

# **Rakai Health Sciences Program**

**Trial of male circumcision:  
safety in HIV+ men and effects in  
women and the community**

**Funded: Bill and Melinda Gates  
Foundation**

# 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"

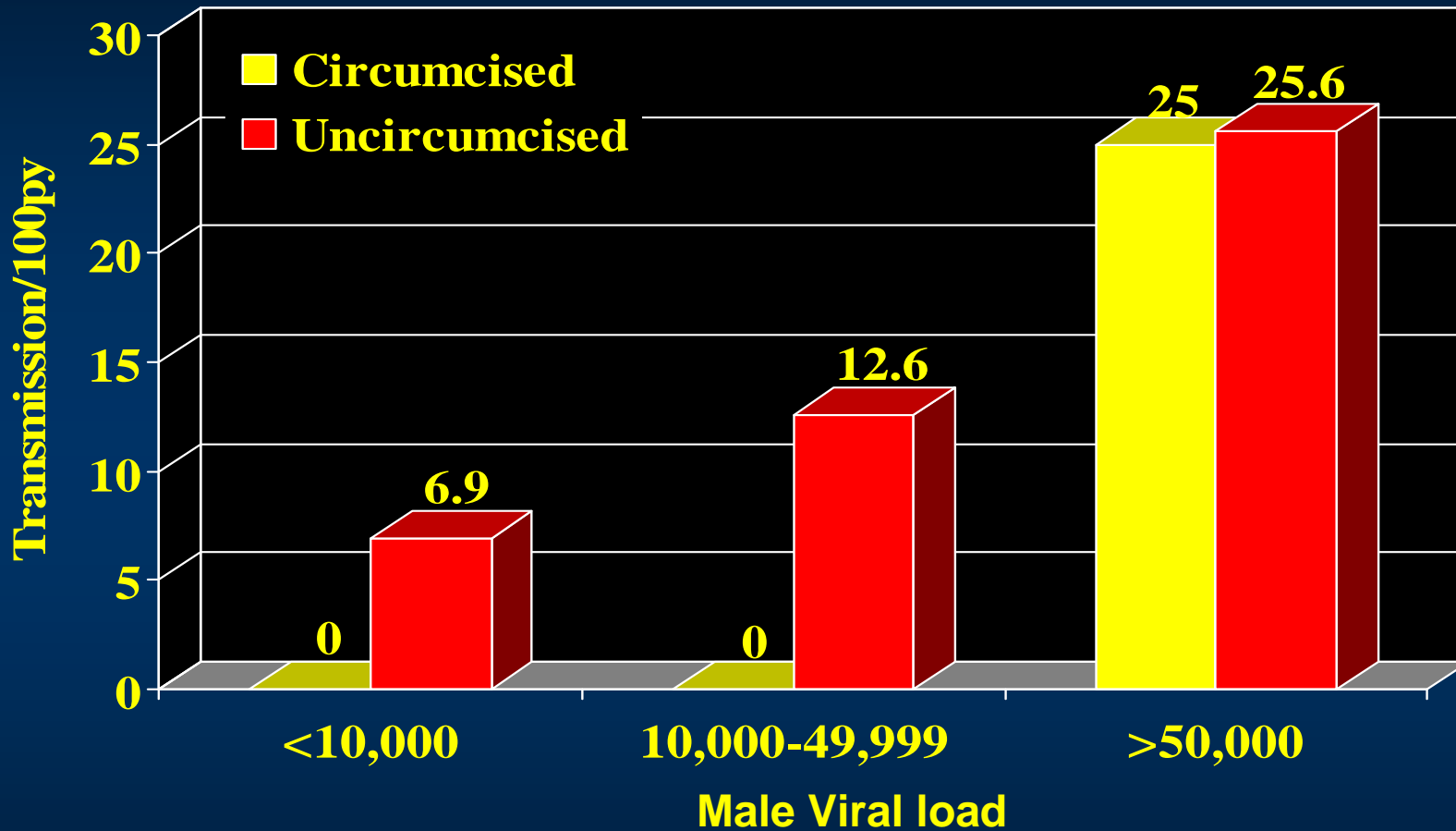
# Why include women?

- **Safety and risk/benefits of male circumcision for women**
  - Assessment of HIV and STI transmission to female partners by male circumcision status
  - Factors influencing potential risk or benefits
- **Behaviors in couples after male circumcision**
- **Women's satisfaction with partner's circumcision status**
- **Effects in women will affect program cost effectiveness**

**The world is not made up solely  
of HIV-negative men...**

**Observational data suggest that male circumcision may reduce transmission of HIV and selected STIs to women partners.**

## Rakai: Male Circumcision Status and HIV Transmission to Women



47 couples with circumcised HIV+ male with VL <50,000 : 0 transmissions in 2 yrs  
143 couples with uncircumcised HIV+ man with VL < 50,000: 26 transmissions  
(9.6/100 py) (p = 0.02).

Gray et al AIDS 2000

## Prospective observational data on the effects of male circumcision on female HIV acquisition

- **Tanzania** (Kapiga et al AIDS 1998)
  - Family planning clinic clients
  - 1022 uncircumcised, 22 circumcised partners
  - Adj IRR = 0.28 (CI 0.09-0.91)

# 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 / traditional**
    - May be correlated with lower risk behaviors, less alcohol use, genital hygiene, etc.
    - Mainly neonatal or puberty rituals  
(i.e, males are generally HIV-neg at time of circumcission)
  - **Possible confounding**

# Complementary trial of male circumcision in HIV+ males, Rakai

- RCT of 900 HIV-positive men (Gates-funded).

Endpoints in HIV+ men, women partners, the community

Circumcision safety in HIV+ men

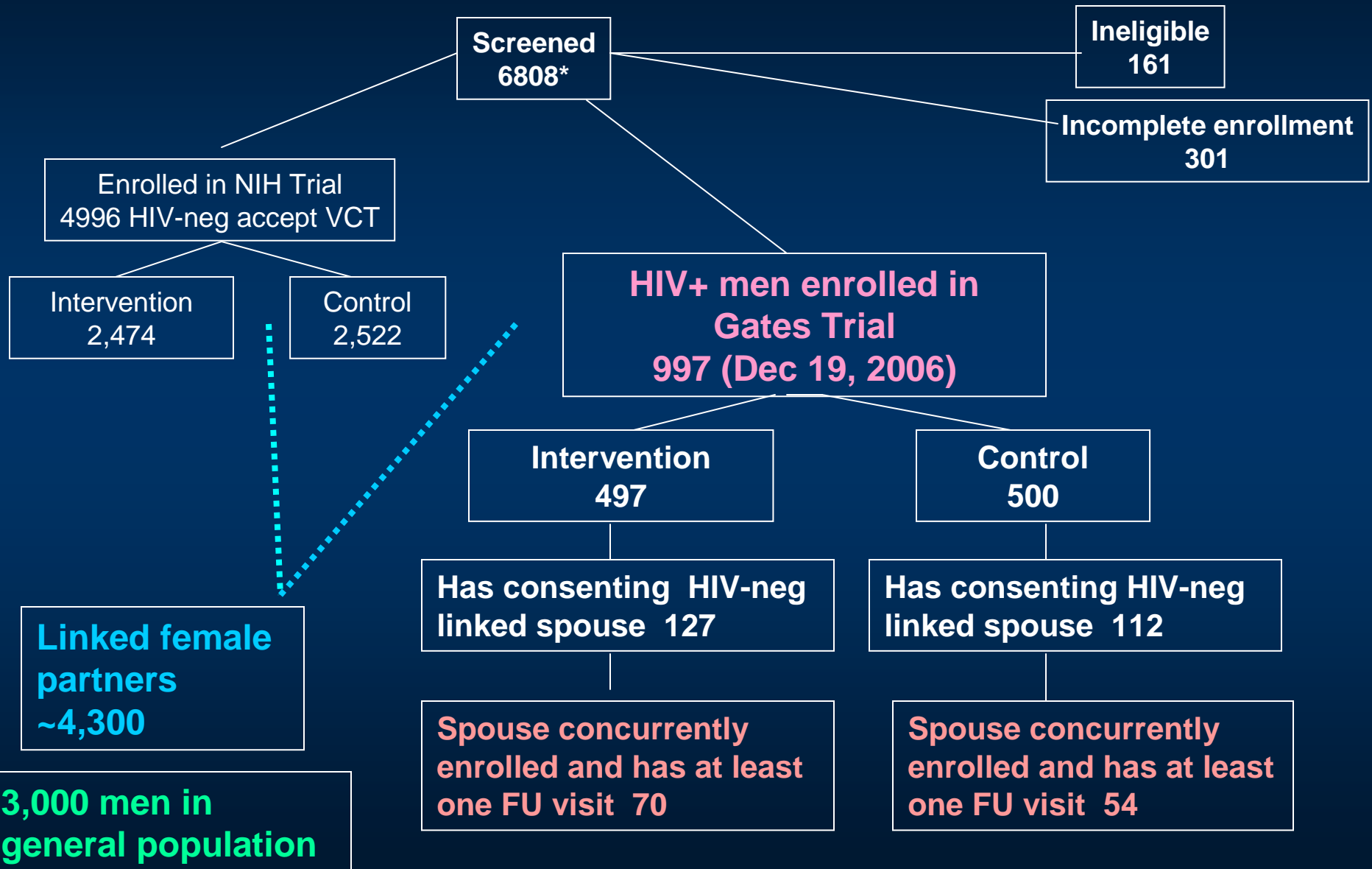
STI acquisition in HIV+ men

HIV acquisition in women

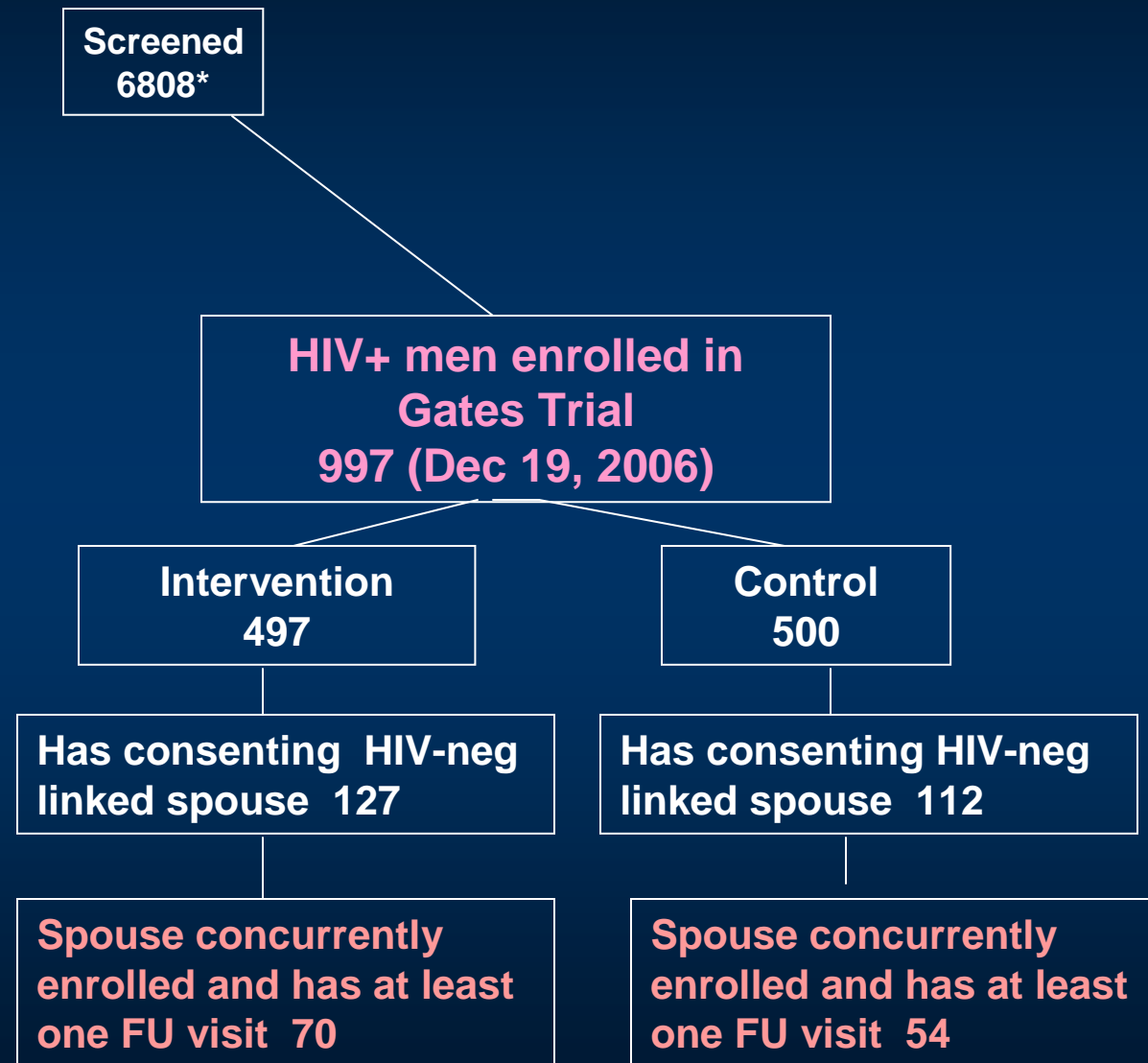
STI acquisition in women

Behaviors in men, women and the general population

# Rakai Male Enrollment in Circumcision Trials



# Rakai Male Enrollment in Circumcision Trials



## Trial oversight

- **Human subjects boards in Uganda**
  - **Science and Ethics Committee, Uganda Virus Research Institute**
  - **Ugandan Council on Science and Technology**
- **Human subjects board in the USA**
  - **Western IRB for JHU**
- **Independent Data Safety and Monitoring Board**
- **Community Advisory Board**

## Enrolment procedures

- Male participants (HIV-neg and HIV+) were recruited into the circ trials from Rakai District
- ~50% of the men were already members of the Rakai Community Cohort Study (RCCS) (in 50 villages since 1994)
- ~50% of men were from outside RCCS villages (“walk-in” men)
- Women partners were linked from within the cohort data set (if the couple were both RCCS member)
- “Walk-in” men were asked to invite their spouse to enroll
- Enrolment was identical for women partners of HIV+ and HIV-neg men

## Enrolment procedures

- Women partners provided written informed consent
- Women were informed that:
  - Their partner is in a trial of male circumcision
  - Trial participation is not an indication of male HIV status
  - MC might result in partial protection against HIV/STI transmission to women, but this is not yet known
  - The couple must adhere to ABC
- Individual and couples VCT are provided free of charge and strongly recommended.
- Improved strategies to promote couples VCT were developed: acceptance of couples VCT is now over 90%.

## Enrolment procedures

- Men represent the index partner
- Women are linked to both HIV-negative and HIV-positive men, whether the men are enrolled in the NIH or the Gates funded trial
- Not a classical discordant couples study: ie., couples do not enroll *a priori* because they are discordant.

## **Women's follow up procedures**

- All women followed at 12 and 24 months
- On the recommendation of the DSMB, partners of HIV+ men (and several hundred HIV-neg men for masking) were also followed at 6 months
- At enrolment and all follow up visits:
  - Detailed behavioral and sexual networks survey
  - Blood for HIV, HSV-2, syphilis
  - Self-administered vaginal swabs for HPV, BV, Tv, GC and Ct

## Unexpected challenges

- Low marriage rates among “walk in” men
- If male had CD4 < 350 cells /ml or on ARVs, not eligible. Many men fell in these categories.
- Original target: 220 Male+/Female-neg couples.
  - Achieved 239 couples overall
  - But as of Dec, 2006, had enrolled only 172 couples where both partners enrolled at the same time (i.e, in some couples, HIV+ women enrolled same months later, so that their HIV status at the time of the male’s enrolment/circumcision could not be known).
- To date, follow up data on 124/174 couples

## **Consequence of challenges**

- **When NIH trial ended, enrolment of HIV+ men and spouses would become more difficult (would require outreach to known discordant couples and enrolment outside of Rakai )**
- **DSMB advice on continuation was requested**
- **DSMB review on Dec 19, 2006**
  - **Stopped trial enrolment for futility**
  - **Requested additional analyses to assess potential of increased risk of HIV transmission**
  - **Requested continued follow up (to Dec 2009)**

**Results in HIV+ men**

**Preliminary and partial**

HIV+ men enrolled 997

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graph TD; A[HIV+ men enrolled 997] --> B[Intervention 497]; A --> C[Control 500];
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Intervention 497

Control 500

## Retention rates, HIV+ men

<b>% followed up</b>	<b>Circumcision arm (N eligible men)</b>	<b>Control arm (N eligible men)</b>
<b>4-6 weeks</b>	<b>97% (341)</b>	<b>88% (349)</b>
<b>6 months</b>	<b>91% (295)</b>	<b>92% (270)</b>
<b>12 months</b>	<b>94% (250)</b>	<b>90% (219)</b>
<b>24 months</b>	<b>88% (49)</b>	<b>87% (60)</b>

# Rates of surgery-related adverse events HIV+ compared to HIV-neg men

	<b>HIV+ men</b> % (N)	<b>HIV-neg men</b> % (N)
<b>Mild</b>	2.8 (16)	3.9 (91)
<b>Moderate</b>	3.6 (13)	3.4 (78)
<b>Severe</b>	0 (0)	0.2 (5)
<b>Total</b>	6.4 (23)	7.5 (174)
	<b>Total # of surgeries = 359</b>	<b>Total # of surgeries = 2328</b>

# Rates of wound healing

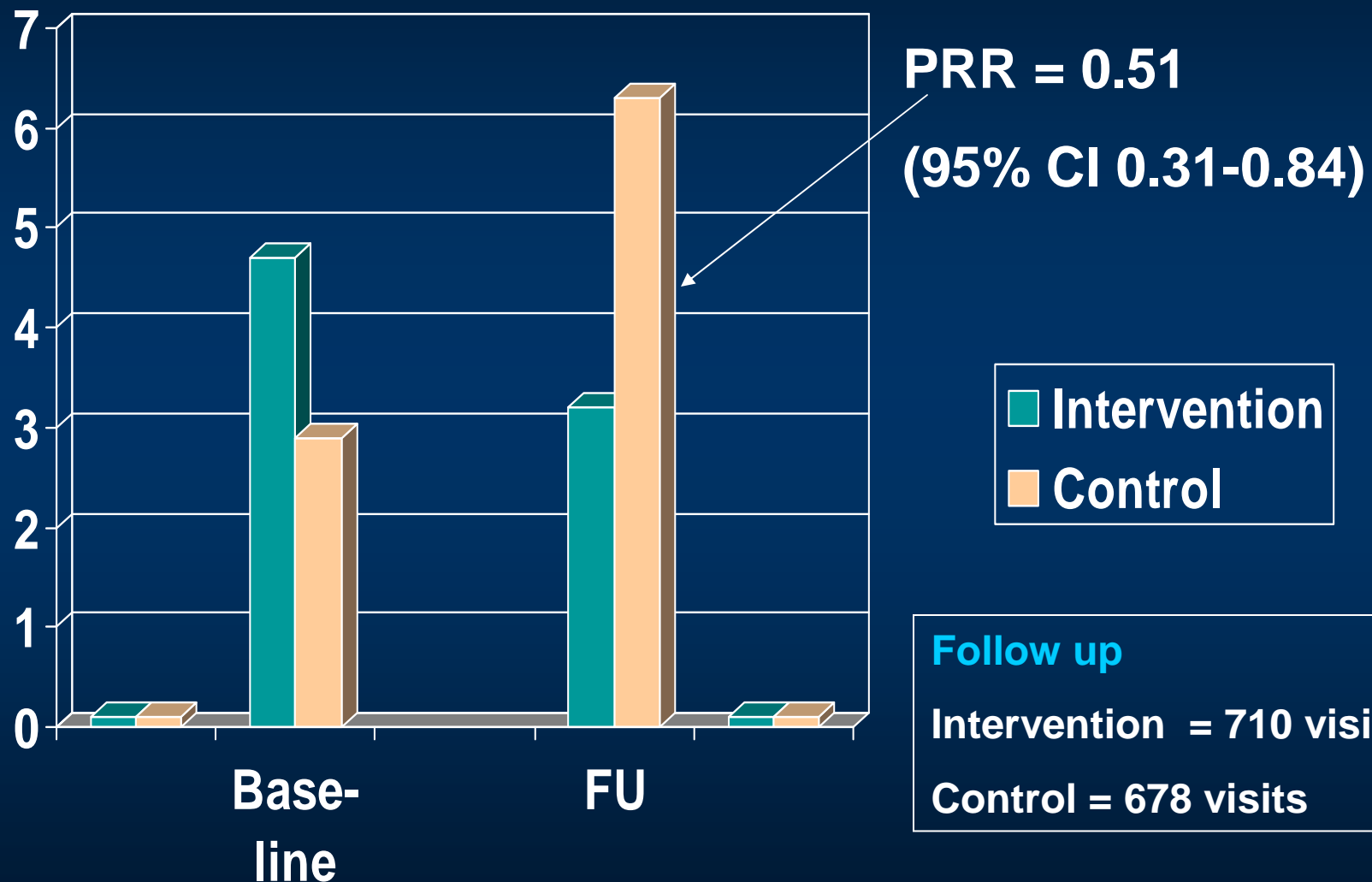
## HIV+ compared to HIV-neg men

Days post op	HIV+ men, Gates trial (% healed by # of days)	HIV-neg men, NIH trial (% healed by # of days)
0-9	0.0	0.1
10-19	0.3	1.1
20-29	70.5	79.6
30+	29.2	19.3
	Total # of surgeries = 420	Total # of surgeries = 2328

# Wound healing and resumption of sex in HIV+ men

	<b>HIV+ circumcisions N = 420</b>
<b>Wounds certified healed by 30 days</b>	<b>71%</b>
<b>% of men who did <u>not</u> resume sex until certified healing</b>	<b>83%</b> <b>(HIV-neg 89%)</b>
<b>Median time from surgery to resumption of sex</b>	<b>43 days</b>

# Current Genital Ulcer Disease (GUD) HIV+ men



HIV+ men enrolled 997

Intervention 497

Control 500

Married 380 (77%)

Married 360 (72%)

Spouse enrolled 302 (79%)

Spouse enrolled 255 (71%)

M+F- Couples 127 (42%)

M+F- Couples 112 (44%)

Concurrent enrol't 94 (74%)

Concurrent enrol't 78 (70%)

Woman has at least 1 FU 70  
(74%)  
(21 have not yet reached 6 mo FU)

Woman has at least 1 FU 54  
(69%)  
(20 have not yet reached 6 mo FU)

**Results in women (preliminary)**  
**Retention rates (among women reaching target follow up date)**

	<b>Intervention arm</b>	<b>Control arm</b>
<b>6 months</b>	<b>98.2%</b>	<b>91.2%</b>
<b>12 months</b>	<b>95.1%</b>	<b>91.1%</b>

## Selected female characteristics (%) by arm

	<b>Intervention (n =70) (%)</b>	<b>Control (%) (n = 54) (%)</b>
<b>Marital status</b>		
<b>Monogamous</b>	<b>80</b>	<b>94</b>
<b>Polygamous</b>	<b>20</b>	<b>4</b>
<b>Alcohol with sex</b>	<b>40</b>	<b>33</b>
<b>&gt;5 coital acts past 30 days</b>	<b>16</b>	<b>30</b>
<b>Condom use past year</b>	<b>17</b>	<b>26</b>
<b>GUD in the past year</b>	<b>13</b>	<b>17</b>

## Selected male partner characteristics (%)

	<b>Intervention (n =64) (%)</b>	<b>Control (%) (n = 54) (%)</b>
<b>Marital status</b>		
<b>Monogamous</b>	<b>81</b>	<b>91</b>
<b>Polygamous</b>	<b>17</b>	<b>9</b>
<b>Alcohol with sex</b>	<b>58</b>	<b>64</b>
<b>HIV viral load &gt; 50,000</b>	<b>33</b>	<b>33</b>
<b>Condom use past year</b>	<b>36</b>	<b>50</b>
<b>GUD in the past year</b>	<b>28</b>	<b>17</b>

## Male-to-female transmission 0-6 months, by arm, and resumption of sex/wound healing

	<b>Intervention arm</b> Sex > 5 days before healing	<b>Intervention arm</b> Sex 5 or <days before healing or after healing	<b>Control arm</b>
<b>N</b>	<b>12</b>	<b>54</b>	<b>46</b>
<b>Number of transmissions</b>	<b>3</b>	<b>5</b>	<b>4</b>
<b>% transmitting</b> <b>Exact 95% CI</b>	<b>25%</b> <b>(5.5-57.2)</b>	<b>9.3%</b> <b>(4.1-22.2)</b>	<b>8.7%</b> <b>(3.9-23.4)</b>

# Preliminary conclusions

- MC in HIV+ men (data available only on ♂ with CD4 >350)
  - Safe wrt surgical AEs, but wound healing slower
  - Reduces symptomatic GUD
- MC in partners of HIV+ men:
  - Transmission may be increased if sex is resumed before full wound healing
  - Longer term effects are not yet known.
- MC in couples:
  - All men (all couples) irrespective of HIV status must be instructed to avoid premature resumption of sex
  - Condom use must be promoted, esp in the first “x” months after surgery
  - ABC remains very important

## WHO Consultation, March 2007

- **Recommendations include:**
- **If male circumcision is requested by HIV+ men following in-depth counseling on the known risks and benefits, it should not be withheld unless it is medically contraindicated.**
- **HIV testing should be recommended for all men seeking male circumcision, but should not be mandatory.**

# Methodological challenges

- In order to avoid stigmatization, study was designed in parallel to RCT of MC in HIV-neg men: complex design and enrolment procedure
- Horizon of ethical concern: in the Rakai setting, not limited solely to HIV-neg men
- Identification of sufficient numbers of couples with HIV+/HIV- partners
- Selection of eligibility criteria for HIV+ men: should trial have had a lower CD4 cut-off?
- DSMB: difficult decision regarding stopping of enrolment

## Rakai: What next?

- **4.5 year follow up of men enrolled in NIH-funded trial has been funded (NIH R01)**  
**Behaviors, HIV incidence, STI incidence/prevalence**
- **MC training center for Uganda (PEPFAR funds)**
- **Gates: proposals for two additional years of FU on HIV+ men and their partners, and on partners of HIV-neg men, is being submitted.**
  - **Long term follow up in the community will be included**