men randomized to immediate circumcision or circumcision delayed for 24 months
 - Orange Farms, South Africa (Auvert PLoS Med 2005),
 - Kisumu, Kenya (Bailey Lancet 2007)
 - Rakai, Uganda (Gray Lancet, 2007)
 - All trials stopped early because of a greater than 50% reduction of HIV infection in the circumcision arm

How does circumcision work?

- Foreskin contains target cells for HIV



Inner mucosal surface of foreskin is lightly keratinized, vulnerable to HIV and ulcers



Outer skin is heavily keratinized, protected from HIV and ulcers



Removing the foreskin removes the tissue vulnerable to HIV infection

Circumcision and Male-to Female HIV transmission (Wawer et al CROI, 2008)

- Circumcision of HIV-infected men
 - No direct reduction in male-to-female HIV transmission
 - Possible increased risk of HIV transmission to women if the couple resumes sex before full wound healing completed

Can circumcision reduce the HIV epidemic?

- **Circumcision can mitigate the epidemic by:**
 - Direct reduction of male HIV acquisition
 - Secondary protection of women if fewer men are infected
 - Probable lifelong protection
- In areas with a high rate of HIV, need ~ 15 circumcisions per HIV infection averted over 10 years
- Likely to be highly cost-effective
- **Challenges:**
 - How do we scale up services
 - Will circumcised men increase their risk behaviors?
 - How to deal with HIV+ men who seek the procedure?

Circumcision is a New Paradigm: We have never used surgery to control an infectious disease

- Priority is Southern and Eastern Africa where circumcision is uncommon and HIV rates are high
- High acceptability and demand
- **Needs**
 - Government & donor support
 - Training thousands of personnel
 - Upgrading facilities
 - Equipment and supplies
 - Costs ~\$1 billion over 5 years
- **Challenges**
 - Changing policies, paradigms and programs is hard

Prevention of Mother-to-Child HIV Transmission (pMTCT) at Birth with Antiretroviral Drugs

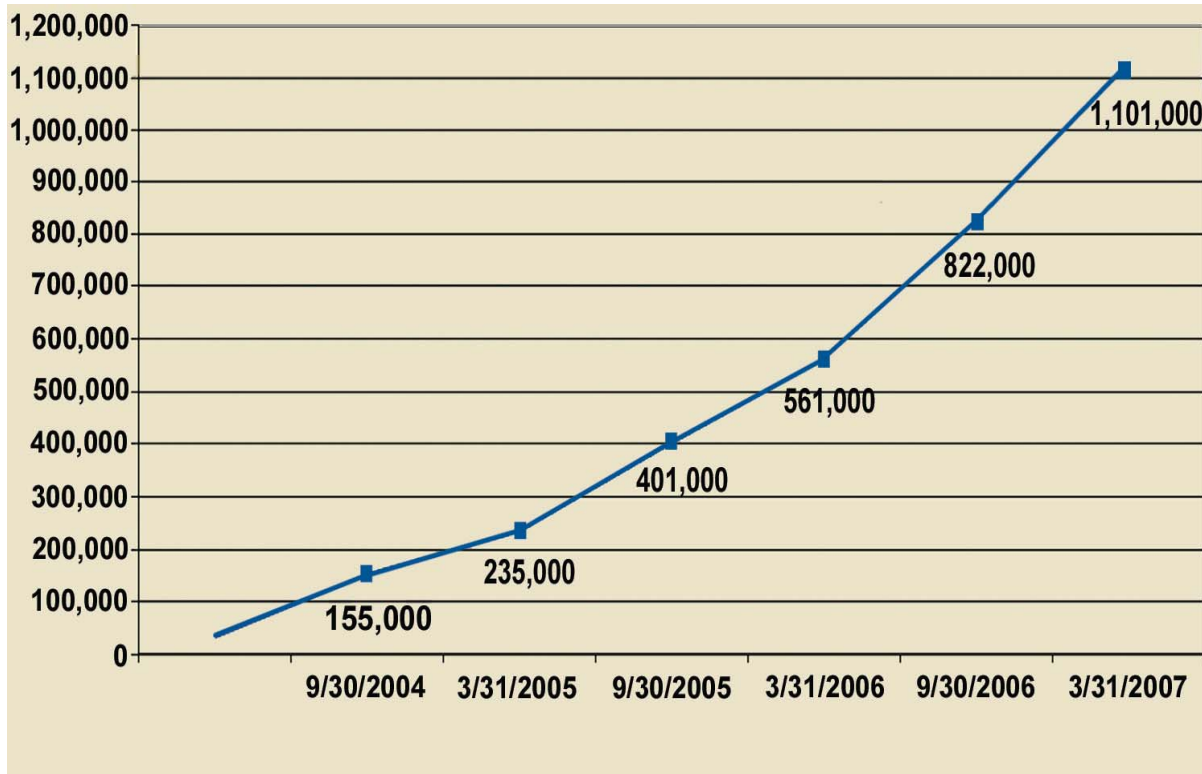
- Major success in developed countries
- **Low Income Countries**
 - Cheap, feasible antiretroviral regimens available
 - Not reaching the population in need
 - Only 9% of HIV+ pregnant women (5% in Africa) receive pMTCT
- **This is a Health Systems failure**
 - Poor infrastructure
 - Home deliveries
 - Reluctance to accept testing

Preventing HIV Transmission via breast milk

- In Africa ~40% of infant HIV infection is through breast milk
- Formula feeding is unsafe in most African settings
- 14 weeks antiretroviral treatment of infant decreased breast milk transmission by 33-44% and reduced mortality (Taha CROI 2008, 42LB)
- Can the health systems deliver care given the system failures for prevention at birth??

Highly Active Antiretroviral Therapy (HAART)

- Sub Saharan Africa: ~1.3 million people on HAART
 - Only 28% of those in need of ART



Patients on
HAART
via PEPFAR

HAART cannot control the epidemic

- HAART reduces HIV transmission by lowering viral load but treatment is initiated late in disease
 - Only ~20% of transmissions occur in late stage HIV disease
 - Most transmissions occur during early or latent infection (Wawer JID, 2005)
- The number of HIV+ persons will increase due to:
 - Longer survival with HAART
 - Continued new infections

What does not work and what needs to be done?

- **STD control for HIV prevention**
 - STD control is a health benefit and should be provided
 - But, promoting STD control for HIV prevention is highly questionable
- **Microbicides. Back to basics**
 - Need better screening of products
 - Must avoid vaginal irritation
 - Improved trial design
- **Vaccines. Back to basics:**
 - Need better understanding of immune response to HIV
 - Need better screening of vaccine candidates
 - Need a new paradigm: **Mucosal vaccines** to block HIV entry?? (Shattock PLoS Med 2008)

What works?

- Biomedical interventions proven to be **efficacious** in randomized trials:
 - Male circumcision
 - Prevention of mother-to-child infection
- What is needed for these interventions to be **effective**?
 - Improved health infrastructure and manpower
 - Political will and funding
 - Acceptance and use of proven interventions

How do Biomedical and Behavioral Interventions Intersect?

- **There is no pure biomedical intervention**
 - All biomedical interventions depend on acceptance, adherence, avoidance of increased risk behaviors
- Behavioral and health systems research is needed to effectively implement proven interventions.
- Need research on translation of science into policy and programs
 - We know what works, we now have to implement it