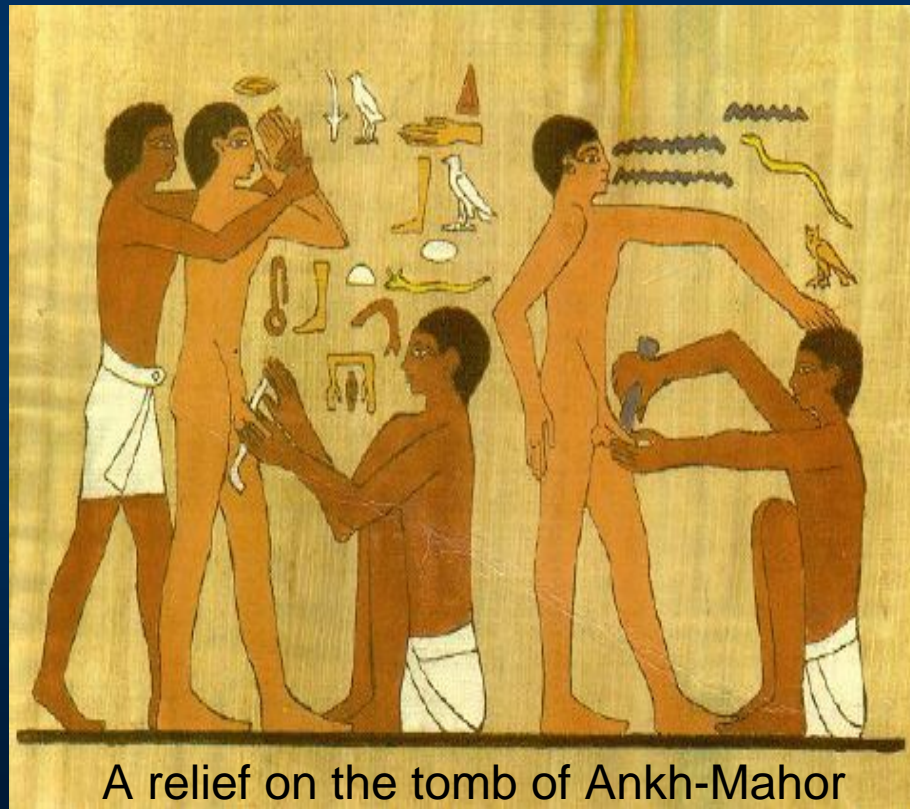


Male circumcision for HIV and STI prevention in men and women

Maria J Wawer, Johns Hopkins



A relief on the tomb of Ankh-Mahor

Acknowledgments

Rakai Health Sciences Program

David Serwadda

Godfrey Kigozi

Fred Nalugoda

Stephen Watya

JHU

Ron Gray

Tom Quinn

Xianbin Li

Michael Chen

U of Versailles

Bertran Auvert

U of Illinois

Robert Bailey

NIH

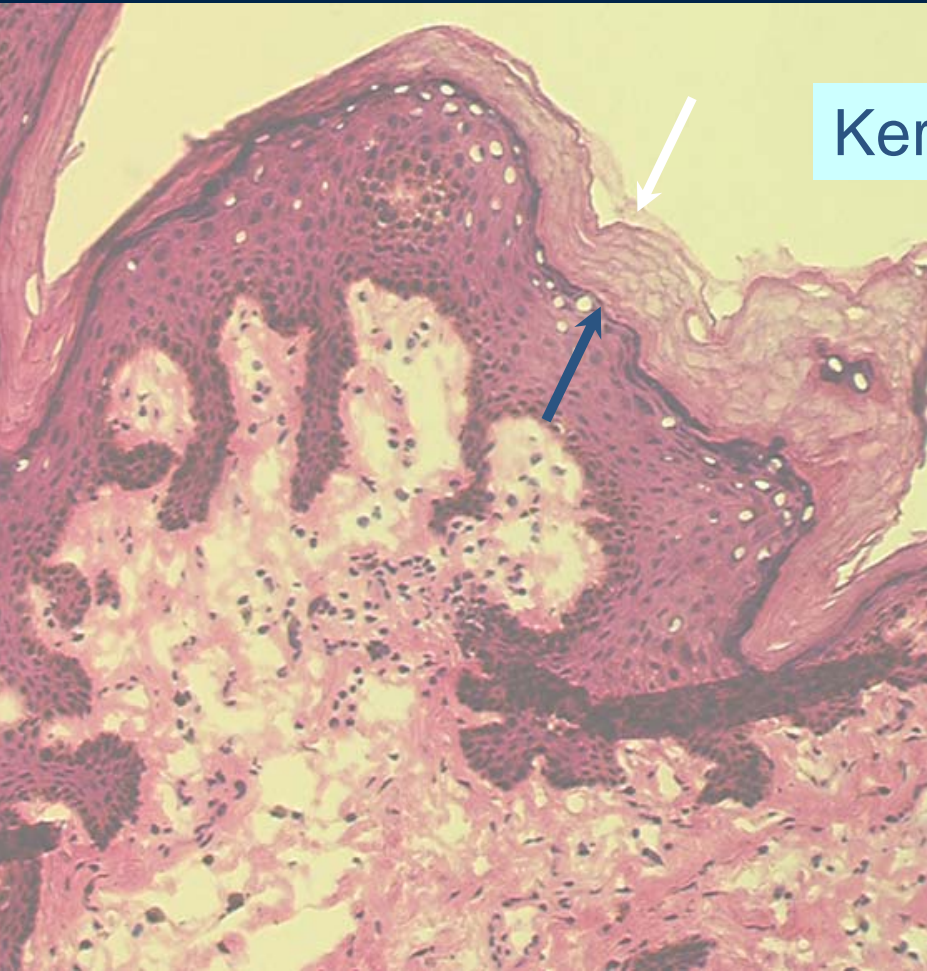
Melanie Bacon, Carlie
Williams

Gates Foundation

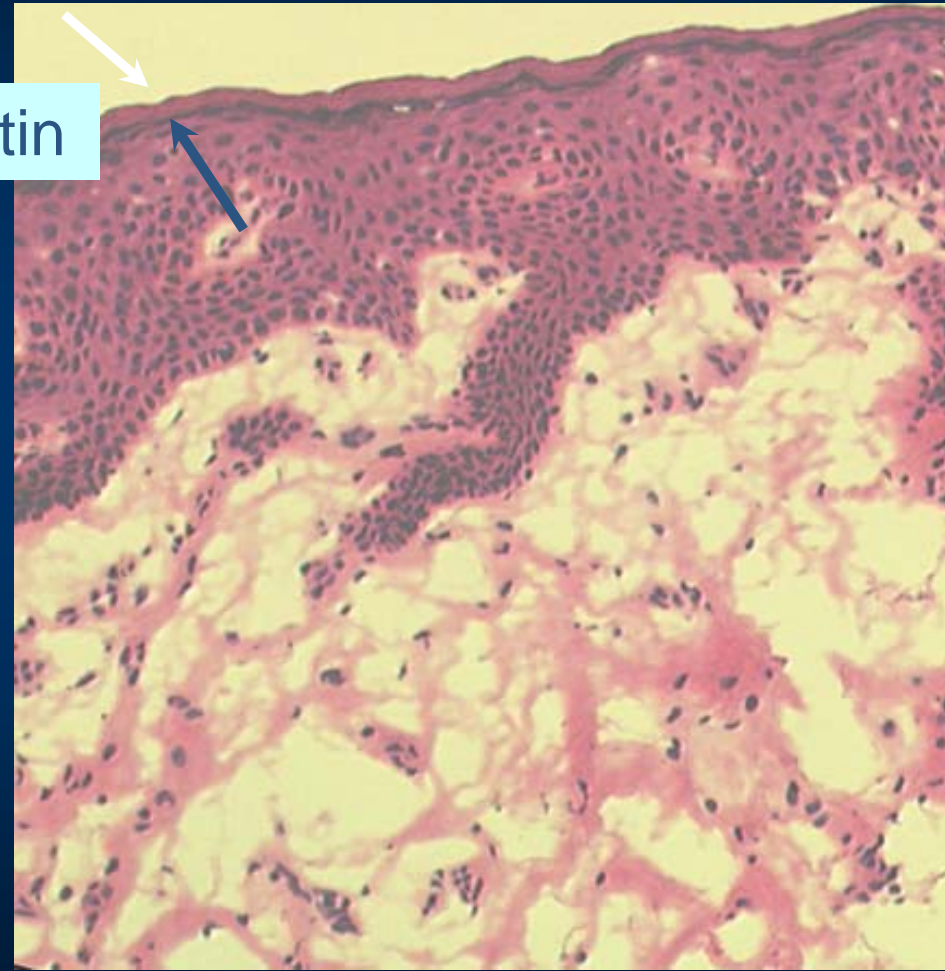
Renee Ridson

- **Biological plausibility**
- **Inner mucosa of foreskin is rich in HIV target cells (9 x cervix)**
 - **External foreskin/ shaft keratinized - not vulnerable**
 - **After circumcision, only remaining vulnerable mucosa is meatus (very small surface area)**
- **Intact foreskin is associated with other infections**
 - **GUD**
 - **Balanitis/phimosis**

KERATIN THICKNESS ON THE EXTERNAL AND INTERNAL MUCOSAL SURFACES OF HUMAN FORESKIN



Keratin

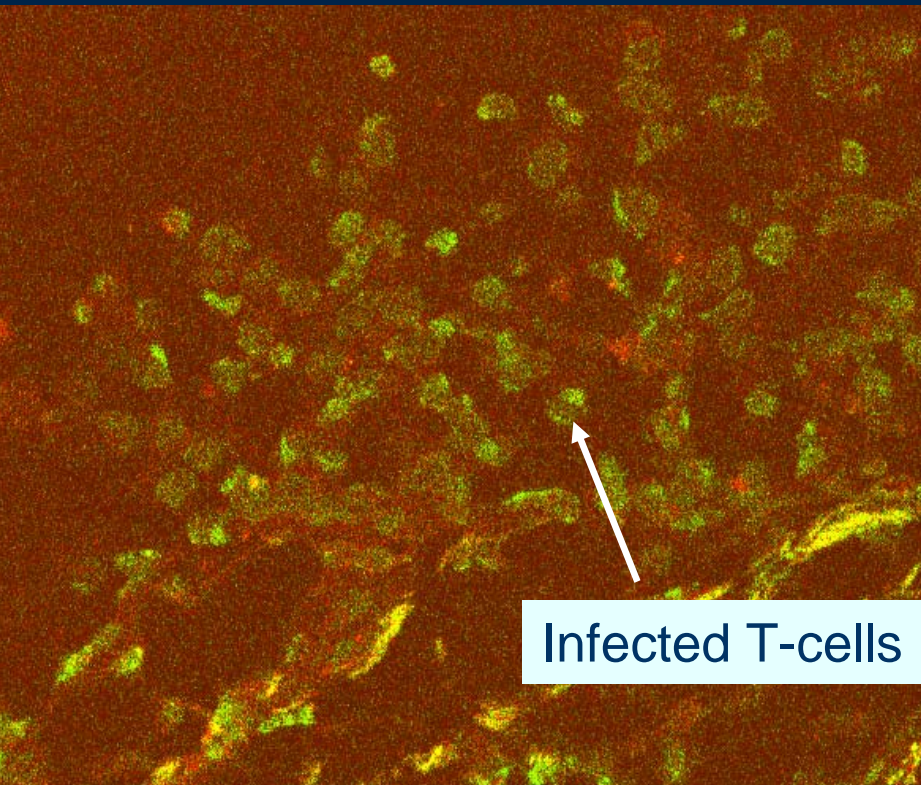


External Surface

Mucosal Surface

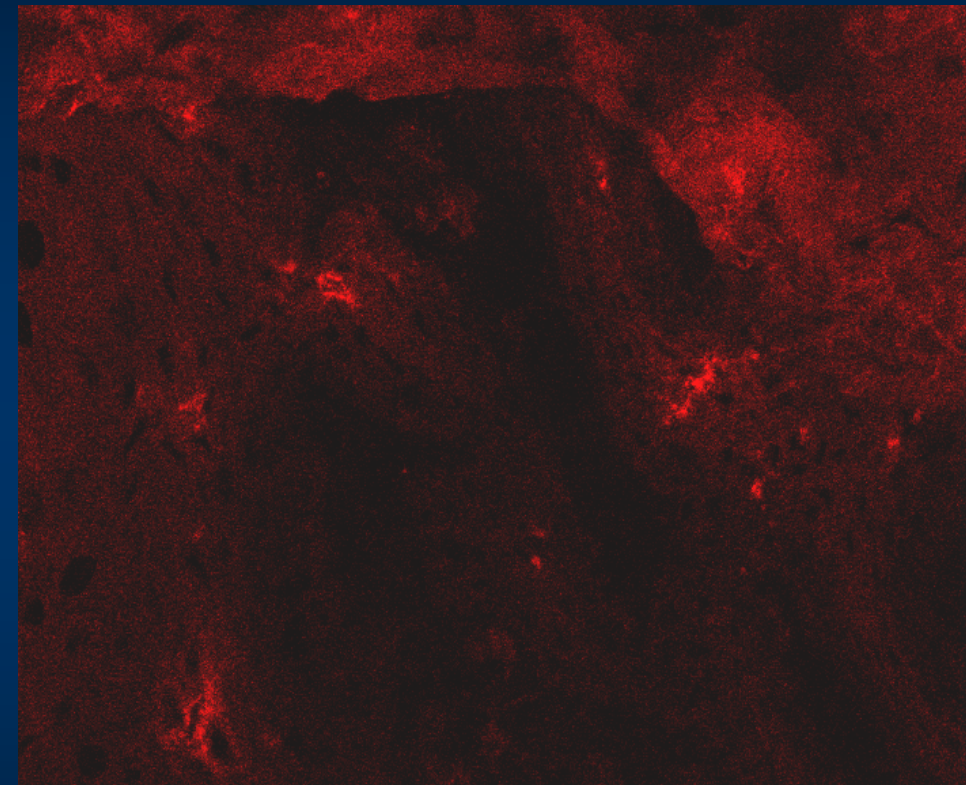
Patterson et al. Am J Pathol 2002

HUMAN FORESKIN INFECTED WITH HIV-1_{Bal} IN EXPLANT CULTURE



Infected T-cells

Mucosal Surface



External Surface

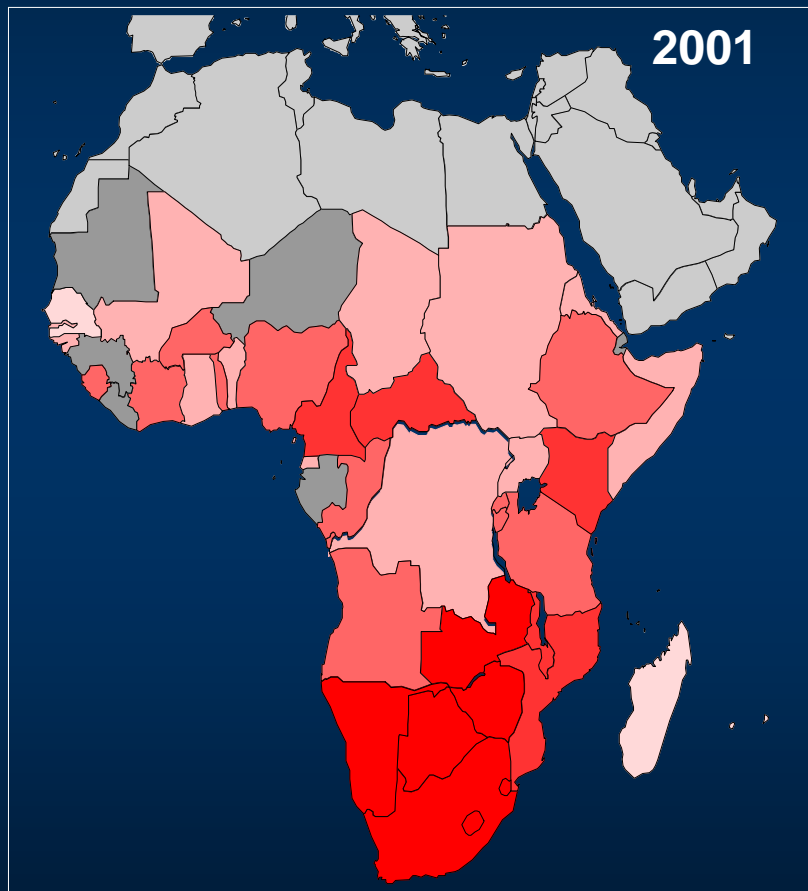
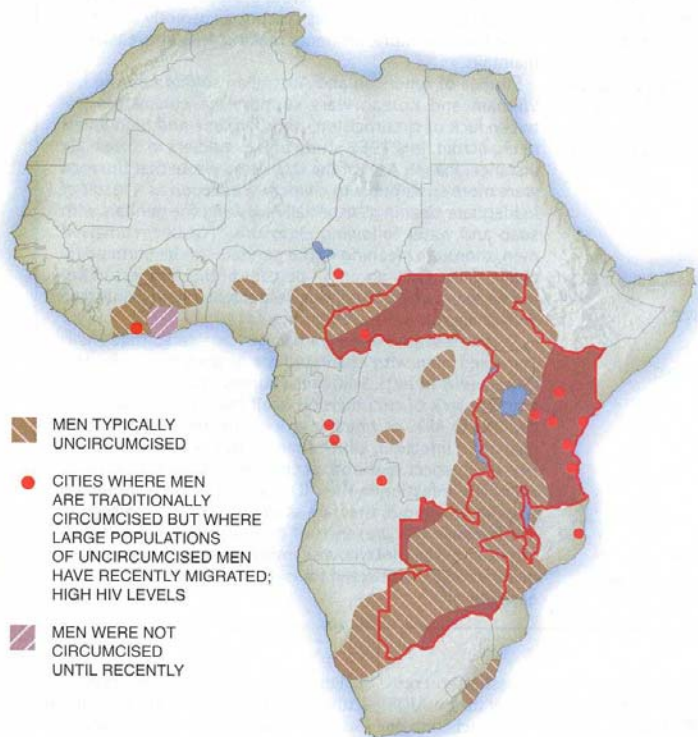
Red - uninfected cells

Green - infected T-cells

Yellow - HIV-1 bound to Langerhan's cells

Circumcision and HIV prevalence in adults in sub-Saharan Africa

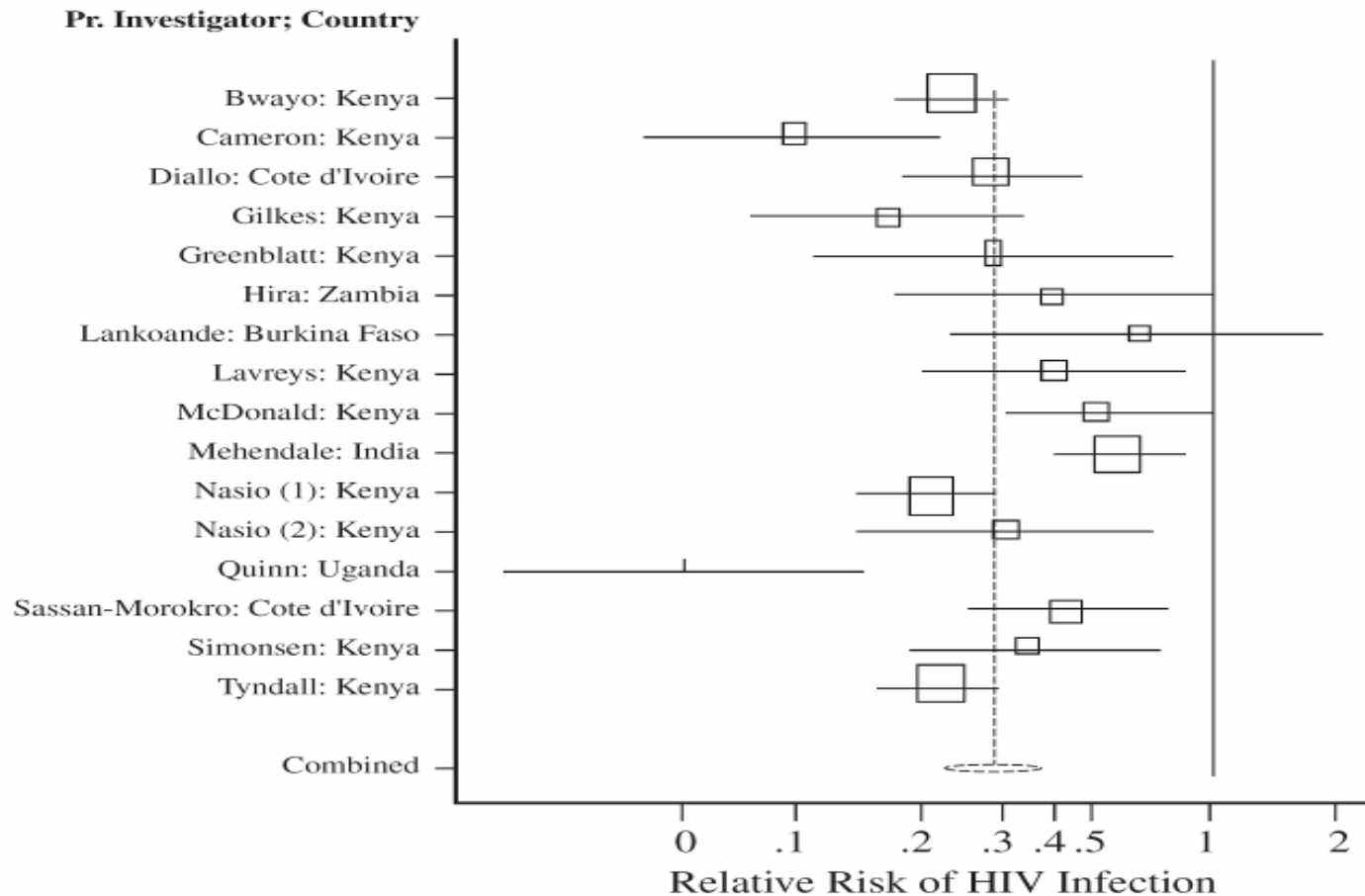
REGIONS WHERE MOST MEN ARE UNCIRCUMCISED



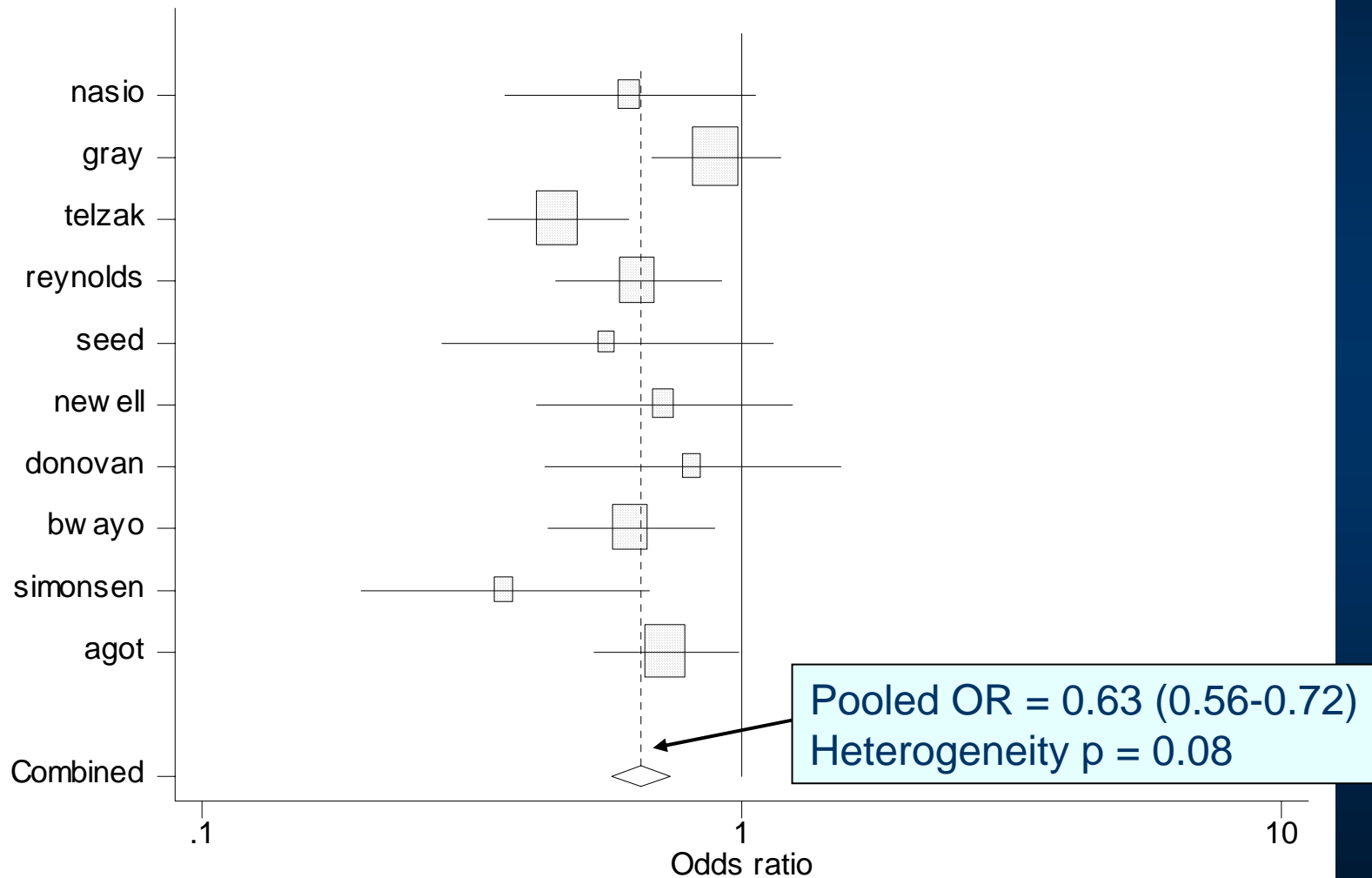
Meta-analysis of circumcision and male HIV acquisition

Weiss *et al* AIDS 2000

Risk Reduction in High-Risk Circumcised Males, Various Studies



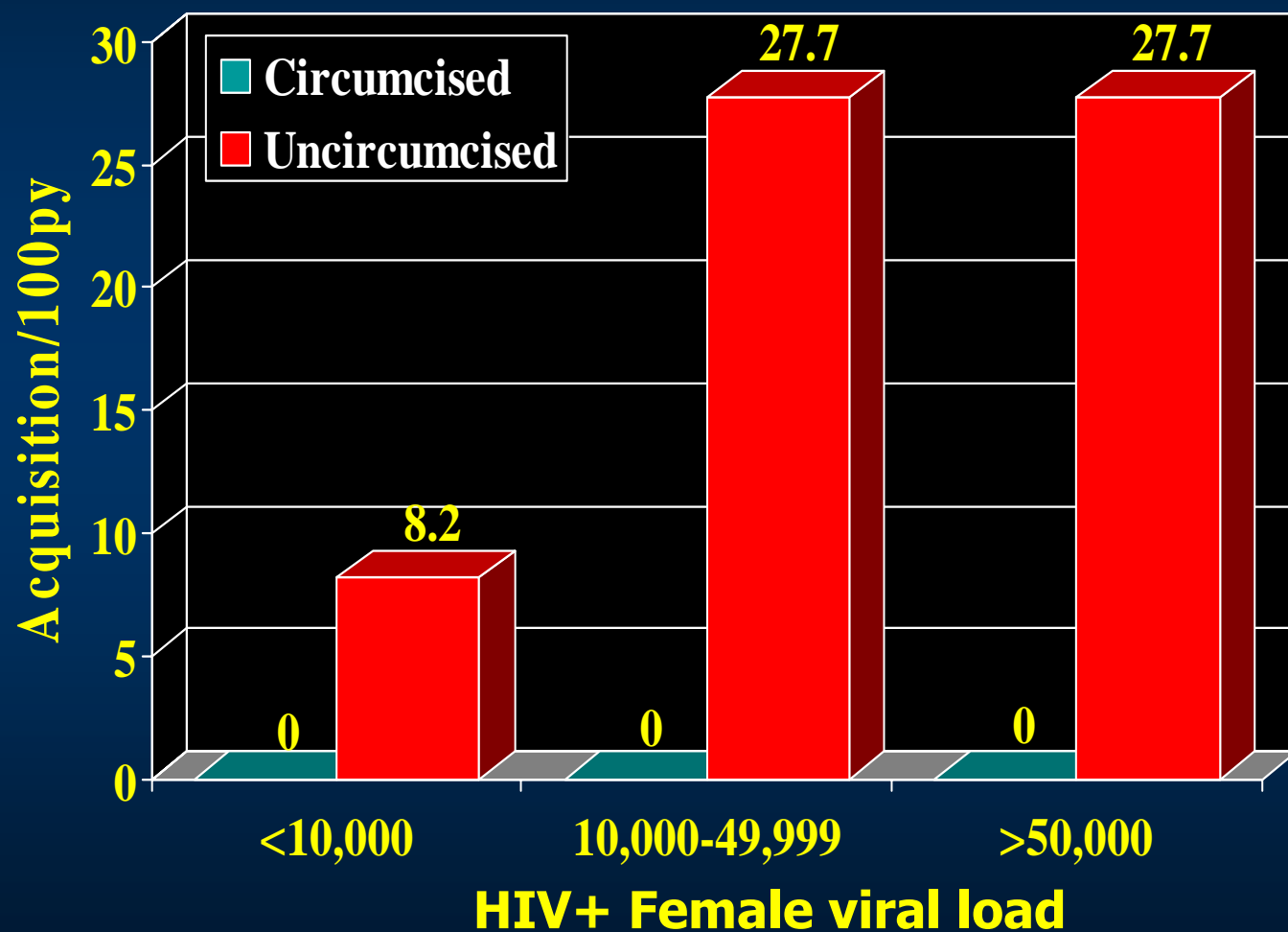
Circumcision and male genital ulcer disease (GUD)



The apparent HIV protection afforded by circumcision may be greater in high risk male populations than in general populations

- **General population (10 studies)**
 - RR = 0.57 (0.47-0.70)
- **High risk populations (10 studies)**
 - RR = 0.31 (0.23-0.42)

Circumcision effect in highly exposed men: HIV acquisition in HIV-neg male partners of HIV+ female partners by male circumcision status and female HIV viral load, Rakai



Gray et al AIDS 2001

Paradox: Why might circumcision be more protective in the most highly exposed?

(Wawer *et al AIDS* 2005)

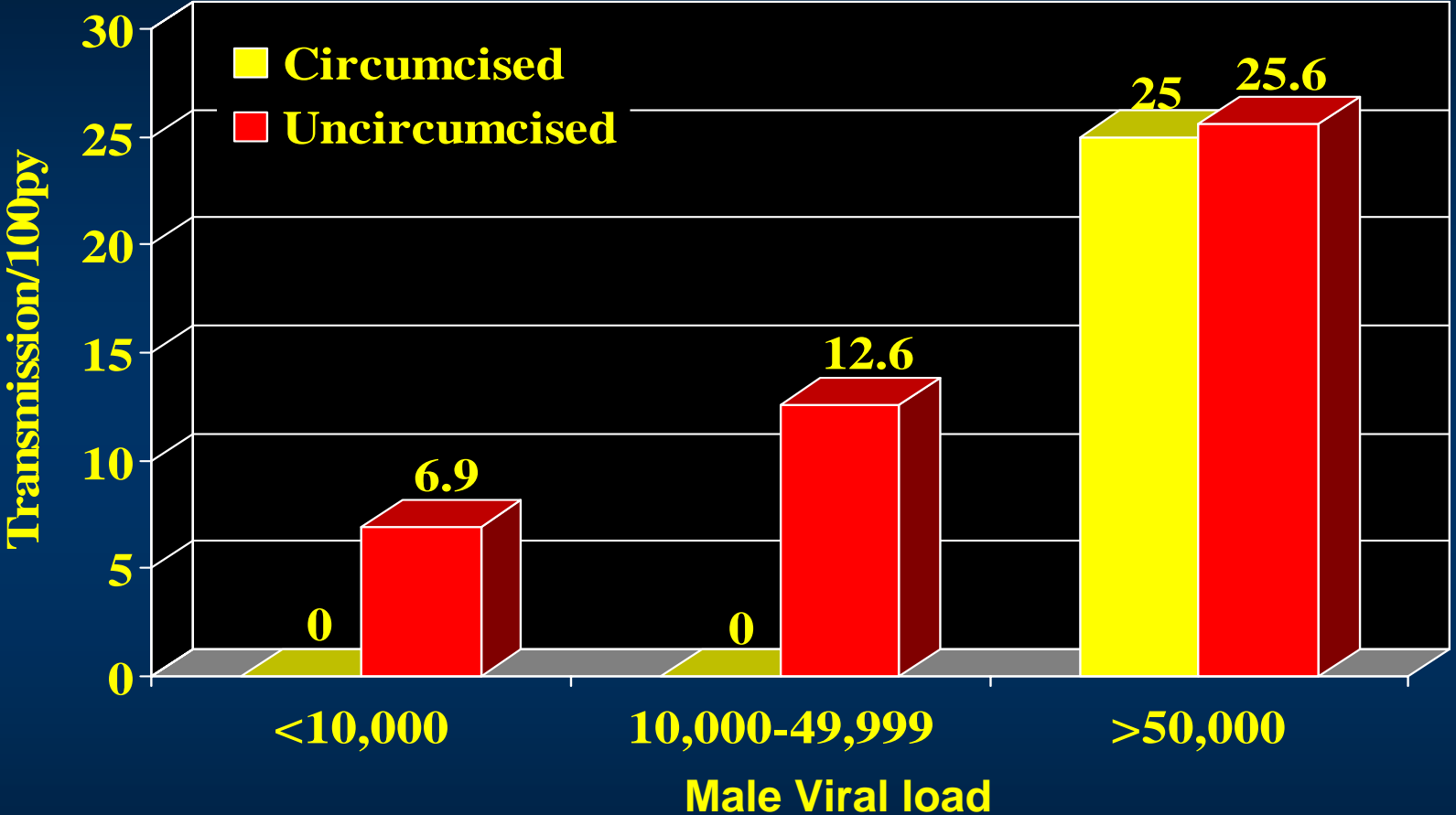
- Possible induced mucosal immunity following repeated subinfectious HIV antigen stimulation of urethral mucosa -- small mucosal surface = low doses
- Analogous to reduced infection in highly exposed but persistent seronegative commercial sex workers (Devito *et al AIDS* 2000, Kaul *et al J Immunol* 2001)
- Circumcision reduces GUD which is a cofactor for HIV. GUD is more common in high risk populations (possible indirect effects)

Male circumcision and female HIV acquisition

Rakai

- Retrospective observational data of M+/F- discordant couples in Rakai (*Gray et al AIDS 2000*)
 - Reduced male-to-female transmission if HIV+ male was circumcised: **IRR ~ 0.41**
- If HIV+ male viral load < 50,000 cps/mL
 - Male circumcised: No transmission
 - Male uncircumcised: Transmission 9.6/100 py (p = 0.02)

Circumcision Status and HIV Transmission to Women



47 couples in which circumcised *male partner* was HIV+ AND whose viral load was <50,000 particles, 0 of female partners were infected after two years, vs. 26 of 143 female partners of uncircumcised HIV+ men (9.6/100 py) (p = 0.02).

Male circumcision and Female HIV & STI rates in Rakai (Gray *et al* CROI 2006)


<u>Female Infection</u>	<u>RR (CI)</u>
Prevalent HIV	0.76 (0.62-0.92)*
HSV-2	0.75 (0.54-1.03)*
BV	0.79 (0.69-0.91)*
Trichomonas	0.65 (0.55-0.77)*
Chlamydia	1.06 (0.61-1.84)
Gonorrhea	1.19 (0.51-2.79)
Syphilis	0.93 (0.76-1.13)
HPV	0.72 (0.46-1.12)

*P<0.05

Limits to observational studies

- **Circumcised men are often highly selected:**
 - **Religion (Islam, Judaism).**
 - May be correlated with lower risk behaviors, less alcohol use, genital hygiene, etc.
 - Mainly neonatal
 - **Traditional / tribal**
 - Behavioral differences
 - Younger age (puberty rituals)
 - **Medical indications (phimosis, GUD)**
 - correlated with higher risk behaviors
 - **Possible confounding**

Randomized trials of male circumcision for HIV prevention in HIV-negative men

- **Three trials:**
 - South Africa (ANRS),
 - Kenya (NIH),
 - Rakai, Uganda (NIH)
- **Similar designs:**
 - Enrolled HIV-neg uncircumcised men, randomized to:
 - Immediate circumcision (Intervention) 
 - Circumcision delayed 21-24 months (Control)
 - Endpoints:
 - HIV incidence
 - Safety
 - Behavioral disinhibition
 - STIs

Community Characteristics, three trials of circumcision for HIV prevention in men (baseline data)

	South Africa	Uganda	Kenya
Trial setting	Semi-urban	Rural	Urban
Study sites	3 clinics	Community	1 clinic
Circumcision (%)	~20%	16%	<10%
HIV incidence	2.7-5.2	1.1-2.1	2.5

Study Characteristics, three trials of male circumcision for HIV prevention in men

	South Africa	Uganda	Kenya
Age	18-24	15-49	18-24
Final N	3,520	5,000	2,784
Enroll completed	Jan 05	Jul 05	Sept 05
Completion date	Mar 05	Jul 07	Sept 07

Surgical procedures and follow up

	South Africa	Uganda	Kenya
Procedure	Clamp/cut	Sleeve	Clamp/cut
Surgeons	General practitioners	Trained surgeons	Medical/ clinical officers
Postoperative follow up	3 months	< 3days, 7-9 days, 1 month	

South African ANRS 1265 Trial

- Trial stopped by DSMB (Nov, 2004) at interim analysis

Incidence rates :

Circumcised : **0.9** (0.6 - 1.3) /100 py

Control : **2.1** (1.6 - 2.8) /100 py

Unadjusted RR : **0.40** (0.24 – 0.68) p=0.0006

Protection (1-RR): **60%** (32% - 76%)

Implications of SA ANRS Trial

- ANRS trial reported a strong protective effect of male circumcision on HIV acquisition by males
 - Consistent with expectations
 - Caveats:
 - Trials stopped early may overestimate efficacy
 - Need to assess longer term effect
 - Need to assess effects in different populations
- Public health response (NIH, UNAIDS)
 - Completion of NIH trials is needed before deciding on policy
 - In the interim, make safe circumcision available to men who request it, but do not promote it for HIV prevention

Rakai Trials of Male Circumcision for HIV/STD prevention and circumcision safety

- in HIV-neg men (NIH-funded)**
- in HIV+ men and in women (Gates-funded)**

Why include HIV+ men?

- **Safety of circumcision in HIV+ men**
 - If circumcision is safe in these men (AEs, healing) future programs will not need to screen them out
- **STI effects in HIV+ men**
 - If circumcision is beneficial in HIV+ men, future circ programs may promote circ for these men
- **Avoidance of stigmatization**
 - Less likely HIV+ men will seek unsafe procedures
- **Potential reduction in behavioral disinhibition**
 - HIV-negative men don't get "proof of negative status"

Why include women?

- **Safety or potential benefits of circumcision for women**
 - If an HIV+ man becomes circumcised, is he more or less likely to transmit HIV to female partners?
 - Are circumcised men (whether HIV-neg or HIV+) less likely to transmit other STDs to women?
 - Determine factors influencing potential risk or benefits
- **Behaviors in couples after male circumcision**
- **Program cost effectiveness will be higher if women also benefit**

Gates-funded trial of male circumcision effects in HIV+ men and in women

■ Populations

~ 800 HIV+ men 15-49

~ 4300 women in the community; linked partnerships to men in the NIH and Gates trials

Primary Endpoints

- Safety in HIV+ men

- STD acquisition in men and women

- HIV transmission to women (safety and efficacy)

- Behavioral effects in participants and partners

Please note: all participants/couples are offered free VCT, couples VCT, condoms and health education; all sign a detailed informed consent

Status of Gates-funded trial

- 847 HIV positive men enrolled
- 4,269 women linked to HIV pos and HIV neg men
- End enrolment Nov 2006
- End FU 2008



Autoclaving procedures



Wound healing and resumption of sex: Rakai Trial

- Median time to certified wound healing 28 days (same in HIV-neg and HIV+ men)
- Median time to resumption of sex 43 days
- Only 11% of men resumed sex before wound healing was certified as complete
- Frequency of all moderate or severe complications requiring treatment ~ 2-4% in the three trials
- Infections, bleeding, hematoma, wound dehiscence, inadequate skin removal
- Complication rates and wound healing are equivalent in HIV+ and HIV-negative men

Condom use at enrolment and use after circumcision, intervention arm men, Rakai trial

	Baseline	Post-circumcision
Any current condom use	19.7%	51.7%
Consistent condom use	13.8%	19.7%

Condom use increased after circumcision

No evidence of behavioral disinhibition

Will this behavioral risk reduction be sustained?

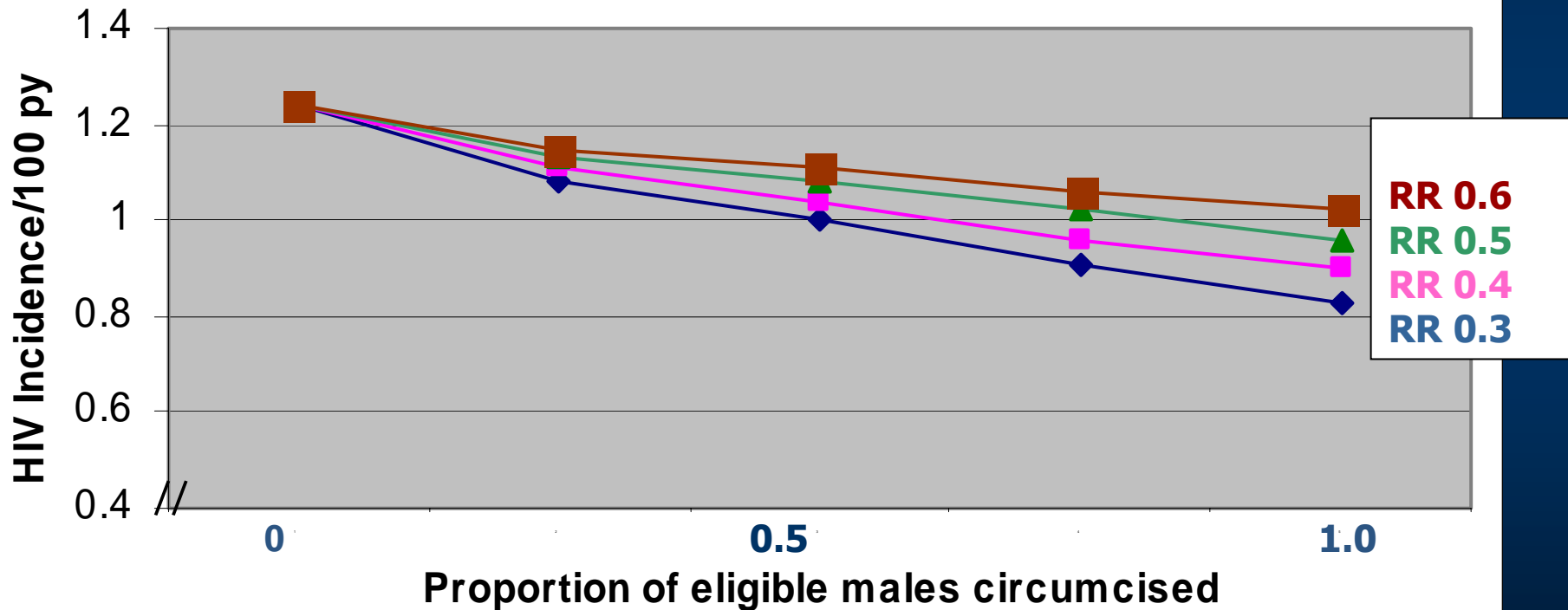
Acceptability in Rakai

- Of general male population, 48 percent enrolled in the trials.
- Focus groups
 - Will circumcision turn men into Muslims?
 - Jesus was circumcised

Acceptability

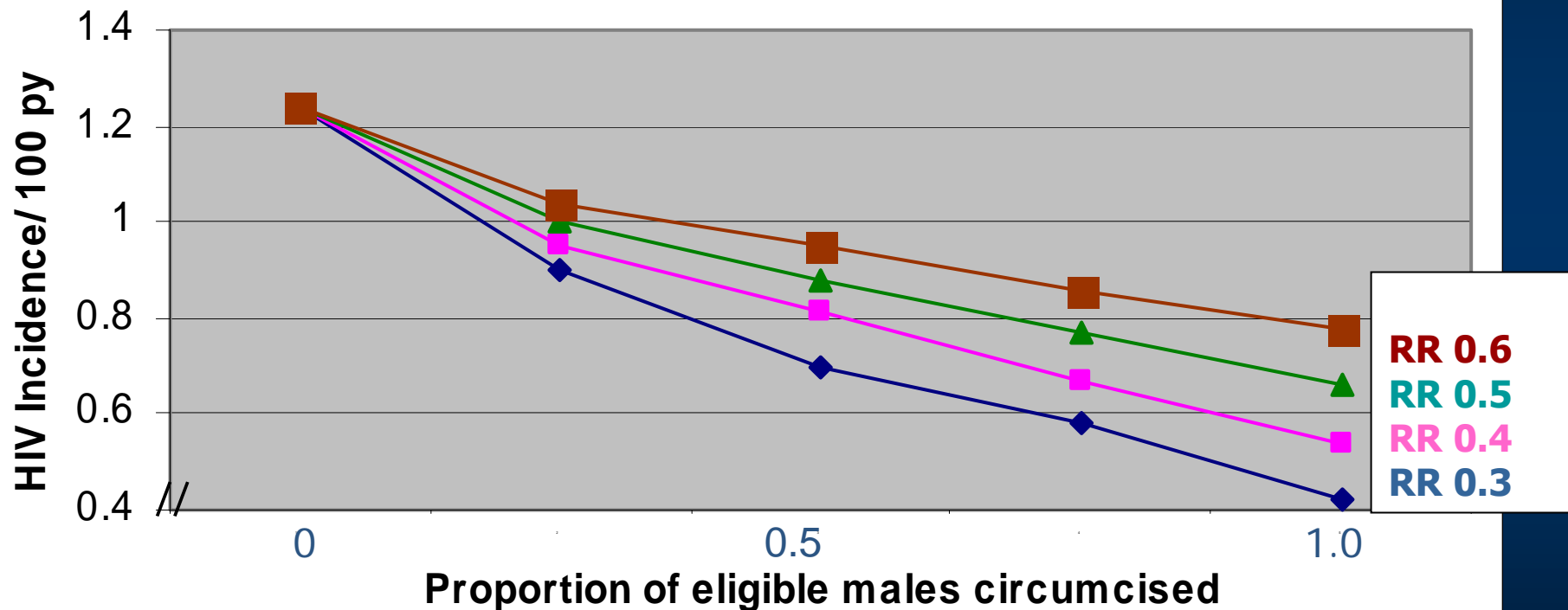
- Kenya, South Africa, Uganda, Botswana, Haiti, Tanzania, Zambia and Zimbabwe acceptability 48-85%. (Rakai ~ 69%)
- Perceived improved hygiene, decreased susceptibility to HIV, and easier condom use.
- Concerns include:
 - Fear of pain
 - Reduced sexual pleasure
 - Limited access to health facilities should complications occur
 - Stigma, religious identity (Islam)

Effect on population HIV incidence if circumcision reduces male HIV acquisition, by program coverage



Stochastic Simulation Model
(Gray *et al* IAS 2005)

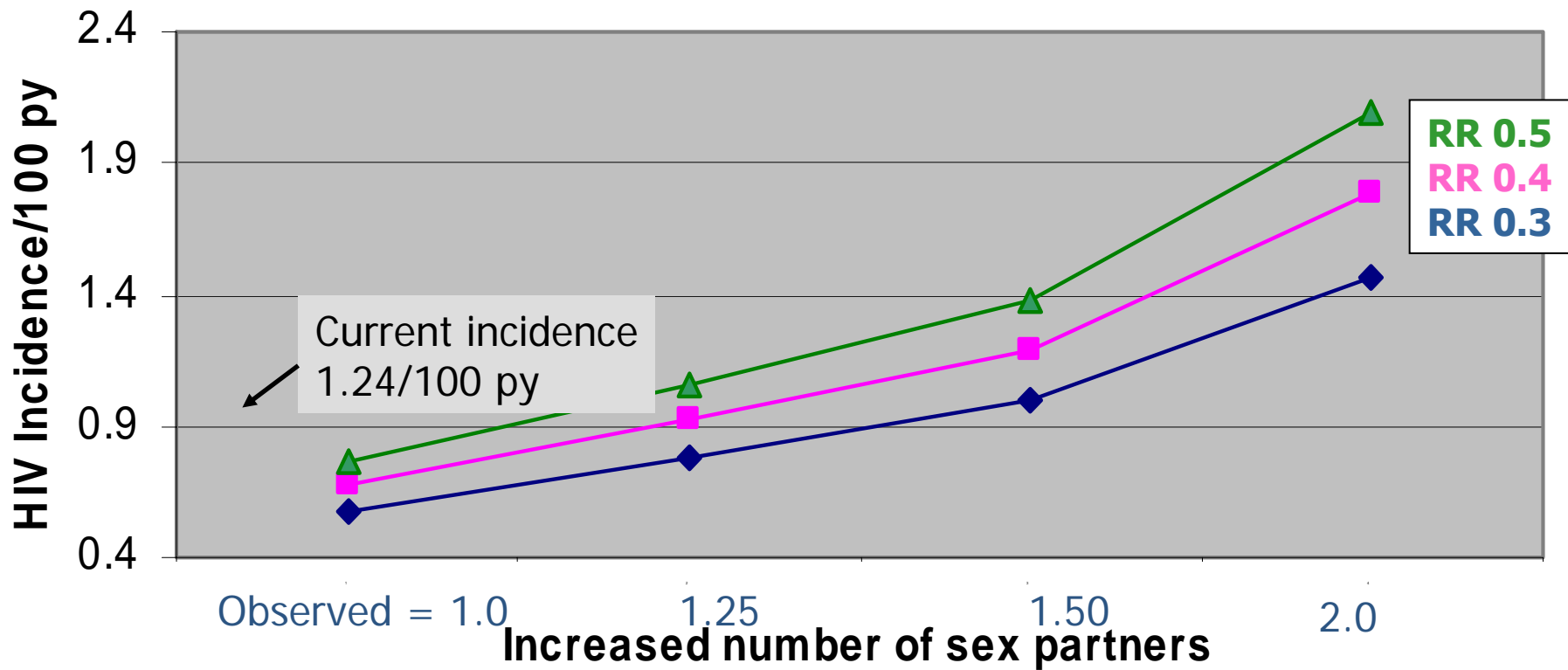
Effect on population HIV incidence if circumcision reduces male and female HIV acquisition, by program coverage



Maximum impact on incidence if circumcision reduces risk in men and women

(Stochastic simulation model, Gray *et al* IAS 2005)

Effect of behavioral disinhibition on HIV incidence, by circumcision IRR in both sexes combined, 75% coverage



Behavioral disinhibition can offset all benefit, even at high circumcision efficacy

Cost-effectiveness of male circumcision for HIV prevention



Rakai: Cost per circumcision ~ **\$69.0**

Research study using physicians and fully equipped theaters.
Program costs are likely to be lower

Cost per HIV infection averted over 10 years

RR	Acquisition in males	Acquisition in females	Acquisition in both sexes
	Cost per infection averted (\$)	Cost per infection averted (\$)	Cost per infection averted (\$)
0.5	3136	2579	1485

- Circumcision is likely to be cost-effective if $RR \leq 0.6$, especially if protective in both sexes.
- Public health impact could be substantial.
- Longer duration of efficacy increases cost-effectiveness
- Nevirapine \$2,517 per infection averted (Sweat et al *AIDS* 2004)

Surgery and risks

- **Adult circumcision is not simple**
- **“Forceps guided” method or clamp:**
 - Draw foreskin over the glans, clamp and cut (South Africa, Kenya trials)
 - Simpler procedure
 - More bleeding
 - Leaves more residual foreskin
- **“Sleeve circumcision”:**
 - Dissect the foreskin and remove all foreskin tissue (Rakai trials)
 - More complex procedure
 - Less bleeding
 - Less residual foreskin

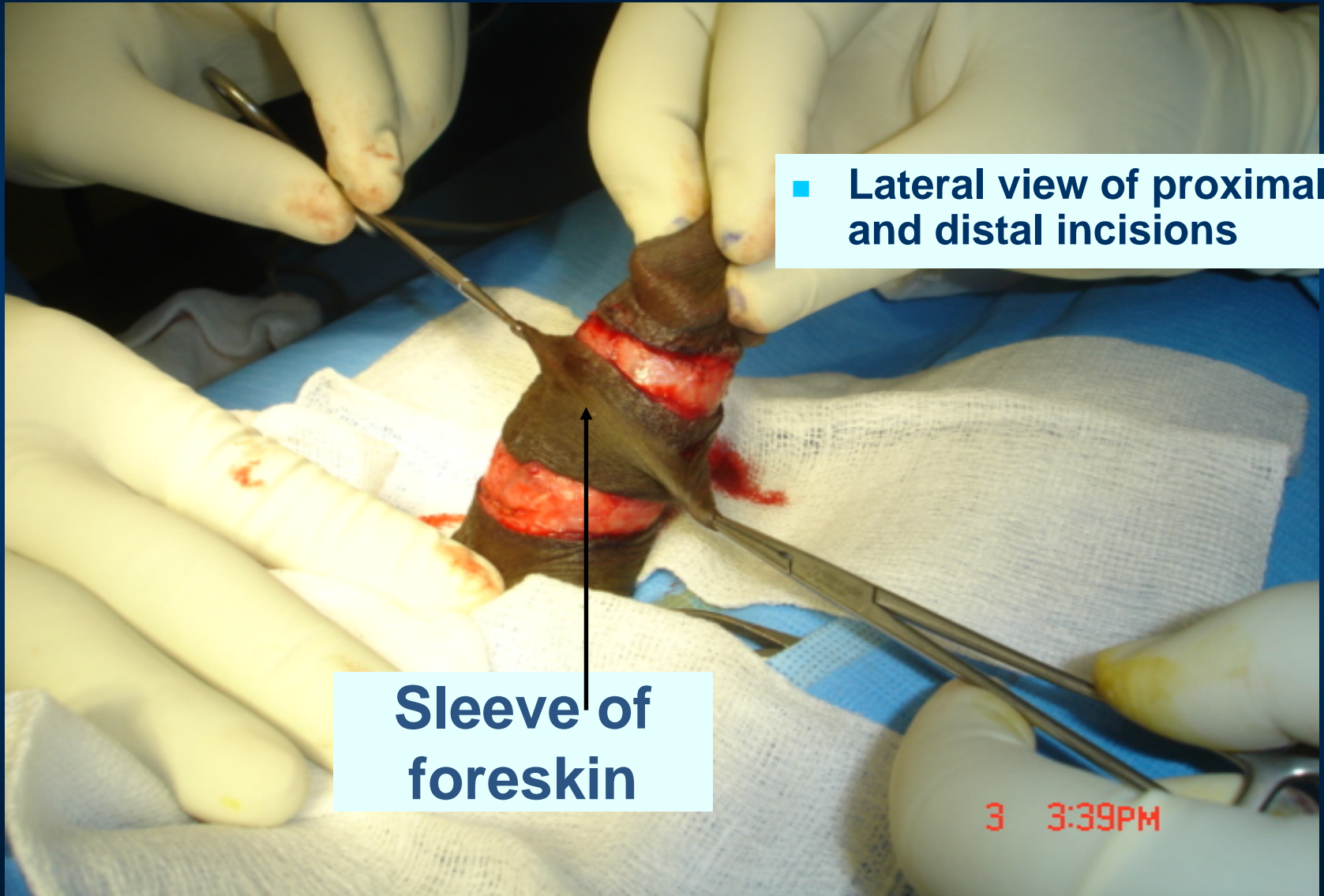
Forceps guided method (Clamp and cut)



Cut foreskin



Sleeve method

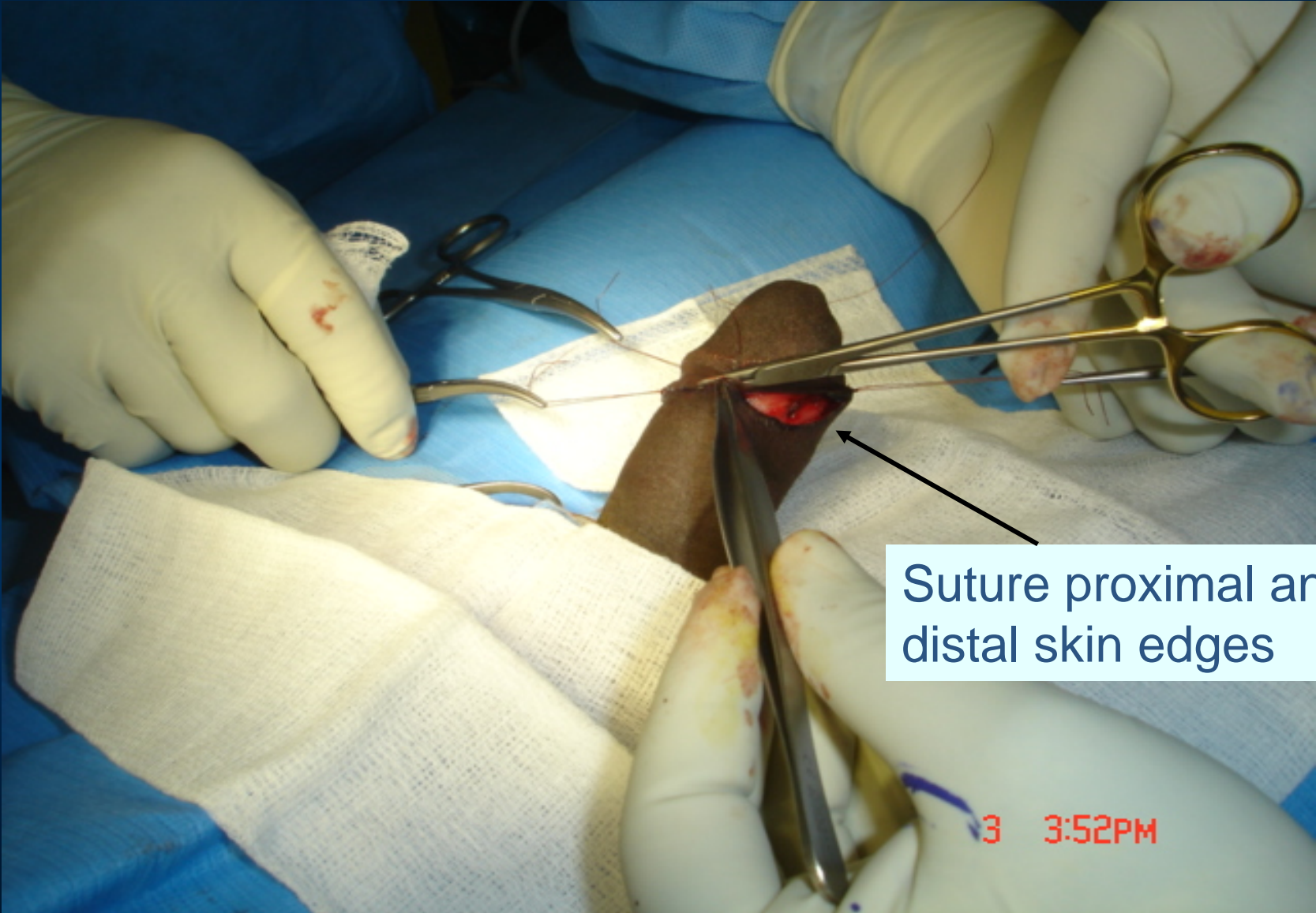


■ Lateral view of proximal and distal incisions

Sleeve of foreskin

3 3:39PM

Approximation of skin edges and suturing



Suture proximal and distal skin edges

Programmatic issues

- **Scale up to provide safe adult circumcision (training, equipment, supplies, etc.)**
- **Specialized surgical centers to maximize quality of surgery and postoperative care**
- **Discourage poorly trained traditional or private practitioners**
- **Provide neonatal circumcision?**
- **Prevent behavioral disinhibition and maintain HIV prevention efforts**

Risks of traditional circumcision

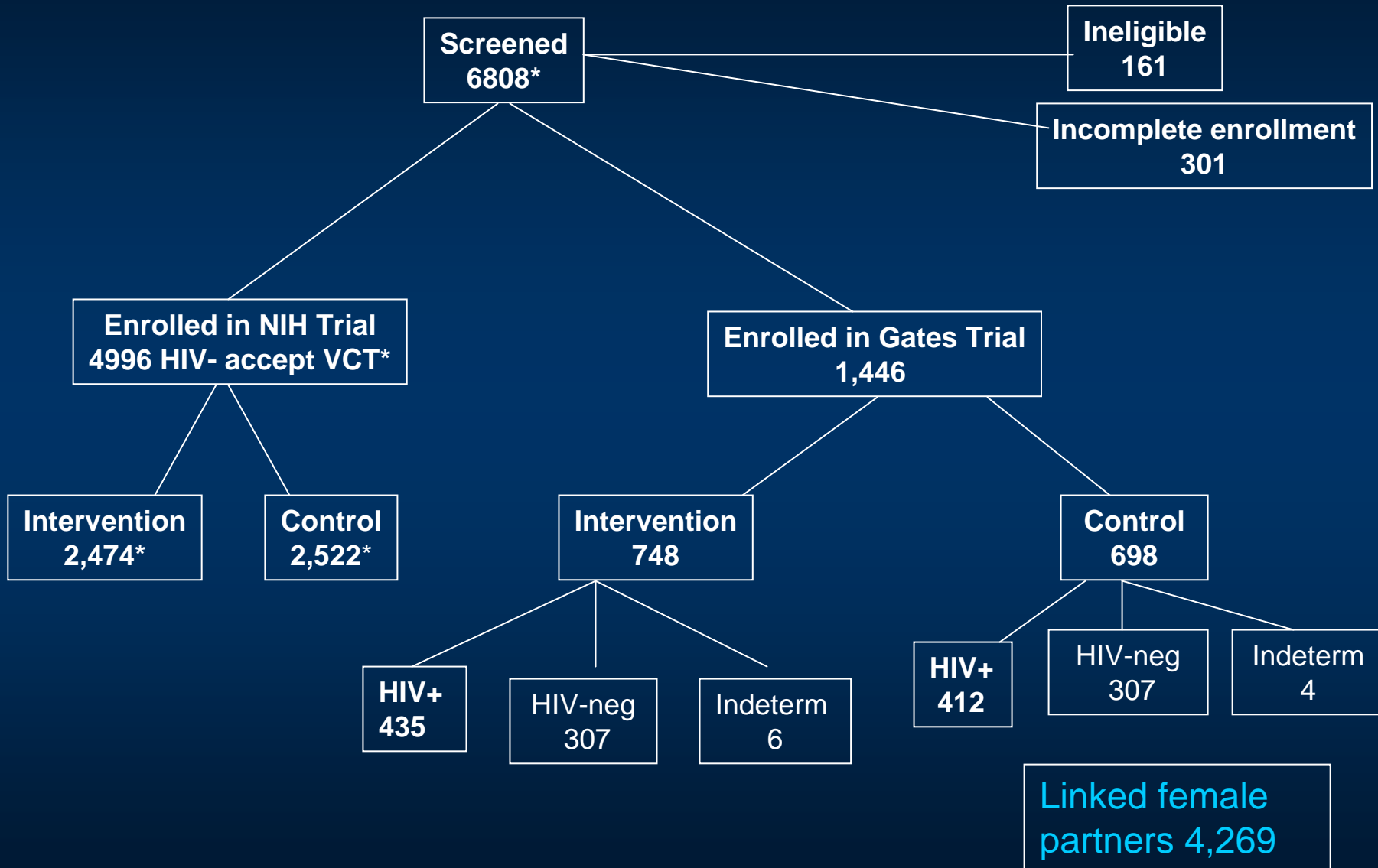
- Traditional circumcision complications:
 - >10%
 - Hemorrhage, infection/septicemia/gangrene, amputation of penis or permanent damage (Mogoha *E Afr Med J* 1999, Ahmed *Ann Trop Ped* 1999)



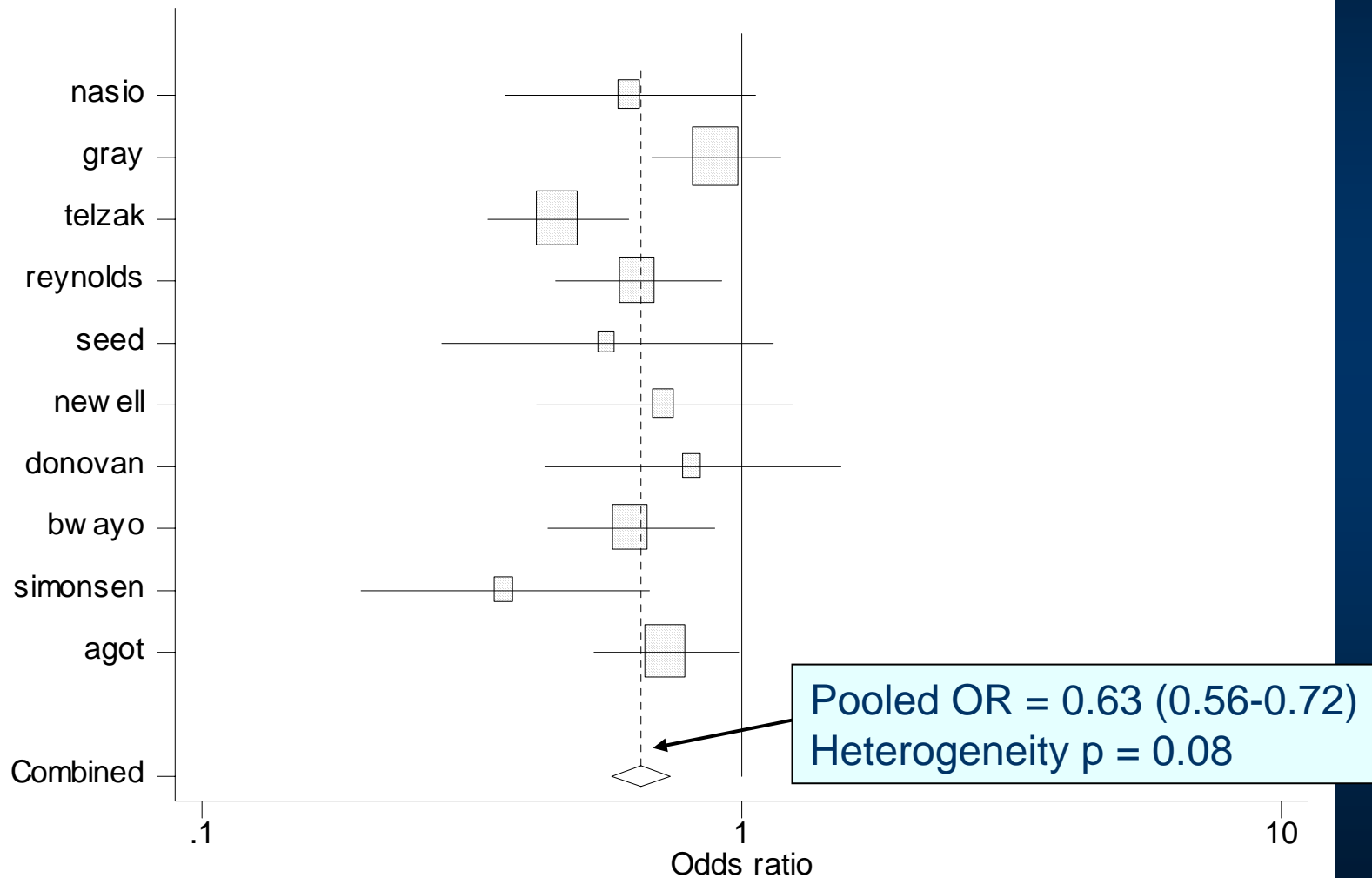
Summary and Conclusions

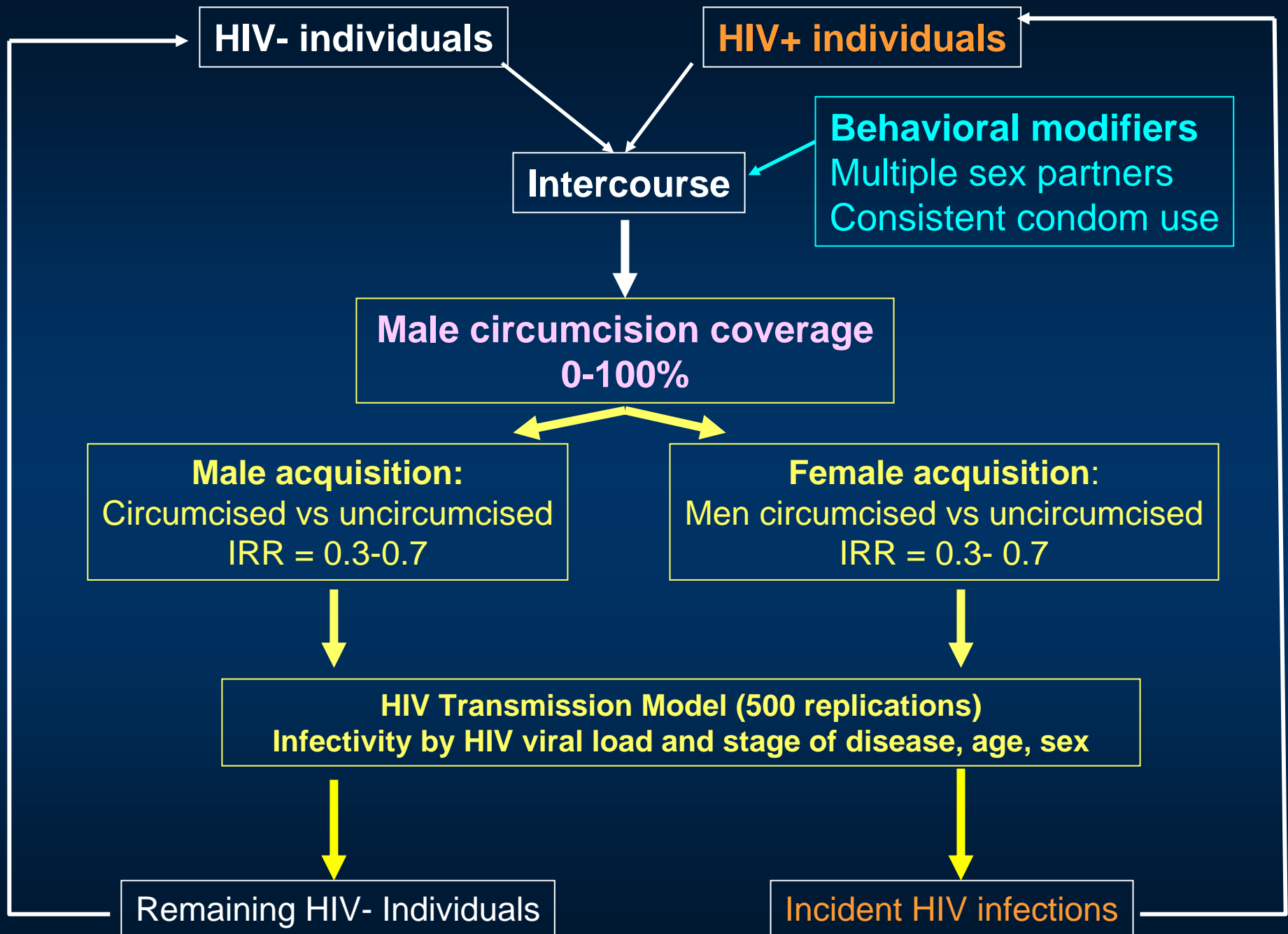
- **Male circumcision could have a major impact on the HIV epidemic, especially if protective in both sexes**
- **Other potential benefits: decreased STIs in both sexes**
- **Behavioral disinhibition could offset benefits; intensive risk reduction and integration with other prevention programs will be required.**

Rakai Male Enrollment in Circumcision Trials

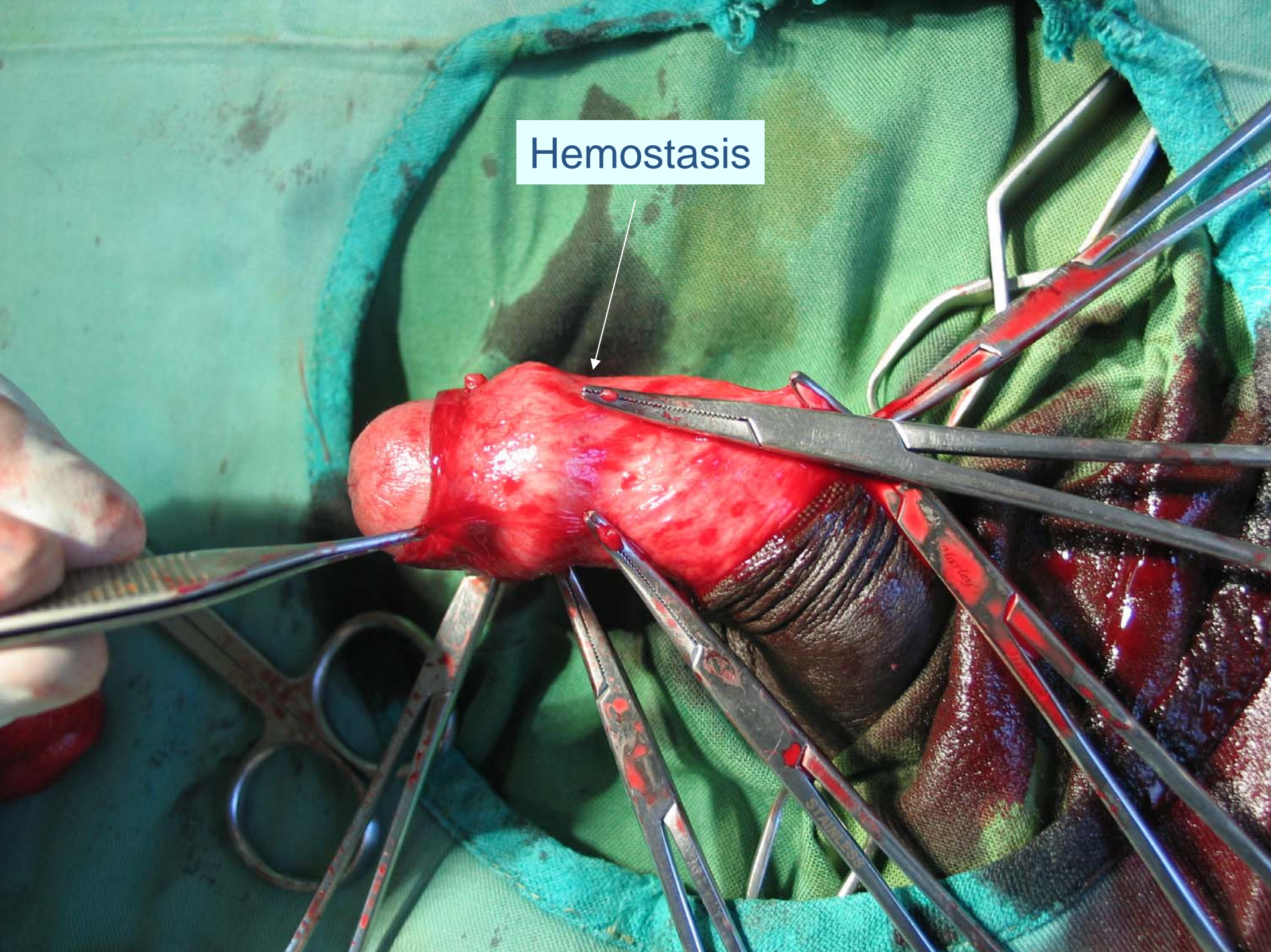


Circumcision and male genital ulcer disease (GUD)





Hemostasis



Number of circumcisions to prevent one incident HIV infection over 10 years with 75% program coverage

RR	Acquisition in males	Acquisition in both sexes
	No. Surgeries per infection averted	No. Surgeries per infection averted
0.5	46	22