Circumcision and Risk of Sexually Transmissible Infections in a Community-Based Cohort of HIV-Negative Homosexual Men in Sydney, Australia

David J. Templeton,1,3 Fengyi Jin,1 Garrett P. Prestage,1 Basil Donovan,1,4 John C. Imrie,2 Susan C. Kippax,2 Phillip H. Cunningham,5 John M. Kaldor,7 Adrian Mindel,6 Anthony L. Cunningham,7 and Andrew E. Grulich1

1National Centre in HIV Epidemiology and Clinical Research and 2National Centre in HIV Social Research, University of New South Wales, 3RPA Sexual Health Clinic, Royal Prince Alfred Hospital, and 4Sydney Sexual Health Centre, Westmead Hospital and University of Sydney, 5Centre for Immunology, St Vincent’s Hospital, Darlinghurst, ¦Sexually Transmitted Infections Research Centre, Westmead Hospital and University of Sydney, and 7Westmead Millennium Institute, Centre for Virus Research, Westmead Hospital, Westmead, Australia

Background. Circumcision status was examined as an independent risk factor for sexually transmissible infections (STIs) in the Health in Men cohort of homosexual men in Sydney.

Methods. From 2001 through 2004, 1427 initially human immunodeficiency virus (HIV)–negative men were enrolled and followed up until mid-2007. All participants were offered annual STI testing. The history of STIs was collected at baseline, and information on sexual risk behaviors was collected every 6 months. At annual face-to-face visits, participants reported STI diagnoses received during the previous year.

Results. Circumcision was not associated with prevalent or incident herpes simplex virus 1, herpes simplex virus 2, or self-reported genital warts. There was also no independent association of circumcision with incident urethral gonorrhea or chlamydia. Being circumcised was associated with a significantly reduced risk of incident syphilis (hazard ratio, 0.35 [95% confidence interval, 0.15–0.84]) but not prevalent (odds ratio, 0.71 [95% confidence interval, 0.35–1.44]) syphilis. The association was somewhat stronger among men who reported predominantly insertive unprotected anal intercourse (hazard ratio, 0.10 [95% confidence interval, 0.01–0.82]).

Conclusions. These are the first prospective data obtained from homosexual men to assess circumcision status as a risk factor for STIs. Circumcised men were at reduced risk of incident syphilis but no other prevalent or incident STIs. Circumcision is unlikely to have a substantial public health impact in reducing acquisition of most STIs in homosexual men.

Men who have sex with men (MSM) bear a disproportionate burden of sexually transmissible infections (STIs) in resource-rich countries. A substantial decrease in rates of many STIs occurred in MSM soon after human immunodeficiency virus (HIV)/AIDS was recognized, but many countries have witnessed a resurgence of STIs among this population [1]. Conventional methods of STI control are clearly failing to control the STI epidemic among MSM, and novel strategies to reduce STI transmission require investigation.

Observational evidence among heterosexual men suggests that circumcision may reduce the risk of syphilis, chancroid, and possibly herpes simplex virus (HSV) type 2 [2]. Recently published data from randomized trials in Africa have demonstrated that circumcised
heterosexual men are at reduced risk of HSV-2 acquisition [3, 4] but not syphilis infection [3]. Compared with uncircumcised men, circumcision also resulted in a lower prevalence of high-risk penile human papilloma virus (HPV) [3, 5] but had no impact on the incidence [6] or prevalence [7] of urethral gonorrhea or chlamydia. Because the range of sexual behaviors of homosexual men is substantially different from those of heterosexual men, it is likely that these results cannot be generalized to homosexual men.

The small number of studies performed among MSM, none of which was prospective, have demonstrated little impact of circumcision on selected STIs [8–10] or STIs overall [11]. The association of circumcision status and STIs was assessed in the community-based Health in Men (HIM) cohort of HIV-negative homosexual men in Sydney, in which the incidence and other risk factors for a wide range of anogenital STIs had already been well characterized [12–15].

METHODS

Participants

Study participants were men who were recruited from a range of community-based sources from June 2001 through December 2004 and followed up through June 2007. Details of recruitment sources and methods of the HIM study have been described elsewhere [15]. Briefly, men eligible for participation in the HIM study met the following criteria: (1) they reported having sex with men in the 5 years before enrollment, (2) they lived in Sydney and/or participated in its gay community, and (3) they tested negative for HIV infection at baseline. Signed, informed consent was obtained from all participants. Ethics approval was granted by the University of New South Wales.

Data Collection

All participants underwent annual face-to-face interviews, with 6-monthly telephone interviews between these visits. Detailed behavioral data were collected every 6 months, including number and position (insertive or receptive) of unprotected anal intercourse (UAI) acts. In addition, each year participants reported their preference for anal intercourse position (preference for insertive or receptive role or no preference). At the annual face-to-face interviews, participants were asked to report whether they had received diagnoses of anogenital gonorrhea, chlamydia, or warts in the past 12 months. They were also asked at the baseline interview whether they had ever received a diagnosis of anogenital warts. As part of the study design, participants were offered annual testing for STIs at the time of the face-to-face interview. Circumcision status was reported by participants at baseline. Self-report was validated by clinical examination in a subgroup of 237 participants and correlated with examination findings in 98% of cases [16].

Laboratory Studies

Detailed information on specimen collection and laboratory diagnostic methods have been published elsewhere [12–15, 17] and are briefly summarized below.

Neisseria gonorrhoeae and Chlamydia trachomatis. Nucleic acid amplification tests (NAATs) for N. gonorrhoeae and C. trachomatis were introduced to the HIM study in January 2003. Consenting participants collected first-void urine and self-obtained anal swab samples annually for NAATs by the BD ProbeTec assay (BD Diagnostics). For anal N. gonorrhoeae diagnosis, all positive ProbeTec results underwent supplementary porA testing. The full methods of this supplementary testing have been described in detail elsewhere [17]. Only porA-positive samples were included as true anal N. gonorrhoeae infections in the analyses.

Syphilis. Consenting participants were screened annually for syphilis by enzyme immunoassay (ICE Syphilis; Murex Biotech). Positive assay results were confirmed with the Treponema pallidum particle agglutination assay and fluorescent treponemal antibody absorption test. The rapid plasma reagin test was used to assist clinical staging and to detect reinfection.

HSV. Baseline serum samples and sequential specimens were tested for antibody to HSV, with use of an algorithm involving the Enzygnost anti-HSV IgG enzyme-linked immunosorbent assay (ELISA) (Behring), and type-specific ELISAs (HerpeSelect 1 and 2 ELISA IgG; Focus Technologies) [15]. Equivocal results were resolved by Western blot analysis.

Anogenital warts. No HPV tests or routine anogenital examinations for warts were performed in the HIM study. Participants self-reported a lifetime history of genital or anal warts at baseline and reported annually whether anogenital warts had been diagnosed since the last face-to-face interview [12].

Incidence Definition

For each STI, incidence was expressed as the number of incident cases per 100 person-years.

N. gonorrhoeae and C. trachomatis. To be able to estimate the incidence of urethral and anal N. gonorrhoeae more comprehensively, participants who reported a diagnosis of urethral or anal N. gonorrhoeae or C. trachomatis or tested positive for such infection at their HIM study visit were treated as having incident cases. Because the NAATs were added to the study in January 2003, this calculation was applicable only from 2003 forward [14].

Syphilis. Incident syphilis was defined as syphilis seroconversion or reinfection during the study period. Reinfection was defined as a 4-fold increase in rapid plasma reagin titer on sequential serum specimens collected at annual visits.

HSV. Incident HSV-1 and HSV-2 infections were defined as HSV-1 and/or HSV-2 seroconversion during the study.

Anogenital warts. For genital and anal warts, prevalent in-
fection was defined as a self-reported lifetime diagnosis of warts at the baseline interview. Incident warts were defined as self-reported diagnoses of anogenital warts during the previous 12-month period.

**Statistical Analysis**

Statistical analyses were performed using Stata software (version 10.0; StataCorp). Participants’ preference for anal intercourse position was correlated with reported UAI behavior (Table 1). Because the data for number of UAI acts were highly skewed, the median was used as the measure of central tendency. The exact binomial method was used to calculate 95% confidence intervals (CIs) for prevalence and incidence values. Crude and adjusted analyses were performed to identify the association of circumcision status with prevalent and incident urethral N. gonorrhoeae, urethral C. trachomatis, syphilis, HSV-1, HSV-2, and anogenital warts. Odds ratios (for prevalent infection) and hazard ratios (for incident infection) and their corresponding 95% CIs were calculated for these associations.

For analyses of the entire cohort, multivariate logistic regression (for prevalent infections) (Table 2) and Cox regression (for incident infections) (Table 3) models included sexual behavioral variables found to be associated with prevalent and incident infections in other HIM study analyses of anogenital N. gonorrhoeae and C. trachomatis [14], syphilis [13], HSV [15], and anogenital warts [12]. Covariates were entered in the multivariate model if they were found to be independent predictors of each STI in these other analyses and are outlined in the footnotes of Tables 2 and 3.

For analyses of participants predominantly practicing the insertive role in anal intercourse, the multivariate Cox regression model (Table 4) included the total number of insertive UAI acts in the past 6 months. Circumcision status and age were a priori covariates in each multivariate model. To avoid the possibility of residual confounding, age was analyzed as a continuous variable because of the strong independent association of age with circumcision status in the HIM study [18] and the association of age with urethral N gonorrhoeae and C. trachomatis infections [14], genital warts [12], and HSV-1 infection [15]. Of other demographic variables associated with circumcision status in the HIM cohort [18], neither country of birth nor ethnicity was associated with any prevalent or incident STI, so these variables were not included as covariates in the multivariate models.

Multiple failures in the subsequent interview(s) were allowed only for incidence calculations involving gonorrhea, chlamydia, and syphilis. For incidence risk factor analyses of these STIs, mixed models were used that allowed for repeated measures in the same individuals. These models, which allow for within- and between-subject variability, provide robust variance estimates and, therefore, appropriate P values and CIs [19].

Participants’ own circumcision status would have had no plausible effect on their STI acquisition via receptive anal sex. We examined circumcision as a risk factor for anal gonorrhea, chlamydia, and warts, only to contrast these findings with the same infections at genital sites.

**RESULTS**

From June 2001 through December 2004, a total of 1427 participants were enrolled. The median age at enrollment was 35 years (range, 18–75 years); 68% of participants were Australian born, 74% were of Anglo ethnicity, and 95% of participants self-identified as gay or homosexual. One participant who reported a surgically reconstructed foreskin was excluded, so analyses of circumcision status and risk of STIs were based on 1426 participants.

By the end of the HIM study in June 2007, the total follow-up time was 5160.7 person-years, and the median follow-up time for participants was 3.9 years. The follow-up time from commencement of gonorrhea and chlamydia NAATs in January 2003 to the end of the HIM study in June 2007 was 3781.5 person-years. The uptake of N. gonorrhoeae and C. trachomatis anal and urine testing was high; a total of 4090 NAATs (90.2% of eligible visits) were performed during this period. All participants consented to HSV and syphilis serological testing. The proportion of circumcised participants among those unavailable for follow-up was very similar to the proportion of circumcised participants in the entire cohort at baseline (65.4% vs 65.8%; P = .879).

**Circumcision status and prevalent STIs.** Results of anal-

### Table 1. Correlation of Reported Preference of Anal Intercourse Position with Anal Intercourse Behavior among Participants Reporting Any Unprotected Anal Intercourse (UAI) in the Health in Men Study

<table>
<thead>
<tr>
<th>Measure</th>
<th>Insertive UAI</th>
<th>Receptive UAI</th>
<th>P</th>
<th>No preference (2120.1 PY)</th>
<th>Insertive UAI</th>
<th>Receptive UAI</th>
<th>P</th>
<th>Insertive UAI</th>
<th>Receptive UAI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acts in past 6 months,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median no (IQR)</td>
<td>5.29 (0.35–21.58)</td>
<td>0 (0–1.48)</td>
<td>&lt;.001</td>
<td>5.44 (0.80–23.0)</td>
<td>5 (0.32–21.63)</td>
<td>.118</td>
<td></td>
<td>1 (0–6.67)</td>
<td>7 (0.33–27.73)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Acts in past 6 months,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median % (IQR)</td>
<td>98.4 (84.1–100)</td>
<td>1.6 (0–15.9)</td>
<td>&lt;.001</td>
<td>51.3 (39.5–68.0)</td>
<td>48.7 (32.0–60.5)</td>
<td>.025</td>
<td></td>
<td>14.6 (0.2–35.0)</td>
<td>85.4 (65.0–99.8)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**NOTE:** IQR, interquartile range; PY, person-years of follow-up. P values determined with Wilcoxon signed rank test.
yses of the association of circumcision status and prevalent (baseline) STIs are shown in Table 2. There was no univariate or multivariate association of circumcision status with syphilis, HSV-1, or HSV-2 seropositivity at baseline, nor any univariate or multivariate association of circumcision status with a lifetime history of genital or anal warts.

**Circumcision status and incident STIs.** The association of circumcision status with incident STIs in the HIM cohort is shown in Table 3. Circumcised participants were at reduced risk of acquiring syphilis during the study period after results were controlled for age, number of male sexual partners, and number of receptive UAI acts with HIV-positive partners or partners of unknown HIV status (HR, 0.35; 95% CI, 0.15–0.84, \(P = .019\)). Circumcision status was not associated with any other incident STI in univariate or multivariate analyses. Comparison of analyses of genital and anal STIs revealed little difference in HRs for incident warts, gonorrhea, and chlamydia.

Only 10.1% of total person-years of follow-up were among men who exclusively practiced insertive, but not receptive, UAI. However, 33.1% of total person-years of follow-up were among participants who reported a preference for the insertive role in anal intercourse and whose sexual behavior closely reflected this preference (Table 1). Among these 404 participants, the protective effect of circumcision on incident syphilis infection remained despite only 6 incident infections in this subgroup (HR, 0.10; 95% CI, 0.01–0.82; \(P = .033\)) (Table 4). There was no association of circumcision status with any other STI in men who predominantly practiced the insertive role in UAI.

**DISCUSSION**

Circumcised participants in the HIM cohort were at significantly reduced risk of incident syphilis infection, although there was no association of circumcision with baseline syphilis seropositivity. Circumcision was not associated with prevalent or incident urethral gonorrhea or chlamydia, HSV, or genital warts.

Only 3 other published studies, all cross-sectional, have examined the relationship between circumcision and specific STIs in homosexual men [8–10]. The first was a study of almost 900 MSM attending an STI clinic in the United States [9], which found no univariate association of being circumcised with prevalent urethral gonorrhea or chlamydia. The second was a small study of mostly uncircumcised Peruvian MSM, quoted in a subsequent meta-analysis [2, 10], in which there was no independent association of circumcision with prevalent syphilis infection among either HIV-positive or HIV-negative MSM [8]. A recent meta-analysis that included some unpublished data also found no overall association of circumcision status with STIs among MSM [11]. Although other published studies of circumcision and STI risk have included MSM, results were not presented separately for this subgroup [20–24].

Of the STIs considered in the HIM study, the published evidence for a protective association with circumcision is strongest for syphilis. However, the majority of other observational studies have been cross-sectional studies of heterosexual men...
in developing countries. Most have found circumcised men to have lower odds of syphilis infection [2]. Recent data from a randomized trial among heterosexual men in Rakai, Uganda, found no effect of circumcision on incident syphilis [3]. However, this finding may have resulted from lack of power attributable to the small number of syphilis infections identified at follow-up testing [25]. Although the adjusted odds ratio for prevalent syphilis in the HIM cohort was 0.71, lower than that of the other prevalent STIs examined (Table 1), it was not statistically significant. Syphilis was very common among Australian homosexual men in the 1970s, but was virtually eliminated during the late 1980s and 1990s [26]. One possible explanation for an association with incident but not prevalent syphilis is that participants who initiated MSM sexual activity during the late 1980s and 1990s would have been at very low risk of acquiring syphilis irrespective of their sexual behavior or circumcision status. Only recently, since 2001, has syphilis reemerged among Australian MSM [13].

Recent publications have described a reduction in HSV-2 risk among circumcised heterosexual men in 2 of the African circumcision trials [3, 4]. We observed no such association of circumcision with incident HSV-2 infection in the HIM cohort, and ours is the first study to assess the association among homosexual men.

In the HIM study, as in most longitudinal studies, HSV and syphilis were diagnosed serologically, and the anatomical site of acquisition was not known [27, 28]. The initial site of infection may have been oral or anal, for which, a man’s own circumcision status could have no plausible protective effect. Should circumcised homosexual men be at reduced risk of genital acquisition of both of these infections, the lack of data on site-specific diagnosis could, in part, explain the lack of association with circumcision in homosexual men.

No reduction in incidence of urethral gonorrhea or chlamydia was observed among circumcised participants in the HIM study. Circumcision had no influence on prevalent or incident urethral gonorrhea or chlamydia in 2 of the African heterosexual circumcision trials [6, 7]. Likewise, the only published study involving MSM [9] found no association of circumcision status with urethral gonorrhea or chlamydia among STI clinic attendees. These findings suggest that circumcision has little impact on acquisition of these urethral bacterial infections.

Data on the association of circumcision status and clinically apparent genital warts among heterosexual men are conflicting [9, 21, 23, 29–33]. Although a lower prevalence of polymerase chain reaction–based diagnoses of high-risk HPV was recently reported among circumcised heterosexual men in 2 circumcision trials [3, 5], observational data are inconsistent regarding

Table 3. Circumcision Status and Incident Sexually Transmissible Infections (STIs) in the Health in Men Cohort

<table>
<thead>
<tr>
<th>STIa</th>
<th>No of incident cases</th>
<th>Circumcised</th>
<th>Uncircumcised</th>
<th>Univariate modeb</th>
<th>Multivariate modéc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Genital warts</td>
<td>39</td>
<td>0.89</td>
<td>1.20</td>
<td>0.74 (0.39–1.41)</td>
<td>0.362</td>
</tr>
<tr>
<td>Anal warts</td>
<td>63</td>
<td>1.87</td>
<td>1.78</td>
<td>1.05 (0.62–1.78)</td>
<td>0.860</td>
</tr>
<tr>
<td>HSV-1</td>
<td>70</td>
<td>7.17</td>
<td>8.21</td>
<td>0.87 (0.53–1.42)</td>
<td>0.571</td>
</tr>
<tr>
<td>HSV-2</td>
<td>75</td>
<td>2.37</td>
<td>2.32</td>
<td>1.00 (0.62–1.63)</td>
<td>0.993</td>
</tr>
<tr>
<td>Syphilis</td>
<td>22</td>
<td>0.33</td>
<td>0.82</td>
<td>0.40 (0.17–0.92)</td>
<td>0.031</td>
</tr>
<tr>
<td>Urethral gonorrhea</td>
<td>127</td>
<td>2.96</td>
<td>2.85</td>
<td>1.04 (0.70–1.58)</td>
<td>0.818</td>
</tr>
<tr>
<td>Anal gonorrhea</td>
<td>113</td>
<td>2.58</td>
<td>2.64</td>
<td>0.98 (0.62–1.54)</td>
<td>0.933</td>
</tr>
<tr>
<td>Urethral chlamydia</td>
<td>275</td>
<td>6.31</td>
<td>6.42</td>
<td>0.99 (0.73–1.34)</td>
<td>0.942</td>
</tr>
<tr>
<td>Anal chlamydia</td>
<td>192</td>
<td>4.49</td>
<td>4.28</td>
<td>1.05 (0.73–1.53)</td>
<td>0.782</td>
</tr>
</tbody>
</table>

NOTE. CI, confidence interval; HR, hazard ratio; HSV, herpes simplex virus.

* The genital and anal wart categories include participants diagnosed within the past year, and the gonorrhea and chlamydia categories (urethral and anal) include those with study visit or self-reported diagnoses in the past 12 months.

b P values determined with test for homogeneity.

c Multivariate models were adjusted a priori for age and for behavioral factors in the previous 6 months independently associated with incidence of each STI [12–15]. For incident genital warts these included frequency of insertive anal fingering with casual partners; for incident anal warts, frequency of insertive anal fingering with casual partners and frequency of insertive fisting with casual partners; for incident HSV-1, number of regular male partners, frequency of insertive oral-anal sex with regular male partners, and frequency of insertive penile-oral sex to ejaculation with casual partners; for incident HSV-2, frequency of insertive anal fingering with casual partners and frequency of receiving a dildo with casual partners; for incident syphilis, number of male sexual partners, number of receptive unprotected anal intercourse acts with human immunodeficiency virus (HIV)—positive partners or partners with unknown HIV status; for incident urethral gonorrhea, sexual contact with gonorrhea, number of casual male partners, and unprotected anal intercourse according to position; for incident anal gonorrhea, sexual contact with gonorrhea, unprotected anal intercourse according to position, and frequency of receptive anal fingering with casual partners; for incident urethral chlamydia, sexual contact with chlamydia, number of casual male partners, unprotected anal intercourse according to position, and insertive oral sex to ejaculation with casual partners; for incident anal warts, frequency of insertive anal fingering with casual partners; for incident syphilis, number of male sexual partners, number of receptive unprotected anal intercourse acts with human immunodeficiency virus (HIV)—positive partners or partners with unknown HIV status; for incident urethral gonorrhea, sexual contact with gonorrhea, number of casual male partners, and unprotected anal intercourse according to position; for incident HSV-1, number of regular male partners, frequency of insertive oral-anal sex with regular male partners, and frequency of insertive fisting with casual partners; for incident HSV-2, frequency of insertive anal fingering with casual partners and frequency of receiving a dildo with casual partners; for incident syphilis, number of male sexual partners, number of receptive unprotected anal intercourse acts with human immunodeficiency virus (HIV)—positive partners or partners with unknown HIV status; for incident urethral gonorrhea, sexual contact with gonorrhea, number of casual male partners, and unprotected anal intercourse according to position; for incident anal gonorrhea, sexual contact with gonorrhea, unprotected anal intercourse according to position, and frequency of receptive anal fingering with casual partners; for incident urethral chlamydia, sexual contact with chlamydia, number of casual male partners, unprotected anal intercourse according to position, and frequency of receptive oral-anal sex (“rimming”) with casual partners.

In the HIM study, as in most longitudinal studies, HSV and syphilis were diagnosed serologically, and the anatomical site of acquisition was not known [27, 28]. The initial site of infection may have been oral or anal, for which, a man’s own circumcision status could have no plausible protective effect. Should circumcised homosexual men be at reduced risk of genital acquisition of both of these infections, the lack of data on site-specific diagnosis could, in part, explain the lack of association with circumcision in homosexual men.

No reduction in incidence of urethral gonorrhea or chlamydia was observed among circumcised participants in the HIM study. Circumcision had no influence on prevalent or incident urethral gonorrhea or chlamydia in 2 of the African heterosexual circumcision trials [6, 7]. Likewise, the only published study involving MSM [9] found no association of circumcision status with urethral gonorrhea or chlamydia among STI clinic attendees. These findings suggest that circumcision has little impact on acquisition of these urethral bacterial infections.

Data on the association of circumcision status and clinically apparent genital warts among heterosexual men are conflicting [9, 21, 23, 29–33]. Although a lower prevalence of polymerase chain reaction–based diagnoses of high-risk HPV was recently reported among circumcised heterosexual men in 2 circumcision trials [3, 5], observational data are inconsistent regarding
the effect of circumcision on penile HPV infection [34]. There was no overall association of circumcision with self-reported genital warts in the HIM study, and this is the first time such a relationship has been examined in MSM.

Several strengths of this study should be noted. First, the prospective nature of the HIM study avoided prevalence-incidence bias which may have been an issue in most other studies that assessed circumcision status and STI risk, employing a cross-sectional design. This may be an important bias; there is some evidence that the presence of a foreskin could lead to an altered clinical expression of infection with sexually transmitted pathogens [3, 29–31, 33].

Second, potential confounding demographic factors were assessed [18] and, where appropriate, included in the multivariate model. Third, the community-based nature of the HIM study avoided selection bias, which may be problematic in clinic-based studies if men of a particular circumcision status more commonly have, or notice, abnormal genital lesions. Fourth, self-reported circumcision status was validated by clinical examination in a subgroup of HIM study participants, and self-report was found to be a valid measure of circumcision status in this group [16]. Fifth, nondifferential misclassification was minimized by the use of highly sensitive and specific diagnostic testing algorithms for gonorrhea, chlamydia, syphilis, and HSV.

In addition, the overall uptake of STI testing offered to HIM study participants was high; >90% of men agreed to STI testing during the study. Importantly, we sought to differentiate genital STIs for which the presence of a foreskin could plausibly affect the risk of acquisition during insertive sexual practices, with use of (1) analyses of site-specific anal gonorrhea and chlamydia infections and anal warts, which allowed direct comparison between anal infections, for which circumcision should afford no protection, and the same infections at genital sites; and (2) analyses of the subgroup of men who predominantly practiced the insertive role in UAI.

A number of limitations of the study also need to be addressed. First, it is possible that some STIs may be associated with circumcision status but that the power of the study was insufficient to detect a significant effect during the study period. Nonetheless, a significant reduced risk of syphilis was observed in the HIM cohort despite the low incidence of infection (Tables 3 and 4). Second, for men with prevalent infections such as HSV and syphilis, especially those in whom life-long seropositivity persists [27, 28], imprecise or inadequate control for past sexual behavioral confounding factors may have influenced the outcome of this analysis. However, no prevalent infection examined in the HIM study was associated with circumcision status at either univariate or adjusted analysis (Table 2). Third, as already mentioned, the results of HSV and syphilis serological tests do not reveal the site of infection, and the lack of association with HSV-2 observed in the HIM study could be a result of infections being acquired at nonpenile sites, for which circumcision would have no plausible benefit. Finally, anogenital warts were self-reported in the HIM study. This may have resulted in some misclassification, as has been described elsewhere for anogenital warts among participants in the United States Multicenter AIDS Cohort Study [35].

Circumcision was associated with a reduced risk of incident syphilis in this cohort. It had little, if any, effect on most other prevalent and incident STIs. To confirm our findings, further prospective studies are warranted among MSM with higher STI incidence. Alternative biological or behavioral public health in-

### Table 4. Circumcision Status and Incident Sexually Transmissible Infections (STIs) in the Health in Men Cohort among Participants Who Predominantly Practiced the Insertive Role in Unprotected Anal Intercourse

<table>
<thead>
<tr>
<th>STI†</th>
<th>No of incident cases</th>
<th>Incidence, cases per 100 person-years</th>
<th>Univariate modelb</th>
<th>Multivariate modelc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Circumcised Uncircumcised</td>
<td>HR (95% CI) P</td>
</tr>
<tr>
<td>Genital warts</td>
<td>13</td>
<td>0.77 1.53</td>
<td>0.50 (0.17–1.46) .203</td>
<td>0.55 (0.18–1.65) .285</td>
</tr>
<tr>
<td>Anal warts</td>
<td>21</td>
<td>1.69 1.89</td>
<td>0.88 (0.35–2.21) .784</td>
<td>0.94 (0.37–2.42) .905</td>
</tr>
<tr>
<td>HSV-1</td>
<td>25</td>
<td>8.69 8.89</td>
<td>0.97 (0.40–2.34) .961</td>
<td>0.93 (0.40–2.17) .868</td>
</tr>
<tr>
<td>HSV-2</td>
<td>20</td>
<td>1.70 2.26</td>
<td>0.73 (0.30–1.79) .497</td>
<td>0.72 (0.30–1.76) .474</td>
</tr>
<tr>
<td>Syphilis</td>
<td>6</td>
<td>0.001 0.01</td>
<td>0.10 (0.01–0.81) .032</td>
<td>0.10 (0.01–0.82) .033</td>
</tr>
<tr>
<td>Urethral gonorrhea</td>
<td>56</td>
<td>4.13 3.50</td>
<td>1.20 (0.63–2.29) .572</td>
<td>1.19 (0.63–2.24) .589</td>
</tr>
<tr>
<td>Anal gonorrhea</td>
<td>17</td>
<td>1.13 1.31</td>
<td>0.85 (0.26–2.75) .782</td>
<td>0.93 (0.29–3.02) .902</td>
</tr>
<tr>
<td>Urethral chlamydia</td>
<td>106</td>
<td>7.23 7.83</td>
<td>0.93 (0.57–1.54) .787</td>
<td>0.93 (0.57–1.53) .778</td>
</tr>
<tr>
<td>Anal chlamydia</td>
<td>33</td>
<td>1.96 3.05</td>
<td>0.67 (0.30–1.49) .324</td>
<td>0.68 (0.30–1.53) .347</td>
</tr>
</tbody>
</table>

**NOTE.** CI, confidence interval; HR, hazard ratio; HSV, herpes simplex virus.

† The genital and anal wart categories include participants with self-reported warts diagnosed within the past year, and the gonorrhea and chlamydia categories (urethral and anal) include those with study visit or self-reported diagnoses in the past 12 months.

b P values determined with test for homogeneity.

c Multivariate models were adjusted a priori for age and for the total number of insertive unprotected anal intercourse acts in the past 6 months.
tventions are needed to combat increasing STI rates among homosexual men.

References