

### **HHS Public Access**

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2017 April 01.

Published in final edited form as:

Author manuscript

J Acquir Immune Defic Syndr. 2016 April 1; 71(4): 444–451. doi:10.1097/QAI.0000000000856.

### Lower HIV risk among circumcised men who have sex with men in China: Interaction with anal sex role in a cross-sectional study

Han-Zhu Qian, MD, PhD<sup>1,2</sup>, Yuhua Ruan, PhD<sup>3,4</sup>, Yu Liu, PhD<sup>1</sup>, Douglas F. Milam, MD<sup>5</sup>, Hans M .L. Spiegel, MD, PhD<sup>6</sup>, Lu Yin, PhD<sup>1</sup>, Dongliang Li, MD<sup>7</sup>, Bryan E. Shepherd, PhD<sup>1,8</sup>, Yiming Shao, MD, PhD<sup>3,4</sup>, and Sten H. Vermund, MD, PhD<sup>1,9,\*</sup>

<sup>1</sup>Vanderbilt Institute for Global Health, Vanderbilt University School of Medicine, Nashville, Tennessee, USA <sup>2</sup>Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, USA <sup>3</sup>Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Hangzhou, 310003, China <sup>4</sup>State Key Laboratory for Infectious Disease Prevention and Control, and National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China <sup>5</sup>Department of Urology, Vanderbilt University School of Medicine, Nashville, Tennessee, USA <sup>6</sup>HJF-DAIDS, a Division of The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Contractor to National Institute of Allergy and Infectious Disease, National Institutes of Health, Bethesda, Maryland <sup>7</sup>Chaoyang District Center for Disease Control and Prevention, Beijing, China <sup>8</sup>Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, Tennessee, USA <sup>9</sup>Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, Tennessee, USA

#### Abstract

**Background**—Voluntary medical male circumcision reduces the risk of HIV heterosexual transmission in men, but its effect on male-to-male sexual transmission is uncertain.

**Methods**—Circumcision status of men who have sex with men (MSM) in China was evaluated by genital examination and self-report; anal sexual role was assessed by questionnaire interview. Serostatus for HIV and syphilis was confirmed.

**Results**—Among1155 participants (242 known seropositives and 913 with unknown HIV status at enrollment), the circumcision rate by self-report (10.4%) was higher than confirmed by genital examination (8.2%). Male circumcision (by exam) was associated with 47% lower odds of being HIV seropositive (adjusted odds ratio [aOR], 0.53; 95% confidence interval [CI], 0.27-1.02) after adjusting for demographic covariates, number of lifetime male sexual partners, and anal sex role. Among MSM who predominantly practiced insertive anal sex, circumcised men had 62% lower odds of HIV infection than those who were uncircumcised (aOR, 0.38, 95%CI, 0.09-1.64). Among those whose anal sex position was predominantly receptive or versatile, circumcised men have 46% lower odds of HIV infection than did men who were not circumcised (aOR, 0.54, 95%CI, 0.25-1.14). Compared to uncircumcised men reporting versatile or predominantly receptive anal sex positioning, those who were circumcised and reported practicing insertive sex had an 85%

<sup>&</sup>lt;sup>\*</sup>Correspondence to: Dr. Sten Vermund, 2525 West End Avenue, Suite 750, Nashville, Tennessee 37203, USA, sten.vermund@vanderbilt.edu.

lower risk (aOR, 0.15; 95% CI, 0.04-0.65). Circumcision was not associated clearly with lower syphilis risk (aOR, 0.91; 95% CI, 0.51-1.61).

**Conclusions**—Circumcised MSM were less likely to have acquired HIV, most pronounced among men predominantly practicing insertive anal intercourse. A clinical trial is needed.

#### Keywords

male circumcision; HIV; syphilis; men who have sex with men; homosexual men; anal sexual role; anal sexual position; China

Randomized controlled trials have shown that male circumcision (MC) reduces the risk of HIV acquisition by over half in heterosexual men living in high prevalence areas of Africa.<sup>1,2,3,4,5</sup> However, the relationship between circumcision and HIV risk among men who have sex with men (MSM) has been inconclusive.<sup>6-16</sup> A meta-analysis of observational studies suggested slightly lower HIV odds among MSM who were circumcised, an association that might have been due to chance.<sup>17,18</sup> A second review suggested that MSM who predominantly practiced insertive anal sex may have had a lower risk of HIV if circumcised.<sup>19</sup> Prior studies among MSM have relied largely on self-report rather than physical exam to assess circumcision status.

Syphilis is another common sexually transmitted infection (STI) in MSM, often associated with HIV transmission.<sup>20</sup> Among MSM<sup>6</sup> and heterosexual men<sup>21</sup> alike, circumcision has not been protective for syphilis. It has been speculated that circumcision status may be behaviorally disinhibiting among men who believe that their circumcised status helps protect them from HIV and STI.<sup>22,23</sup> More risky behaviors in circumcised men could confound the assessment of an effect of circumcision on HIV infection and syphilis infection.<sup>24,25</sup>

As circumcision is thought to protect men from acquiring HIV via the glans penis, sexual role preference or position (i.e., practicing insertive versus receptive anal intercourse) may be a key factor. Men practicing insertive anal sex (analogous to insertive vaginal sex) may be protected by circumcision more than men predominantly practicing receptive anal sex. Only a few studies have considered this factor carefully.<sup>9,10,16</sup> We sought to evaluate the relationship between circumcision and HIV and syphilis among Chinese MSM, along with interactions of anal sexual role.

#### Methods

#### Study design and population

Through local gay-friendly community based organizations (CBOs), we recruited participants into a cross-sectional study during 2010-2011 in Beijing, China. We used advertisements on an MSM-oriented website (http://www.hivolunt.net). Outreach to MSM-frequented venues including bars, public bathhouses, parks, and MSM clubs, and snowball sampling via peer recruitment. Inclusion criteria were: (1) male; (2) self-reported ever having had sex with men; (3) willingness to receive a genital exam and blood sample; and (4) written informed consent. HIV-infected MSM from ongoing epidemiologic studies in the same community were also recruited; equivalent recruitment approaches were used to find

participants for these ongoing studies.<sup>26</sup> All participants provided consent for study participation, completed questionnaires, agreed to genital exams, and provided needed blood specimens. If participants provided definitive evidence of confirmed HIV-seropositive status, HIV testing was not repeated. According to the national HIV/AIDS diagnostic criteria, diagnosis of HIV infection must be confirmed by Western Blot (WB) test, and confirmed HIV infections should be reported and entered to national database. The study protocol was approved by the institutional review boards of National Center for AIDS/STD Control and Prevention (NCAIDS) of the Chinese Center for Disease Control and Prevention (China CDC) and Vanderbilt University.

#### Data collection

A questionnaire was administered by a trained interviewer to collect data on sociodemographic characteristics, drug and alcohol use, history of STIs, circumcision status, and sexual behaviors, including the number of male and female sexual partners, frequency of partner change, condom use, and pattern of homosexual activities, including anal sexual role. Participants were asked, "Which one of the following statements best describes your sexual activities with male partners in your life?" Choices were "exclusively receptive (or 100% receptive)," "mainly receptive (>75-99% receptive)," "versatile (25-75% receptive)," "mainly insertive (1-<25% receptive)," and "exclusively insertive (0% receptive)." Circumcision status was also assessed through genital examination performed by Chinese clinicians trained in Beijing by a US board-certified urologist (DFM).

A blood sample was collected to test for HIV and syphilis infections according to Chinese national testing protocols. An enzyme-linked immunosorbent assay (ELISA, Wantai Biological Medicine, Beijing) was used as a screening test for HIV-1 antibody, and a positive sample was confirmed by HIV-1/2 Western blot (HIV Blot 2.2 WB<sup>™</sup>; Genelabs Diagnostics, Singapore). The rapid plasma reagin (RPR) assay (Shanghai Kehua Biotechnology Ltd., China) was used to screen for syphilis, and a positive RPR result was confirmed by the *Treponema pallidum* particle assay (TPPA) (Fujirebio Inc., Japan). Participants who were positive for both RPR and TPPA were classified as syphilis-infected. All participants were offered their study results with counseling and linkage to care when needed for treatment.

#### Statistical analysis

We performed descriptive analyses of demographic, sexual, and behavioral characteristics, using medians and interquartile ranges for continuous variables. We compared self-report and genital exam methods for assessing circumcision status. We described demographic and behavioral characteristics by HIV and syphilis status. We examined the associations between circumcision and HIV and syphilis infections separately using multivariable logistic regression.

In multivariable logistic regression analyses, predominant anal sexual role was dichotomized as insertive ("mainly insertive" or "exclusively insertive") versus receptive/versatile ("exclusively receptive," "mainly receptive," or "versatile"), based on preliminary analysis of HIV risk across the original five categories of anal sexual role. Our primary model

assessed the associations adjusting for variables perceived to be selected *a priori* as potential confounders: age, ethnicity (Han or other), years of education (6, 7-9, 10-12, or >12), local residency (Beijing or other), anal sexual role, and, as a reviewer's suggestion (so strictly not *a priori*) number of lifetime male sexual partners. Secondary models included (1) a model that adjusted for all variables that were significant at the level of *P* 0.2 in bivariate analyses, and (2) a model that adjusted for all variables which contributed to 10% or larger change in the effect estimate of the primary predictor variable (circumcision) based on a backward stepwise elimination strategy. During model fitting, we included an interaction term of circumcision and anal sexual role, but they were not statistically significant (*P*>0.05) and were not included in the reported models. We assessed condom use during the past six months in the questionnaire interview. As condom use was not associated with circumcision status in preliminary analysis, we did not include this variable in the multivariable analyses.

We further performed stratified analyses of circumcision and HIV infection by anal sex role while adjusting for age, ethnicity, marriage, education, occupation, number of lifetime male sexual partners, and Beijing residency status. Using uncircumcised, receptive/versatile-sex subgroup as the reference, we assessed the individual and joint effects of circumcision and insertive-sex. We also performed a subgroup analysis among participants who exclusively or mainly practiced insertive anal sex over their lifetime. STATA 12.0<sup>TM</sup> (StataCorp LP, College Station, Texas) was used for all analyses.

#### Funding Sources

The study was supported by the National Institutes of Health (grants UL1RR024975, UL1TR000445, and R01AI094562) and by the Chinese State Key Laboratory for Infectious Disease Development Grant (2012SKLID103).

**Role of the funding source**—The content is solely the responsibility of the authors and does not represent the views of the NIH of the China CDC. Dr. Spiegel is a coauthor from the NIH and Drs. Ruan and Shao are co-authors from the China CDC, but none was responsible for grant funding.

#### Results

#### Study population and prevalence of infections

We recruited 1155 MSM who provided informed consent for participation in this study, including 913 with unknown HIV status and 242 with confirmed HIV-positive status at enrollment. Of all participants, 27.2% were married to women; 52.8% had attended college; 66.1% had Beijing legal residency (i.e., non-migrants); 5.9% were of minority (non-Han) ethnicity; 82.7% were employed, and 5.0% were students. Age ranged from 18 to 68 years (median 30 years). Among 913 participants with unknown HIV status at enrollment, 48 (5.3%) were HIV-infected; HIV status was unable to be assessed for 18 (2.0%) participants. Therefore, the study included 1137 participants (98.4%) with Western blot-confirmed HIV status, including 290 HIV-infected and 847 HIV-uninfected. Of 1140 participants (98.7%) with syphilis results, 298 (26.1%) were confirmed seropositive.

#### Prevalence of circumcision by self-report and genital exam

Of 964 (83.5%) MSM who self-reported their circumcision status and also received a genital exam, 100 (10.4%) self-reported circumcision and 79 (8.2%) were circumcised based on genital exam. With genital exam as the gold standard, the positive predictive value and negative predictive value of self-report in assessing circumcision were 74% and 99%, respectively (Table 1).

Sexual and drug using behaviors were similar between circumcised and uncircumcised participants. Drug abuse was reported among 2.5% of circumcised and 3.0% of uncircumcised participants had abused drugs. Female sex partners were reported by 49% of circumcised and 46% of uncircumcised men. A history of STIs was reported by 28% of circumcised and 30% of uncircumcised men.

#### Demographic and behavioral characteristics by HIV and syphilis status

The distribution of age, ethnicity, education and marital status was similar between HIV infected and uninfected men (Table 2). However, HIV-infected participants were more likely to be unemployed/retired (13.1% vs. 5.2%; P<0.01) and without Beijing residency status (39.4% vs. 31.8%; P=0.02). HIV-infected participants were more likely to self-identify as homosexuals instead of bisexuals (73.4% vs. 65.3%; P=0.04); had more lifetime male sexual partners (median 15 vs.10; P<0.01); were more likely to predominantly practice receptive anal sex (41.6% vs. 29.5%; P<0.01); and were more likely to be syphilis-infected (58.3% vs.15.0%; P<0.01) and have a history of an STI (52.0% vs. 22.9%; P<0.01). HIV-infected men were less likely to report current alcohol use (17.9% vs. 24.9%; P<0.01; Table 2).

Compared to uninfected participants, participants with syphilis infection were older (median age: 32 vs. 30 years; P<0.01), had lower educational attainment (less than middle school: 33.9% vs. 16.3%; P<0.01), and were more likely to be unemployed/retired (9.4% vs. 6.5%; P<0.01). Syphilis-infected participants were also more likely to have a history of STIs (59.7% vs. 19.9%; P<0.01) or a history of trading sex for money (7.5% vs. 4.2%; P=0.03), and had more lifetime male sexual partners (median 17 vs.10; P<0.01). Syphilis-infected men were less likely to currently consume alcohol (18.8% vs. 24.7%; P=0.02) and predominantly practice insertive anal sex (35.7% vs. 46.4%; P<0.01; Table 2).

#### Association of circumcision and infection

Table 3 shows HIV risk across the original five categories of anal sexual role among 1053 (91.2%) participants who had no missing data on three variables: circumcision, HIV status, and anal sex role/position. As HIV risk in two strata of mainly and exclusively insertive sex was lower than that in the other three strata, anal sex role was dichotomized as insertive versus receptive/versatile in multivariable logistic regression analyses.

In our primary model adjusting for age, ethnicity, education, Beijing residency, number of lifetime male sexual partners, and anal sexual role, men who were circumcised had 47% lower odds of being HIV positive than those who were not circumcised (adjusted OR [aOR], 0.53; 95% confidence interval [CI], 0.27-1.02). Results were similar in our two secondary

models, one that adjusted for occupation, Beijing residency, alcohol drinking, sexual orientation, history of STI, number of lifetime male sexual partners, and anal sexual role (all covariates with significance 0.2 in bivariate analyses), and the second that adjusted for education (Table 4).

The association between circumcision and syphilis infection was not statistically significant (aOR, 0.91; 95% CI, 0.51-1.61). Results were similar for secondary models adjusted for the same covariates as did for HIV models (Table 4).

#### Association of circumcision and HIV infection by strata of anal sexual role

Table 5 shows individual and joint associations of circumcision and anal sexual role on HIV risk. MSM who predominantly practiced insertive anal sex had lower odds of HIV infection than those whose anal sex was predominantly receptive or versatile regardless of circumcision status: 60% lower among uncircumcised men (aOR, 0.40; 95% CI, 0.29-0.55) and 72% lower among circumcised men (aOR, 0.28; 95% CI, 0.06-1.41) (Table 5).

MSM who were circumcised had lower (but not statistically significant) odds of HIV infection than those who were uncircumcised regardless of anal sexual role: 46% lower (aOR, 0.54; 95% CI, 0.25-1.14) among those predominantly practicing receptive or versatile anal sex and 62% lower (aOR, 0.38; 95% CI, 0.09-1.64) among those practicing insertive anal sex (Table 5).

Compared to uncircumcised men reporting practicing dual or predominantly receptive anal sex, those who were circumcised and reported predominantly practicing insertive anal sex had 85% lower odds (aOR, 0.15; 95% CI, 0.04-0.65) (Table 5).

#### Discussion

Our study found the strongest HIV protective association to date of circumcision among MSM,  $^{15,27-30}$  at the borderline of statistical significance (2-tailed  $\alpha$ =0.05). A meta-analysis of 20 observational studies with 65,784 participants showed a weaker, also marginally significant association (OR, 0.86; 95% CI, 0.70-1.06).<sup>6</sup> As expected, the protective odds were strongest among circumcised MSM who practiced insertive anal sex,<sup>31</sup> which is consistent with the finding from that meta-analysis (OR, 0.27; 95% CI, 0.17-0.44).<sup>6</sup> The stronger association in our population of uncircumcised status and higher HIV odds may be partially explained by our objective assessment of male circumcision status through genital examination, which eliminated misclassification in our study (Table 1). Chinese MSM do not have risk indices quite as high as in other MSM populations; the magnitude of risk in other populations could conceivably overwhelm the biological protective effects of circumcision. In addition, the sample sizes and number of events (HIV infection) were small in some strata, e.g., only 31 men who were circumcised and reported insertive anal sex and only two circumcised men were HIV-infected (Table 5); therefore, we do not believe that the protective effect that is suggested by the strong association observed here is a robust point estimate in the absence of confirmatory studies.

It is biologically plausible that circumcision offers a prophylactic effect for HIV acquisition among MSM who practice insertive anal intercourse, and that the mechanism is same for the protective effect in penile-vaginal intercourse among heterosexual men. The inner mucosa of the foreskin has less keratinization and a higher density of target cells for HIV infection.<sup>32</sup> Removal of the foreskin among circumcised MSM will likely reduce the likelihood of HIV infection during insertive anal sex.

It is well-known that the per-act probability of acquiring HIV from an infected source is higher through receptive anal sex than through insertive anal sex;<sup>33</sup> this result was also observed in our study (insertive vs. receptive/versatile: aOR, 0.40 (95% CI, 0.29-0.55) among uncircumcised MSM, while aOR, 0.28 (95% CI, 0.06-1.41) was among circumcised MSM. Circumcision would not be expected to protect persons who exclusively engage in receptive anal sex, though too few men fell into this category for us to do meaningful subgroup analyses. We note, however, that the association between circumcision status and HIV infection did not statistically differ between those who reported primarily engaging in insertive anal sex versus those who reported primarily engaged in receptive/versatile anal sex. This could be due to insufficient power, our collapsing predominantly receptive and versatile sex into a single category, misclassification of role due to the self-report nature of anal sex role, and/or evolving sexual behaviors within individuals over their lifetime. Most Chinese MSM are versatile, having practiced both receptive and insertive anal intercourse; we assessed their preferences over the past six months. Nonetheless, our results suggest that a future randomized clinical trial should not be limited only to those who engage in predominantly insertive anal sex.

Only about 8% of MSM enrolled in our study were circumcised; if circumcision is perceived to protect against HIV (not widely known in China), circumcised men could have higher risk behaviors due to risk disinhibition (also known as risk compensation). We found no differences in sexual risk taking between circumcised and uncircumcised participants. That syphilis was also not significantly different between the two groups suggests that sexual behavior differences are unlikely to explain our findings of lower odds of HIV in circumcised MSM.

Our study was hypothesis-driven, ascertained circumcision status through genital examination by trained physicians, and assessed HIV and syphilis infections with state-of-the-art serology and confirmatory testing. Hence, our study reduced information bias by eliminating recall bias for the ascertainment of the main exposure (circumcision) and the outcome (HIV and syphilis) variables. Our assessment of predominant sexual role/position during anal sex permitted an assessment of this interactive variable.

Our study's limitations include the following. First, the key confounding variable—anal sex role in lifetime—was assessed based on response to one question. We defined insertive anal sex as >75% of anal sexual activities in lifetime being insertive (only 14% were exclusively insertive). MSM may change their role behavior over time, and some may take both insertive and receptive positions during one sex encounter with the same partner.<sup>34</sup> If social desirability bias resulted in men over-reporting engaging in insertive anal intercourse, then it is likely that our odds ratio for protection would have been underestimated. Second, our

cross-sectional design could invite unmeasured confounders that interfered with correct inferences. Since Han ethnic Chinese men are circumcised for medical indications, rather than religious or cultural reasons, we think the circumcision effect is unlikely to be explained by an unmeasured confounding factor, unless men with phimosis (usually from childhood) are different in some systematic way from others.<sup>35</sup> Routine infant circumcision is a rare practice in China; Muslims were <1% of our sample. Third, data on prospective condom use were not available due to the cross-sectional nature of this survey. Theoretically, if men believed that their circumcised status helped protect them from HIV, circumcised men might be behaviorally disinhibiting, so condom use could have distorted the relationship between circumcision and HIV risk. Our survey had one question about condom use during the past six months, and no association of condom use with circumcision status was noted, so this variable was not adjusted for in multivariable analyses. Future prospective studies or clinical trials should examine condom use and sexual risk taking carefully. Finally, the use of one site in the capital city Beijing may limit our study's generalizability.

In the US, circumcision rates are lower among black MSM, while HIV rates are higher, compared to white MSM.<sup>36-38</sup> Since the global prevalence of circumcision is only 30% among males aged 15, we suggest that a considerable public health benefit of circumcision in MSM is plausible, if proven effective and acceptable in MSM in clinical trials.<sup>39</sup> Most MSM are versatile in their anal sex roles,<sup>40</sup> and <10% exclusively practice receptive sex; hence, most MSM could benefit from circumcision.<sup>41</sup> In Peru, circumcision prevalence is low and HIV incidence is high in MSM; a transmission model estimated that one HIV infection could be averted per six circumcisions, but the putative protective benefits of circumcision may have been underestimated, judging from parameters that are suggested by our study.<sup>42</sup>

HIV prevention strategies among MSM are still limited in their availability and uptake.<sup>43,44</sup> Only a clinical trial will resolve the issue of the efficacy of male circumcision for MSM to prevent HIV, given inherent limitations of observational studies. Future work must consider: (1) Objective ascertainment of circumcision status via genital examination; (2) Careful assessment of anal sex role/positioning;<sup>45,46</sup> (3) Detailed data on condom use and sexual risk taking; (4) Local acceptability of adult circumcision, whether favorable<sup>35,47-50</sup> or less so;<sup>31,51</sup> (5) Appropriate study design.<sup>52-54</sup> Before clinical trials are initiated, feasibility studies may be necessary for evaluating cultural contextual factors that may affect recruitment and external validity, surgery-alternative techniques,<sup>55-59</sup> decision analysis models of costs vs. benefits of circumcision among MSM, and community views of circumcision and willingness to engage circumcision efficacy trials. In a registered clinical trial (NCT01068015) where circumcision is one component of a package of integrated interventions, 50% of Chinese MSM participants stated willingness, but only 15% eventually accepted circumcision (personal communication, Dr. Jie Xu).

In summary, our study suggests that circumcision may be a tool to reduce the risk of HIV acquisition among MSM. If community support and willingness to participate is confirmed, an adequately powered, multi-center (to improve generalizability) randomized clinical trial could provide a definitive assessment of efficacy in the context of different populations of

MSM with careful assessment and adjustment of sexual role/positioning and risky behaviors.

#### Acknowledgments

HZQ, YR and SHV conceptualized and designed the study; YR, DFM and DL contributed to data collection; HZQ, YL and LY analyzed the data; HZQ, YL, YS, BES, and SHV interpreted the data, HZQ and YL drafted the manuscript; all authors contributed to revising the manuscript, and all authors have reviewed and approved the final version of the manuscript.

**Primary Funding Sources:** NIH (NCRR Grant UL1RR024975, NCATS Grant UL1TR000445, and NIAID Grant R01AI094562) and Chinese State Key Laboratory for Infectious Disease (Development Grant 2012SKLID103).

#### References

- Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. PLoS Med. 2005; 2(11):e298. [PubMed: 16231970]
- Bailey RC, Moses S, Parker CB, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. Lancet. 2007; 369(9562):643–656. [PubMed: 17321310]
- 3. Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. Lancet. 2007; 369(9562):657–666. [PubMed: 17321311]
- Weiss HA, Quigley MA, Hayes RJ. Male circumcision and risk of HIV infection in sub-Saharan Africa: a systematic review and meta-analysis. AIDS. 2000; 14(15):2361–2370. [PubMed: 11089625]
- Mehta SD, Moses S, Parker CB, Agot K, Maclean I, Bailey RC. Circumcision status and incident herpes simplex virus type 2 infection, genital ulcer disease, and HIV infection. AIDS. 2012; 26(9): 1141–1149. [PubMed: 22382150]
- 6. Wiysonge CS, Kongnyuy EJ, Shey M, et al. Male circumcision for prevention of homosexual acquisition of HIV in men. Cochrane Database Syst Rev. 2011(6) CD007496.
- Beyrer C. Global prevention of HIV infection for neglected populations: men who have sex with men. Clin Infect Dis. 2010; 50(Suppl 3):S108–113. [PubMed: 20397938]
- 8. Fankem SL, Wiysonge CS, Hankins CA. Male circumcision and the risk of HIV infection in men who have sex with men. Int J Epidemiol. 2008; 37(2):353–355. [PubMed: 17951274]
- Doerner R, McKeown E, Nelson S, Anderson J, Low N, Elford J. Circumcision and HIV Infection among Men Who Have Sex with Men in Britain: The Insertive Sexual Role. Arch Sex Behav. 2013; 42(7):1319–26. [PubMed: 23358857]
- Gust DA, Wiegand RE, Kretsinger K, et al. Circumcision status and HIV infection among MSM: reanalysis of a Phase III HIV vaccine clinical trial. Aids. 2010; 24(8):1135–1143. [PubMed: 20168206]
- Jameson DR, Celum CL, Manhart L, Menza TW, Golden MR. The association between lack of circumcision and HIV, HSV-2, and other sexually transmitted infections among men who have sex with men. Sex Transm Dis. 2010; 37(3):147–152. [PubMed: 19901865]
- Jozkowski K, Rosenberger JG, Schick V, Herbenick D, Novak DS, Reece M. Relations between circumcision status, sexually transmitted infection history, and HIV serostatus among a national sample of men who have sex with men in the United States. AIDS Patient Care STDS. 2010; 24(8):465–470. [PubMed: 20666578]
- Londish GJ, Templeton DJ, Regan DG, Kaldor JM, Murray JM. Minimal impact of circumcision on HIV acquisition in men who have sex with men. Sex Health. 2010; 7(4):463–470. [PubMed: 21062588]
- Sanchez J, Sal YRVG, Hughes JP, et al. Male circumcision and risk of HIV acquisition among MSM. Aids. 2011; 25(4):519–523. [PubMed: 21099672]

- Schneider JA, Michaels S, Gandham SR, et al. A protective effect of circumcision among receptive male sex partners of Indian men who have sex with men. AIDS Behav. 2012; 16(2):350–359.
  [PubMed: 21681562]
- Zhou C, Raymond HF, Ding X, et al. Anal Sex Role, Circumcision Status, and HIV Infection Among Men Who Have Sex with Men in Chongqing, China. Arch Sex Behav. 2013; 42(7):1275– 83. [PubMed: 23070532]
- Millett GA, Flores SA, Marks G, Reed JB, Herbst JH. Circumcision status and risk of HIV and sexually transmitted infections among men who have sex with men: a meta-analysis. Jama. 2008; 300(14):1674–1684. [PubMed: 18840841]
- Vermund SH, Qian HZ. Circumcision and HIV prevention among men who have sex with men: no final word. JAMA. 2008; 300(14):1698–1700. [PubMed: 18840846]
- Templeton DJ, Millett GA, Grulich AE. Male circumcision to reduce the risk of HIV and sexually transmitted infections among men who have sex with men. Curr Opin Infect Dis. 2010; 23(1):45– 52. [PubMed: 19935420]
- Mayer KH. Sexually transmitted diseases in men who have sex with men. Clin Infect Dis. 2011; 53(Suppl 3):S79–83. [PubMed: 22080272]
- 21. Tobian AA, Serwadda D, Quinn TC, et al. Male circumcision for the prevention of HSV-2 and HPV infections and syphilis. N Engl J Med. 2009; 360(13):1298–1309. [PubMed: 19321868]
- 22. Mattson CL, Campbell RT, Bailey RC, Agot K, Ndinya-Achola JO, Moses S. Risk compensation is not associated with male circumcision in Kisumu, Kenya: a multi-faceted assessment of men enrolled in a randomized controlled trial. PLoS One. 2008; 3(6):e2443. [PubMed: 18560581]
- Agot KE, Kiarie JN, Nguyen HQ, Odhiambo JO, Onyango TM, Weiss NS. Male circumcision in Siaya and Bondo Districts, Kenya: prospective cohort study to assess behavioral disinhibition following circumcision. J Acquir Immune Defic Syndr. 2007; 44(1):66–70. [PubMed: 17019365]
- 24. Buchacz K, Greenberg A, Onorato I, Janssen R. Syphilis epidemics and human immunodeficiency virus (HIV) incidence among men who have sex with men in the United States: implications for HIV prevention. Sex Transm Dis. 2005; 32(10 Suppl):S73–79. [PubMed: 16205297]
- 25. Ruan Y, Li D, Li X, et al. Relationship between syphilis and HIV infections among men who have sex with men in Beijing, China. Sex Transm Dis. 2007; 34(8):592–597. [PubMed: 17325622]
- 26. Li D, Li S, Liu Y, et al. HIV incidence among men who have sex with men in Beijing: a prospective cohort study. BMJ Open. 2012; 2(6)
- Lane T, Raymond HF, Dladla S, et al. High HIV prevalence among men who have sex with men in Soweto, South Africa: results from the Soweto Men's Study. AIDS Behav. 2011; 15(3):626–634. [PubMed: 19662523]
- Buchbinder SP, Vittinghoff E, Heagerty PJ, et al. Sexual risk, nitrite inhalant use, and lack of circumcision associated with HIV seroconversion in men who have sex with men in the United States. J Acquir Immune Defic Syndr. 2005; 39(1):82–89. [PubMed: 15851918]
- Kreiss JK, Hopkins SG. The association between circumcision status and human immunodeficiency virus infection among homosexual men. J Infect Dis. 1993; 168(6):1404–1408. [PubMed: 8245525]
- Reisen CA, Zea MC, Poppen PJ, Bianchi FT. Male circumcision and HIV status among Latino immigrant MSM in New York City. J LGBT Health Res. 2007; 3(4):29–36. [PubMed: 19002268]
- Pando MA, Balan IC, Dolezal C, et al. Low frequency of male circumcision and unwillingness to be circumcised among MSM in Buenos Aires, Argentina: association with sexually transmitted infections. J Int AIDS Soc. 2013; 16(1):18500. [PubMed: 23746302]
- Hirbod T, Bailey RC, Agot K, et al. Abundant expression of HIV target cells and C-type lectin receptors in the foreskin tissue of young Kenyan men. Am J Pathol. 2010; 176(6):2798–2805. [PubMed: 20395432]
- 33. Patel P, Borkowf CB, Brooks JT, Lasry A, Lansky A, Mermin J. Estimating per-act HIV transmission risk: a systematic review. Aids. 2014; 28(10):1509–1519. [PubMed: 24809629]
- 34. Lyons A, Pitts M, Smith G, et al. Versatility and HIV vulnerability: investigating the proportion of Australian gay men having both insertive and receptive anal intercourse. J Sex Med. 2011; 8(8): 2164–2171. [PubMed: 21269403]

- 35. Ruan Y, Qian HZ, Li D, et al. Willingness to be circumcised for preventing HIV among Chinese men who have sex with men. AIDS Patient Care STDS. 2009; 23(5):315–321. [PubMed: 19335172]
- 36. Maulsby C, Millett G, Lindsey K, et al. HIV Among Black Men Who Have Sex with Men (MSM) in the United States: A Review of the Literature. AIDS Behav. 2014; 18(1):10–25. [PubMed: 23620241]
- 37. Fenton KA, Imrie J. Increasing rates of sexually transmitted diseases in homosexual men in Western europe and the United States: why? Infect Dis Clin North Am. 2005; 19(2):311–331. [PubMed: 15963874]
- Millett GA, Ding H, Lauby J, et al. Circumcision status and HIV infection among Black and Latino men who have sex with men in 3 US cities. J Acquir Immune Defic Syndr. 2007; 46(5):643–650. [PubMed: 18043319]
- WHO. Male circumcision: Global trends and determinants of prevalence, safety and acceptability. Geneva, Switzerland: World Health Organization and Joint United Nations Programme on HIV/ AIDS; 2007.
- 40. Hemmige V, Snyder H, Liao C, et al. Sex position, marital status, and HIV risk among Indian men who have sex with men: clues to optimizing prevention approaches. AIDS Patient Care STDS. 2011; 25(12):725–734. [PubMed: 21682588]
- Tieu HV, Li X, Donnell D, et al. Anal Sex Role Segregation and Versatility Among Men Who Have Sex With Men: EXPLORE Study. J Acquir Immune Defic Syndr. 2013; 64(1):121–125. [PubMed: 23945255]
- 42. Goodreau SM, Carnegie NB, Vittinghoff E, et al. Can Male Circumcision Have an Impact on the HIV Epidemic in Men Who Have Sex with Men? PLoS One. 2014; 9(7) e102960.
- 43. Sullivan PS, Carballo-Dieguez A, Coates T, et al. Successes and challenges of HIV prevention in men who have sex with men. Lancet. 2012; 380(9839):388–399. [PubMed: 22819659]
- 44. Beyrer C, Baral SD, van Griensven F, et al. Global epidemiology of HIV infection in men who have sex with men. Lancet. 2012; 380(9839):367–377. [PubMed: 22819660]
- Williams JK, Wyatt GE, Resell J, Peterson J, Asuan-O'Brien A. Psychosocial issues among gayand non-gay-identifying HIV-seropositive African American and Latino MSM. Cultur Divers Ethnic Minor Psychol. 2004; 10(3):268–286. [PubMed: 15311979]
- Fields EL, Bogart LM, Smith KC, Malebranche DJ, Ellen J, Schuster MA. HIV risk and perceptions of masculinity among young black men who have sex with men. J Adolesc Health. 2012; 50(3):296–303. [PubMed: 22325136]
- 47. Begley EB, Jafa K, Voetsch AC, Heffelfinger JD, Borkowf CB, Sullivan PS. Willingness of men who have sex with men (MSM) in the United States to be circumcised as adults to reduce the risk of HIV infection. PLoS One. 2008; 3(7):e2731. [PubMed: 18628946]
- Chariyalertsak S, Kosachunhanan N, Saokhieo P, et al. HIV incidence, risk factors, and motivation for biomedical intervention among gay, bisexual men, and transgender persons in Northern Thailand. PLoS One. 2011; 6(9) e24295.
- 49. Kelly A, Kupul M, Fitzgerald L, et al. "Now we are in a different time; various bad diseases have come." Understanding men's acceptability of male circumcision for HIV prevention in a moderate prevalence setting. BMC Public Health. 2012; 12:67. [PubMed: 22264256]
- Andersson N, Cockcroft A. Male circumcision, attitudes to HIV prevention and HIV status: a cross-sectional study in Botswana, Namibia and Swaziland. AIDS Care. 2012; 24(3):301–309. [PubMed: 21933035]
- Thornton AC, Lattimore S, Delpech V, Weiss HA, Elford J. Circumcision among men who have sex with men in London, United Kingdom: an unlikely strategy for HIV prevention. Sex Transm Dis. 2011; 38(10):928–931. [PubMed: 21934567]
- 52. Weiss HA, Halperin D, Bailey RC, Hayes RJ, Schmid G, Hankins CA. Male circumcision for HIV prevention: from evidence to action? Aids. 2008; 22(5):567–574. [PubMed: 18316997]
- Gray RH, Wawer MJ, Polis CB, Kigozi G, Serwadda D. Male circumcision and prevention of HIV and sexually transmitted infections. Curr Infect Dis Rep. 2008; 10(2):121–127. [PubMed: 18462586]

- 54. Macdonald A, Humphreys J, Jaffe HW. Prevention of HIV transmission in the UK: what is the role of male circumcision? Sex Transm Infect. 2008; 84(3):158–160. [PubMed: 18283093]
- 55. Kanyago S, Riding DM, Mutakooha E, Lopez de la OA, Siedner MJ. Shang Ring versus forcepsguided adult male circumcision: a randomized controlled effectiveness study in southwestern Uganda. J Acquir Immune Defic Syndr. 2013; 64(2):130–3. [PubMed: 23599013]
- Bratt JH, Zyambo Z. Comparing direct costs of facility-based shang ring provision versus a standard surgical technique for voluntary medical male circumcision in zambia. J Acquir Immune Defic Syndr. 2013; 63(3):e109–112. [PubMed: 23481667]
- 57. Yue C, Ze-Jun Y, Wu KR, et al. A randomized clinical study of circumcision with a ring device versus conventional circumcision. J Urol. 2012; 188(5):1849–1854. [PubMed: 22999700]
- Barone MA, Awori QD, Li PS, et al. Randomized trial of the Shang Ring for adult male circumcision with removal at one to three weeks: delayed removal leads to detachment. J Acquir Immune Defic Syndr. 2012; 60(3):e82–89. [PubMed: 22343180]
- McIntyre JA. Can devices for adult male circumcision help bridge the implementation gap for HIV prevention services? J Acquir Immune Defic Syndr. 2011; 58(5):506–508. [PubMed: 21963938]

### Table 1

Agreement of male circumcision status based on self-report and genital examination among men who have sex with men in China

Note: Using genital exam as the definitive method for assessing circumcision: Kappa=0.81; sensitivity=94%; specificity=97%; positive predictive value (PPV)=74%, negative predictive value (NPV)=94%, specificity=99%.

Demographic and behavioral characteristics by HIV and syphilis status among men who have sex with men in China

Age in years	Positive ( <i>n</i> =290); n (%)	Negative ( <i>n</i> =847); n (%)	<i>P</i> -value	Positive ( <i>n</i> =298); n (%)	Negative ( <i>n</i> =842); n (%)	<i>P</i> -value
* (101) :F - 34			0.78			<0.01
Median (IQK)	31(26-36)	30 (26-35)		32 (27-38)	30 (26-35)	
Ethnicity			0.79			0.67
Han majority	272 (93.8)	798 (94.2)		279 (93.6)	794 (94.3)	
Minorities	18 (6.2)	49 (5.8)		19 (6.4)	48 (5.7)	
<b>Current marital status</b>			0.75			0.10
Unmarried	213 (73.4)	614(72.5)		206 (69.1)	624 (74.1)	
Married	72 (26.6)	233(27.5)		92 (30.9)	218 (25.9)	
Education in years			0.58			<0.01
Primary (<=6)	10 (3.4)	21 (2.5)		10 (3.4)	21 (2.5)	
Middle school(7-9)	51 (17.6)	128 (15.1)		64 (21.5)	116 (13.8)	
Secondary (10-12)	82 (28.3)	243 (28.7)		89 (30.0)	237 (28.1)	
College (>12)	147 (50.7)	454 (53.7)		134 (45.1)	468 (55.6)	
Occupation			<0.01			<0.01
Employed	222 (76.6)	717 (85.0)		245 (82.2)	696 (83.0)	
Unemployed/retired	38 (13.1)	44 (5.2)		28 (9.4)	55 (6.5)	
Student	12 (4.1)	45 (5.3)		4 (1.3)	53 (6.3)	
Other	18 (6.2)	38 (4.5)		21 (7.1)	35 (4.2)	
Beijing local residence (Hukou)	Hukou)		0.02			0.20
No	114 (39.4)	269 (31.8)		110 (36.9)	275 (32.7)	
Yes	175 (60.6)	577 (68.2)		188 (63.1)	565 (62.3)	
Illicit drug use			0.98			0.89
No	281 (97.2)	821 (97.0)		289 (97.0)	816 (97.1)	
Yes	8 (2.8)	25 (3.0)		9 (3.0)	24 (2.9)	
Alcohol drinking, past 4 weeks	weeks		<0.01			0.02
Never	99 (34.1)	213 (25.2)		100 (33.6)	214 (25.5)	
Rarely	139 (47.9)	422 (49.9)		142 (47.6)	419(49.8)	

Characteristic	H	HIV (N=1137)		Syp	Syphilis $(N = 1140)$	
	Positive (n=290); n (%)	Negative ( <i>n</i> =847); n (%)	<i>P</i> -value	Positive (n=298); n (%)	Negative ( <i>n</i> =842); n (%)	<i>P</i> -value
>2 times weekly	40 (13.8)	172 (20.3)		42 (14.1)	171 (20.3)	
Daily	12 (4.1)	39 (4.6)		14 (4.7)	37 (4.4)	
Sexual orientation			0.04			0.30
Homosexual	210 (73.4)	547 (65.3)		210 (71.0)	549 (66.1)	
Heterosexual	2 (0.7)	10 (1.2)		2 (0.7)	10 (1.2)	
Bisexual	74 (25.9)	281 (33.5)		84 (28.3)	271 (32.7)	
Number of lifetime male sexual partners	ile sexual partners		<0.01			<0.01
Median (IQR)	15 (7-10)	10 (5-30)		17 (8-50)	10 (5-26)	
Predominant anal sexual role ${\not f}$	ıal role∔		<0.01			0.01
Receptive	116 (41.6)	241 (29.5)		101 (35.7)	257 (31.4)	
Insertive	82 (29.4)	397 (48.5)		101 (35.7)	379 (46.4)	
Versatile	81(29.0)	180 (22.0)		81 (28.6)	181 (22.2)	
Concurrent male partı	Concurrent male partners in past 12 months		0.11			0.13
No	258 (90.8)	788 (93.1)		266 (90.5)	782 (93.2)	
Yes	26 (9.2)	58 (6.9)		28 (9.5)	57 (6.8)	
Traded sex for money in past 12 months	in past 12 months		0.15			0.03
No	266 (93.3)	808 (95.5)		273 (92.5)	804 (95.8)	
Yes	19 (6.7)	38 (4.5)		22 (7.5)	35 (4.2)	
Ever had forced sex with a male partner	ith a male partner		0.28			0.34
No	272 (95.4)	819 (96.8)		282 (95.6)	812 (96.8)	
Yes	13 (4.6)	27 (3.2)		13(4.4)	27 (3.2)	
Ever had sex with a female partner	male partner		06.0			0.96
No	157 (54.1)	462 (54.5)		162 (54.4)	459 (54.5)	
Yes	133 (45.9)	385 (45.5)		136 (45.6)	383 (45.5)	
Circumcision status by exam	/ exam		0.02			0.22
Uncircumcised	263 (96.0)	750 (91.7)		266 (94.3)	749 (92.1)	
Circumcised	11 (4.0)	68 (8.3)		16 (5.7)	64 (7.9)	
History of sexually transmitted diseases	nsmitted diseases		<0.01			<0.01
No	132 (48.0)	634 (77.1)		115 (40.3)	653 (80.1)	
Yes	143 (52.0)	188 (22.9)		170 (59.7)	162 (19.9)	

\* IQR: interquartile range

cript Author Manuscript

 ${}^{\sharp}_{k}$ Receptive or Insertive sexual roles refer to exclusively or mainly, combined. Versatile indicates no marked preference for receptive or insertive role.

Qian et al.

HIV risk stratified by anal sex role among men who have sex with men in China

Anal sex role	HIV statu	HIV status (N=1053)	Odds Ratio (95% confidence interval) P value	P value
	Positive (N=264)	Positive (N=264) Negative (N=789)		
Exclusively receptive	57	94	Reference	:
Mainly receptive	53	138	0.63(0.40, 1.00)	0.05
Versatile	76	170	0.74 (0.48,1.13)	0.16
Mainly insertive	49	216	0.37 (0.24,0.59)	<0.001
Exclusively insertive	29	171	$0.28\ (0.17, 0.47)$	<0.001

## Table 4

Association between male circumcision and HIV, syphilis or HIV/syphilis co-infection among men who have sex with men in China

<b>Circumcision status</b>	Circumcision status Sample size (N=1053)*	Adjusted	Adjusted odds ratio; OR (95% confidence interval)	fidence interval)
		A priori model $^{\dagger}$	A priori model $^{\dagger}$ Secondary model (1) $^{\sharp}$ Secondary model (2) $^{\$}$	Secondary model (2) $\S$
HIV infection				
Uncircumcised	975	Reference	Reference	Reference
Circumcised	78	0.53 (0.27, 1.02)	0.52 (0.25, 1.06)	0.47 (0.24, 0.90)
Syphilis infection				
Uncircumcised	975	Reference	Reference	Reference
Circumcised	78	0.91 (0.51, 1.61)	0.94 (0.49, 1.78)	0.75 (0.42, 1.32)
* N=1053 due to missing	N=1053 due to missing data on variables of circumcision, HIV status, or anal sex role/position.	ncision, HIV status, c	r anal sex role/position.	
$t^{\dagger}$ Adjusted for age, ethnic	Adjusted for age, ethnicity, education, Beijing residency, number of lifetime male sexual partners, and anal sexual role/position	idency, number of lif	stime male sexual partners	, and anal sexual role/po
, , , , , , , , , , , , , , , , , , ,		-	2 2 2 2	

Adjusted for those covariates in Table 2, including anal sexual role, that were significant at P<0.2.

 $^{\$}$ Adjusted for education after stepwise backward selection based on a 10% change in estimates.

~
$\rightarrow$
-
<u> </u>
t
-
~
0
_
~
ิล
2
ิท
anusc
anus
anuscrij
anuscri

# Table 5

Association between circumcision and HIV risk stratified by anal sexual role/position among men who have sex with men in China

Anal sex role Circumcised	Circumcised	HIV status	HIV status (N=1053)*	Adjusted odds rauo (95%	Aujusteu ouus ratio (35 %	Adjusted odds ratio (95%
		Positive (N=264)	Negative (N=789)	confidence interval)/	confidence interval)'	confidence interval)/
Receptive/versatile	No	177	364	Reference		
Insertive	No	76	358	$0.40\ (0.29,\ 0.55)$		Reference
Receptive/versatile	Yes	6	38	0.54 (0.25, 1.14)	Reference	
Insertive	Yes	2	29	0.15(0.04, 0.65)	0.28~(0.06, 1.41)	$0.38~(0.09, 1.64)^{\#}$

 $^{\dagger}$  Adjusted for age, ethnicity, education, number of lifetime male sexual partners, and Beijing residency.

 ${}^{\sharp}$ Compared with circumcised, receptive/versatile-sex subgroup.