The Long Term Efficacy of Medical Male Circumcision against HIV Acquisition

[1]Supriya D. Mehta, MHS, PhD

[2]Stephen Moses, MD, MPH

[3]Kawango Agot, PhD

[4]Elijah Odoyo-June, MBCHB, MSc

[1]Hong Li, MS

[2]Ian Maclean, PhD

[1]Donald Hedeker, PhD

[1]Robert C. Bailey, PhD, MPH

[1] Division of Epidemiology and Biostatistics, University of Illinois at Chicago School of Public Health, Illinois, USA

[2] Departments of Medical Microbiology, Community Health Sciences and Medicine, University of Manitoba, Winnipeg, Canada

[3] Impact Research & Development Organization, Kisumu, Kenya

[4] Department of Medical Microbiology, University of Manitoba, Winnipeg, Canada

Corresponding Author: Dr. Supriya Mehta, 958 SPHPI M/C 923; 1603 W. Taylor St.; Chicago, IL 60622; phone: (312) 413-7485; fax (312) 996-0064; email: supriyad@uic.edu

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Background: In three randomized trials, medical male circumcision (MMC) reduced HIV acquisition in heterosexual men in sub-Saharan Africa by approximately 60%, after 21-24 months of follow-up. We estimated the 72-month efficacy of MMC against HIV among men retained in the Kisumu randomized trial, where HIV acquisition was reduced by 60% after 24 months.

Methods: From 2002-2005, 2,784 men aged 18-24 were enrolled and randomized 1:1 to immediate circumcision or control. At trial end in December 2006, control men were offered free circumcision. Follow-up continued through September 2010. Cox proportional hazards regression incorporating stabilized inverse probability of treatment and censoring weights generated through marginal structural modeling, was used to account for potential time-varying confounding and censoring to estimate the efficacy of MMC on HIV risk.

Results: The cumulative 72-month HIV incidence was 7.21% [95% CI: 5.98 – 8.68%]: 4.81% among circumcised men, 11.0% among uncircumcised men. The crude hazard ratio (HR) of HIV seroconversion for circumcised vs. uncircumcised men was 0.38 [95% CI: 0.26 – 0.55]. In weight-adjusted Cox regression, the HR was 0.42 [95% CI: 0.26 – 0.66].

Conclusions: The efficacy of MMC was sustained at 58% at 72 months, similar to overall findings of the three trials under conditions of randomization. These findings provide an estimate of the long-term efficacy of circumcision against HIV acquisition. Our results support programmatic scale-up recommendations that are based on assumptions of sustained efficacy.

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Introduction

Three randomized controlled trials (RCTs) show that medical male circumcision (MMC) reduces the risk of HIV acquisition in heterosexual men by approximately 60% over 24 months. [1-3] The World Health Organization (WHO) recommends MMC as an important element of HIV prevention programs. [4] It is estimated that programmatic implementation of adult MMC in several sub-Saharan African countries could in 10 years reduce HIV acquisition in men by at least 60%, with up to a 30-40% reduction in women, potentiating a 40-50% decrease in HIV population prevalence. [5] In Nyanza province, Kenya, 80% MMC uptake over 10 years would result in the female HIV prevalence decreasing from 22% to 10%, and male HIV prevalence decreasing from 17% to 7%.[6] These long-term projections assume a sustained efficacy of circumcision in preventing HIV. The three RCTs were stopped early once efficacy was determined, and participants randomized to the control arm were free to choose circumcision. If men choose to become circumcised differentially, their behavioral risk may mitigate or exaggerate the protective effect of MMC.

We sought to determine the effectiveness of MMC on HIV acquisition over 72-months of follow-up among men participating in the Kisumu trial. If time-varying covariates were associated with the decision to become circumcised and also with risk of HIV acquisition (e.g., condom use, number of sex partners, transactional sex, STI history), then this time-varying confounding would not be adequately addressed by simply adjusting for the time-varying covariates. [7] To address this concern, we evaluated the effectiveness of MMC on HIV risk over extended follow-up using marginal structural models (MSM). [8-9]

Methods

This study was approved by the Institutional Review Boards of the University of Illinois at Chicago, the Kenyatta National Hospital, RTI International, and the University of Manitoba, and was overseen by a Data and Safety Monitoring Board. From 2002-2005, the MMC trial in Kisumu enrolled 2,784 men aged 18-24 years. For inclusion men had to be: uncircumcised, HIV-negative, sexually active in the previous 12 months, and aged 18-24 years; have a hemoglobin > 9.0 gm/dL; and reside in Kisumu District. Exclusion criteria included: foreskin covering less than half of the glans, a bleeding disorder, keloid formation, other conditions that might increase the risks of elective surgery, or a medical indication for circumcision. Participants with sexually transmitted infections (STIs) or other treatable medical conditions were deferred until cured. Trial recruitment, enrollment, reasons for refusing enrollment, and follow-up have been previously described. [1] Following written informed consent, participants were randomized 1:1 to either immediate circumcision or delayed circumcision after a two-year follow-up period (the control group).

Both groups underwent STI and HIV risk reduction counseling and were provided unlimited supplies of free condoms. Detailed evaluations were conducted at baseline, 1 month, 3 months, and every 6 months from randomization for all men. At each visit, participants underwent a standardized medical history and physical examination. For this analysis, genital ulcer disease (GUD) was defined as clinically detected ulcers or self-reported genital ulcers occurring in the past 6 months. For planned visits occurring 6 months from randomization or later, subjects underwent personal interviews to obtain socio-demographic information, measures of sexual behavior and genital hygiene practices, and attitudes towards circumcision. Endorsement of

circumcision was assessed through a series of 5 questions asking who had greater: ease of penile cleanliness; protection against HIV; protection against STIs; sexual pleasure for men; and sexual pleasure for women. Response categories were "circumcised men", "uncircumcised men", "no difference", and "don't know". A response that favored circumcision was assigned one point, and points were summed to create a score ranging from zero to five, generated for each study visit.

HIV Testing

Testing for HIV infection was conducted using a parallel double rapid test protocol, using Determine® HIV 1/2 (Abbott Diagnostic Division, Hoofddorp, The Netherlands), and the Uni-Gold Recombigen™ HIV Test (Trinity Biotech, Wicklow, Ireland). Men who were concordant negative were eligible for the study. Concordant positive results were confirmed by double ELISA, and men were informed of their HIV status and followed-up at the study clinic or referred to the New Nyanza Provincial Hospital. Men with discordant results were followed up with additional tests to determine their HIV status, but were not enrolled. For determination of HIV seroconversion for analysis, positive rapid tests and ELISA test results were confirmed by Health Canada's National HIV Reference Laboratory (Ottawa, Canada) by line immunoassay (INNO-LIA HIV 1/2, Immunogenetics NV, Ghent, Belgium). Specimens indeterminate by line immunoassay were tested by polymerase chain reaction (PCR) at Health Canada or the Fred Hutchinson Cancer Research Center (Seattle, WA, USA), with the PCR result deemed to be definitive.

Sexually Transmitted Infection Testing

STI testing methods have been reported in detail previously. [10] Briefly, men were tested for urogenital infection with *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis* at baseline and each planned 6-month study visit, and at interim visits where symptoms or signs of infection were elicited. Men were tested for HSV-2 serum antibody at baseline and at each planned 6-month study visit.

Study Sample

On recommendation of the data monitoring and safety board, the trial was stopped at the third interim analysis on December 12, 2006. Of the 1,740 men still enrolled and eligible to participatein extended follow-up, 1,545 (89%) provided additional consent to do so. Of the 1,545 men consenting to extended follow-up, 778 (50.4%) were initially randomized to the control group. The follow-up visit schedule and procedures were identical to those of the trial, with scheduled visits every 6 months that included personal interview, physical examination, and STI and HIV testing. Extended follow-up was completed on September 30, 2010, and the remaining cohort was discharged at that time. This analysis excluded three men found to be HIV-infected at baseline after detailed testing and three HIV-uninfected men who were found to be outside the inclusion age range. [1]

Marginal Structural Model Analysis

Marginal structural models reduce the bias introduced by self-selection to become circumcised through application of stabilized weighting at each time point for the time-dependent confounders. The effect of these weights is to create at each time point, a pseudopopulation in which the time-dependent covariates no longer predict HIV seroconversion (i.e. the confounding

effect is removed), and the causal association between circumcision status and HIV risk approximates the original randomized population.[11] The denominator of the weights is the probability that each subject was circumcised at a particular time point, given his past circumcision status, and his baseline and time-varying prognostic factors. The numerator of the weight is the probability that each subject was circumcised at each particular timepoint, conditional on his past circumcision status and baseline covariates. Hernán et al. report that these stabilized inverse-probability-of-treatment-weights (IPTWs) are preferred to the non-stabilized IPTW for more efficient and accurate 95% confidence intervals [CIs].[6] For our marginal structural approach, we generated the above described stabilized IPTW and stabilized inverse-probability-of-censoring-weights (IPCW) to account for time-dependent confounding and loss to follow-up.

To obtain stabilized IPTWs, we fitted a weighted pooled logistic regression model for circumcision using each 6-month study visit as an observation. The weighted logistic model was fitted using generalized estimating equations assuming an exchangeable correlation structure, with robust variance estimation, to account for correlated observations. A similar approach was taken to generate stabilized weights for censoring. Following methods by Hernán et al., the overall weights for subjects were calculated as the product of stabilized treatment and censoring weights.[6] Baseline and time-varying covariates used to estimate treatment and censoring probabilities were selected *a priori* based on a conceptual framework. This approach was taken to avoid the addition of non-confounding variables, which would decrease statistical efficiency, or the addition of too many confounding variables, which could introduce bias.[11] The marginal structural modeling approach does not adjust for time-varying covariates to avoid over-

adjustment, as the stabilized weight already considers the effects of the time-varying covariates. Behavioral and socio-demographic data were not collected at the 1-month and 3-month visit. Therefore, HIV seroconversions occurring at the 1-month (n=3) and 3-month (n=3) study visits were analyzed as occurring at the 6-month visit so that these seroconversions would be included from analysis.

To identify other risks for HIV seroconversion, we used a conventional Cox regression model to show HIV seroconversion risk as a function of circumcision status, conditional on covariates of interest. Circumcision status was analyzed as a time-varying covariate by status (as treated). The assumption of proportionality for Cox proportional hazards was assessed by graphical inspection of Nelson-Aalen curves and by testing for a non-zero slope in a generalized linear regression of the scaled Schoenfeld residuals on functions of time. Standard errors were estimated using a robust variance estimate. Data were analyzed using Stata/SE 11.2 for Windows (Stata Corporation, College Station, Texas).

Results

As previously reported, the control and treatment arms were well-balanced at baseline regarding socio-demographic and behavioral characteristics, STI prevalences, and rates of follow-up (Table 1).[1]

Within 12 months of the end of the trial, 24% of the men randomized to delayed circumcision became circumcised, and by the end of the extended follow-up period, approximately 50% (n=395) had done so (Figure 1). Circumcision was opted for more frequently by men who were

aged 21-24 (vs. 18-20 years) at baseline, those with greater than a primary education, married or cohabiting men, those who lived in Kisumu over follow-up, used condoms at baseline, and had greater endorsement of circumcision at follow-up (Table 2). Circumcision was less likely among men who lived in Kisumu at baseline, had GUD during follow-up, self-reported penile coital injury during follow-up, or had 1 or more sex partners in the past 6 months during follow-up.

Post-trial retention among men consenting to extended follow-up was 84% at 36 months, 72% at 48 months, 68% at 60 months, and 52% at 72 months. Censoring by loss to follow-up was less likely among married/cohabiting men, men who were employed, those who lived in Kisumu at baseline, those with greater endorsement of circumcision over follow-up, those who used condoms over follow-up, and those with 1 or more sex partner in the past 6 months at baseline (Table 2). Men with greater endorsement of circumcision at baseline were more likely to be lost to follow-up.

MMC and HIV Seroconversion

The cumulative 72-month HIV incidence was 7.21% [95% CI: 5.98 – 8.68%]: 4.81% among circumcised men, 11.0% among uncircumcised men (Figure 2). The crude hazard ratio (HR) was 0.38 [95% CI: 0.26 – 0.55] (Table 3). The results of Cox regression incorporating weights from the marginal structural model (Table 3) indicates the protective efficacy of MMC against HIV seroconversion was 58% [HR=0.42; 95% CI: 0.26 – 0.66] over 6 years of observation.

A traditional multivariable Cox regression model adjusted for all other variables significant at the $p<0.05$ level demonstrated a 55% protective effect of MMC against HIV acquisition

[adjusted HR = 0.45; 95% CI: 0.30-0.65]. Other factors associated with HIV seroconversion included HSV-2 infection [aHR=2.25; 95% CI: 1.54-3.28], genital ulcer disease [aHR=3.55; 95% CI: 1.70-7.40], infection with *N. gonorrhoeae* [aHR=2.91; 95% CI: 1.33-6.39], and self-reported scratches, cuts, abrasions or bleeding of the penile skin after sex [aHR=1.68; 95% CI: 1.14-2.48]. Condom use at last sexual intercourse was associated with reduced risk of HIV seroconversion by 42% [aHR=0.58; 95% CI: 0.39-0.84]. Variables that were significant risks for HIV seroconversion ($p<0.05$ level) in univariate analysis but not in multivariable analysis included: increasing number of sex partners in the past 6 months or past 12 months; and cleaning penis more than 1 hour after sexual intercourse. Condom use at last sex violated the proportional hazards assumption. Inclusion of an interaction term for condom use by time period (before or after the end of the trial) produced a main effects measure of aHR=0.38 [95% CI: 0.22-0.65] for condom use at last sex, with an HR=2.25 [95% CI: 1.06 – 4.77] for the interaction with time. Inclusion of the interaction term did not alter the magnitude or significance of other terms in the model [aHR for circumcision: 0.44; 95% CI: 0.30 – 0.65].

Discussion

Accounting for differences in who becomes circumcised and who is lost to follow-up, the protective effect of MMC was maintained at 58% over 6 years of observation, virtually the same as the 58% protective effect observed under trial conditions.[1] Our results show that the protective efficacy does not wane at up to 6 years. Programmatic implementation and scale-up of voluntary MMC services in sub-Saharan Africa is relatively recent, beginning largely in 2008.[12] Because long-term follow-up of circumcised men with an appropriate comparison group of uncircumcised men is generally not feasible in programmatic implementation, surveillance of programmatic

effectiveness over time will need to rely on regular cross-sectional surveillance of men's circumcision status and HIV status. Thus assessment of the long-term effectiveness of MMC is currently limited to data collected through post-trial surveillance. Our results showing long-term protective efficacy of MMC against HIV support the assumptions of studies modeling the population impact of MMC on HIV, and the recommendations for scale-up that are based in part on these model assumptions.[5-6,13-15]

In post-trial surveillance of men initially enrolled in the control arm of the Ugandan MMC trial, the protective effect of circumcision against HIV was 67%,[16] somewhat stronger than the 57% protective effect of MMC against HIV seroconversion observed in the intention-to-treat analysis under their trial conditions.[2] Although Gray et al. found no differences in sociodemographic or behavioral risks between control arm men who chose circumcision and those who did not, comparisons were restricted to the last visit under randomization, and the authors acknowledge that there may have been unmeasured higher risk among men who chose to remain uncircumcised.[16] Their multivariable analysis adjusted for confounders as time-varying covariates, but did not account for the potential of time-varying confounding associated with choosing circumcision or being lost to follow-up.

In post-trial follow-up, circumcision uptake was approximately 50% among men initially randomized to control in our trial, which may indicate significant selection bias, and is significantly less than the 78% circumcision uptake among Rakai trial participants.[16] Reasons for the disparity in uptake in MMC between the two trial populations may have been due to differences: in age (men enrolled in the Rakai trial were ages 15-49 years), factors affecting

decision to become circumcised, messages or delivery of promotion of MMC following the trial. Men opting for MMC may be a mixture of potentially lower risk and higher risk men. We found that control men with potentially lower risk for HIV (at baseline used condoms, were married or cohabiting, were not sexually active) were more likely to choose circumcision during post-trial follow-up, although men with more sex partners over follow-up were more likely to become circumcised.. Unsurprisingly, greater endorsement of circumcision over follow-up was associated with greater likelihood of becoming circumcised. The WHO/UNAIDS implementation guidance for rapid MMC scale-up recommends that voluntary MMC programs understand reasons for seeking circumcision (situational analysis) and assessment of behavior and practices related to HIV (monitoring and evaluation), so that additional services may be incorporated as needed.[17] Results of our analyses determined specific sexual risk behaviors were associated with choosing circumcision. This highlights the importance of routine HIV testing, counseling to promote protective behaviors, reinforcing that MMC does not reduce HIV risk completely, and syndromic STI screening and treatment, as essential components of voluntary MMC programmatic scale-up. Moreover, while Kenya is over 50% of the way towards reaching the 80% male circumcision target needed to achieve desired population level reductions in HIV prevalence,[12] these results provide insight for advocacy and education that could lead to greater circumcision endorsement to increase service uptake.

In our conventional multivariable Cox regression model, risks for HIV seroconversion were primarily STIs (HSV-2 infection, genital ulcer disease, and urogenital gonococcal infection), highlighting the need for screening and treatment. Similar to results of our 24-month analysis,[18] both HSV-2 infection [aHR=2·26] and GUD [aHR=3·59] were strong, independent risks for HIV

seroconversion, suggesting HSV-2 and GUD have different mechanisms of increased HIV risk. Approximately 60% of clinically detected GUD in our trial was not associated with HSV-2, chancroid or syphilis by PCR and serology.[19] Rather, pyrosequencing of clinically detected genital ulcers demonstrated that such non-STI GUD was associated with specific anaerobic bacteria that have cytotoxic and tissue destructive properties. The extent to which increased risk of HIV acquisition is a function of dermal compromise and/or inflammation may differ between HSV-2 infection and GUD. The increased risk of HIV acquisition associated with HSV-2 may also reflect differential infectivity of the two viruses when exposed to a co-infected partner, and studies involving discordant couples could assess this. Additionally, controlling for HSV-2 serostatus and GUD, self-reported penile epithelial trauma nearly doubled the risk of HIV seroconversion. From our previous analysis, uncircumcised men are more likely to have epithelial disruptions of the penile skin, which are likely to be mechanical in origin.[20] We previously hypothesized this could represent misclassification of HSV-2 or GUD, but results of this analysis and our previous analyses suggest otherwise.[18-20] Further study characterizing this potential dermal compromise and mechanisms of increased HIV risk are needed, as genital mucosal trauma was commonly reported among men in our cohort,[18] and in other populations in sub-Saharan Africa.[21-22]

Limitations

One of the assumptions of marginal structural models, exchangeability – or the assumption of no measured confounding – cannot be empirically verified[11]. To address this assumption, we attempted to model a sufficient number of joint predictors of becoming circumcised and HIV seroconversion, while balancing this against introduction of too many predictors, which may

result in non-positivity. As reported by Cole and Hernán, estimated weights that are not mean centered or have wide range are indicative of non-positivity or misspecification.[11] Our weights were mean centered with a narrow range of minimums and maximums for both censoring and treatment. To the extent possible, our models were developed to minimize unmeasured confounding, non-positivity, and misspecification. The application of marginal structural modeling provides confidence in the causal interpretation of the data.

Post-trial retention among men consenting to extended follow-up was high, and while we accounted for the effect of differential circumcision and loss to follow-up, this still affects the generalizability of our findings. Moreover, this analysis reflects men enrolled in a long-term cohort, with counseling on sexual behavioral risk reduction and testing and treatment of STIs every six months.

Conclusion

The efficacy of MMC was sustained at 58% at 6 years of follow-up, similar to findings of the three trials under conditions of randomization at 24 months of follow-up. These findings provide an estimate of the long-term efficacy of medical male circumcision against HIV acquisition.

Author Contributions:

Study concept and design: Bailey, Moses

Acquisition of data: Agot, Bailey, Maclean, Moses, Odoyo-June

Drafting of the manuscript: Mehta

Critical revision of the manuscript for important intellectual content: Agot, Bailey, Hedeker, Li, Maclean, Mehta, Moses, Odoyo-June

Statistical analysis: Hedeker, Li, Mehta

Analysis and interpretation of data: Bailey, Hedeker, Li, Mehta

Obtained funding: Bailey, Moses

Administrative, technical, or material support: Agot, Bailey, Mehta, Moses, Odoyo-June

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Table 1. Selected Baseline Sociodemographic Characteristics and Behaviors by Treatment Assignment.

Characteristic[1]	Circumcision Group, N=1386 n (%)	Control Group, N=1389 n (%)
Reported age in years		
18-20	710 (51.2)	705 (50.7)
21-24	678 (48.8)	685 (49.3)
Marital status		
Not married or living with a female sex partner	1294 (93.5)	1288 (93.1)
Married or living with a female sex partner	90 (6.5)	95 (6.9)
Number of sex partners in the past 30 days		
0	597 (43.0)	626 (45.2)
1	552 (39.8)	547 (39.5)
2 or more	238 (17.2)	213 (15.4)
Number of sex partners in the past 6 months		
0	192 (13.8)	191 (13.8)
1	609 (44.0)	616 (44.4)
2 or more	584 (42.2)	579 (41.8)
Used a condom the last time you had sexual intercourse		
No	703 (50.7)	734 (53.0)
Yes	684 (49.3)	652 (47.0)
How many hours until you washed your penis after the last time you had sex?		
< 1 hour	305 (22.2)	288 (20.9)
$\geq$ 1 hour	1071 (77.8)	1089 (79.1)
Median (range) score: endorsement of circumcision	3 (0 – 5)	3 (0 – 5)
Self-reported scratches, cuts, abrasions, or bleeding of skin of penis after sex in the past 6 months		
No	685 (49.5)	696 (50.3)
Yes	700 (50.5)	687 (49.7)
Painless or painful genital ulcer in past 6 months or currently (by report), or ulcer on exam		
No	1326 (95.7)	1339 (96.4)
Yes	60 (4.3)	50 (3.6)
HSV-2 Status at Baseline		
Seronegative	1001 (72.2)	1043 (75.0)
Seropositive	387 (27.9)	347 (25.0)
Non-ulcerative sexually transmitted infection		
N. gonorrhoeae	32 (2.3)	25 (1.8)
C. Trachomatis	72 (5.2)	55 (4.0)
T. vaginalis	27 (2.0)	31 (2.2)
Infection with NG, CT, and/or TV	118 (8.5)	97 (7.0)

[1/] Sample sizes vary slightly by characteristic due to a few missing responses.

Figure 1. Circumcision Status Among Men Originally Randomized to Control: Proportion of Men Circumcised by Study Visit.

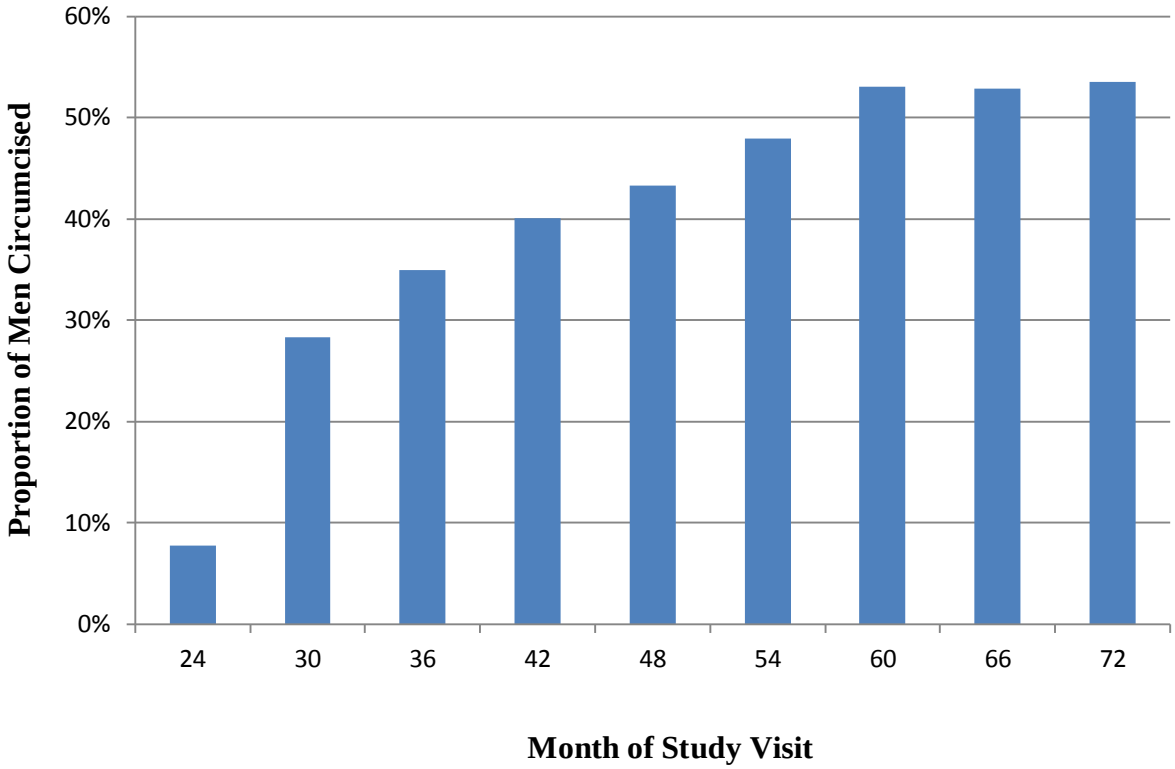

Table 2. Results of Logistic Regression Models to Generate Weights for Treatment and Censoring[*].

Variables	Treatment, OR (95% CI)	Censoring, OR (95% CI)
Baseline covariates		
Age 21-24 years (vs. 18-20 years)	1.19 (1.03 – 1.36)	1.07 (0.96 – 1.19)
Highest completed educational attainment		
None, primary 1 – 8	ref	ref
Some secondary	1.39 (1.15 – 1.68)	0.96 (0.83 – 1.12)
Secondary or higher	1.41 (1.19 – 1.67)	1.08 (0.95 – 1.23)
Married or cohabiting (vs. not married and not cohabiting)	1.56 (1.19 – 2.06)	1.09 (0.87 – 1.38)
Resides in Kisumu District (vs. other district)	0.76 (0.55 – 1.04)	0.72 (0.55 – 0.93)
Income source		
None	ref	ref
Self-employed	1.05 (0.83 – 1.33)	1.00 (0.83 – 1.19)
Salaried	1.02 (0.81 – 1.29)	0.97 (0.82 – 1.16)
Condom used at last intercourse (Yes vs. No)	1.37 (1.20 – 1.57)	0.93 (0.83 – 1.04)
Number of sex partners in past 6 months		
None	ref	ref
One	0.78 (0.63 – 0.98)	0.83 (0.71 – 0.98)
Two or more	0.81 (0.65 – 1.02)	0.76 (0.65 – 0.90)
Endorsement of circumcision	0.98 (0.94 – 1.02)	1.06 (1.02 – 1.09)
HSV-2 seropositive	0.90 (0.72 – 1.11)	1.15 (0.95 – 1.38)
Self-reported or clinically detected GUD	0.93 (0.61 – 1.44)	1.11 (0.85 – 1.46)
Urogenital infection with *N. gonorrhoeae*, *C. trachomatis*, or *T. vaginalis*	1.27 (0.95 – 1.71)	1.00 (0.80 – 1.25)
Self-reported scratches, cuts, abrasions, bleeding of skin of penis after sexual intercourse, occurring in the past 6 months	0.97 (0.84 – 1.11)	0.99 (0.89 – 1.10)
Time-varying covariates		
Circumcised		0.98 (0.87 – 1.09)
Married or cohabiting (vs. not married and not cohabiting)	0.91 (0.76 – 1.08)	0.76 (0.66 – 0.87)
Resides in Kisumu District (vs. other district)	1.30 (0.95 – 1.78)	0.99 (0.77 – 1.28)
Income source		
None	ref	ref
Self-employed	0.89 (0.75 – 1.05)	0.78 (0.68 – 0.88)
Salaried	1.14 (0.92 – 1.40)	0.85 (0.73 – 0.99)
Condom used at last intercourse (Yes vs. No)	0.94 (0.80 – 1.10)	0.86 (0.76 – 0.97)
Number of sex partners in past 6 months		
None	ref	ref
One	1.42 (1.12 – 1.79)	1.04 (0.87 – 1.23)
Two or more	1.52 (1.19 – 1.95)	1.04 (0.87 – 1.25)
Endorsement of circumcision	1.38 (1.32 – 1.44)	0.92 (0.89 – 0.96)
HSV-2 seropositive	1.05 (0.88 – 1.27)	0.89 (0.75 – 1.05)

Self-reported or clinically detected GUD	0.50 (0.25 – 1.00)	1.06 (0.70 – 1.61)
Urogenital infection with *N. gonorrhoeae*, *C. trachomatis*, or *T. vaginalis*	1.16 (0.85 – 1.59)	1.06 (0.83 – 1.36)
Self-reported scratches, cuts, abrasions, bleeding of skin of penis after sexual intercourse, occurring in the past 6 months	0.55 (0.46 – 0.66)	1.05 (0.92 – 1.20)

* Models presented are the denominators for the stabilized weights: pooled logistic regression models for circumcision and for censoring.

OR = Odds ratio; CI = Confidence Interval
HSV-2 = Herpes Simplex Virus Type 2
GUD = Genital ulcer disease

Figure 2. Cumulative HIV seroincidence across follow-up visits by circumcision status.

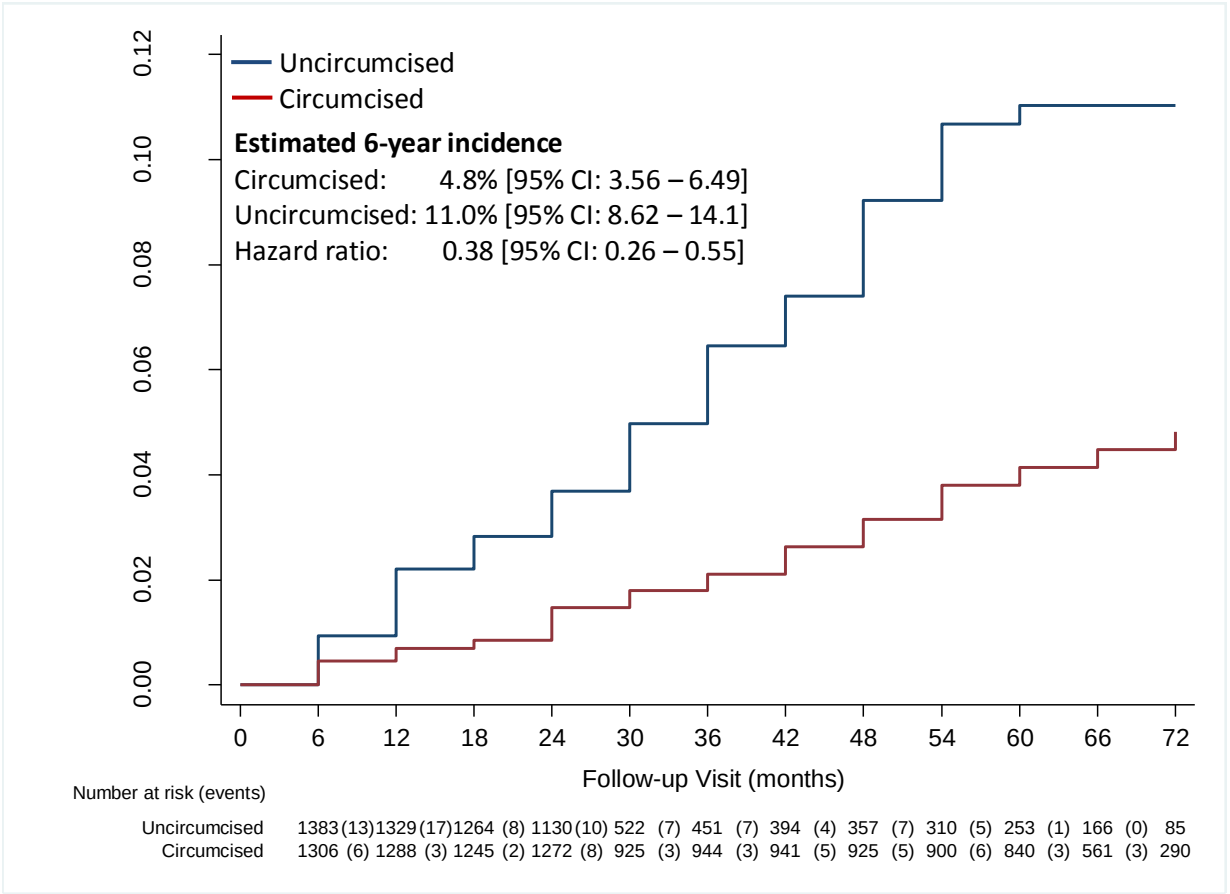

Table 3. Male Circumcision Status and Risk of HIV Seroconversion.

Variables	Conventional Cox Model Unadjusted HR [95% CI]	Cox Regression with Weights from Marginal Structural Modeling[§] HR [95% CI]	Conventional Cox Model Adjusted for Time-Varying Factors^ HR [95% CI]
Circumcised	0.38 [0.26 – 0.55]	0.42 [0.26 – 0.66]	0.45 [0.30 – 0.65]
Aged 21-24 at baseline (vs. 18-20)			0.69 [0.47 – 0.99]
HSV-2 seropositive			2.26 [1.55 – 3.29]
Self-reported* or clinically detected GUD			3.59 [1.72 – 7.49]
Infection with *N. gonorrhoeae*			2.99 [1.36 – 6.54]
Skin of penis ever gets scratches or bleeds during or after sex*			1.69 [1.14 – 2.49]
Used a condom at last vaginal intercourse			0.56 [0.38 – 0.81]

"HR" = Hazard Ratio; "CI" = Confidence Interval

HSV-2 = Herpes Simplex Virus Type 2; GUD = Genital ulcer disease

[§]Weighted marginal structural model is adjusted for month of visit (5-knot cubic spline with knots at the 5^{th}, 27.5^{th}, 50^{th}, 72.5^{th}, and 95^{th} percentile).

^All covariates are time-varying except for age at baseline.

* Recall period is past 6 months