



Trials of Male Circumcision for HIV and STI Prevention in Men and Women

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Two circumcision trials
HIV-negative men (NIH funded)
HIV+ men (Gates funded)

Both trials were population based

Consenting HIV-negative and HIV+Men were enrolled
and randomized to circumcision or control arms

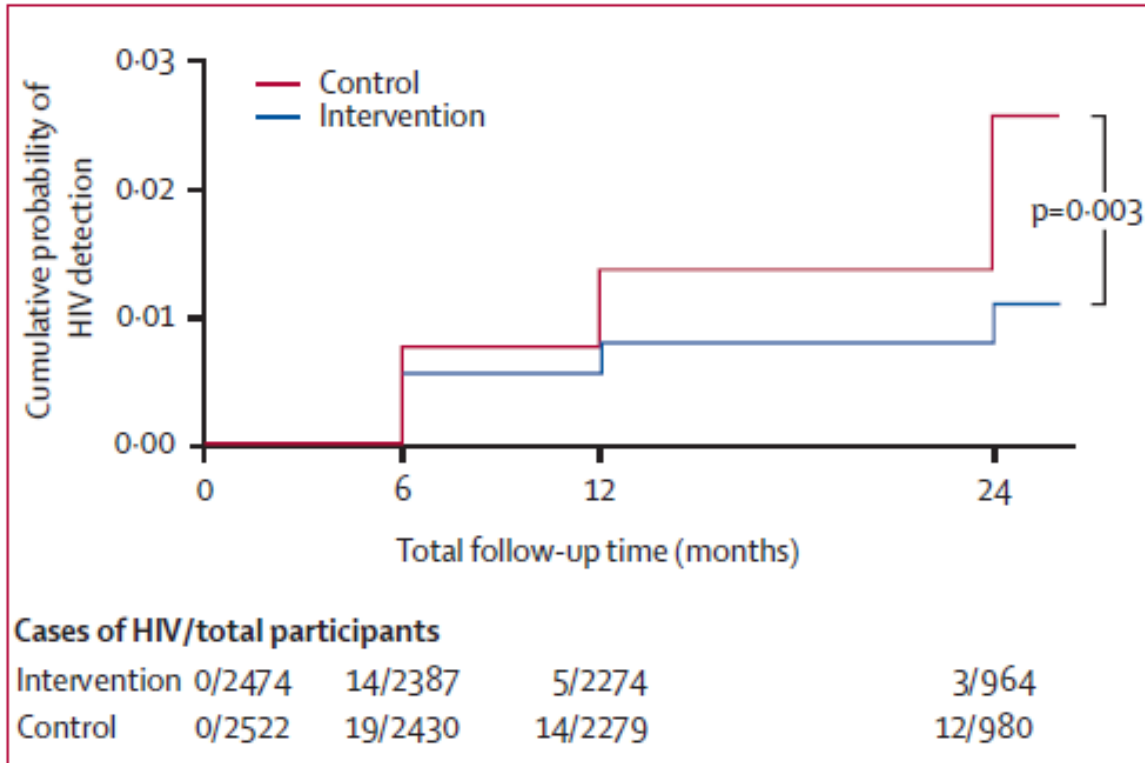
Consenting wives of married male participants were enrolled into
A follow up study

Trial of Male Circumcision for HIV Prevention in Men

- Enroll HIV-negative uncircumcised men, randomize to:
 - Immediate MC (Intervention n= 2474)
 - MC delayed 24 months (Control n=2522)
 - Follow up at 6, 12 and 24 months
- **Endpoints:**
 - HIV incidence
 - Safety
 - Behavioral disinhibition
 - STIs and STI symptoms



HIV incidence over 24 months by Circumcision Status



Intervention HIV Incidence /100 py	Control HIV Incidence /100 py	HR (95% CI)
0.66	1.33	0.40 (0.23-0.70)

HIV reduction - 60%

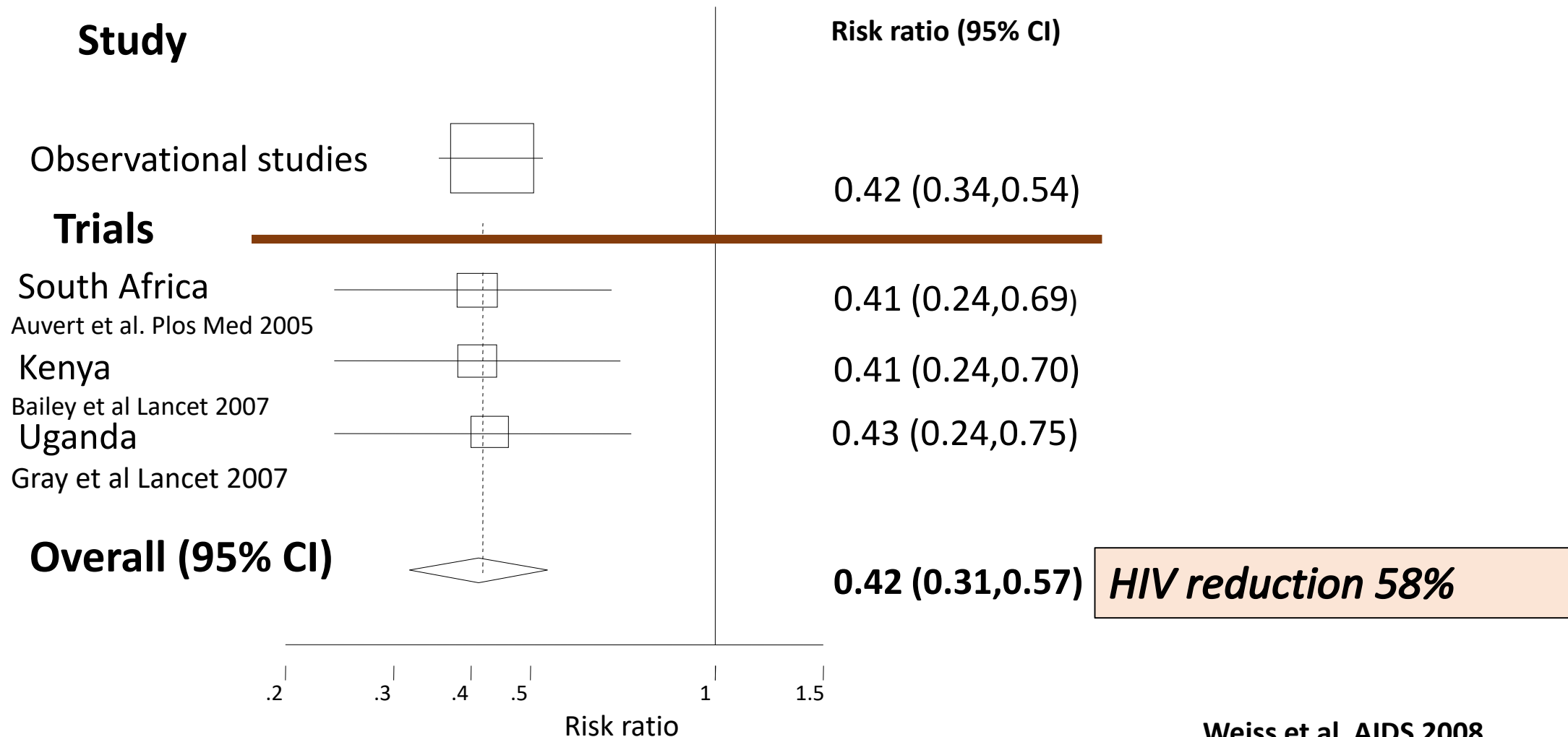
Figure 2: Kaplan-Meier cumulative probabilities of HIV detection by study group

Gray et al Lancet 2007



Meta-analysis: Circumcision

For HIV prevention in HIV-neg men



Weiss et al AIDS 2008



Circumcision and Sexual satisfaction/dysfunction in men and women

- Sexual satisfaction in men was 98.4% in circumcised and 99.9% among controls.
- 57.3% of women partners of circumcised men reported no change and 39.8% an improvement in sexual satisfaction



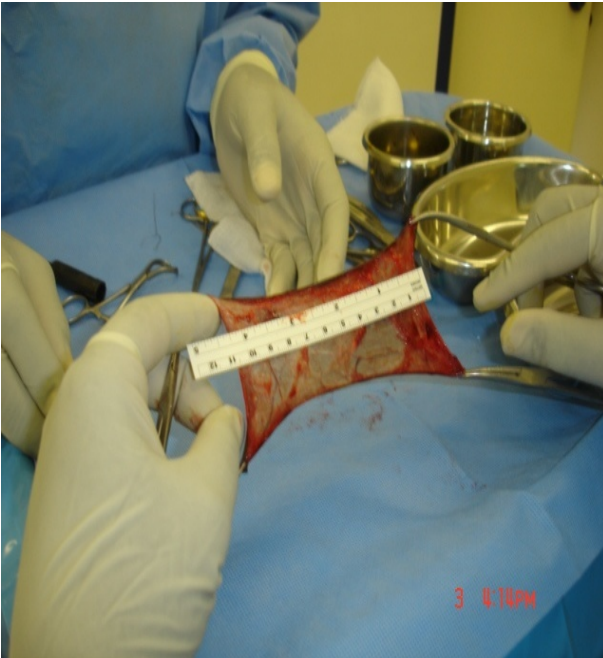
No adverse effects on male and female sexual satisfaction or function

(Kigozi et al Brit J Urol 2008)

Reduction of STIs with Circumcision in Men

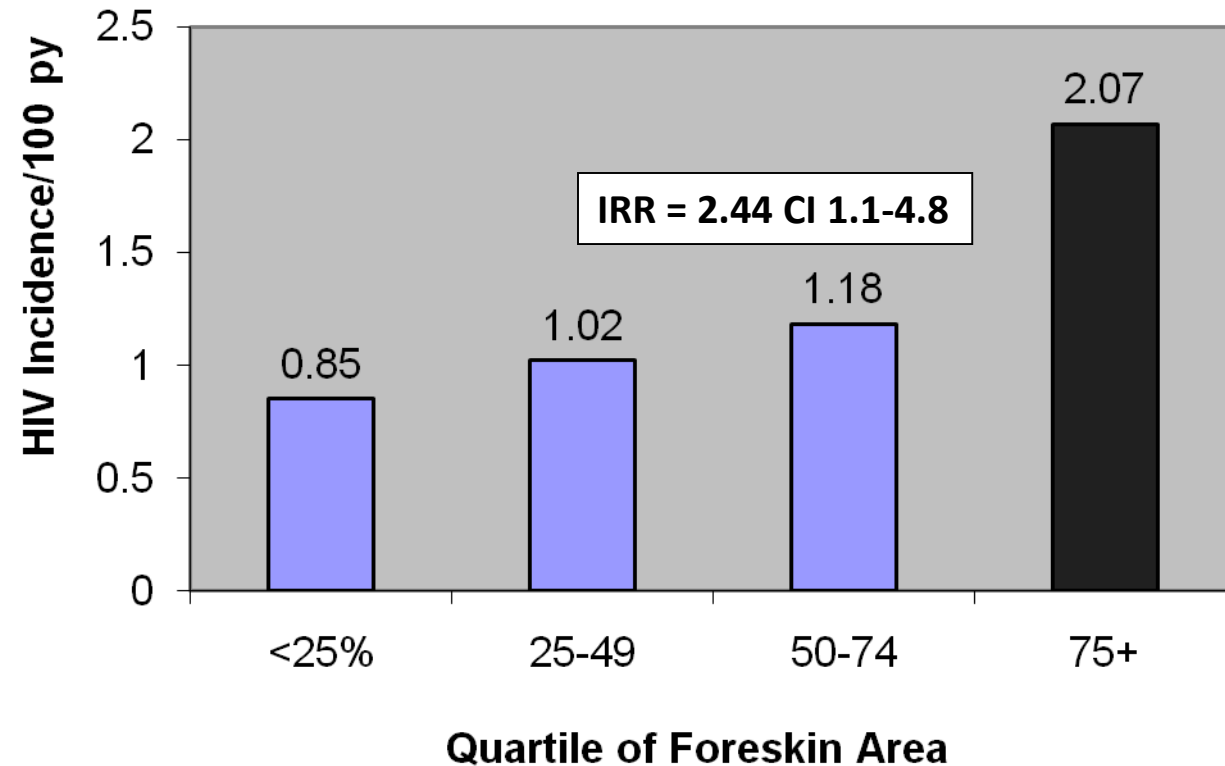
- Genital Ulcer Disease (GUD)
 - RR = 0.53 (0.43-0.64) *Gray et al Lancet 2007*
- HSV-2
 - RR = 0.72 (0.56-0.92) *Tobian et al NEJM 2009*
- HPV
 - RR = 0.67 (0.51-0.82) *Gray et al JID 2010*
- Pro-inflammatory anaerobes
 - Marked reduction following circumcision (*Price et al Plos One 2010, Liu et al Mbio 2013*)

HIV Incidence higher with larger foreskin surface area: Size matters!



Comparison of pre-MC HIV incidence by foreskin surface area measured after circumcision

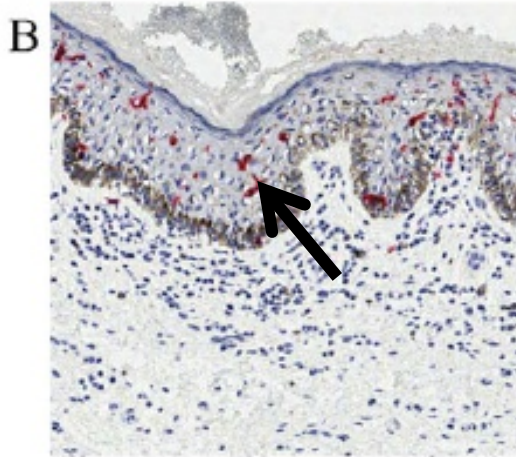
HIV Incidence by Foreskin Surface Area



Kigozi et al, AIDS 2009

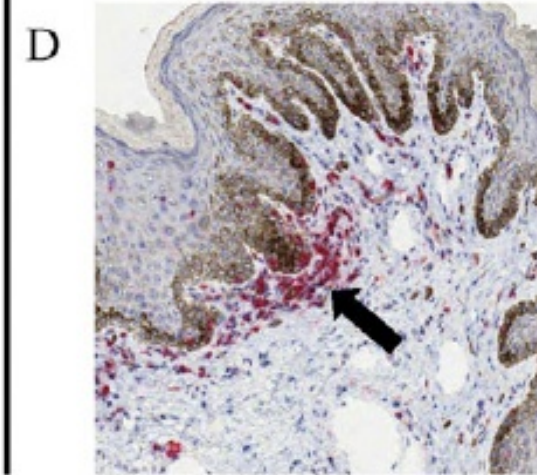
The Foreskin Contains HIV Target Cells

CD1A Dendritic cells



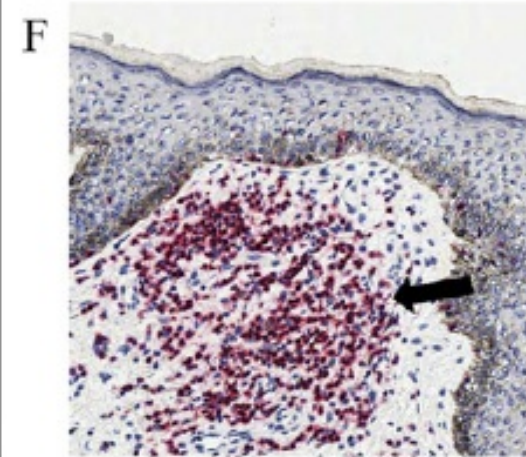
Cells for HIV entry
in epidermis

CD4 T-cells



Cells for HIV replication and dissemination
in dermis

CD8 T-cells



*The larger the foreskin the more
the dendritic and CD4/CD8 T cells*

(Johnson, Redd et al JID 2011)

Trial of Circumcision in HIV+ Men

Rationale: Cannot deny MC to HIV+ men

- Stigma in HIV+ men
- Behavioral disinhibition in HIV-neg men

• End points

- Safety in HIV+ men
- STI effects in HIV+ men



Surgery-related adverse events in HIV+ compared to HIV-neg men

	HIV+ men % (N=420)	HIV-neg men % (N=2326)
Moderate	3.1	3.1
Severe	0	0.2
Total	3.1	3.2

Healed

Safety is comparable in HIV+ and HIV-neg men

Genital Ulceration and HPV Infections in HIV+ Men

	Circumcised HIV+ Men (%)	Uncircumcised HIV+ Men (%)	RR (95% CI)
Genital Ulcers	10.0	16.0	0.63 (0.5-0.8)
HR-HPV Prevalence	55.3	71.7	0.77 (0.62-0.97)

Circumcision provides benefit to HIV+ men by reducing genital ulceration and HR-HPV infections



Serwadda et al. JID 2010

Effects of MC on HIV Acquisition in HIV-negative Women

- HIV-negative female partners of HIV+ male circumcision trial participants were invited to be followed up.
- Identified and followed -
 - 93 HIV-ve partners of circumcised men and
 - 70 HIV-ve partners of un-circumcised men
- Followed at 6, 12 and 24 months
- **Endpoint:**
 - HIV incidence in women
 - STI in Women



(Wawer et al Lancet, 2009)

Female HIV Acquisition by Male HIV+ Circumcision Status

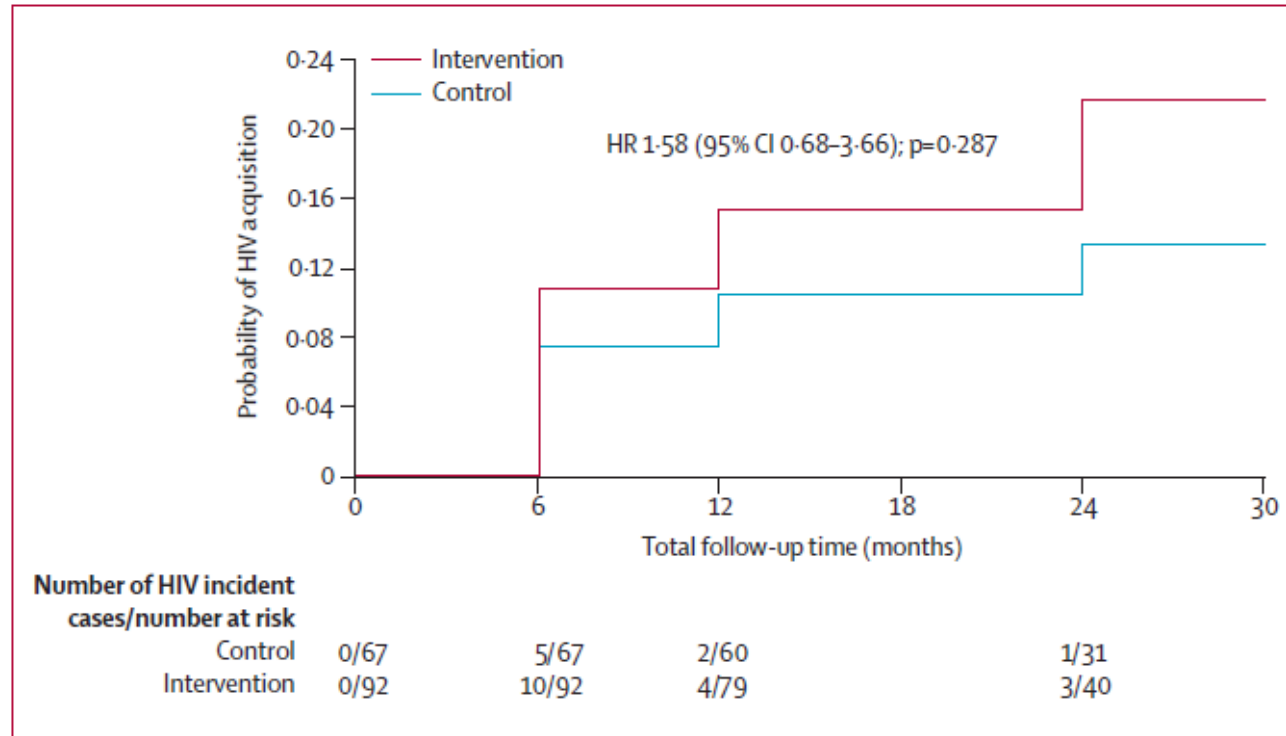
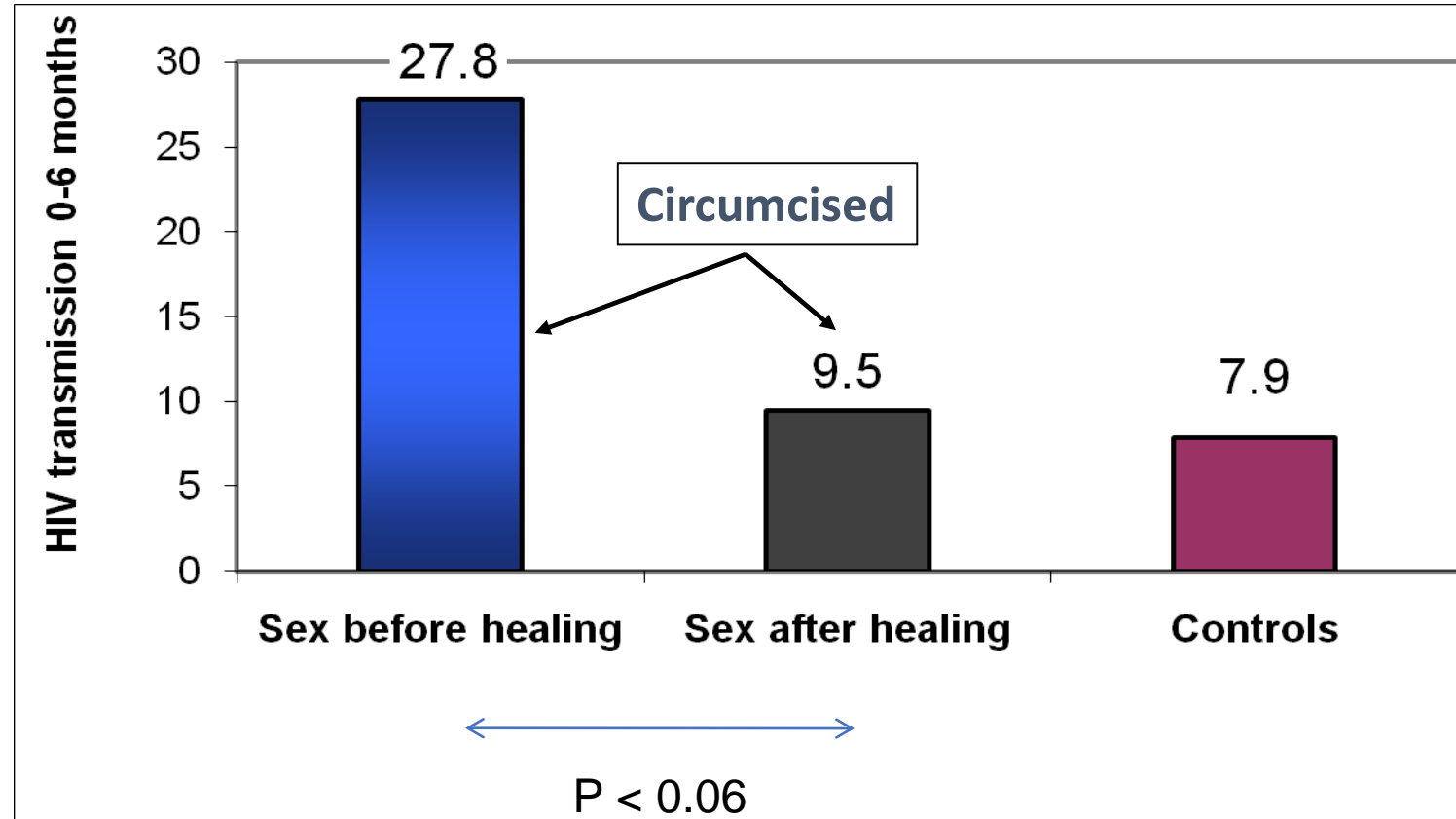


Figure 2: Kaplan-Meier cumulative probability of female HIV acquisition by study group

No significant difference in HIV acquisition by partner circumcision status

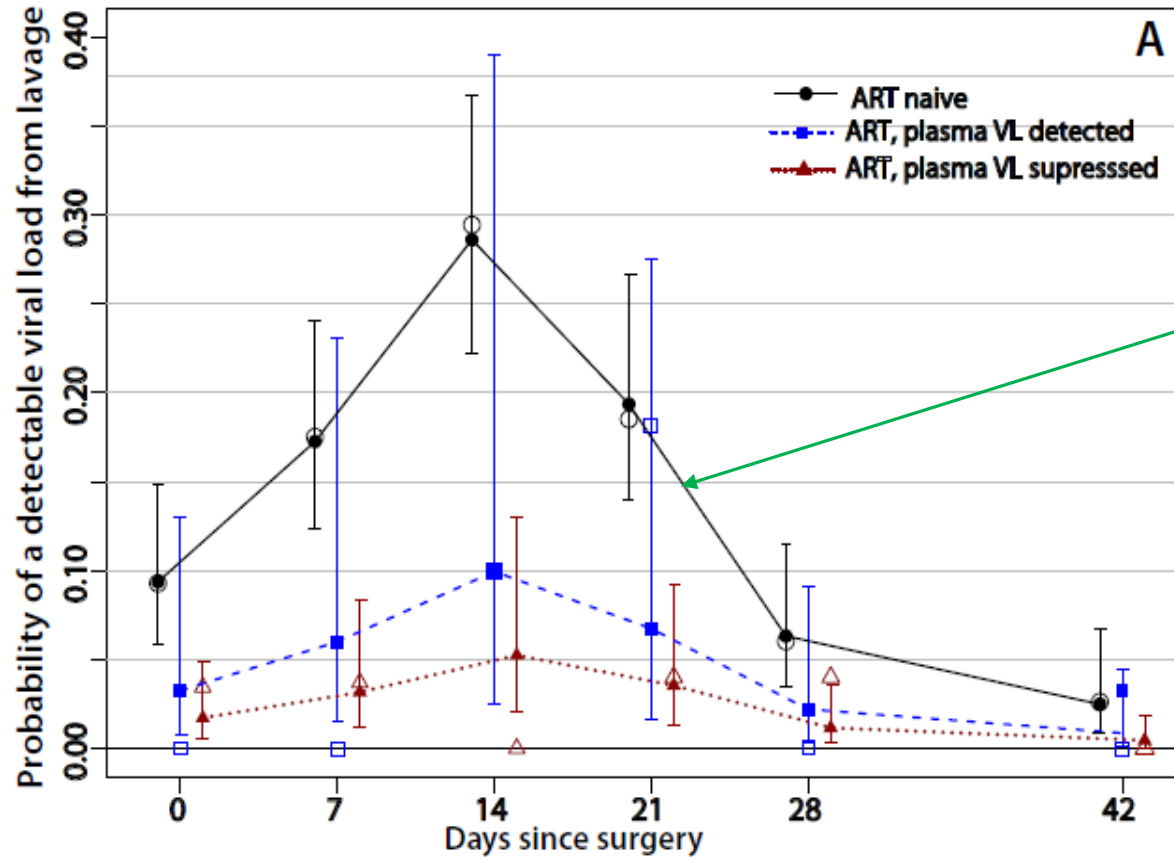
(Wawer et al Lancet, 2009)

Female HIV acquisition 0-6 months by resumption of sex and partners' circumcision wound healing



Resumption of sex before wound healing increased HIV transmission

HIV Shedding is Increased After Circumcision of ART Naïve HIV+ men



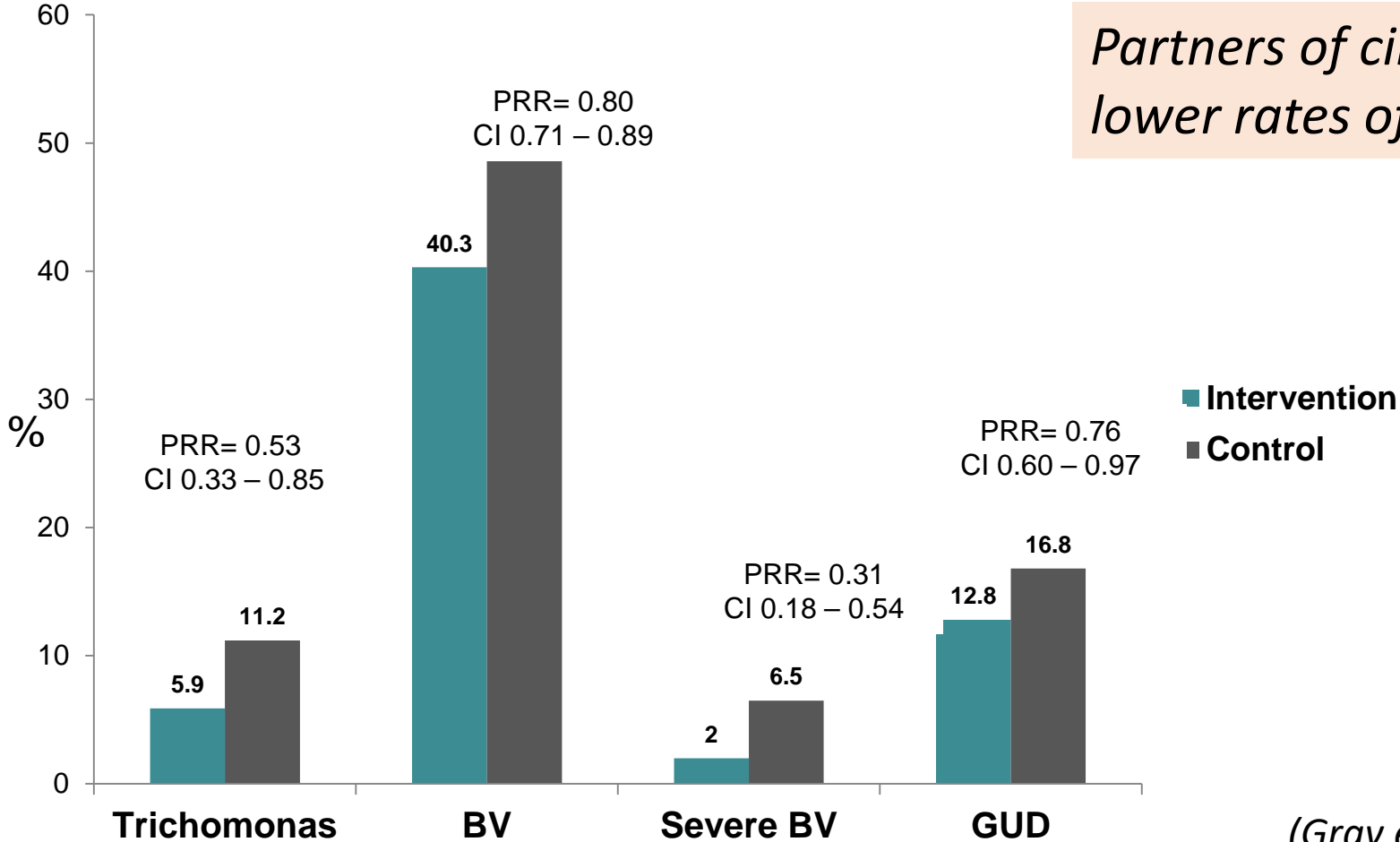
Shedding was increased for 3 weeks after circumcision especially in ART Naïve HIV+ve men

Genital Infections in HIV-negative Women by Male Partner's Circumcision Status

- HIV-negative women with HIV-negative male partners were followed up over 24 months
- Males were randomized to circumcision (n=648) or uncircumcised controls (n=597)
- Women were assessed for vaginal infections and HPV

Gray et al. Amer J Obstet Gynecol 2008
Wawer et al. Lancet 2011

Vaginal infections and GUD at 24 months by HIV-negative Male Circumcision Status



(Gray et al Am J Obs Gynecol 2008)



HR-HPV Infection in HIV-negative Females by Male Partner's Circumcision Status

	Male Circumcised %	Male Uncircumcised %	RR (95% CI)
HR-HPV Prevalence	27.6	38.6	0.71 (0.68-0.85)

Male circumcision decreased HPV infection in women and could reduce cervical cancer.

Wawer et al. Lancet 2011



Thanks