Rush to Judgment

Understanding the STI-HIV Trials

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Burden of STIs in sub-Saharan Africa

Average bacterial STI burden in SSA
= 6 times higher than outside the region

Age-adjusted DALYS per 100,000
WHO, *Global Burden of Disease*, 2004

Poor access to medication promotes high prevalence of STIs

STIs and other genital infections promote HIV transmission and acquisition

- Genital ulcers
- Genital inflammation
- Increased viral shedding in genital tract

Mwanza

Method: – Randomized controlled trial (RCT)

– community-based

– syndromic treatment of STIs

Results: – HIV incidence

~40% less in treatment arm

9 subsequent RCTs

- 4 community- and 5 individual-based trials
- Diverse interventions
- Focus on either bacterial or viral STIs
- Study sites in 10 countries

None found a significant difference

in HIV incidence

between control and treatment arms

The 10 STI-HIV Trials

Community-based interventions targeting bacterial STIs

- Mwanza, Tanzania–Grosskurth et al. 1995
- Rakai, Uganda–Wawer et al. 1999
- Rakai, Uganda–Gray et al. 2001
- Masaka, Uganda–Kamali et al. 2003
- Manicaland, Zimbabwe–Gregson et al. 2007

Individual-based interventions targeting bacterial STIs

- Abidjan, Côte d'Ivoire–Ghys et al. 2001
- Nairobi, Kenya–Kaul et al. 2004

Individual-based interventions targeting herpes simplex (HSV-2)

- Northwest Tanzania–Watson-Jones et al. 2008
- Johannesburg, Lusaka, Harare–Celum et al. 2008
- 14 Cities–Celum et al. 2010

Policy conclusion drawn from the trials

STI control

should not be part of HIV-prevention programs

Ronald Gray and Maria Wawer

Lancet **371**:2064-2605, , 2008.

Heidi Larson, Stefano Bertozzi, and Peter Piot

Bulletin of the World Health Organization, **89**: 846-852, 2011.

We argue . . .

The results of the 10 trials do not support that judgment.

RCTs are inappropriate vehicles for producing evidence about the link between STI treatment and HIV.

There is abundant evidence that shows the causal pathway from STIs to HIV.

Fundamental Principle of Statistical Inference

One cannot prove the null hypothesis.

None of the trials measured *change* in HIV incidence

Nevertheless, all of the trials conclude either

– the trial *reduced* HIV incidence (Mwanza)

or

– the trial *failed to reduce* HIV incidence (9 other trials).

Without measuring the *change* in incidence, however, the trials could not show if the intervention reduced or did not reduce HIV incidence.

None of the trials measured change in HIV incidence

The trials could only measure whether the interventions in the treatment and control arms had different effects on HIV incidence.

The substitution of “reduction” for “difference”

leads to critically important confusion

None of the trials measured change in HIV incidence

Gray and Wawer: “the hypothesis that control of sexually transmitted infections can prevent the spread of HIV in populations has been extensively tested and is not supported by evidence.” *Lancet* 2009.

The trials could not provide evidence about the spread of HIV because they did not measure it.

Consequence I.

If interventions in the treatment and control arms are similar, those small differences would produce small differences in HIV incidence between the arms.

(All of the trials were underpowered making it difficult to detect small differences between the arms.)

Consequence II.

Even if the interventions were very successful

in reducing HIV incidence in both arms,

the trials were not designed to show that success

(since they did not measure change in HIV incidence)

Comparing interventions between arms

Only the Mwanza trial had

substantially different interventions

in the treatment and control arms.

Interventions in 5 individual-based trials

the only differences between arms

in 4 individual-based trials		
daily or monthly presumptive medication	or	medicated if diagnosed with STI upon examination at periodic visits
in 1 individual-based trial		
monthly examinations and antibiotics if indicated	or	monthly visits and antibiotics if participant reported symptoms

Celum et al. 14-city trial

- all participants treated aggressively for bacterial STIs
- all participants instructed in HIV prevention
- all HIV+ participants treated with ART
- HIV incidence remarkably low in both arms

Correct Conclusion:

Daily prophylactic acyclovir or treating diagnosed ulcers with acyclovir are equally effective in reducing HIV incidence.

Wrong Conclusion:

Treating HSV will not reduce HIV.

Two trials in Rakai

- Both arms had the same BCC and condom distribution
- The only difference between arms was:

Treatment community	Control community
presumptive antibiotic administration	presumptive anti-helminthics and vitamin and mineral supplements plus antibiotic treatment of diagnosed STIs

Note:
Helminth infections and nutritional deficiencies have been linked to HIV transmission.

Small differences in risky sexual behavior between treatment and control arms

Except in Mwanza, reductions in risky sexual behavior in control arms could have confounded the results.

Summing up so far

The trials measured the effect of their interventions by looking at the differences in HIV incidence between treatment and control arms. They did not measure change in HIV incidence over the course of the trial.

In all 9 trials after Mwanza,

interventions in treatment and control arms

were very similar.

Failure to account for all STIs

All of the trials focused on either

herpes simplex (HSV-2) or bacterial STIs

but not both.

Failure to account for all STIs

None of the trials tried to measure effect of treating all STIs.

7 trials treated only bacterial STIs.

3 trials treated all STIs, but only measured the effect of treating viral STIs (herpes simplex).

In some trials after Mwanza, bacterial STIs were far less common than herpes simplex.

Failure to account for all genital infections

In Rakai and Masaka,

STIs accounted for only *half* of genital ulcers.

Pickering et al. 2005. *Sexually Transmitted Infections* **81**:488-493.

Wawer et al. 1999, *Lancet*, **353**(9152): 530.

(The other 8 trials do not report the proportion,
and 6 trials did not perform lab tests necessary
to determine the pathogen infecting the ulcer.)

Schistosomiasis (bilharzia)

has the same symptoms as STIs that promote HIV transmission and acquisition

- Worms and ova of *S. hematobium* infect the vagina, uterus, vulva, cervix, urethra
- *S. hematobium* lesions are indistinguishable from STIs without biopsy
- Schistosomal lesions provide direct pathway for HIV
- Worms and ova produce inflammation, attracting CD 4+ cells to the cervix and other sites in the reproductive tract

Schistosomiasis (bilharzia)

Genital lesions of *S. hematobium*

increase women's risk of HIV

3- to 4-fold.

Sources:

Kjetland, et al. 2006, *AIDS* **20**(4):593.

Downs, et al., 2011, *American Journal of Tropical Medicine and Hygiene,* 84(3) 364.

Schistosomiasis (bilharzia)

leads to hematuria (blood in the urine)

Failure to account for all genital infections

Genital ulcers infected with staph and strep and

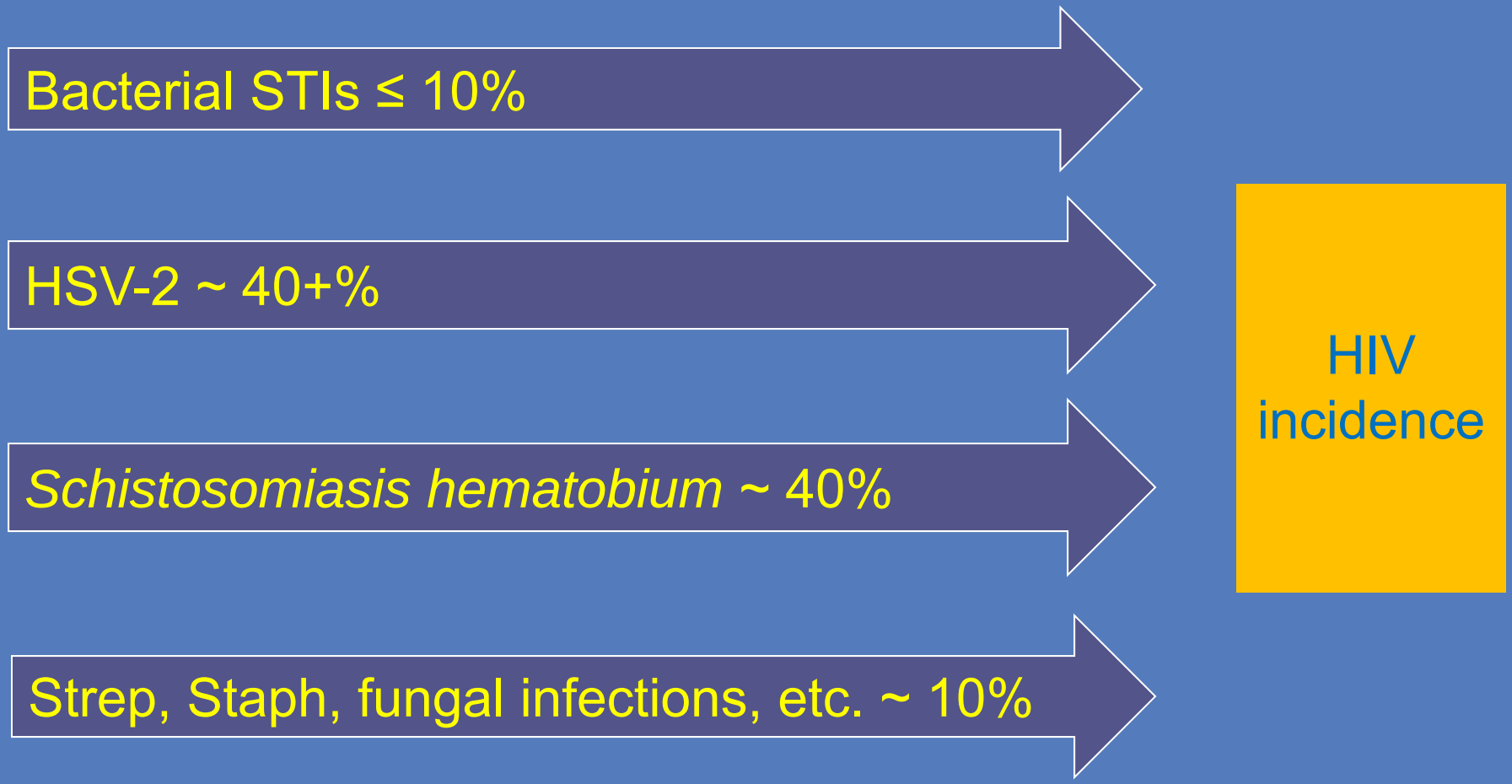
fungal infections that produce inflammation

cannot be treated by antibiotics or acyclovir.

It is likely that ulceration and inflammation from these infections have a similar effect as ulceration and inflammation from STIs.

Failure to account for all genital infections

(Percentages based on Pickering, Wawer, Kjetland, and others)



Failure to account for all genital infections

3 of many possible interactions

Additive:

each additional ulcer increases risk of HIV transmission by the same amount

Multiplicative:

having additional ulcers multiplies HIV transmission risk

No interaction:

risk of HIV transmission is independent of the number of ulcers

Failure to account for all genital infections

interaction of genital infections is unknown

very little is known about genital microbial communities

100s of species of bacteria inhabit the genitals

NIH has recently launched an effort to research the topic

Failure to account for other genital infections

Labeling the bias

Economists:

missing variable bias

Epidemiologists:

incomplete exposure contrast

information bias due to non-differential misclassification

confounding (under certain assumptions)

Whatever we call it, failure to account for all genital infections reduces the ability of all 10 trials to measure the connection between interventions and HIV incidence.

Discussion I.

All of the trials after Mwanza had treatment and control arms with similar interventions. Those interventions produced similar changes in HIV incidence.

All of the trials measured the effect on HIV incidence of only a small subset of genital infections.

For both reasons, the ability to detect the effect of the intervention on HIV incidence was weakened or eliminated.

Discussion II.

The solution is not more trials.

Ethical considerations will again lead to negligible differences in interventions between arms.

Why RCTs cannot answer the question

When the treatment in question is

- inexpensive
- has minor side effects
- is clearly efficacious and effective

it is unethical not to treat controls.

Treating controls leaves the trial unable to discern an effect.

Discussion III.

RCTs can answer questions in situations where confounding can be reduced to manageable proportions.

RCTs cannot work in complex environments investigating multiple, interacting causes, or where ethical considerations lead to similar interventions in arms.

Discussion IV.

In sum, the STI-HIV trials do not show that STI control cannot slow the spread of HIV.

There is abundant evidence that genital infections promote HIV transmission.

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Discussion V.

TREATMENT IS PREVENTION.

Of course, we should continue to expand coverage of ART.

But also treating STIs and other genital infections

- – enhances the preventative effect of ART
- – can postpone need for second-line therapy
- – reduces HIV transmission in those not yet on ART.

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Thank you.

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