

STD CONTROL AND HIV PREVENTION

Current status of the evidence

Review STDs as cofactors for HIV

Bacterial STDs

- Observational studies
- STDs in HIV+ increase HIV shedding
- Randomized trials of bacterial STD control for HIV prevention

Viral STDs (Mainly HSV-2)

1. Observational studies
2. Randomized trials of HSV-2 suppression in HIV+ persons and HIV shedding in the genital tract
3. Randomized trials of HSV-2 suppression and HIV acquisition/transmission

INDIVIDUAL LEVEL vs POPULATION LEVEL

STDs as cofactors in HIV transmission

STDs increase HIV transmission

- ↑ HIV replication**
- ↑ viral shedding in genital secretions**

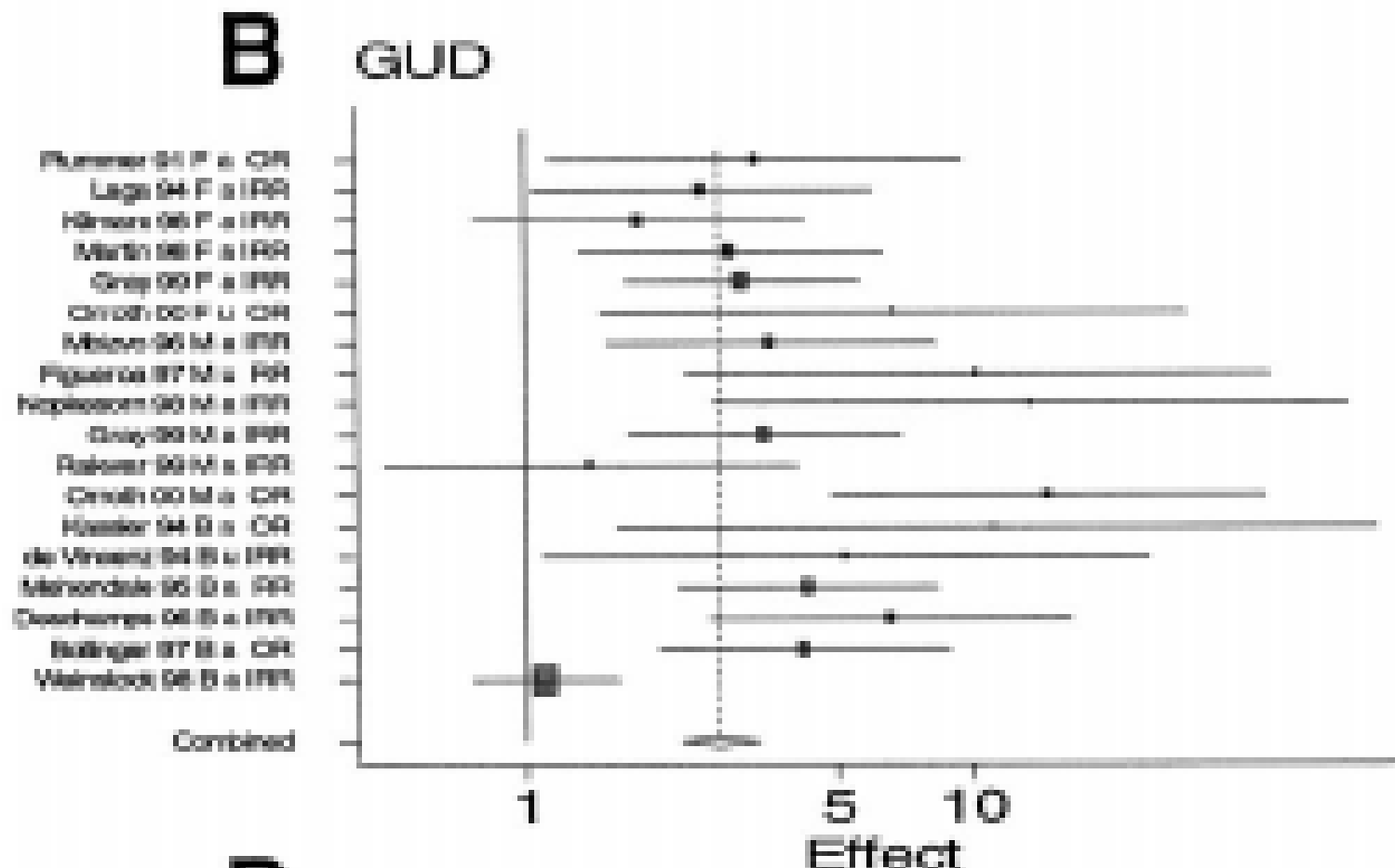
STDs increase susceptibility to HIV

- Disrupt mucosal barrier (e.g., GUD)**
- ↑ number of HIV target cells in genital tract**
- ↑ receptors expressed per cell**

Epidemiologic studies of bacterial STDs and HIV acquisition

Meta-analysis of GUD and HIV

(Rottingen et al STDs 2001)

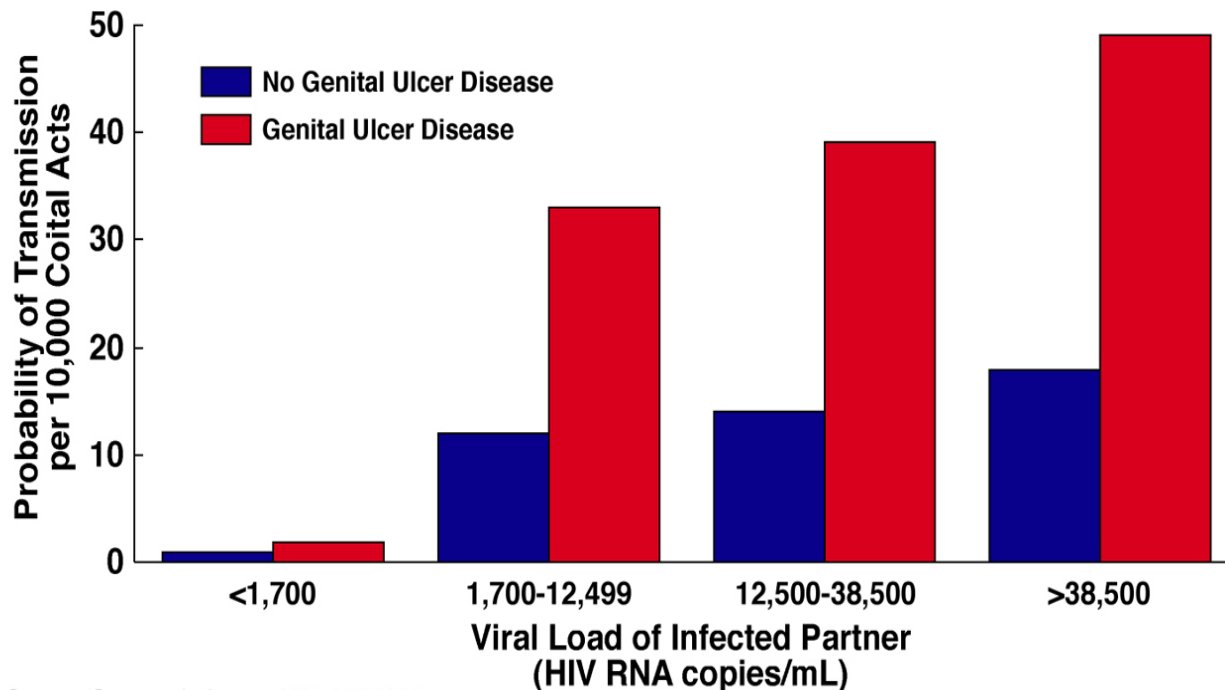


18 studies, in 14 GUD significantly increased HIV risk

GUD, viral load and HIV transmission per coital act in discordant couples, Rakai

(Gray Lancet 2001)

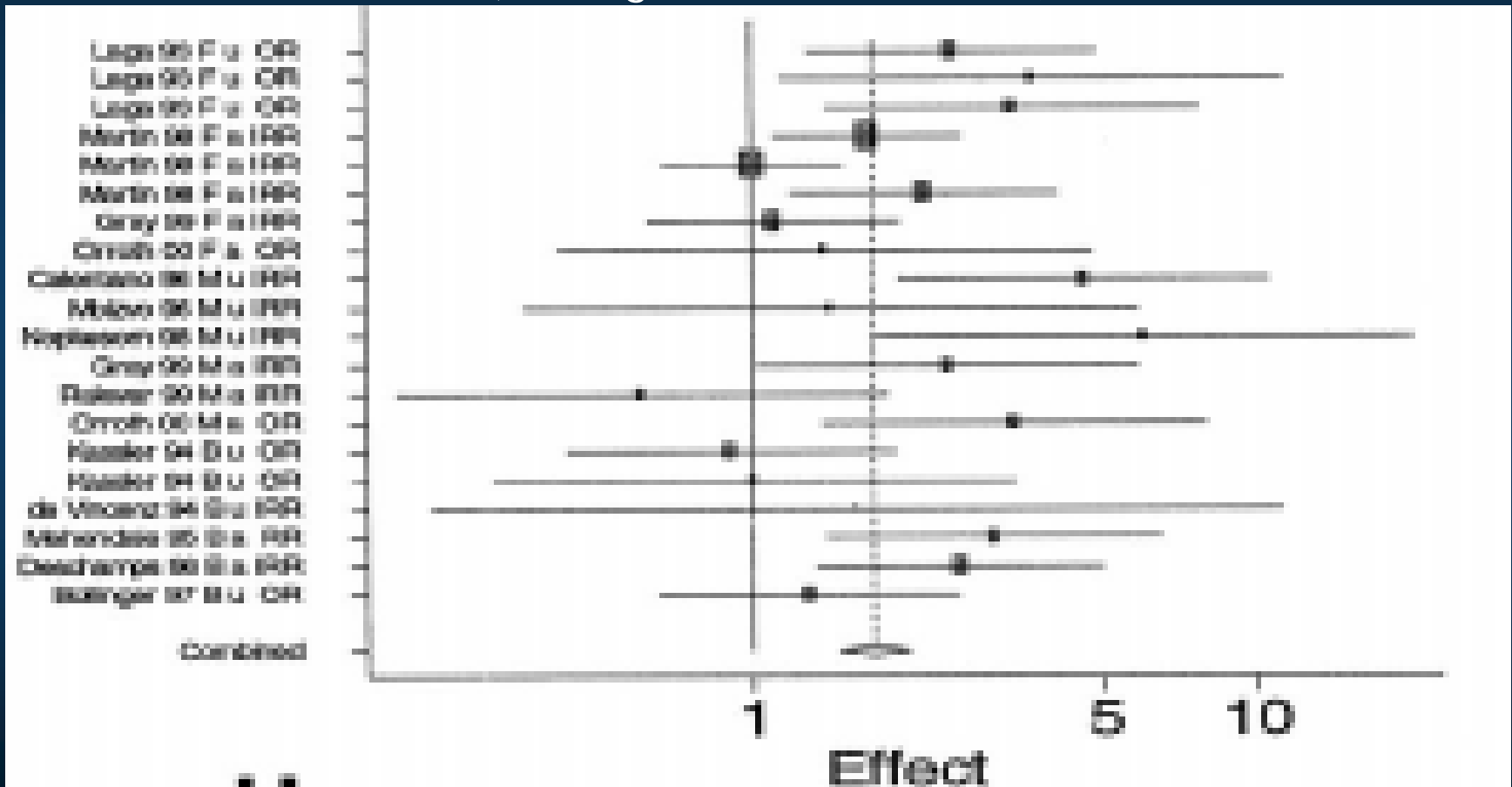
Probability of HIV Transmission per Coital Act in Monogamous, Heterosexual, HIV-Discordant Couples in Rakai, Uganda



Source: Gray et al., *Lancet* 2001;257:1149

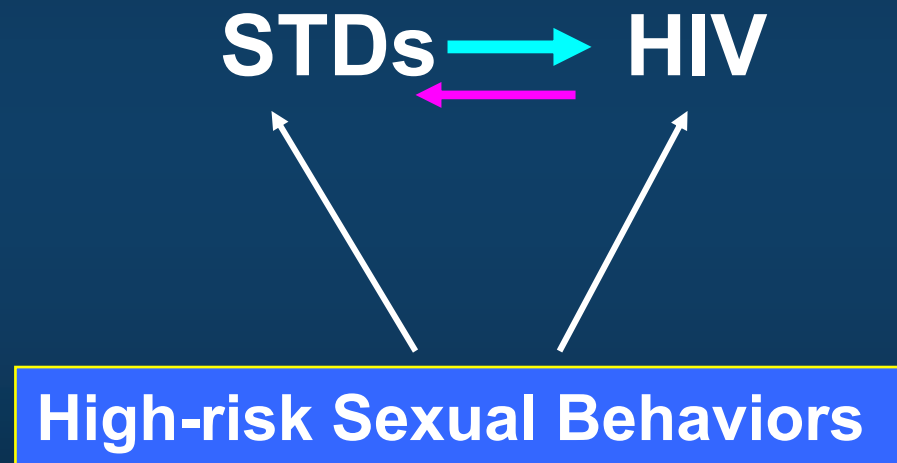
Meta-analysis of Non-Ulcerative STDs and HIV acquisition

(Rottingen et al STDs 2001)



20 studies, in 10 significant increased HIV risk with Non-ulcerative STDs

Problem of Confounding by Sexual Behavior



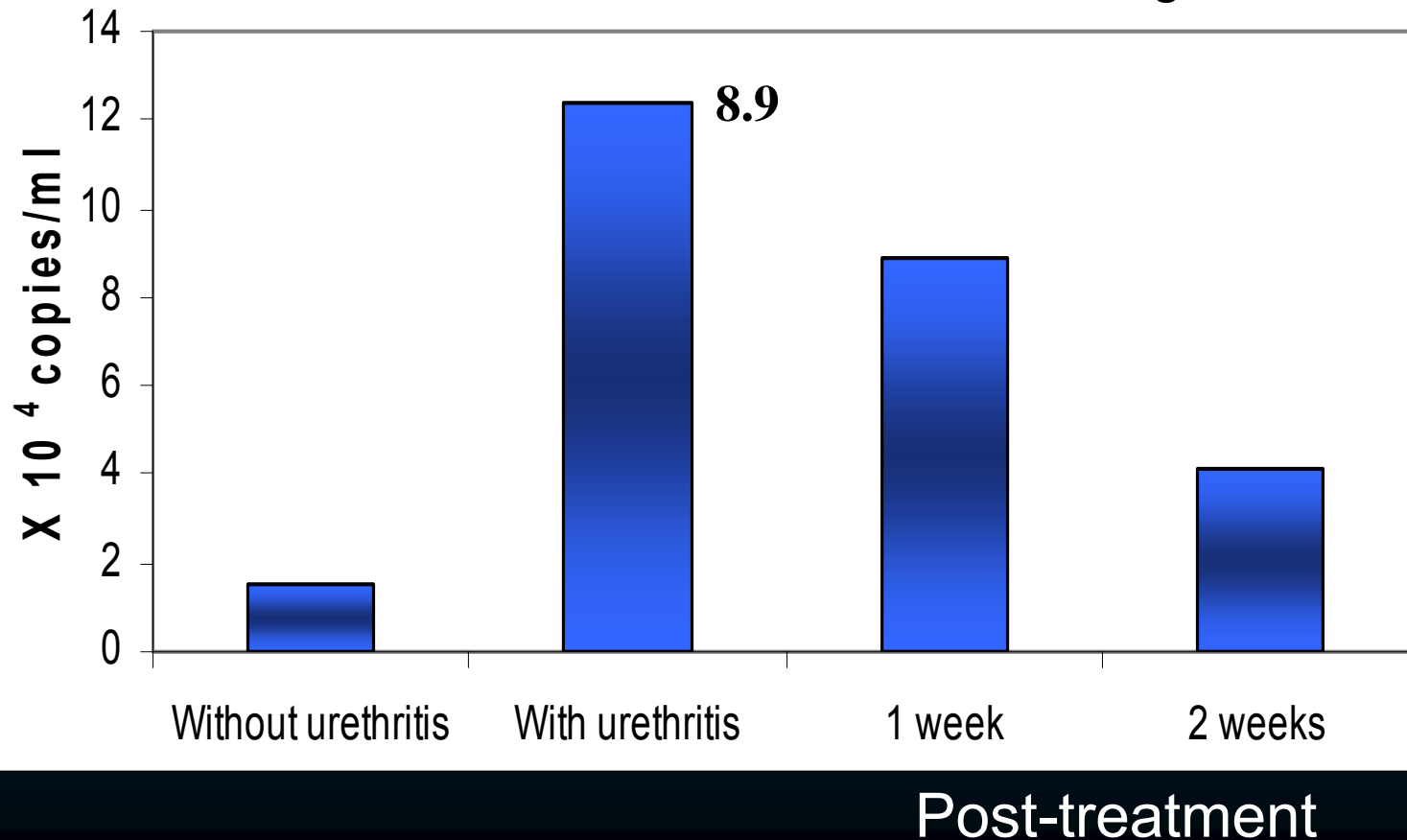
Need randomized trials to avoid confounding

Bacterial STDs and genital tract shedding of HIV

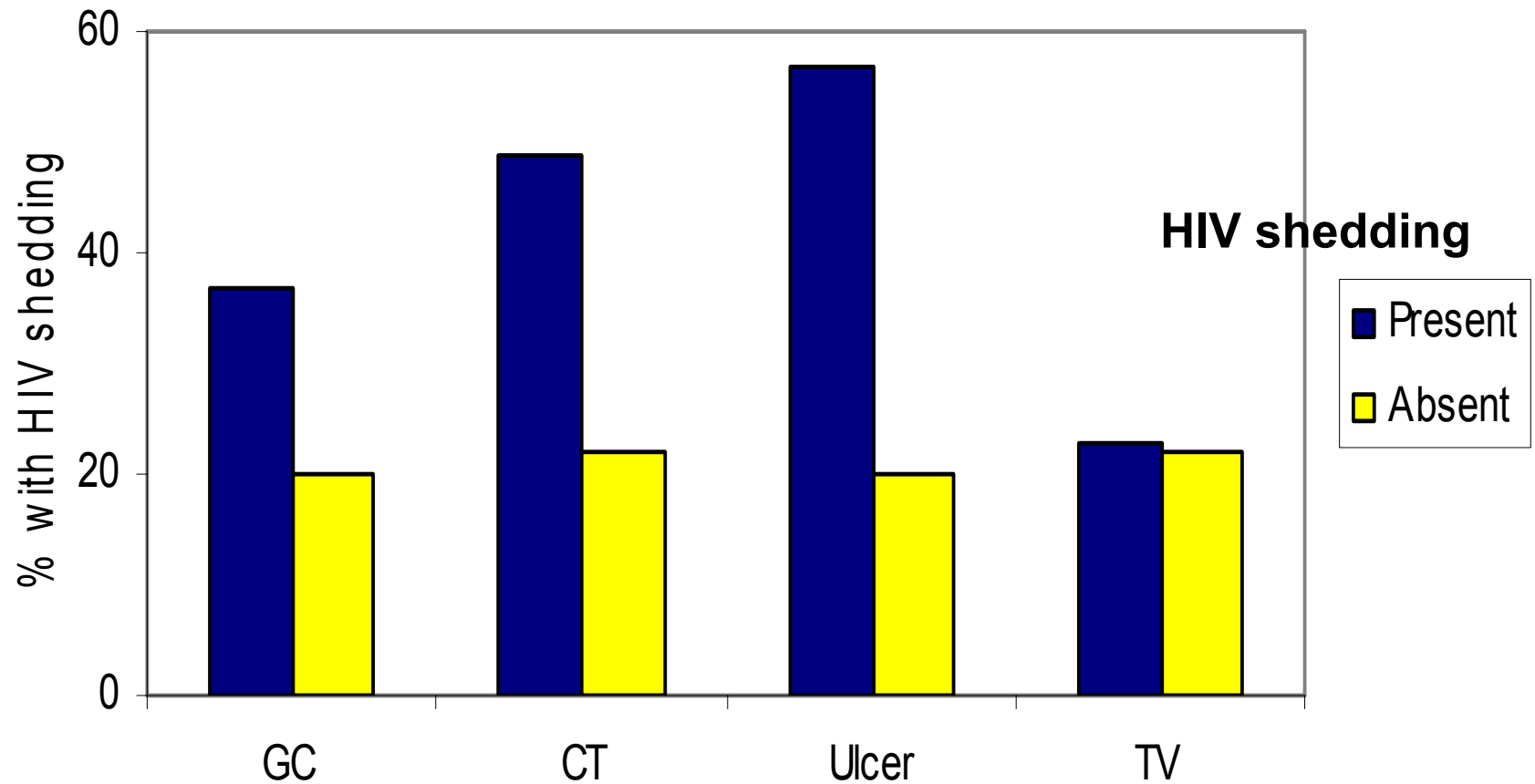
Semen HIV-RNA and urethritis

Cohen et al, Lancet 1997

Median concentration of HIV-1 RNA in semen,
104 men with and without urethritis in Malawi,
baseline and in first two weeks following Rx



Association between presence of STD and cervico-vaginal HIV-1 shedding



Randomized Trials of Bacterial STD Control for Heterosexual HIV Prevention

- **Community randomized trials:**
 - **Mwanza, Tanzania** (Grosskurth, Lancet 2005)
 - **Rakai, Uganda:** Two trials: Adult HIV and MTCT (Wawer Lancet 1999, Gray Amer J Obstet Gynecol 2001)
 - **Masaka, Uganda:** Two interventions STD control \pm IEC (Kamali, Lancet 2003)
 - **Manicaland, Zimbabwe** (Gregson PLoS 2007)
- **Individually randomized trial:**
 - **Commercial sex workers, Nairobi, Kenya** (Kaul JAMA 2004)

STD Interventions

- Mwanza, Tanzania (syndromic)
- Rakai, Uganda (mass treatment)
- Rakai Mother/infant (mass treatment)
- Masaka, Uganda (syndromic)
- CSW, Nairobi, Kenya (mass treatment)
- Manicaland, Zimbabwe (syndromic)
- **All tested the hypothesis that control of bacterial STI & trichomonas can reduce HIV incidence**

Comparison of STD control trials

	% HIV + baseline	HIV-neg enrolled	Arms	Cluster/ arm
• Mwanza	4%	12,000	2	6
• Rakai	16%	12,700	2	5
• Masaka	10%	14,500	3	6
• CSW Nairobi	27%	466	2	-
• Zimbabwe	~22%	9,400	2	6

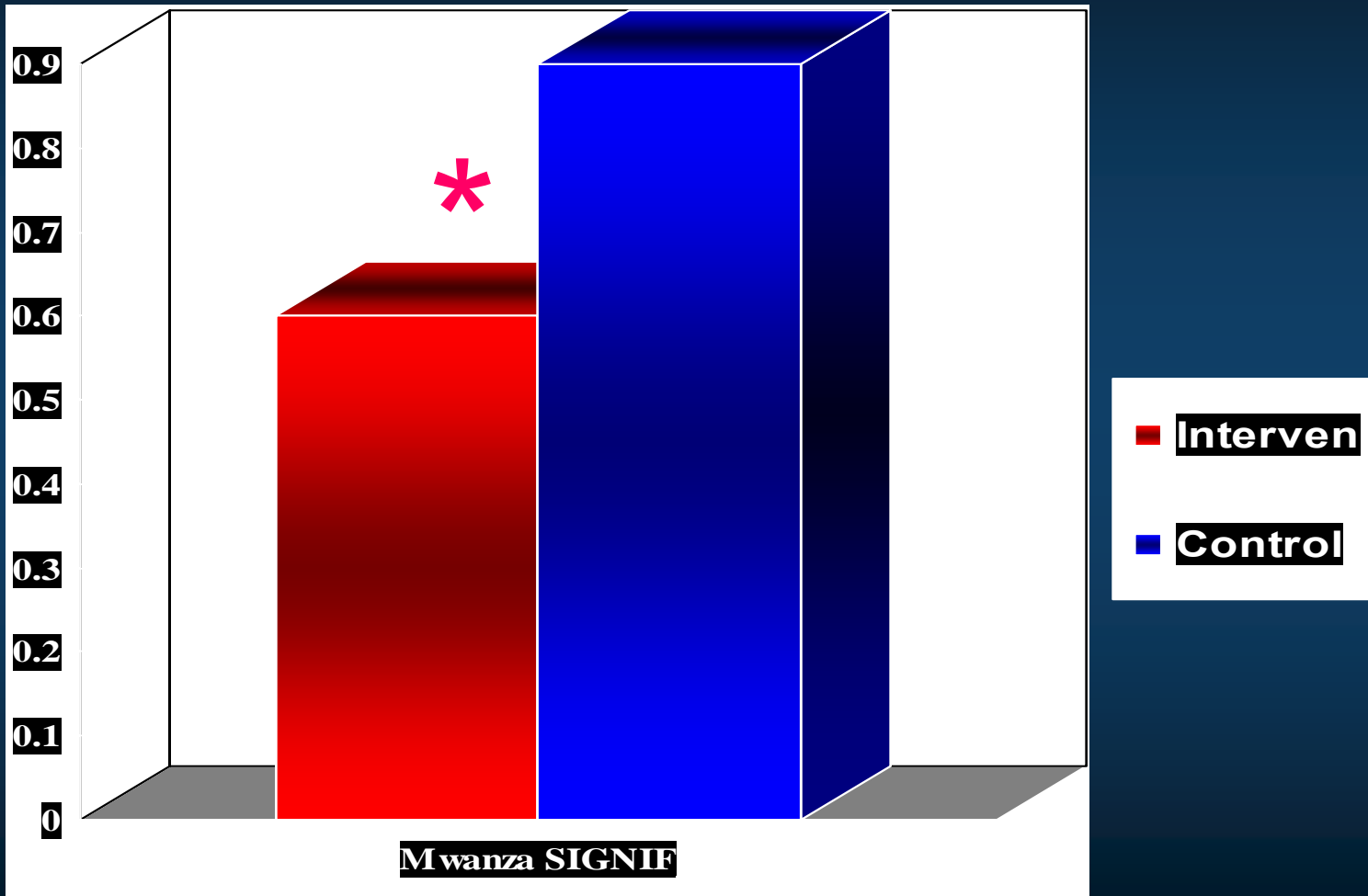
Comparison of STD control trials

Follow up rates

- Rakai 77%
- Mwanza 71%
- Masaka 70%
- CSW Nairobi 73%
- Manicaland 55%

Mwanza: HIV Incidence Intervention and Control Arms

(Grosskurth et al, Lancet, 1995)



✖ Significant (~38%) lower incidence in intervention arm

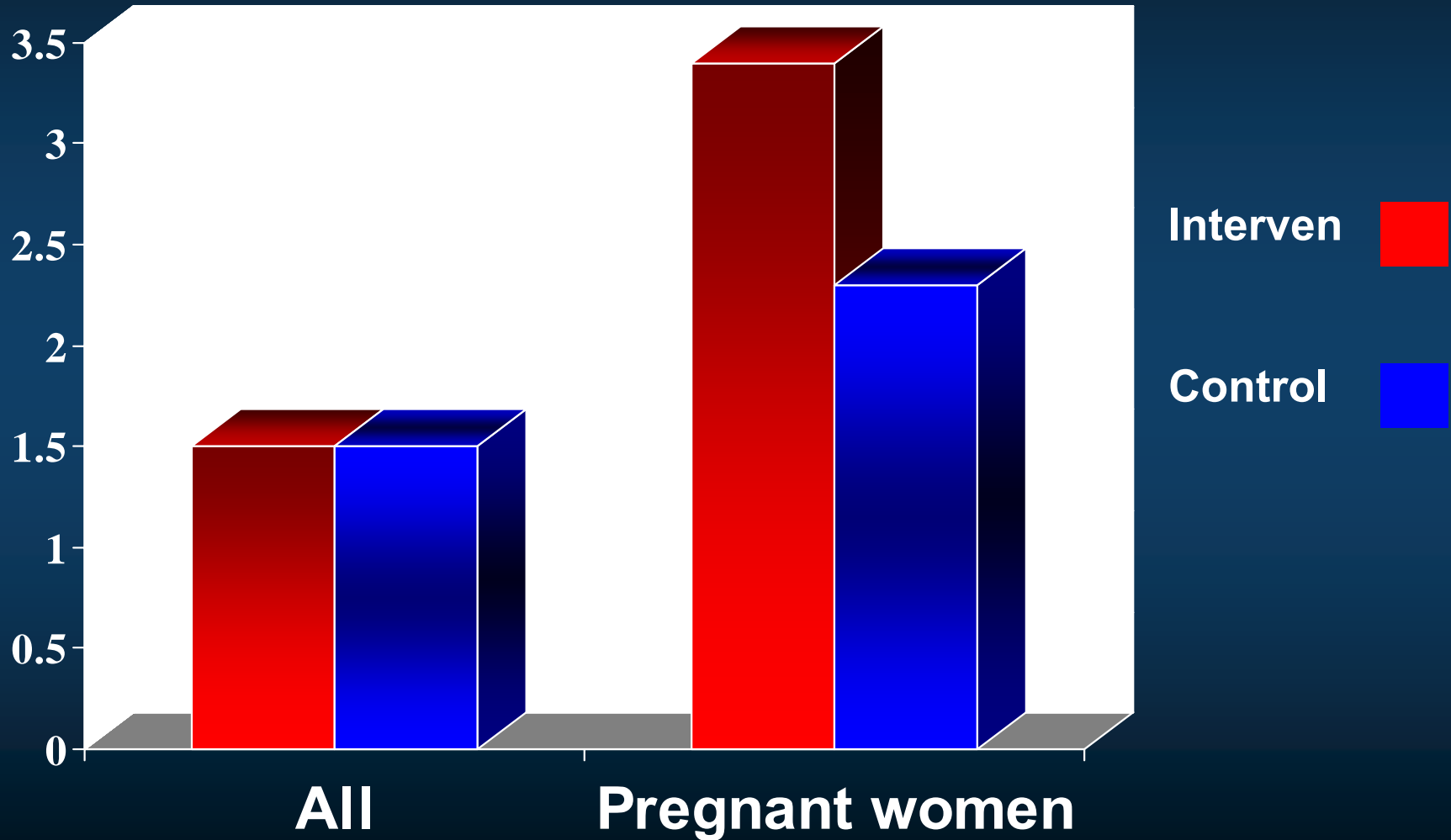
Commentary: Maria Laga, Lancet 1995

STD control for HIV prevention—it works!

Tanzania. As the researchers note, the magnitude of the effect on HIV incidence observed in this trial is the clearest evidence so far that a large proportion of HIV infections in this population are attributable to the enhancing effect of STDs. Even more important, this study shows that simple replicable STD care activities integrated into primary healthcare services can lead to a considerable reduction of HIV. Although there were

Rakai HIV Incidence Intervention and Control Arms

(Wawer et al, Lancet, 1999, Gray et al Amer J Obstet Gynecol 2001)



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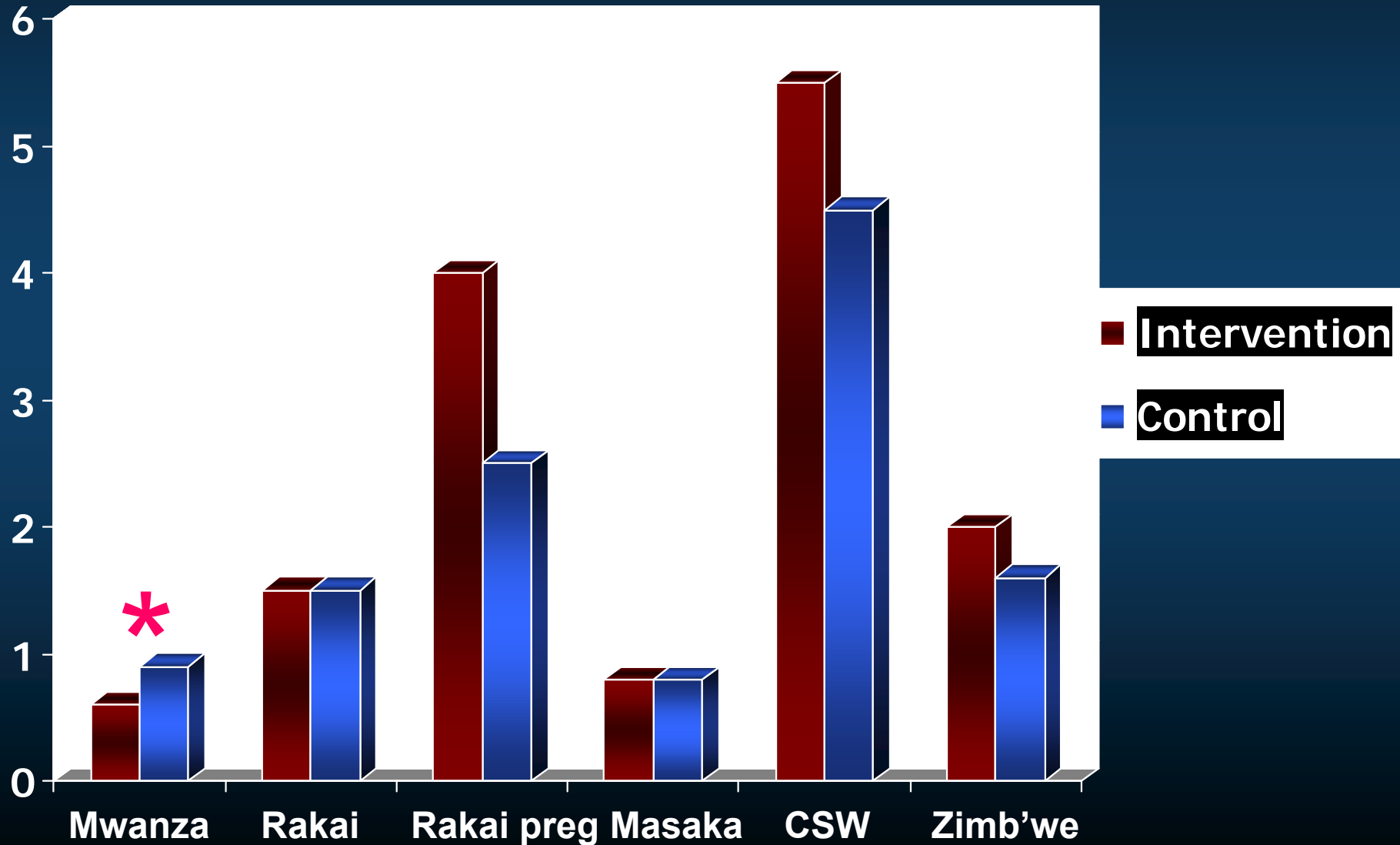
Response to Rakai STD results



QUELLE HORREUR

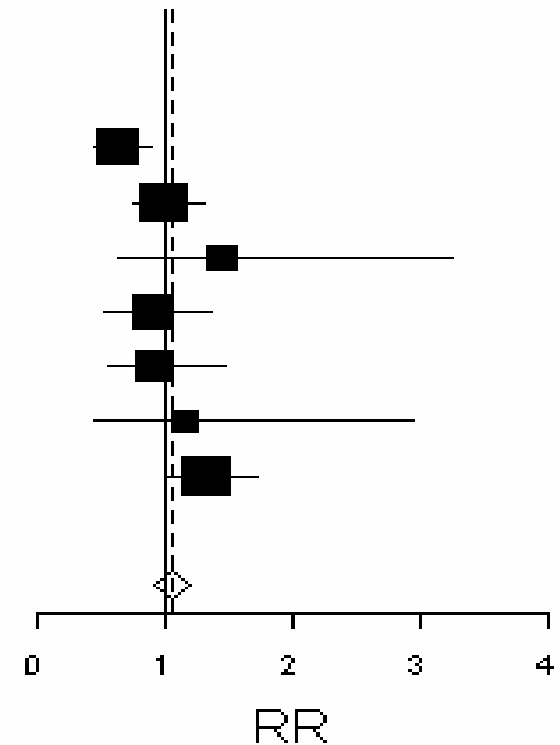
HIV Incidence in Trials of STD Control for Heterosexual HIV prevention

HIV incidence



Meta-analysis of Trials of Bacterial STD Control for Heterosexual HIV Prevention

STUDY	RR (95%CI)
Tanzania Groskurth	0.63 (0.45,0.89)
Rakai, Uganda Wawer	1.00 (0.75,1.32)
Rakai, Uganda Pregnant Gray	1.44 (0.64,3.25)
Masaka, Uganda Kamali A	0.92 (0.52,1.37)
Masaka, Uganda Kamali B	0.91 (0.56,1.47)
Nairobi, CSW Kaul	1.15 (0.45,2.94)
Zimbabwe Gregson	1.33 (1.01,1.74)
Combined	1.06 (0.92,1.21)



1 out of 7 trials showed significant protection

STI effects (laboratory diagnoses)

	Mwanz	Rakai	Rakai Preg	Masak	Nairobi CSW	Zimbab we*
Syphil	↓	↓				
Syphil Incid'ce	↓			↓		
GC			↓	↓	↓	
Ct			↓		↓	
Trich		↓	↓		↓	
BV			↓			

* Lab data not reported. No effects on STI symptoms.

STD control in Pregnancy and Maternal-to-Child HIV Transmission (MTCT)

	Intervention MTCT %	Control MTCT%	RR (CI)
Gray Am J Obstet Gynecol 2001	18.9	22.3	0.92 (0.29-2.91)
Taha et al AIDS 2006;20:1313	16.2	15.8	1.03

Summary of Bacterial STD Control Trials

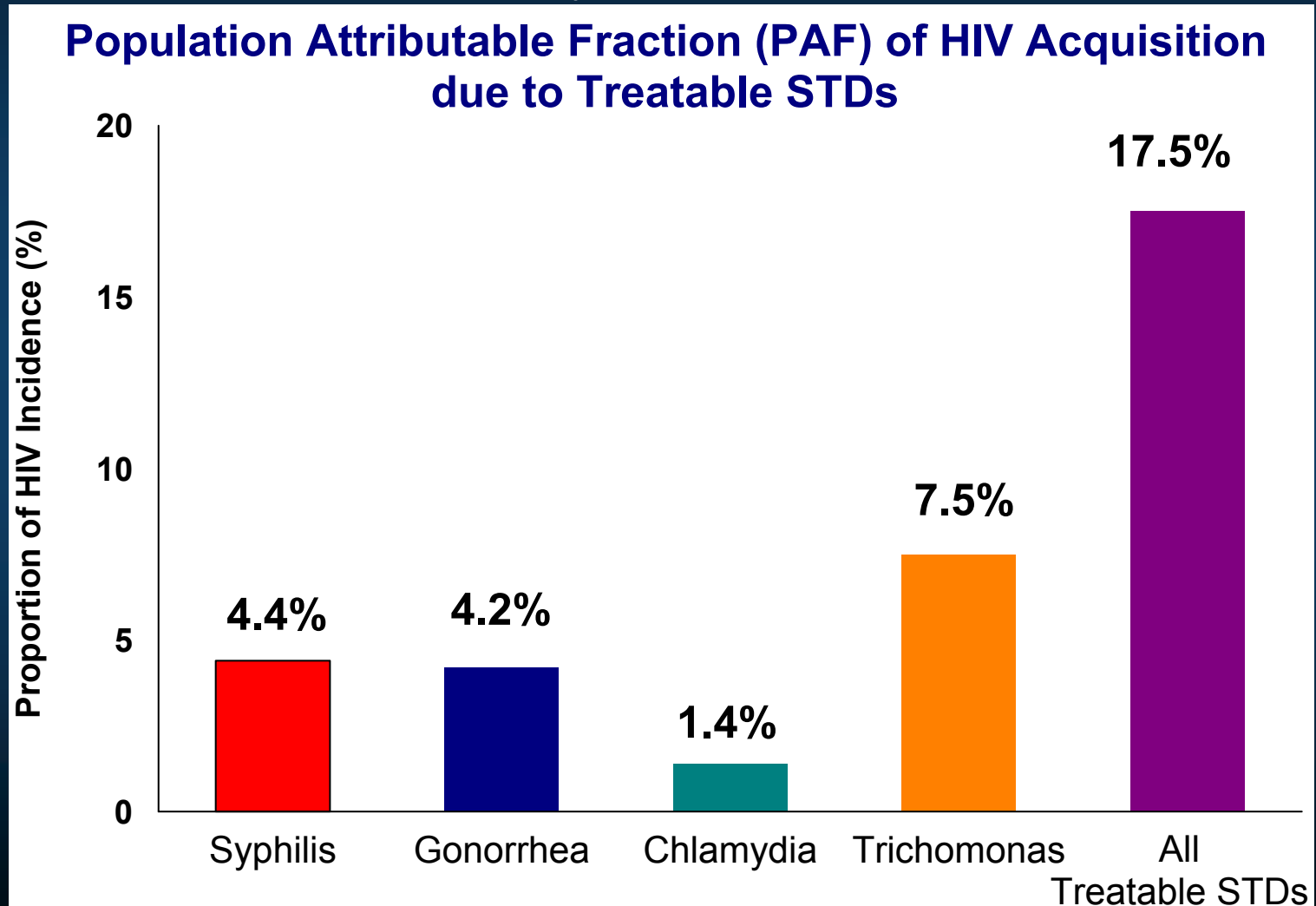
- 6/7 trials of STD control for heterosexual HIV prevention show no impact on adult HIV incidence despite reduced STDs
- 2/2 trials of STD control during pregnancy show no impact on MTCT despite reduced STDs

Population Attributable Fraction (PAF)

- Proportion of incident HIV attributable to STD cofactors
- Depends on:
 - Relative risk of HIV with or without STD
 - Prevalence of STDs in the population

Population Attributable Fraction (PAF) of HIV acquisition associated with STDs in Rakai

Gray AIDS 2000

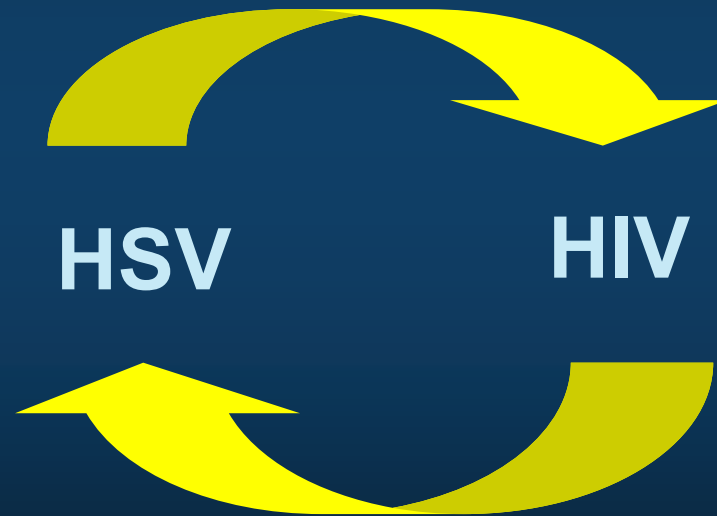


Possible Explanations:

- At the individual level, bacterial STIs increase risk of transmission and acquisition,
- At the population level, the PAF is limited due to low bacterial STD prevalence or modest RR of HIV acquisition
- Modeling suggests bacterial STDs play a small role in mature, generalized epidemics
- HIV viral load and GUD due to HSV-2 may be the main drivers of the epidemic

HSV-2 and HIV Interactions

HSV-Increases HIV susceptibility and infectivity,
and upregulates HIV plasma viral load

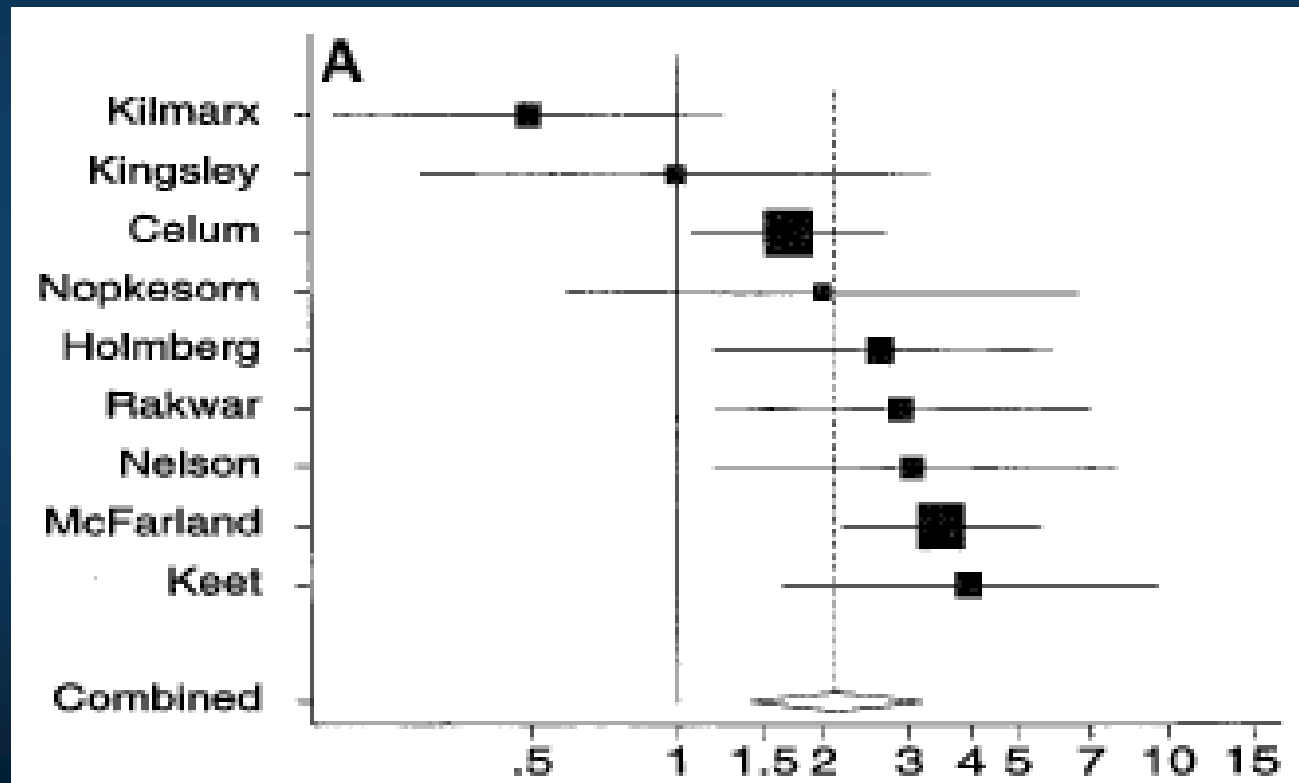


HIV increases frequency and duration of
GUD with HSV-2 coinfection

Meta-analysis of serologic HSV-2 and HIV acquisition

Wald & Link, JID 2002

Longitudinal and Nested case-control studies

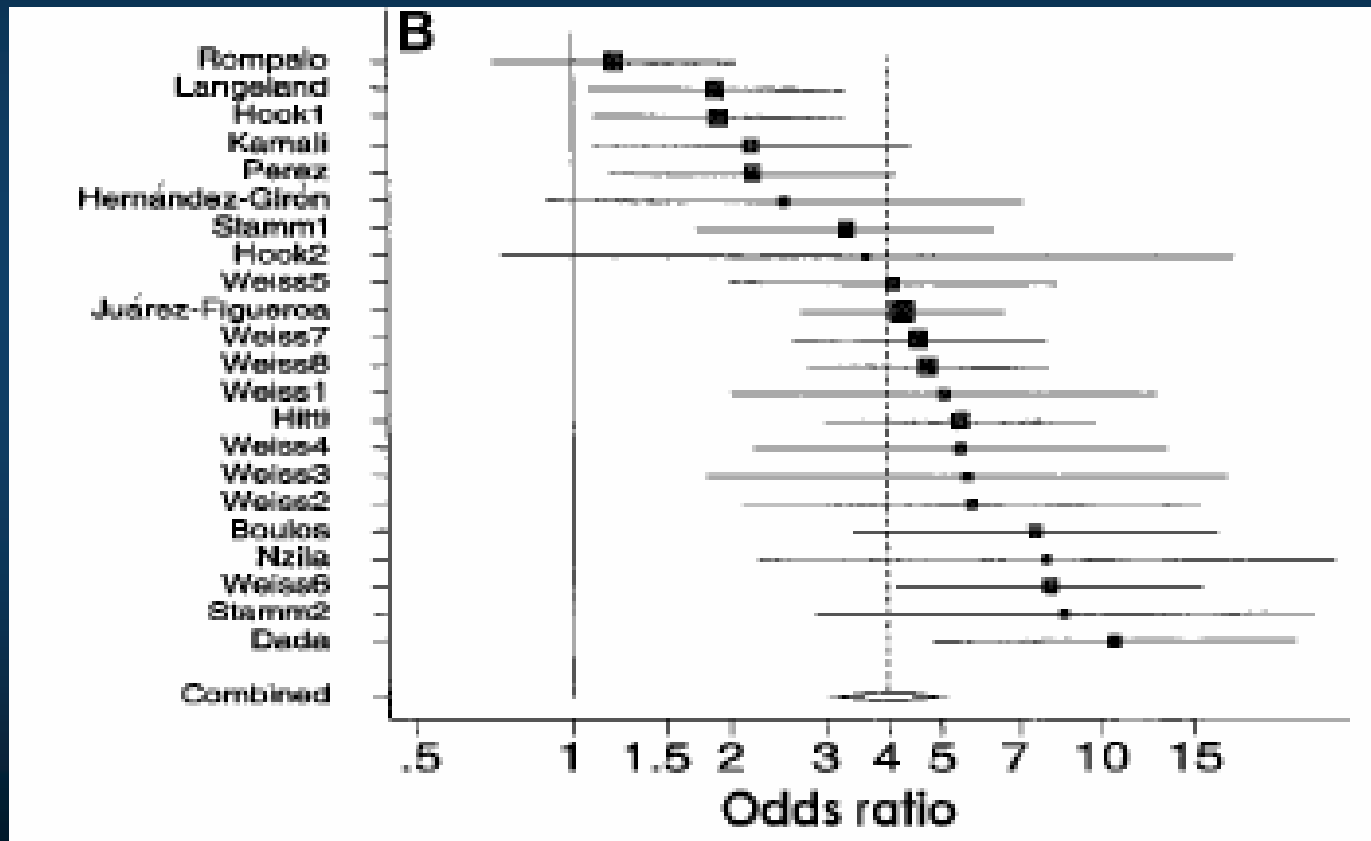


9 studies 6 significant increased risk of HIV with HSV-2

Meta-analysis of serologic HSV-2 and HIV acquisition

Wald & Link, JID 2002

Cross-sectional and case-control studies



22 studies, 19 significant association of HSV-2 with HIV

Trials of HSV-2 Suppressive therapy

- Objectives:
- Reduce HIV shedding in HIV+ individuals
- Prevent HIV transmission from HIV+ and acquisition in HIV- individuals

Trials of Valocyclovir in HIV+ persons: HIV genital shedding and plasma viral load

	Burkina Faso (ANRS 1285)		Peru
	60 Women on HAART ¹	136 women HAART naive ²	20 MSM HAART naive ³
HIV shedding	OR 0.90	OR 0.41**	
Δ Genital HIV log cps/mL	-0.33	-0.29**	-0.16**
Δ Plasma HIV log cps/mL	-0.41	-0.53**	-0.33

1. Ouedraogo et al AIDS 2006
2. Nagot et al NEJM 2007
3. Zuckerman et al IAS Sydeny, 2007

Trials of acyclovir in HIV+ persons: HIV shedding and plasma viral load

	Sth Africa ¹	Thailand ²	Tanzania ³
	N 269	N = 67	N = 383
HIV shedding	OR = 0.56**		OR = 0.83
Δ Genital HIV log cps/mL	-0.12	-0.44**	-0.03
Δ Plasma HIV log cps/ ml	-0.37**	na	na

1. Delaney et al CROI 2007 Abstr 154LB
2. Dunne et al CROI 2007 Abstr30
3. Tarton et al IAS Sydney

HSV-2 SUPPRESSION TRIALS TO PREVENT HIV INFECTION

- **MRC Mwanza, Tanzania**.(Watson-Jones, IAS Sydney, 2007)
 - Acyclovir Rx in HSV-2 positive HIV-uninfected
- **Washington Univ, Multi-site** (C Cellum)
 - Acyclovir HSV-2 suppression in:
 - HIV-negative persons for acquisition
 - HIV+ partner in discordant couples for transmission
 - Results available in 2008

Mwanza HSV-2 suppression Trial to Prevent HIV Acquisition

Watson-Jones et al. IAS Conference; 2007; Sydney,

	Acyclovir N = 400	Placebo N = 421
Follow up	53%	59%
HIV incidence /100 py	4.5	4.1
IRR	1.08 (0.64-1.83)	

Summary of HSV-2 Suppression Trials

- **HSV-2 Suppression in HIV+ individuals**
- Evidence for:
 - Reduced genital tract HIV shedding
 - Reduced plasma viral load
- **HSV-2 Suppression in HIV-negative individuals**
- No evidence of reduced HIV acquisition with HSV-2 suppression only one trial reported & one pending
- **HSV-2 suppression in HIV+ to prevent transmission**
- No data yet available

What do the RCTs tell us?

- **Bacterial STI control at the population level is difficult**
- **Control of bacterial STIs is important for public health, but should it be promoted for population-level HIV control?**
- **HSV-2 suppression in HIV+ may be warranted in high risk settings (e.g., discordant couples) to reduce shedding, but efficacy trial results are not yet available**
- **HSV-2 suppression in HIV-negatives is not of proven efficacy, but one trial has not yet reported**