

Quarterly Research Digest on Voluntary Medical Male Circumcision for HIV Prevention

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Combination HIV prevention

1. Chang, L. W., et al. **Novel community health worker strategy for HIV service engagement in a hyperendemic community in Rakai, Uganda: A pragmatic, cluster-randomized trial.** *PLoS Med* 2021;18(1): e1003475.

Online at:

<https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1003475>.

BACKGROUND: Effective implementation strategies are needed to increase engagement in HIV services in hyperendemic settings. We conducted a pragmatic cluster-randomized trial in a high-risk, highly mobile fishing community (HIV prevalence: approximately 38%) in Rakai, Uganda, to assess the impact of a community health worker-delivered, theory-based (situated Information, Motivation, and Behavior Skills), motivational interviewing-informed, and mobile phone application-supported counseling strategy called "Health Scouts" to promote engagement in HIV treatment and prevention services.

METHODS AND FINDINGS: The study community was divided into 40 contiguous, randomly allocated clusters (20 intervention clusters, n = 1,054 participants at baseline; 20 control clusters, n = 1,094 participants at baseline). From September 2015 to December 2018, the Health Scouts were deployed in intervention clusters. Community-wide, cross-sectional surveys of consenting 15 to 49-year-old residents were conducted at approximately 15 months (mid-study) and at approximately 39 months (end-study) assessing the primary programmatic outcomes of self-reported linkage to HIV care, antiretroviral therapy (ART) use, and male circumcision, and the primary biologic outcome of HIV viral suppression (<400 copies/mL). Secondary outcomes included HIV testing coverage, HIV incidence, and consistent condom use. The primary intent-to-treat analysis used log-linear binomial regression with generalized estimating equation to

estimate prevalence risk ratios (PRR) in the intervention versus control arm. A total of 2,533 (45% female, mean age: 31 years) and 1,903 (46% female; mean age 32 years) residents completed the mid-study and end-study surveys, respectively. At mid-study, there were no differences in outcomes between arms. At end-study, self-reported receipt of the Health Scouts intervention was 38% in the intervention arm and 23% in the control arm, suggesting moderate intervention uptake in the intervention arm and substantial contamination in the control arm. At end-study, intention-to-treat analysis found higher HIV care coverage (PRR: 1.06, 95% CI: 1.01 to 1.10, $p = 0.011$) and ART coverage (PRR: 1.05, 95% CI: 1.01 to 1.10, $p = 0.028$) among HIV-positive participants in the intervention compared with the control arm. Male circumcision coverage among all men (PRR: 1.05, 95% CI: 0.96 to 1.14, $p = 0.31$) and HIV viral suppression among HIV-positive participants (PRR: 1.04, 95% CI: 0.98 to 1.12, $p = 0.20$) were higher in the intervention arm, but differences were not statistically significant. No differences were seen in secondary outcomes. Study limitations include reliance on self-report for programmatic outcomes and substantial contamination which may have diluted estimates of effect.

CONCLUSIONS: A novel community health worker intervention improved HIV care and ART coverage in an HIV hyperendemic setting but did not clearly improve male circumcision coverage or HIV viral suppression. This community-based, implementation strategy may be a useful component in some settings for HIV epidemic control.

TRIAL REGISTRATION: ClinicalTrials.gov NCT02556957.

2. Jewell, B. L., et al. **Predicting HIV Incidence in the SEARCH trial: a mathematical modeling study [abstract]**. *J Acquir Immune Defic Syndr* 2021 Mar 23. Online ahead of print.

Online at:

https://journals.lww.com/jaids/Abstract/9000/Predicting_HIV_Incidence_in_the_SEARCH_Trial_A.95905.aspx.

BACKGROUND: The SEARCH study provided community-based HIV and multi-disease testing and antiretroviral therapy (ART) to 32 communities in East Africa and reported no statistically significant difference in three-year HIV incidence. We used mathematical modelling to estimate the effect of control arm viral suppression and community mixing on SEARCH trial outcomes. **SETTING:** Uganda and Kenya.

METHODS: Using the individual-based HIV modeling software EMOD-HIV, we configured a new model of SEARCH communities. The model was parameterized using demographic, HIV prevalence, male circumcision, and viral suppression data, and calibrated to HIV prevalence, ART coverage, and population size. Using assumptions about ART scale-up in the control arm, degree of community mixing, and effect of baseline testing, we estimated comparative HIV incidence under multiple scenarios.

RESULTS: Prior to the trial results, we predicted that SEARCH would report a 4-40% reduction between arms, depending on control arm ART linkage rates and community mixing. With universal baseline testing followed by rapidly expanded ART eligibility and uptake, modelled effect sizes were smaller than the study was powered to detect. Using interim viral suppression data, we estimated three-year cumulative incidence would have been reduced by up to 27% in the control arm and 43% in the intervention arm compared to a counterfactual without universal baseline testing.

CONCLUSIONS: Our model suggests that the active control arm substantially reduced expected effect size and power of the SEARCH study. However, compared to a counterfactual "true control" without increased ART linkage due to baseline testing, SEARCH reduced HIV incidence by up to 43%.

Cost and cost-effectiveness

1. Thomas, R., et al. **Cost and cost-effectiveness of a universal HIV testing and treatment intervention in Zambia and South Africa: evidence and projections from the HPTN 071 (PopART) trial.** *Lancet Glob Health* 2021 Mar 12;S2214-109X(21)00034-6. Online ahead of print.

Online at: [https://www.thelancet.com/journals/langlo/article/PIIS2214-109X\(21\)00034-6/fulltext](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(21)00034-6/fulltext).

BACKGROUND: The HPTN 071 (PopART) trial showed that a combination HIV prevention package including universal HIV testing and treatment (UTT) reduced population-level incidence of HIV compared with standard care. However, evidence is scarce on the costs and cost-effectiveness of such an intervention.

METHODS: Using an individual-based model, we simulated the PopART intervention and standard care with antiretroviral therapy (ART) provided according to national guidelines for the 21 trial communities in Zambia and South Africa (for all individuals aged >14 years), with model parameters and primary cost data collected during the PopART trial and from published sources. Two intervention scenarios were modelled: annual rounds of PopART from 2014 to 2030 (PopART 2014-30; as the UNAIDS Fast-Track target year) and three rounds of PopART throughout the trial intervention period (PopART 2014-17). For each country, we calculated incremental cost-effectiveness ratios (ICERs) as the cost per disability-adjusted life-year (DALY) and cost per HIV infection averted. Cost-effectiveness acceptability curves were used to indicate the probability of PopART being cost-effective compared with standard care at different thresholds of cost per DALY averted. We also assessed budget impact by projecting undiscounted costs of the intervention compared with standard care up to 2030.

FINDINGS: During 2014-17, the mean cost per person per year of delivering home-based HIV counselling and testing, linkage to care, promotion of ART adherence, and voluntary

medical male circumcision via community HIV care providers for the simulated population was US\$6.53 (SD 0.29) in Zambia and US\$7.93 (0.16) in South Africa. In the PopART 2014-30 scenario, median ICERs for PopART delivered annually until 2030 were \$2111 (95% credible interval [CrI] 1827-2462) per HIV infection averted in Zambia and \$3248 (2472-3963) per HIV infection averted in South Africa; and \$593 (95% CrI 526-674) per DALY averted in Zambia and \$645 (538-757) per DALY averted in South Africa. In the PopART 2014-17 scenario, PopART averted one infection at a cost of \$1318 (1098-1591) in Zambia and \$2236 (1601-2916) in South Africa, and averted one DALY at \$258 (225-298) in Zambia and \$326 (266-391) in South Africa, when outcomes were projected until 2030. The intervention had almost 100% probability of being cost-effective at thresholds greater than \$700 per DALY averted in Zambia, and greater than \$800 per DALY averted in South Africa, in the PopART 2014-30 scenario. Incremental programme costs for annual rounds until 2030 were \$46.12 million (for a mean of 341 323 people) in Zambia and \$30.24 million (for a mean of 165 852 people) in South Africa.

INTERPRETATION: Combination prevention with universal home-based testing can be delivered at low annual cost per person but accumulates to a considerable amount when scaled for a growing population. Combination prevention including UTT is cost-effective at thresholds greater than \$800 per DALY averted and can be an efficient strategy to reduce HIV incidence in high-prevalence settings.

FUNDING: US National Institutes of Health, President's Emergency Plan for AIDS Relief, International Initiative for Impact Evaluation, Bill & Melinda Gates Foundation.

Epidemiological studies

1. Merzouki, A., et al. **Clusters of sub-Saharan African countries based on sociobehavioural characteristics and associated HIV incidence.** *PeerJ* 2021 Jan 15;9: e10660.

Online at: <https://peerj.com/articles/10660/>.

INTRODUCTION: HIV incidence varies widely between sub-Saharan African (SSA) countries. This variation coincides with a substantial sociobehavioural heterogeneity, which complicates the design of effective interventions. In this study, we investigated how sociobehavioural heterogeneity in sub-Saharan Africa could account for the variance of HIV incidence between countries.

METHODS: We analysed aggregated data, at the national-level, from the most recent Demographic and Health Surveys of 29 SSA countries (2010-2017), which included 594,644 persons (183,310 men and 411,334 women). We preselected 48 demographic, socio-economic, behavioural and HIV-related attributes to describe each country. We used Principal Component Analysis to visualize sociobehavioural similarity between countries, and to identify the variables that accounted for most sociobehavioural

variance in SSA. We used hierarchical clustering to identify groups of countries with similar sociobehavioural profiles, and we compared the distribution of HIV incidence (estimates from UNAIDS) and sociobehavioural variables within each cluster.

RESULTS: The most important characteristics, which explained 69% of sociobehavioural variance across SSA among the variables we assessed were: religion; male circumcision; number of sexual partners; literacy; uptake of HIV testing; women's empowerment; accepting attitude toward people living with HIV/AIDS; rurality; ART coverage; and, knowledge about AIDS. Our model revealed three groups of countries, each with characteristic sociobehavioural profiles. HIV incidence was mostly similar within each cluster and different between clusters (median (IQR); 0.5/1000 (0.6/1000), 1.8/1000 (1.3/1000) and 5.0/1000 (4.2/1000)).

CONCLUSIONS: Our findings suggest that the combination of sociobehavioural factors play a key role in determining the course of the HIV epidemic, and that similar techniques can help to predict the effects of behavioural change on the HIV epidemic and to design targeted interventions to impede HIV transmission in SSA.

2. Hines, J. Z., et al. **HIV incidence by male circumcision status from the population-based HIV impact assessment (PHIA) surveys-eight sub-Saharan African countries, 2015-2017 [abstract].** *J Acquir Immune Defic Syndr* 2021 Mar 16. Online ahead of print.

Online at:

https://journals.lww.com/jaids/Abstract/9000/HIV_incidence_by_male_circumcision_status_from_the.95908.aspx.

BACKGROUND: Male circumcision (MC) offers men lifelong partial protection from heterosexually-acquired HIV infection. The impact of MC on HIV incidence has not been quantified in nationally-representative samples. Data from the Population-based HIV Impact Assessments (PHIAs) were used to compare incidence by MC status in countries implementing voluntary medical MC (VMMC) programs.

METHODS: Data were pooled from PHIAs conducted in Eswatini, Lesotho, Malawi, Namibia, Tanzania, Uganda, Zambia and Zimbabwe from 2015-2017. Incidence was measured using a recent infection testing algorithm, and analyzed by self-reported MC status distinguishing between medical and non-medical MC. Country, marital status, urban setting, sexual risk behaviors, and mean population HIV viral load among women as an indicator of treatment scale-up were included in a random effects logistic regression model using pooled survey weights. Analyses were age-stratified (15-34 and 35-59 years). Annualized incidence rates and 95% confidence intervals (CIs) and incidence differences were calculated between medically circumcised and uncircumcised men.

RESULTS: Men 15-34 years reporting medical MC had lower HIV incidence than uncircumcised men (0.04% [95% CI: 0.00, 0.10%] versus 0.34% [95% CI: 0.10, 0.57%], respectively; p-value = 0.01); whereas among men 35-59 years, there was no significant incidence difference (1.36% [95% CI: 0.32, 2.39%] versus 0.55% [95% CI: 0.14, 0.67%], respectively; p-value = 0.14).

DISCUSSION: Medical MC was associated with lower HIV incidence in men aged 15-34 years in nationally-representative surveys in Africa. These findings are consistent with the expected ongoing VMMC program impact and highlight the importance of VMMC for the HIV response in Africa.

3. Mapingure, M., et al. **Understanding HIV and associated risk factors among religious groups in Zimbabwe.** *BMC Public Health* 2021;21(1):375.

Online at: <https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-021-10405-8>.

BACKGROUND: The influence of religion and belief systems is widely recognized as an important factor in understanding of health risk perception and myths in the general fight against the HIV pandemic. This study compares the understanding of HIV risk factors and utilization of some HIV services among religious groups in Zimbabwe.

METHODS: We conducted secondary data statistical analysis to investigate the understanding of HIV and associated risk factors among religious groups in Zimbabwe using 2015-2016 Zimbabwe Demographic and Health Survey (ZDHS) data. We began by investigating associations between understanding of HIV and associated risk factors among religious groups. A multivariate stepwise backward elimination method was carried out to explore factors determining understanding of HIV risk after controlling for confounding factors using the most recent ZDHS data (2015-2016).

RESULTS: The results from the three surveys showed that, in general apostolic sector had low understanding of HIV and associated risk factors compared to other religious groups. Analysis of the 2015-2016 ZDHS data showed that women belonging to the apostolic sector were less likely to know where to get an HIV test odds ratio (OR) and 95% confidence interval, 0.665 (0.503-0.880) and to know that male circumcision reduces HIV transmission OR 0.863 (0.781-0.955). Women from this group had no knowledge that circumcised men can be infected if they do not use condoms OR 0.633 (0.579-0.693), nor that it is possible for a healthy-looking person to have HIV, OR 0.814 (0.719-0.921). They would not buy vegetables from a vendor with HIV OR 0.817 (0.729-0.915) and were less likely to support that HIV positive children should be allowed to attend school with HIV negative children OR 0.804 (0.680-0.950). Similar results were obtained for men in the apostolic sector. These men also did not agree that women were justified to use condoms if the husband has an Sexually Transmitted Infection (STI) OR 0.851 (0.748-0.967).

CONCLUSIONS: Our results suggest that apostolic sector lack adequate knowledge of HIV and associated risk factors than other religious groups. Targeting HIV prevention programmes by religious groups could be an efficient approach for controlling HIV in Zimbabwe.

Enhancing uptake of VMMC

1. Msungama, W., et al. **Sexually transmitted infections (STI) and antenatal care (ANC) clinics in Malawi: effective platforms for improving engagement of men at high HIV risk with voluntary medical male circumcision services.** *Sex Transm Infect* 2021 Jan 4;sextrans-2020-054776. Online ahead of print.

Online at: <https://sti.bmj.com/content/early/2021/01/03/sextrans-2020-054776.long>.

INTRODUCTION: Voluntary medical male circumcision (VMMC), an effective HIV prevention programme for men, is implemented in East and Southern Africa. Approximately 50% of VMMC clients are aged below 15 years. More targeted interventions to reach older men and others at higher short-term HIV risk are needed.

METHODS: We implemented a quality improvement project testing the effectiveness of an active referral-based VMMC recruitment approach, targeting men attending STI clinics and those escorting partners to antenatal care (ANC) clinics, at Bwaila Hospital in Lilongwe, Malawi. We compared the proportions aged older than 15 years among men who received VMMC following referral from STI and ANC clinics with those among men referred from standard community mobilisation. We also analysed referral cascades to VMMC.

RESULTS: In total, 330 clients were circumcised after referral from STI (242) and ANC (88) clinics, as compared with 3839 other clients attributed to standard community mobilisation. All clients from ANC and STI clinics were aged over 15 years, as compared with 69% from standard community mobilisation. STI clinics had a higher conversion rate from counselling to VMMC than ANC (12% vs 9%) and a higher contribution to total circumcisions performed at the VMMC clinic (6% vs 2%).

CONCLUSIONS: Integrating VMMC recruitment and follow-up in STI and ANC clinics co-located with VMMC services can augment demand creation and targeting of men at risk of HIV, based on age and STI history. This approach can be replicated at least in similar health facilities with ANC and STI services in close proximity to VMMC service delivery.

Impact and coverage

1. Davis, S. M., et al. **Brief report: modeling the impact of voluntary medical male circumcision on cervical cancer in Uganda.** *J Acquir Immune Defic Syndr* 2021;86(3): 323-328.

Online at:

https://journals.lww.com/jaids/Fulltext/2021/03010/Brief_Report_Modeling_the_Impact_of_Voluntary.11.asp.

BACKGROUND: In addition to providing millions of men with lifelong lower risk for HIV infection, voluntary medical male circumcision (VMMC) also provides female partners with health benefits including decreased risk for human papillomavirus (HPV) and resultant cervical cancer (CC).

SETTING: We modeled potential impacts of VMMC on CC incidence and mortality in Uganda as an additional benefit beyond HIV prevention.

METHODS: HPV and CC outcomes were modeled using the CC model from the Spectrum policy tool suite, calibrated for Uganda, to estimate HPV infection incidence and progression to CC, using a 50-year (2018-2067) time horizon. 2016 Demographic Health Survey data provided baseline VMMC coverage. The baseline (no VMMC scale-up beyond current coverage, minimal HPV vaccination coverage) was compared with multiple scenarios to assess the varying impact of VMMC according to different implementations of HPV vaccination and HPV screening programs.

RESULTS: Without further intervention, annual CC incidence was projected to rise from 16.9 to 31.2 per 100,000 women in 2067. VMMC scale-up alone decreased 2067 annual CC incidence to 25.3, averting 13,000 deaths between 2018 and 2067. With rapidly-achieved 90% HPV9 vaccination coverage for adolescent girls and young women, 2067 incidence dropped below 10 per 100,000 with or without a VMMC program. With 45% vaccine coverage, the addition of VMMC scaleup decreased incidence by 2.9 per 100,000 and averted 8000 additional deaths. Similarly, with HPV screen-and-treat without vaccination, the addition of VMMC scaleup decreased incidence by 5.1 per 100,000 and averted 10,000 additional deaths.

CONCLUSIONS: Planned VMMC scale-up to 90% coverage from current levels could prevent a substantial number of CC cases and deaths in the absence of rapid scale-up of HPV vaccination to 90% coverage.

2. Matoga, M., et al. **Effects of HIV voluntary medical male circumcision programs on sexually transmitted infections [abstract]**. *Curr Opin Infect Dis* 2021;34(1): 50-55.

Online at: https://journals.lww.com/co-infectiousdiseases/Abstract/2021/02000/Effects_of_HIV_voluntary_medical_male_circumcision.8.aspx.

PURPOSE OF REVIEW: Evidence of the protective effect of voluntary medical male circumcision (VMMC) against HIV is well established. However, evidence of the protective effect of VMMC against other sexually transmitted infections (STIs) has been inconsistent or scarce across different populations and settings. This review summarizes the current evidence on the effect of VMMC for HIV prevention on acquisition and transmission of other STIs in heterosexual men, women, and men who have sex with men (MSM).

RECENT FINDINGS: Recent findings continue to strongly support the protective effect of male medical circumcision against acquisition and transmission of herpes simplex virus type 2 (HSV-2), human papillomavirus (HPV) and syphilis infections in heterosexual men and women, and bacterial vaginosis and trichomoniasis in women. There is emerging evidence on the protective effect of VMMC against acquisition of hepatitis B and *Mycoplasma genitalium* infections in heterosexual men, and HSV-2, HPV, and syphilis in MSM.

SUMMARY: Evidence on the protective effect of VMMC against acquisition and transmission of common STIs is available for heterosexual men and women but more evidence is required for MSM. This review supports policy recommendations for the protective benefits of VMMC against STIs.

3. Korenromp, E. L., et al. **The impact of the program for medical male circumcision on HIV in South Africa: analysis using three epidemiological models**. *Gates Open Res* 2021;5: 15.

Online at: <https://gatesopenresearch.org/articles/5-15/v1>.

BACKGROUND: South Africa began offering medical male circumcision (MMC) in 2010. We evaluated the current and future impact of this program to see if it is effective in preventing new HIV infections.

METHODS: The Thembisa, Goals and Epidemiological Modeling Software (EMOD) HIV transmission models were calibrated to South Africa's HIV epidemic, fitting to household survey data on HIV prevalence, risk behaviors, and proportions of men circumcised, and to programmatic data on intervention roll-out including program-reported MMCs over 2009-2017. We compared the actual program accomplishments through 2017 and program targets through 2021 with a counterfactual scenario of no MMC program.

RESULTS: The MMC program averted 71,000-83,000 new HIV infections from 2010 to 2017. The future benefit of the circumcision already conducted will grow to 496,000-518,000 infections (6-7% of all new infections) by 2030. If program targets are met by 2021 the benefits will increase to 723,000-760,000 infections averted by 2030. The cost would be \$1,070-1,220 per infection averted relative to no MMC. The savings from averted treatment needs would become larger than the costs of the MMC program around 2034-2039. In the Thembisa model, when modelling South Africa's 9 provinces individually, the 9-provinces-aggregate results were similar to those of the single national model. Across provinces, projected long-term impacts were largest in Free State, KwaZulu-Natal and Mpumalanga (23-27% reduction over 2017-2030), reflecting these provinces' greater MMC scale-up.

CONCLUSIONS: MMC has already had a modest impact on HIV incidence in South Africa and can substantially impact South Africa's HIV epidemic in the coming years.

Male circumcision methods, including devices

1. Hohlfeld, A., et al. **Circumcision devices versus standard surgical techniques in adolescent and adult male circumcisions.** *Cochrane Database Syst Rev* 2021 Mar;3: CD012250.

Online at:

<https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012250.pub2/full>.

BACKGROUND: Medical circumcisions are among the most common surgical procedures performed in males. The usual indications are phimosis (inability to completely retract the foreskin and expose the glans due to a congenital or acquired constriction of the prepuce), paraphimosis (when the foreskin is not pulled back over the glans after retraction resulting in a tight constricting band which causes swelling of the distal penis and acute discomfort), balanoposthitis (erythema and edema of the prepuce and glans) and balanitis (inflammation is confined to the glans; the foreskin is usually non-retractile). Circumcision devices have been developed to shorten the operative time, simplify techniques, and improve safety and cosmetic outcomes. The devices generally aim to crush the foreskin while simultaneously creating hemostasis, the foreskin is then excised or allowed to slough off. Their use is supposedly safer and easier to replicate than the standard dissection techniques. There are at least 20 devices for male circumcision on the market, yet their effectiveness has not been reviewed to date.

OBJECTIVES: To assess the effects of device-based circumcisions compared with standard surgical techniques in adolescent and adult males (10 years old and above).

SEARCH METHODS: We performed a comprehensive search with no restrictions to the language of publication or publication status. We searched the Cochrane Library,

MEDLINE (PubMed), Embase, Web of Science, trials registries, grey literature sources and conference proceedings up to 16 April 2020.

SELECTION CRITERIA: We included randomized controlled trials of device-based circumcisions (crush or ligature circumcision devices) compared to standard surgical dissection-based circumcision conducted by health professionals in a medical setting.

DATA COLLECTION AND ANALYSIS: At least two review authors independently assessed study eligibility and extracted data from the included studies. We classified adverse events into serious, moderate or mild. We reported study results as risk ratios (RR) or mean differences (MD) using 95% confidence intervals (CI) and a random-effects model. We used the GRADE approach to evaluate the overall certainty of the evidence for each outcome.

MAIN RESULTS: Eighteen trials met the inclusion criteria. Trials were conducted in China, South Africa, Kenya and Zambia, Mozambique, Rwanda, Uganda and Zimbabwe.

Primary outcomes: there were no serious adverse events in either treatment arm (11 trials, 3472 participants). Moderate adverse events: there may be a slight increase in moderate adverse events when devices are used compared to standard surgical techniques (RR 1.31, 95% CI 0.55 to 3.10; $I(2) = 68\%$; 10 trials, 3370 participants; low-certainty evidence); this corresponds to 8 more (ranging from 15 fewer to 84 more) moderate adverse events per 1000 participants. We downgraded the certainty of the evidence for study limitations and imprecision.

Secondary outcomes: Mild adverse events: we are uncertain about the difference in mild adverse events between groups when devices are used compared to standard surgical techniques (RR 1.09, 95% CI 0.44 to 2.72; $I(2) = 91\%$; 10 trials, 3370 participants; very low-certainty evidence). We downgraded the certainty of the evidence for study limitations, imprecision and unexplained inconsistency. Operative time: operative time is probably about 17 minutes shorter when using a device rather than standard surgical techniques, which constitutes a clinically meaningful decrease in a procedure (MD -17.26 minutes, 95% CI -19.96 to -14.57; $I(2) = 99\%$; 14 trials, 4812 participants; moderate-certainty evidence). We downgraded the certainty of the evidence for serious study limitations. The standard surgical technique generally takes about 24 minutes. There may be less postoperative pain during the first 24 hours when circumcision devices are used compared to standard surgical techniques (measured using a visual analog scale [VAS]; MD 1.30 cm lower, 95% CI 2.37 lower to 0.22 lower; $I(2) = 99\%$; 9 trials, 3022 participants; low-certainty evidence). We downgraded the certainty of the evidence for study limitations and unexplained heterogeneity. There may be little or no difference in postoperative pain experienced during the first seven days when compared with standard surgical techniques (measured using a VAS; MD 0.11 cm higher,

95% CI 0.89 lower to 1.11 higher; $I(2) = 94\%$; 4 trials, 1430 participants; low-certainty evidence). We downgraded the certainty of the evidence for study limitations and unexplained inconsistency. A higher score on the VAS indicates greater pain. Participants may slightly prefer circumcision devices compared to standard surgical techniques (RR 1.19, 95% CI 1.04 to 1.37; $I(2) = 97\%$; 15 trials, 4501 participants; low-certainty evidence). We downgraded the certainty of the evidence for study limitations and unexplained inconsistency. We recorded satisfaction as a dichotomous outcome. Higher rates reflected greater satisfaction.

AUTHORS' CONCLUSIONS: We found that there were no serious adverse events reported when using a circumcision device compared to standard surgical techniques, but they may slightly increase moderate adverse effects, and it is unclear whether there is a difference in mild adverse effects. Use of circumcision devices probably reduces the time of the procedure by about 17 minutes, a clinically meaningful time saving. For patients, use of the circumcision device may result in lower pain scores during the first 24 hours and patients may be slightly more satisfied with it compared with standard surgical techniques. Clinicians, patients and policymakers can use these results in conjunction with their own contextual factors to inform the approach that best suits their healthcare settings. High-quality trials evaluating this intervention are needed to provide further certainty regarding the rates of adverse effects and postoperative pain of using devices compared to standard approaches.

Safety

1. Shabanzadeh, D. M., et al. **Male circumcision complications - a systematic review, meta-analysis and meta-regression [abstract]**. *Urology* 2021 Feb 2;S0090-4295(21)00113-8.

Online at: [https://goldjournal.net/article/S0090-4295\(21\)00113-8/fulltext](https://goldjournal.net/article/S0090-4295(21)00113-8/fulltext).

OBJECTIVE: To determine the risk of complications requiring treatment following male circumcision by health-care professionals and to explore the impact of participant characteristics, type of circumcision and study design.

METHODS: We identified studies through systematic searches in online databases (MEDLINE, EMBASE and CENTRAL) and hand searches. We performed random-effects meta-analysis to determine risk of circumcision complications and mixed-effects metaregression analyses to explore the impact of participant characteristics, type of circumcision and study design. Methods were prespecified in a registered protocol (Prospero CRD42020116770) and according to PRISMA guidelines.

RESULTS: We included 351 studies with 4,042,988 participants. Overall complication risk was 3.84% (95% confidence interval 3.35-4.37). Our meta-analysis revealed that therapeutic circumcisions were associated with a 2-fold increase in complications as

compared to nontherapeutic (7.47% and 3.34%, respectively). Adhesions, meatal stenosis and infections were the most frequent complication subgroups to therapeutic circumcisions. Bleeding, device removals and infections occurred more frequently in nontherapeutic circumcisions. Additionally, adjusted metaregression analyses revealed that children above 2 years, South American continent, older publication year and smaller study populations increased complication risk. Type of circumcision method, provider and setting were not associated with complication risk. Sensitivity analyses including only better-quality studies reporting indication, age at circumcision, treatment for complications, full-text articles, and adequate follow-up clinically for a minimum of one month or through databases confirmed our main findings while accounting better for heterogeneity.

CONCLUSION: Circumcision complications occur in about 4 per hundred circumcisions. Higher risks of complications were determined by therapeutic circumcisions and by childhood age when compared to infant. Future studies should assess therapeutic and childhood circumcisions separately.

2. Lucas, T., et al. **Urethrocutaneous fistulas after voluntary medical male circumcision for HIV prevention-15 African Countries, 2015-2019.** *BMC Urol* 2021;21(1): 23.

Online at: <https://bmcurol.biomedcentral.com/articles/10.1186/s12894-021-00790-y>.

BACKGROUND: Voluntary medical male circumcision (VMMC) is an HIV prevention strategy recommended to partially protect men from heterosexually acquired HIV. From 2015 to 2019, the President's Emergency Plan for AIDS Relief (PEPFAR) has supported approximately 14.9 million VMMCs in 15 African countries. Urethrocutaneous fistulas, abnormal openings between the urethra and penile skin through which urine can escape, are rare, severe adverse events (AEs) that can occur with VMMC. This analysis describes fistula cases, identifies possible risks and mechanisms of injury, and offers mitigation actions.

METHODS: Demographic and clinical program data were reviewed from all reported fistula cases during 2015 to 2019, descriptive analyses were performed, and an odds ratio was calculated by patient age group.

RESULTS: In total, 41 fistula cases were reported. Median patient age for fistula cases was 11 years and 40/41 (98%) occurred in patients aged < 15 years. Fistulas were more often reported among patients < 15 compared to \geq 15 years old (0.61 vs. 0.01 fistulas per 100,000 VMMCs, odds ratio 50.9 (95% confidence interval [CI] = 8.6-2060.0)). Median time from VMMC surgery to appearance of fistula was 20 days (interquartile range (IQR) 14-27).

CONCLUSIONS: Urethral fistulas were significantly more common in patients under age 15 years. Thinner tissue overlying the urethra in immature genitalia may predispose

boys to injury. The delay between procedure and symptom onset of 2-3 weeks indicates partial thickness injury or suture violation of the urethral wall as more likely mechanisms of injury than intra-operative urethral transection. This analysis helped to inform PEPFAR's recent decision to change VMMC eligibility policy in 2020, raising the minimum age to 15 years.