

HIV prevention: Where is the evidence of interventions that work?



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1. Introduction

- Remarkable advances in the molecular biology of HIV and major therapeutic discoveries in the past 28 years of the epidemic.
- Many interventions have been developed and implemented – some were tested for evidence of efficacy or effectiveness and some were not.
- In 2009, we are not sure which interventions work! We need to identify and use best and good evidence HIV prevention interventions that work.
- Policymakers, implementers, researchers, funders and the community - all need evidence that an HIV prevention intervention works...
- We present evidence of HIV prevention interventions that work and also present their level of effectiveness or efficacy.

2. What is evidence?

- Evidence refers to “**facts** or testimony in support of a conclusion, statement or belief” and “something serving as **proof**”.
- Proof that something works.
- The Law uses witnesses and other forms of evidence to prove guilt beyond reasonable doubt.
- Epidemiology uses p-value to show level of significance e.g. $p \leq 0.05$ says we are 95% confident that the observed difference is not due to chance.



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The Evidence Pyramid



Source: <http://library.downstate.edu/EBM2/2100.htm>

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Proposed levels of evidence

Level of evidence	% Effectiveness or efficacy (in RCT)
 Best Evidence	80% +
 Good evidence	60-79%
 Promising evidence	30-59%
 NO Evidence	0-29%

3.1. Biomedical HIV prevention interventions

3.1.1. Male circumcision (MC)

3.1.2. Highly Active Antiretroviral Therapy (HAART)

3.1.3. Prevention of mother to child transmission (PMTCT)

3.1.4. Condoms (Male and Female)

3.1.5. Treatment of Sexually Transmitted Infections (STI)

3.1.6. Microbicides and cervical barriers

3.1.7. HIV vaccine

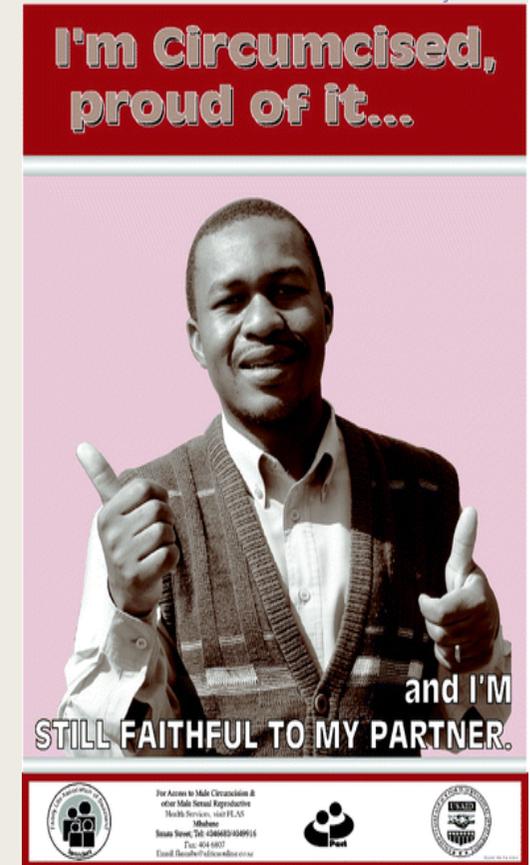
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3.1.1. Male Circumcision (MC)

Good evidence

- RCTs on MC in South Africa, Uganda, and Kenya^[1] :
"There is **compelling evidence** that MC is **65% effective** in reducing the risk of acquiring HIV in circumcised men..."
- A **Cochrane review** assessed data from trials in SA, Uganda, and Kenya between 2002 and 2006 that enrolled 11,054 males said that **research on the effectiveness of MC for preventing HIV in heterosexual men is conclusive.**

Reviewers concluded that **no further trials are required** to establish that HIV infection rates are reduced in heterosexual men for at least the first two years after circumcision^[2]



[1] Gray, H. et al. (2007). MC for HIV prevention in young men in Rakai: A RCT. *Lancet* 369:657-66.

[2] Siegfried N, Muller M, Volmink J, Deeks JJ,. MC for prevention of heterosexual acquisition of HIV in men. *Cochrane Database of Systematic Reviews*, Issue 4, 7 October 2009

3.1.2. Highly Active Antiretroviral Therapy (HAART)



Good evidence

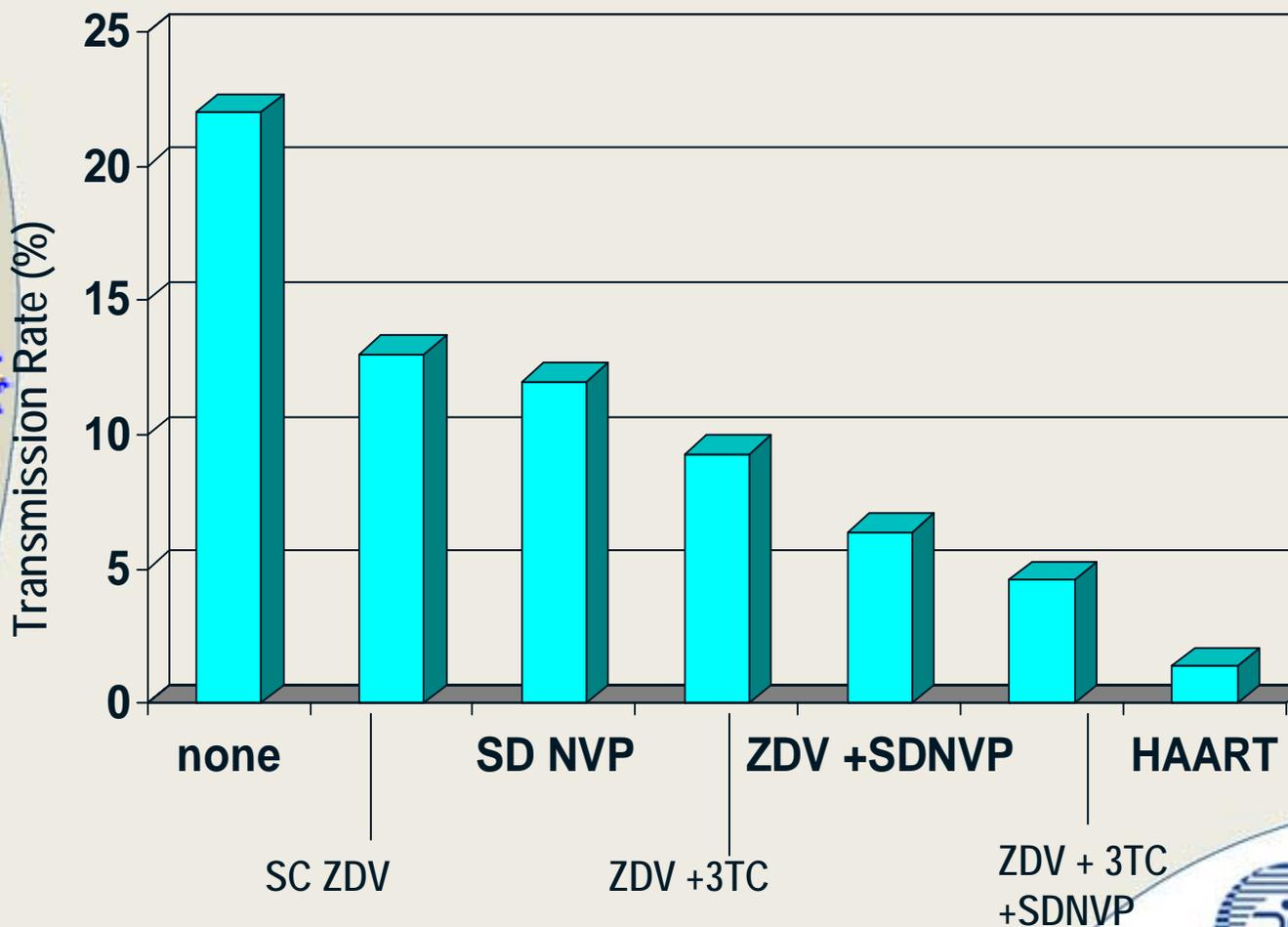
- RCTs on HAART* reported 60% to 80% reductions in new AIDS illnesses, hospitalizations and deaths
- A meta-analysis** of 54 antiretroviral clinical trials has demonstrated that:
 - Using one antiretroviral reduced progression to AIDS or death by 30% against placebo.
 - Using two antiretrovirals reduced progression to AIDS or death by 40% against one antiretroviral
 - Using three antiretrovirals reduced progression to AIDS or death by 40% against two antiretrovirals

*Jordan *et al.* (2002) *Systematic review and meta-analysis of evidence for increasing numbers of drugs in antiretroviral combination therapy*. BMJ 2002;324:757 <http://www.bmj.com/cgi/content/full/324/7340/757>

**Palella *et al.* (1998) *Declining morbidity and mortality among patients with advanced HIV infection*. NEJM, 338:853-860.

3.1.3. Preventing Mother-To-Child Transmission (PMTCT) of HIV

ARV and Perinatal Transmission in Africa, 1995-2006

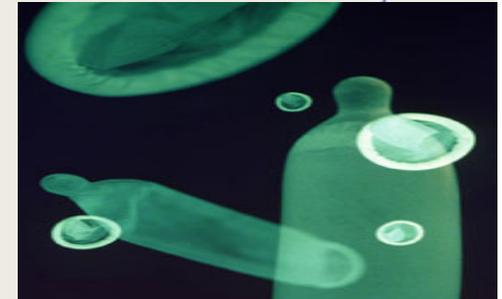


Transmission rates are as high as 35% when there is no intervention and below 5% when antiretroviral treatment and appropriate care are available



3.1.4. Condoms

Weapons of mass protection!



Best Evidence

- A meta-analysis commissioned by UNAIDS* = male condom use is **90% effective** in preventing HIV transmission.
- "Evidence from Family Planning programs over many years makes it abundantly clear that the condom is a safe and relatively effective method..."

Best Evidence

- Based on laboratory and clinical evidence, the US FDA approved the **female condom** as **94-97% effective** in reducing the risk of HIV infection, if used correctly and consistently**.

*Hearst N and Chen S, *Condom promotion for AIDS prevention in the developing world: is it working?* Studies in Family Planning, 2004, 35(1):39-47. <http://www.usp.br/nepaids/condom.pdf>

**AVERT, "The Female Condom" fact sheet, available online at <http://www.avert.org/femcond.htm>

3.5. STI treatment

Promising
evidence

- Evidence from a **cluster RCT in Mwanza, Tanzania**, suggests that improved STI treatment services were shown to reduce HIV transmission by about 40%.

NO
evidence

- Two trials (Mwanza & Rakai) indicate no evidence for substantial benefit from STI treatment of all community members.

Promising
evidence

- Cochrane Reviewers concluded that limited evidence from RCTs indicates that STI control serves as an effective HIV prevention strategy.

Schulze KF (2004) Population-based interventions for reducing sexually transmitted infections, including HIV infection. *The WHO Reproductive Health Library*, Geneva

Wilkinson D, Rutherford G. Population-based interventions for reducing sexually transmitted infections, including HIV infection. *The Cochrane Library*, Issue 1 2003.

3.1.6. Microbicides and cervical barriers

NO
evidence

- Studies of **early-generation microbicides** have **failed** to detect a prevention benefit, and disappointing results were reported on the HIV prevention potential of female diaphragms.

Promising
evidence

- **HPTN 035**: A multi-centre clinical trial conducted at 7 sites (6 in Africa) evaluated the safety and effectiveness of two candidate microbicides, BufferGel and PRO 2000 with 3,099 participants. **PRO 2000** was **30% effective** compared with no gel but BufferGel had no detectable effect on preventing HIV infection.

NO
evidence

- **Topical microbicides** **have not performed well** in human HIV prevention studies, with 10 trials of surfactant and polyanionic compounds yielding **negative results**.



3.1.7. HIV vaccine



Promising
evidence

- The Thai Phase III HIV vaccine clinical trial (RV 144), tested the “prime-boost” combination of two vaccines: ALVAC[®] HIV vaccine (the prime), and AIDSVAX[®] B/E vaccine (the boost). The vaccine combination was based on HIV strains that commonly circulate in Thailand. The trial demonstrated that the vaccine regimen was safe and modestly effective in preventing HIV infection. The results show that the prime-boost combination lowered the rate of HIV infection by 31.2%*

NO
evidence

- HIV Vaccine Trials Network (HVTN) launched the first large-scale study to evaluate a candidate clade B HIV HIV vaccine. The phase IIb or “test of concept” efficacy trial involved 3,000 participants at 5 sites in South Africa. Unfortunately, the trials were halted in September 2007 owing to the vaccine’s lack of efficacy

*Rerks-Ngarm R, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J et al. Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand. *NEJM* 20 October 2009

Summary: Evidence of Biomedical HIV prevention interventions

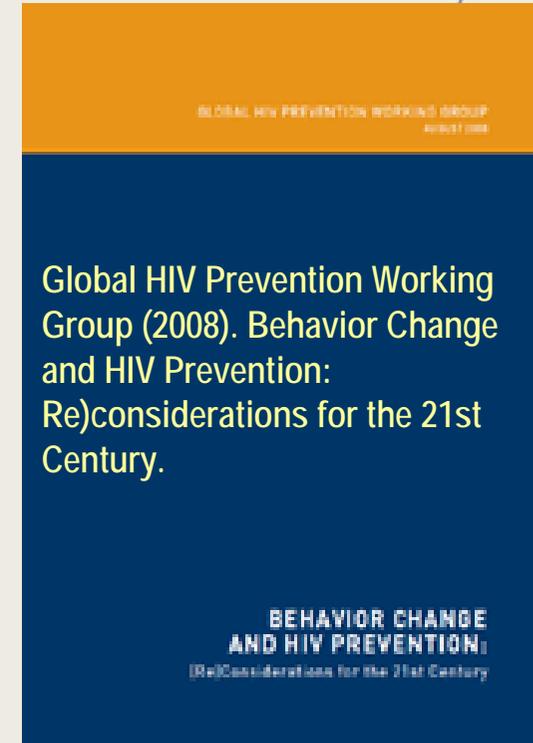
Level of evidence	Interventions	% Effectiveness or efficacy
	Male Condoms Female Condoms PMTCT [Dual & triple therapy]	80-95% [Natural experiment] 94-97% [Natural experiment] 92-98% [RCTs]
	HAART Male Circumcision	60-80% [RCTs] 65% [3 RCTs]
	HPTN 035 (PRO 2000) STI treatment RV 144 Thai vaccine trial	30% [1 RCT] 40% [1 RCT] 31.2% [1 RCT]
	HIV Vaccine Trials Network (HVTN) Early-generation microbicides & topical microbicides	No efficacy [RCT] Failed [RCTs] and negative results [10 RCTs]

3.2. Behavioural HIV prevention interventions

- 3.2.1. Abstinence-only and ABC interventions
- 3.2.2. Voluntary Counselling & Testing (VCT)
- 3.2.3. Stepping Stones counselling intervention
- 3.2.4. Concurrent sexual partnerships

“Behavioral HIV prevention works. Some have been pessimistic that it’s possible to reduce HIV risk behaviors on a large scale, but this concern is misplaced”

Dr. Helene Gayle, co-chair of the Working Group



3.2.1. Abstinence-only and ABC interventions

NO
evidence

A Cochrane review of 13 RCTs comparing abstinence-only programs to various control groups in the US concluded that ...abstinence-only programs do not appear to reduce or exacerbate HIV risk among participants in high-income countries, although this evidence might not apply beyond US youth. Of the 13 trials, 7 trials reported incidence of vaginal sex.



NO
Evidence?

"It is time to scrap the ABCs and elevate the debate on HIV prevention beyond the incessant controversies over individual interventions. Small scale, isolated HIV prevention programs, however effective, will not bring the AIDS epidemic under control...Policy makers, donors and advocates need to demand national prevention efforts...ABC infantilizes prevention, oversimplifying what should be an ongoing, strategic approach to reducing incidence."

Collins et al, *AIDS*, 2008

Underhill K, Operario D, Montgomery P. Abstinence-only programs for HIV infection prevention in high-income countries. *Cochrane Database of Systematic Reviews* 2007, Issue 4.

3.2.2. HIV Counseling and Testing (HCT)



Good evidence

- Meta-analysis of 11 studies of the impact of counseling and testing for PLWH/A*
 - 68% reduction in high risk sexual behaviors with partners not already HIV+ (95% CI: 59% - 76%)
 - Very similar findings for men and women

NO evidence

- Examining pool of 27 studies, a meta-analysis** found no significant impact of “counseling *and* testing” bundle on behavior relative to the untested

*Marks G et al. *JAIDS* 2005;39:446-453.

**Weinhardt LS et al. *Am J Public Health*. 1999;89:1397-1405.

3.2.3. Stepping Stones counseling intervention: Impact on HIV-1, HSV-2 & Behaviour

Promising
evidence

- *Stepping Stones*, a 50-hour “participatory learning” counseling program, lowered the risk of herpes simplex virus type 2 (HSV-2) infection by 34.9 per 1000 people exposed in a community RCT of 70 E.Cape villages. Compared with a shorter program, Stepping Stones did not lower incidence of HIV-1 infection and had variable impacts on risk behavior in the young adults studied.

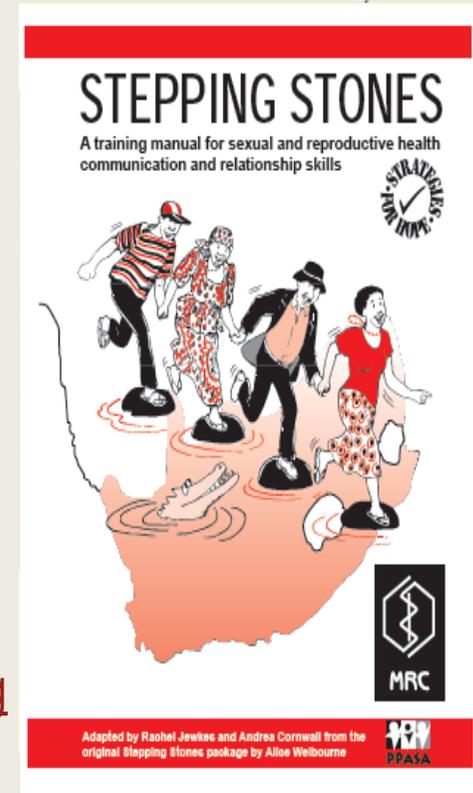
NO
evidence

Promising
evidence

Men who completed the *Stepping Stones* program reported less intimate partner violence (IPV) over 2 years, less transactional sex over 12 months, and less problem drinking over 12 months.

NO
evidence

But Stepping Stones women reported more transactional sex than women in the control program.



Jewkes, Nduna, Levin, Jama, Dunkle, Puren, Duvvury. Impact of Stepping Stones on incidence of HIV and HSV-2 and sexual behaviour in rural South Africa: Cluster randomised controlled trial. *BMJ*. 2008;337:a506

3.2.4. Concurrent Sexual Partnerships

- Taken together, the evidence that concurrency is driving the Africa AIDS epidemics is limited. There is as yet no conclusive evidence that concurrency:
 - (1) is associated with HIV prevalence;
 - (2) increases the size of an HIV epidemic;
 - (3) increases the speed of HIV transmission;
 - (4) increases the persistence of HIV in a population; or
 - (5) that this relationship has a large magnitude of effect.
- Current data on MCP comes from cross-sectional and ecological studies only; no RCTs or observational studies.

NO
evidence

Lurie M and Rosenthal S (2009) Concurrent Partnerships as a Driver of the HIV Epidemic in Sub-Saharan Africa? **The Evidence is Limited**. AIDS and Behavior

Mah T. L. and Halperin D. T. (2008). Concurrent sexual partnerships and the HIV epidemics in Africa: Evidence to move forward. AIDS and Behavior

3.3. Structural HIV prevention interventions

IMAGE study on micro-finance

Promising
evidence

- Intervention with Microfinance for AIDS and Gender Equity (IMAGE) RCT in rural Limpopo assessed a structural intervention that combined a microfinance programme with a gender and HIV training curriculum. They study found that experience of intimate-partner violence (IPV) was reduced by 55%.
- The intervention did not affect the rate of unprotected sex with a non-spousal partner (aRR 1.02, 0.85–1.23), and there was no effect on the rate of unprotected sex at last occurrence with a non-spousal partner (0.89, 0.66–1.19) or HIV incidence (1.06, 0.66–1.69) in cohort three

NO
evidence

Pronyk P, Hargreaves J, Kim J, et al. (2006) Effect of a structural intervention for the prevention of intimate-partner violence and HIV in rural South Africa: a cluster randomised trial. Lancet Vol 368: 1973-83



Summary: Behavioural and Structural HIV prevention interventions that work

Level of evidence	Interventions	% Effectiveness or efficacy
		
	HCT for PLWHA	68% reduction in high risk sexual behaviors [1 comm RCT]
	Stepping Stones IMAGE study	Lowered the risk of HSV-2 by 34.9 per 1000 people exposed; less IPV and less transactional sex [comm RCT] IPV was reduced by 55% [comm RCT].
	Abstinence-only interv's HCT on untested Stepping Stones IMAGE Concurrency	7/13 reported sex [SR] no impact of C&T on behavior of untested did not lower incidence of HIV-1 No effect on HIV incidence [comm RCT] No conclusive evidence

The AIDS epidemic has taught us to be innovative and to invent, test and implement new interventions.
We now have evidence of HIV prevention strategies that work!



Picture source: Naidoo D (2007). Science, Technological and Innovation – A Strategic Imperative for South Africa

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However, despite our innovation, inventiveness and compelling evidence of effective strategies, the “killer virus” is still chasing and killing us!



Picture source: Naidoo D (2007). Science, Technological and Innovation – A Strategic Imperative for South Africa

5. Conclusion

No “Magic Bullet” for HIV

“It is critical to note that there is no “magic bullet” for HIV prevention. None of the new prevention methods currently being tested is likely to be 100 percent effective, and all will need to be used in combination with existing prevention approaches if they are to reduce the global burden of *HIV/AIDS*.”

Source: Global HIV Prevention Working Group (2008)

Thanks

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