

Hepatitis B Prevention: An Interdisciplinary Model for STI Prevention

King Holmes
University of Washington
Department of Medicine
Center for AIDS and STD



Research on Preventing Sexual Transmission of HBV in Overall Context of STI Prevention Research

- MEDLINE
- Cochrane Central Registry of Controlled Trials
- Papers presented at international conferences 2002-2005, but not yet published
- Papers cited in literature reviewed, but not identified through above methods

Inclusion Criteria

- Randomized controlled trials
- Prevention of sexual acquisition or transmission of STI or HIV
- Systematic objective measurements of STI outcomes

Why focus on RCTs?

Parachute Use to Prevent Death and Major Trauma Related to Gravitational Challenge: Systematic Review of Randomized Controlled Trials

Gordon C S Smith, Jill P Pell

BMJ VOLUME 327 20-27 DECEMBER 2003

Abstract

Conclusions: We think that everyone might benefit if the most radical protagonists of evidence-based medicine organized and participated in a double blind, randomized, placebo-controlled, crossover trial of the parachute.



Parachutes' effectiveness has not been proven with randomized controlled trials.

December 3, 2005



Prevention and (STD or STI or HIV) = 37,381

How many were RCTs? = 88

How many had objective STI endpoints? = 46

reduced transmission of HIV? = 2

How many were effective
against other STIs? = 24

Classification of Interventions to Prevent Sexual Transmission of Infection

Level of randomization	1° Modality of intervention	Outcome measured
<ul style="list-style-type: none">• Individual	<ul style="list-style-type: none">• Behavior	<ul style="list-style-type: none">• Acquisition
<ul style="list-style-type: none">• Group	<ul style="list-style-type: none">• Treatment	<ul style="list-style-type: none">• Transmission
<ul style="list-style-type: none">• Community	<ul style="list-style-type: none">• Vaccine• Microbicide• Male circumcision	

How Well Have Behavior Change Interventions Worked?





THE LANCET

Volume 366 Number 9490 Pages 957-1050 September 17-23, 2005

www.thelancet.com

A quote from:
Sexual and
reproductive
health: call for
papers. Lancet
2005;366:969-70.

“Unsafe sex is the second most important risk factor leading to disease, disability, or death in the poorest countries in the world.”

See Comment page 969

|||||
AUTO ***** 5-DIGIT 98104
LNU/0538/03349176-9/S/LND 01 00/002
K HOLMES /LANCET917 0080
325 9TH AVE . NO. 359931
SEATTLE WA 98104 2420

Articles

Radiation therapy for low-grade astrocytoma and oligodendroglioma
See page 985

Articles

Worldwide distribution of HPV
See page 991

Articles

Effect of zinc supplementation on childhood pneumonia and diarrhoea
See page 999

Seminar

Invasive mycoses
See page 1013

Review

Performance of health workers in low-resource settings
See page 1026

The Lancet (ISSN 0099-5355) is published weekly by Elsevier Ltd. ©2005 Elsevier Ltd. All rights reserved. This year, the last issue in December will be a treble issue. Elsevier Ltd's North American agent is Elsevier Inc., 360 Park Avenue South, New York, NY 10010-1710, USA. Tel: 212-633-3800. Fax: 212-633-3853. Periodicals postage paid at New York, NY 10010, and at additional mailing offices. # 585-880 USPS CDN PM#0905372
POSTMASTER: Send undeliverable journals to The Lancet, Elsevier, Subscription Customer Service, 6277 Sea Harbour Drive, Orlando, FL 32887-4800, USA.

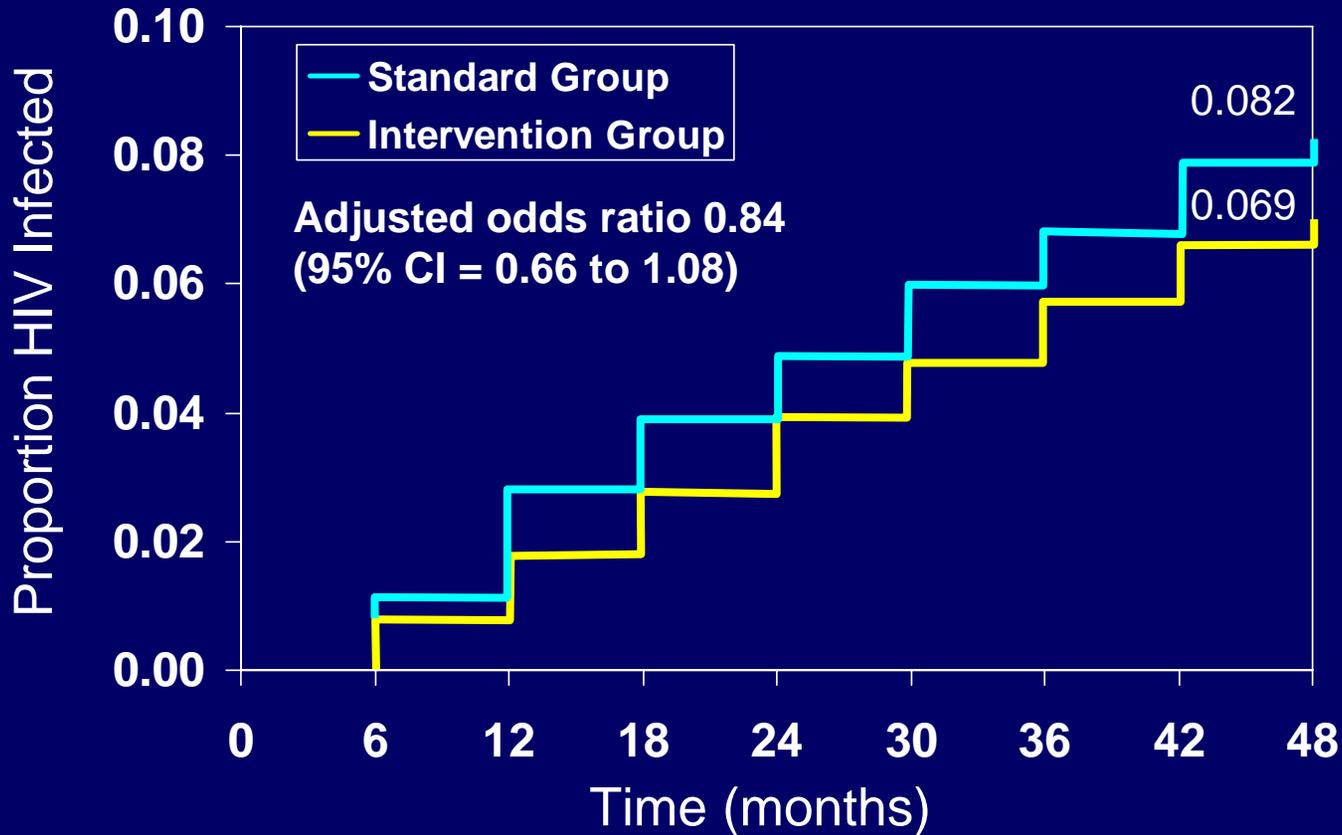
The Lancet® is a registered trademark of Elsevier Properties S.A., used under license. Printed in USA.

Founded 1823 · Published weekly

EXPLORE: RCT of a Behavioral Intervention to Prevent Acquisition of HIV Infection by MSM *Lancet 2004;364:41-50*

- 6 US cities
- 4296 HIV 1 seronegative MSM at risk randomized
- Intervention: 10 core counseling modules over 4-6 months (Chesney MA et al., Am J Public Health 2003;93:933-38)
- “Maintenance sessions” every 3 months thereafter
- F/U every 6 months (interviews, serology) for 4 years

EXPLORE: No Significant Difference in HIV Incidence



Kaplan-Meier curve: proportion infected with HIV (Lancet 2004;364:45)

Efficacy of Risk-Reduction Counseling to Prevent Human Immunodeficiency Virus and Sexually Transmitted Diseases

A Randomized Controlled Trial

Mary L. Kamb, MD, MPH; Martin Fishbein, PhD; John M. Douglas, Jr, MD; Fen Rhodes, PhD; Judy Rogers, MS; Gail Bolan, MD; Jonathan Zenilman, MD; Tamara Hoxworth, PhD; C. Kevin Malotte, DrPH; Michael Iatesta, MA; Charlotte Kent, MPH; Andrew Lentz, MPA; Sandra Graziano, PhD; Robert H. Byers, PhD; Thomas A. Peterman, MD, MSc; for the Project RESPECT Study Group

JAMA 1998; 280:1161-67

See also Am J Epid 2004; 159: 242



Proportion of Participants with a new STI Through the 3, 6, 9, & 12 Mo. Visits



Summary

- 14 behavioral RCTs with objective STI outcomes.
- Most showed self-reported behavior change.
- Only five (36%) showed a significant impact on STI.
- No obvious explanation for why some succeeded and some did not, except:
 - Effects were modest
 - Unsuccessful studies were often underpowered for STI outcomes.
- Sustainability of effect was a common problem.
- Of 5 behavioral RCTs with STI outcomes involving adolescents, only one reduced STIs.
- **Impact on HBV transmission?**

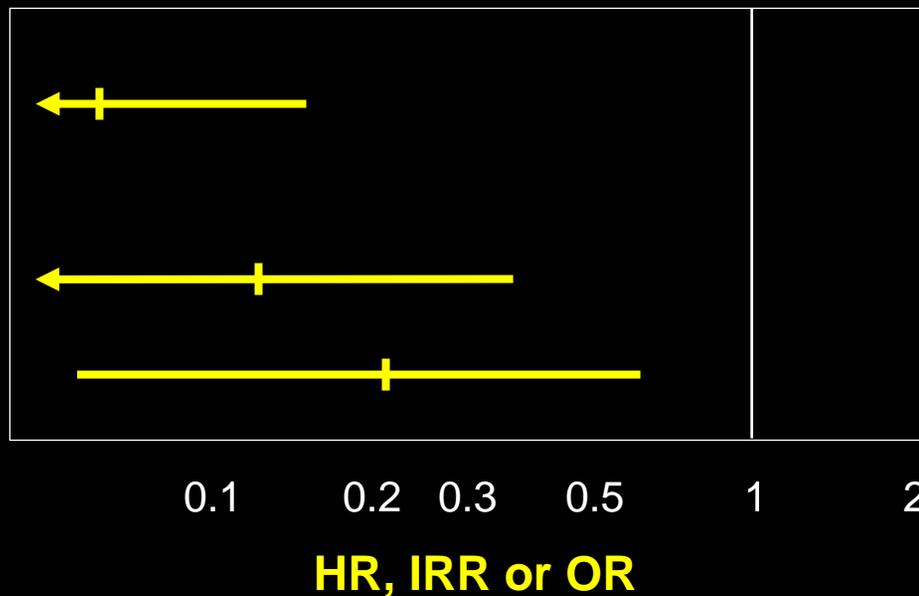


Copyright © 2005, [Chicago Tribune](#)

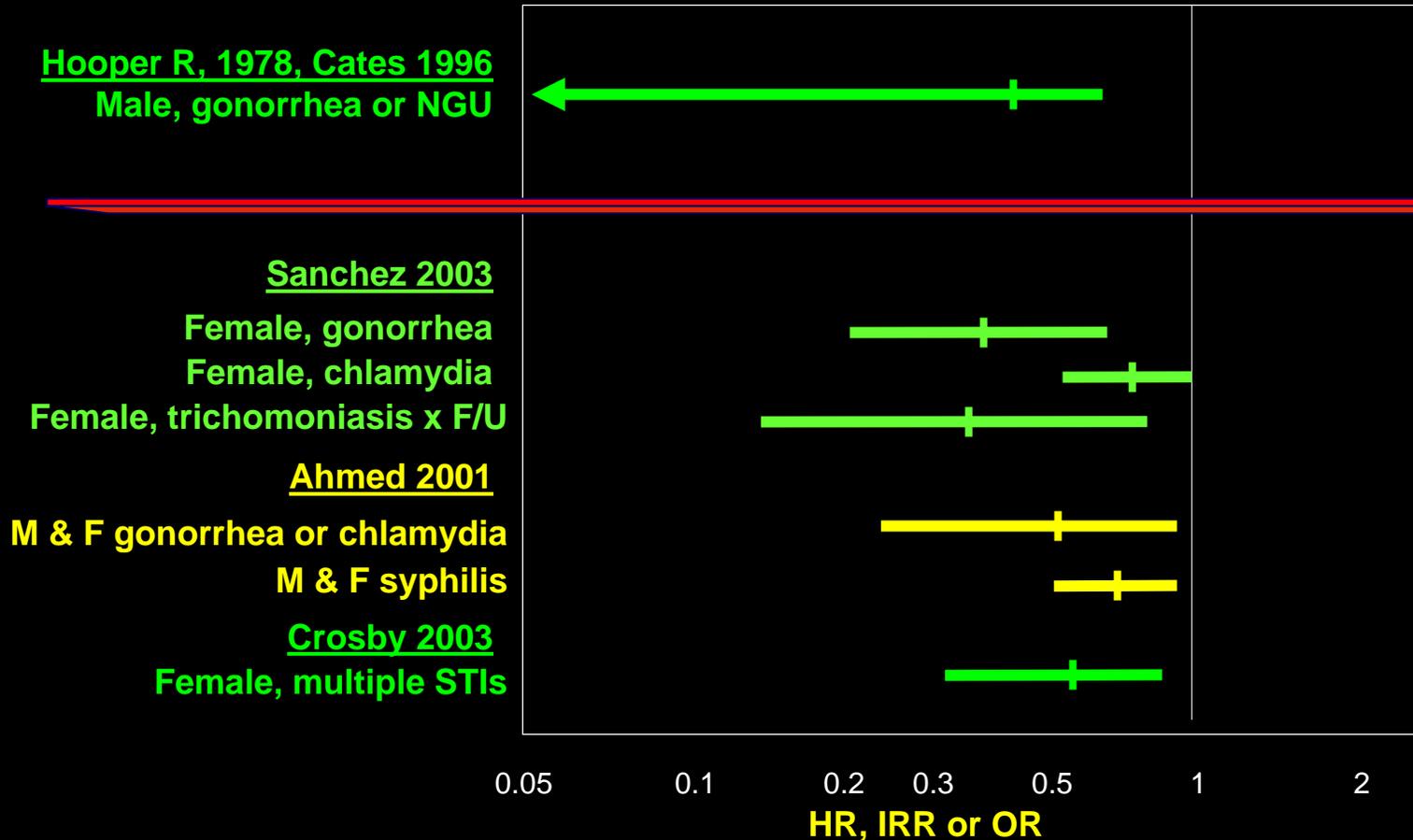
World AIDS Day-The traditional obelisk in downtown Buenos Aires, Argentina, is covered with a giant condom Thursday 12/1/05 to mark this year's World AIDS Day with campaigns for HIV/AIDS prevention.

80-95% Effectiveness of Condoms in Preventing HIV

Pinkerton 1997
Davis & Weller 1999
Weller & Davis 2004



Effectiveness of Condoms in Preventing Curable STI



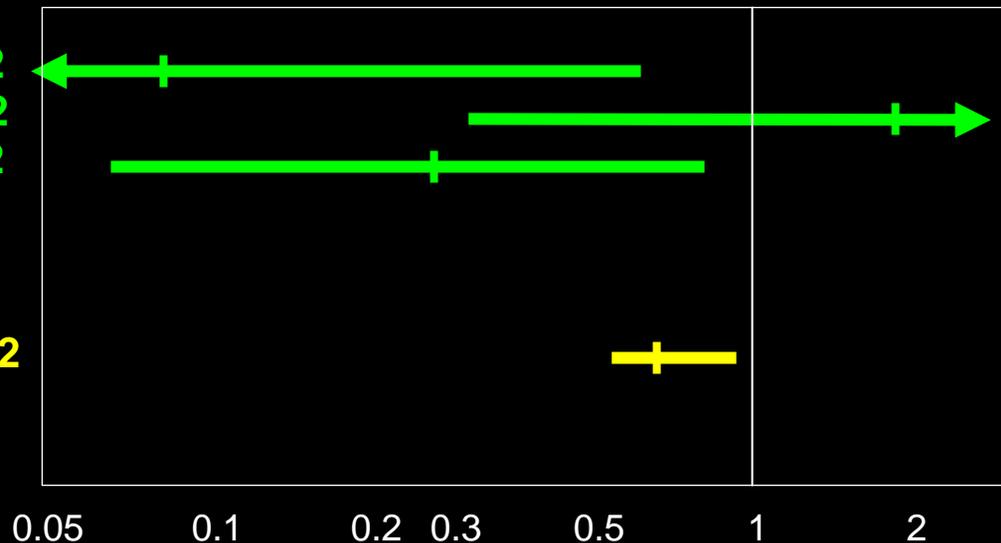
Effectiveness of Condoms in Preventing Transmission of Herpes Simplex Virus

Wald

2001 Female, HSV-2
Male, HSV-2
HSV-2

Wald

2005- Male, HSV-2



HR, IRR or OR

Summary: Condom Efficacy

Despite bias towards null effect (e.g., social desirability, selective use of condoms with high risk partners, recall, incorrect use, etc.):

Longitudinal Studies in Males and Females Show:

HIV	: ↓ 80 – 95%
CT, GC	: ↓ at least 50%
HSV-2	: ↓ at least 30 – 70%
Vaginal infections (TV, BV)	: ↓ modestly
Syphilis	: ↓ about 25%
HPV	: ↓ 72%

What about HBV?

Sexually Transmitted Infections in Female Sex Workers: Less Common in Consistent Condom Users

	Crude Odds Ratio	Adjusted Odds Ratio (95% CI)	p
Current STDs			
<i>N. gonorrhoeae</i> isolated	0.3	0.4 (0.2, 1.0)	.07
<i>C. trachomatis</i> isolated	0.8	0.9 (0.5, 1.6)	.70
VDRL \geq 1:4 and FTA-ABS reactive	0.3	0.3 (0.1, 1.2)	.09
Current or Past STDs			
FTA-ABS reactive	0.4	0.4 (0.2, 0.8)	.01
<i>C. trachomatis</i> antibody	0.5	0.6 (0.4, 1.0)	.05
<i>H. ducreyi</i> antibody	0.6	0.8 (0.5, 1.4)	.40
HSV-2 antibody	0.4	0.7 (0.4, 1.3)	.20
Anti-HBc	0.5	0.6 (0.3, 0.9)	.03
HTLV-1 antibody	0.2	0.3 (0.1, 0.8)	.02

Sanchez J, et al. Sex Transm Dis 1998;25:82-9.

Impact of a Condom Promotion Intervention on HBV Infection Incidence

- 334 FSW from intervention district (2.25 km²) and 207 FSW from control district (9 km²) in Bombay.
- Intervention: promotion & provision of condoms.



HBsAg

HIV

TPHA

	Incidence Density/6 mo F/U		
	Intervention (N=334)	Control (N=190)	
HBsAg	.03 (.02-.06)	.11 (.07-.18)	(p=.001)
HIV	.05 (.03-.10)	.16 (.09-.26)	(p=.002)
TPHA	.08 (.04-.13)	.22 (.13-.35)	(p=.002)

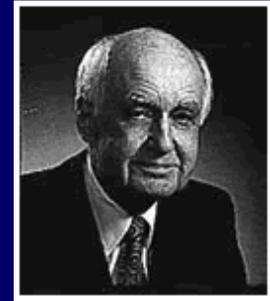


Bhave G, et al. AIDS
1995;9:S21-S30.

STI Immunizations?



Hepatitis B Vaccine: Prevention of Hepatitis B in MSM in Randomized Placebo-Controlled Trials



- **Szmunness W, et al. NEJM 1980;303:833-41.**
 - Vaccine efficacy 92%; nearly 100% after 3 doses
- **Coutinho RA, et al. Br Med J 1983;286:1305.**
 - HBV acquisition by 4.8% given vaccine vs. 23.8% given placebo
- **Francis DP, et al. Ann Intern Med 1982;97:362.**
 - HBV acquisition in 13/1000 person-years for placebo vs. 2/1000 person-years for vaccine



HBV Vaccination – MSM, GUM Clinics England

- For eligible MSM, dose 1 coverage increased from 85% in 2003 to 90% (2753/3499) in 2004.
 - Target was 90% for dose 1 by 2006.
 - Consistent trend in 8 of 9 regions.
-

Munro HL. Health Protection Agency, UK ISSTDR 2005, TP-034.

Coverage in US STD clinics?

Impact of Prison Vaccination Program in HBV Vaccine Coverage Among IDU

- 1988 UK Government recommended to vaccinate IDUs.
- 4/99 – Scottish Prison Service Initiative for HBV.
- In Glasgow, vaccine uptake among community-recruited IDU.
 - 1993 : 16% of 166
 - 1994 : 19% of 138
 - 1999 : 15% of 128
 - 2001-2: 52% of 387 (of whom 56% had been vaccinated in prison)

HBV Vaccination Practices – HIV Outpatient Study (HOPS)

- 1998 – 9/30/2002; 1st visit '98 or later

1,071 Patients

877 (82%) screened for HBV infection or vaccination

612 (57%) eligible for HBV vaccine

198 \geq 1 dose

104 \geq 3 doses

19 (37%) of 51 Respond

**HMC Madison HIV Clinic: EMR Search of
Active Patients (2+ PHC visits/yr).
% Eligible for HBV Vaccine, % Vaccinated**

Year	Active	Eligible for Vaccine	% Eligible	Vaccinated	% Eligible Vaccinated
1998	309	166	54%	39	23%
1999	443	203	46%	56	28%
2000	614	226	37%	49	22%
2001	727	238	33%	48	20%
2002	845	264	31%	67	25%
2003	929	241	26%	50	21%
2004	1024	270	26%	67	25%

Unresolved Issues

- Should providers wait until CD4 returns to > 200 cells?
- “The provider’s intention to delay vaccination until there is a degree of immune restoration places the patient at risk never to receive the vaccination.” (Tedaldi, et al.)
- What interventions for HBV transmission are offered for HBV infected persons?
- How should vaccines against OIs be included in the HIV “positive prevention” package?
- How can HBV vaccine uptake and response be improved?

States With AIDS Drug Assistance Programs (ADAP) That Cover Hepatitis Vaccine (2002)

Alaska	Florida	New York
Arkansas	Massachusetts	North Dakota
California	Michigan	Virginia
Connecticut	Missouri	Washington (HBIG only)
Delaware	New Hampshire	

National ADAP Monitoring Report April 2003
NASTAD/Kaiser Family Fund/ATDN

**Koutsky LA, et al. A Controlled Trial
of a Human Papilloma-virus Type 16
Vaccine. *NEJM* 2002; 347: 1645**



HPV 16 Infections

HPV 16 vaccine group	0 (0 per year)
Placebo vaccine group	41 (3.8% per year)

Mao C, et al ICAAC 2004

**HPV 16 – Associated
Mod-Severe CIN**

HPV-16 vaccine group	0
Placebo vaccine group	12



Summary – STI Vaccine RCTs

HBV: Effective, underutilized to prevent sexually acquired HBV

HPV L1 VLP: A slam dunk! Multi-type trials underway

HSV-2: GSK gD2 alum MPL vaccine, induces neutralizing antibody, with 73-74% reduction in symptomatic GHD, 38-42% reduction in acquisition of HSV-2 infection, but only in HSV-1 and -2 seronegative women

Summary – Microbicide RCTs

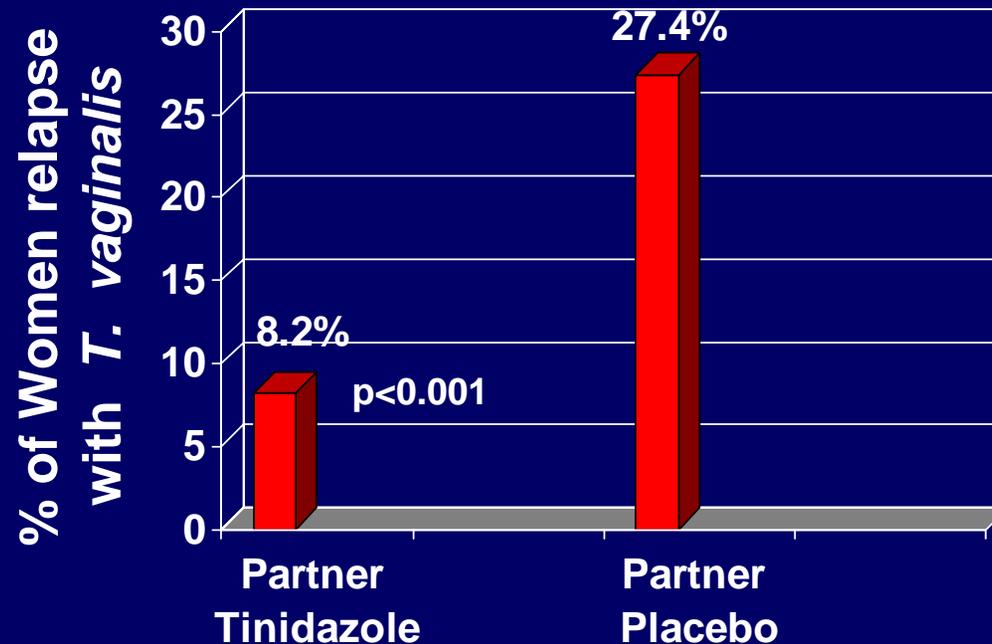
- Five RCTs of N-9 since 1990 – all in women
- No benefit against HIV, other STI
- One trial: significantly increased HIV acquisition!
- N-9 – Rest in Peace
- Other products (e.g. Pro2000, Buffergel, Carraguard) now undergoing phase III trials



Preventive Treatment



Double-Blind Randomized Trial of Giving 2 gm Tinidazole to Male Partners of Females Treated With 2 gm Tinidazole for Trichomoniasis



Lyng J, Christensen J. Acta Obstet Gynecol Scand 1981;60:199

Summary – STI Preventive Treatment

- Treatment of infected sex partners to prevent (re)infection of the susceptible partner
 - Effective vs. trichomonas, HSV-2, GC-PDPT
 - Impact of ARVs on HIV transmission?
- STD Rx for HIV prevention
 - ↓ HIV transmission in Mwanza (emerging HIV epidemic, high STI rates)
- Effect of treating Hep B on HBV transmission?

Randomized Trial of Male Circumcision

- Bertrand Auvert – Orange Farm Intervention Trial (ANRS 1285)
- International AIDS Society – 27 July, 2005
Rio de Janeiro

Results 2/3

Incident cases :

	<u>M0-M3</u>	M4-M12	M13-M21	Total
Intervention	2	7	9	18
Control	9	15	27	51
Total	11	22	36	69

Incidence rates :

Intervention : 0.77 (0.49 - 1.23) /100 py

Control : 2.2 (1.7 - 2.9) /100 py

Total : 1.5 (1.2 - 1.9) /100 py

Unadjusted RR : 0.35 (0.20 - 0.60) $p=0.00013$

Protection (1-RR): 65% (40% - 80%)

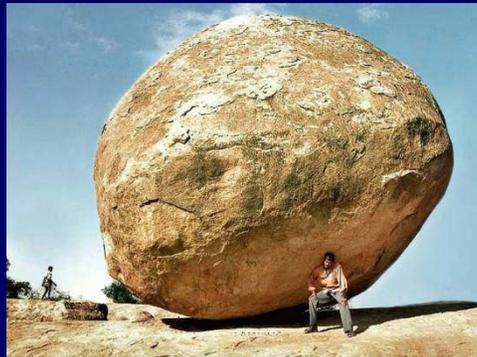
The intervention prevented 6 to 7 out of 10 potential HIV infections

Conclusions

1. Several rigorously designed and evaluated RCTs of STI prevention. Half worked!
2. Only two (STD Rx, Mwanza and male circumcision, So. Africa) showed impact on sexual transmission of HIV.
3. Since HBV vaccine trials of late 1970s, no RCT has yet shown impact of any preventive intervention on STI/HIV among MSM.
4. Remarkably, few of the effective STI interventions widely implemented.
5. Prevention in HIV seropositive persons beginning, and becoming the standard of care.
6. Prevention in HBsAg + persons?

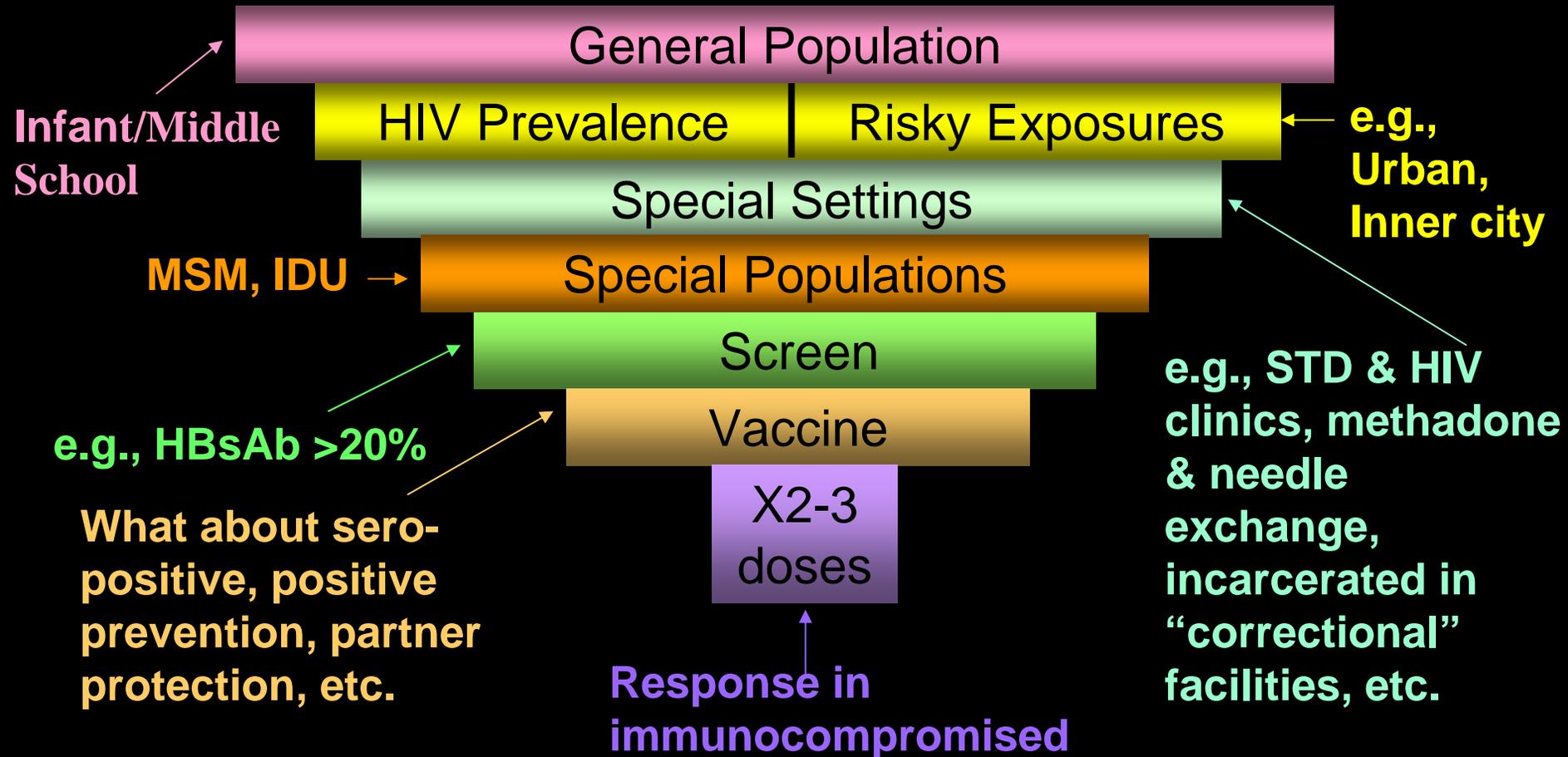
Need for Structural and Policy Supports for Interventions to Prevent HIV and Other STI

- How effective have they been in the U.S.?



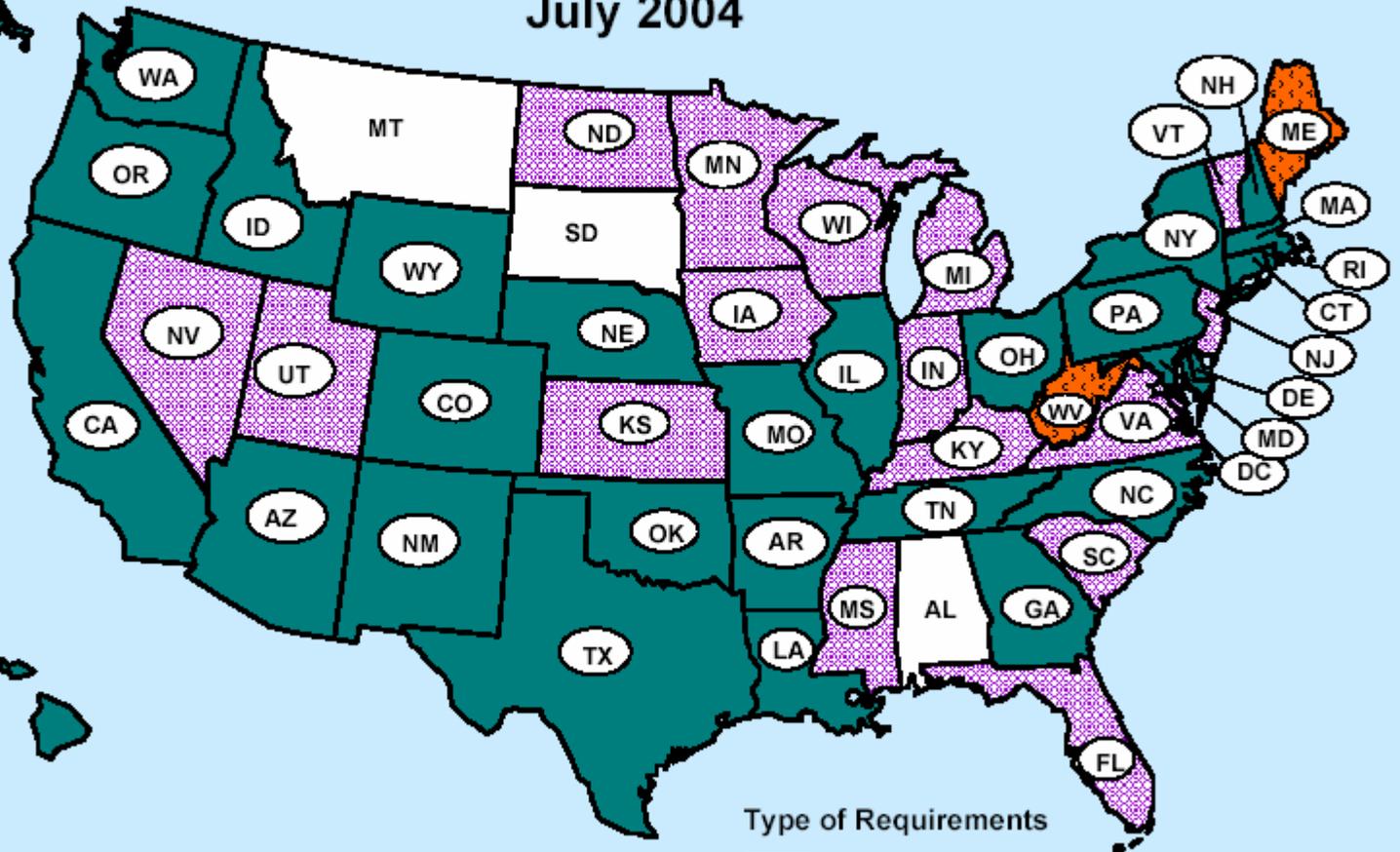
“Why Women Think Men are Immature”

Hepatitis Prevention Pyramid



Hepatitis B Prevention Mandates for Children in Day Care and Schools

July 2004



Type of Requirements

Day care & school

School only

Day care only

Age-Specific Incidence of Acute HBV Infection – US 2004

- Females – peak ages 25 – 44
- Males – peak ages 25 - 49

Cost-Effectiveness and Time Until Impact of Targeted HBV Immunization of High Risk Adults in STD Clinics

Transmission dynamic model showed that for UK:

- Universal infant vaccination became more cost-effective than STD clinic-based vaccination only after **40 years**.
- For MSM, clinic-based vaccination with prior screening was **always** more effective.

Williams JR, Nokes DJ, Medley GF, Anderson RM.

1. J Epidemiol Common Health 1996;50:667-73.
2. Epidemiol Infect 1996;116:71-89.



“Tactics is knowing what to do when there is something to do. Strategy is knowing what to do when there is nothing to do.”

Savielly Tartakover
Polish Chess Grand Master

Perspectives on Hepatitis B Vaccination as Interdisciplinary Model for STI/HIV Prevention

- How can HBV vaccine uptake and response be improved in cross-discipline practice settings?
- Positive prevention for HBV: Where is the HBsAg-positive individual in HBV prevention? (e.g., Behavior change, condoms, partners).
- Include (or recapture) HBV as endpoint in STI prevention trials e.g., condom efficacy, microbicides, behavioral intervention, circumcision.
- Apply CQI techniques to integration of hepatitis prevention into cross-discipline practice settings.
- Policies and structural support for integration of services
- We spend \$15B on PEPFAR, millions on HIV vaccine research; we can spend 1/100th that on closing the gap in US adults with a highly effective HBV vaccine.

Psychosocial Correlates of HBV Vaccine Uptake in US STD Clinics

- A-CASI interview on beliefs and intent to accept vaccination.
- 73% intended to accept, 58% accepted 1st dose.
- Acceptance predicted by greater intent, less fear of vaccine, less worry about infection, perceived benefits, and belief vaccination was normative.

Zimet GD, et al. ISSTD 2005, TP-035.

THANK YOU!