

Quarterly Research Digest on Voluntary Medical Male Circumcision for HIV Prevention

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Biological mechanisms

1. Galiwango, R. M., et al. **Immune milieu and microbiome of the distal urethra in Ugandan men: impact of penile circumcision and implications for HIV susceptibility.** *Microbiome*. 2022;10(1):7.

Online at: <https://microbiomejournal.biomedcentral.com/articles/10.1186/s40168-021-01185-9>.

BACKGROUND: Coronal sulcus (CS) anaerobe abundance and IL-8 levels are linked to HIV acquisition, and are dramatically reduced after penile circumcision (PC). The distal urethra may be the site of some HIV acquisition before PC, and presumably most acquisition post PC. We describe the immune milieu and microbiome of the distal urethra in uncircumcised Ugandan men, and define the impact of PC. Participants consisted of HIV-negative, genital symptom-free adult Ugandan men undergoing PC (n = 51). Urethral and coronal sulcus swabs were collected at baseline and at 6- and 12-months post-PC. Soluble immune factors were quantified by multiplex ELISA, and bacterial abundance assessed by 16S rRNA qPCR and sequencing.

RESULTS: At baseline, the urethra was enriched compared to the CS for most cytokines (including IL-8 and MIP-1beta) and soluble E-cadherin (sE-cadherin, an epithelial disruption marker), although CS levels of IL-1alpha and IL-1beta were higher. Baseline total bacterial abundance was \geq 20-fold higher in the CS than the urethra (median 27,100 vs. 1200 gene copies/swab, $p = 0.001$), and anaerobes comprised 58% of CS bacteria vs. 42% of urethral bacteria. PC did not alter urethral IL-8 (median 806 at baseline vs. 1130 pg/ml at 12 months; $p = 0.062$) and urethral sE-cadherin increased

(113,223 vs. 158,385 pg/ml, $p = 0.009$), despite five- and sevenfold drops in total bacterial and anaerobe abundance after PC, respectively. However, PC dramatically reduced CS levels of sE-cadherin (15,843 vs. 837 pg/ml, $p < 0.001$) and most cytokines (IL-8; 34 vs. 3 pg/ml, $p < 0.001$), while reducing total bacterial and anaerobe abundance by 13-fold and 60-fold, respectively (both $P \leq 0.004$).

CONCLUSIONS: The urethra is immunologically rich with characteristics of an HIV-susceptible tissue site. However, PC had no impact on urethral immunology and may have reduced epithelial integrity, despite modest reductions in total bacteria and anaerobes, suggesting that HIV protection from PC is not mediated via immune or microbiome alterations in the urethra.

Combination HIV prevention

1. Conserve, D. F., et al. **Assessing the efficacy of an integrated intervention to create demand for fishermen's schistosomiasis and HIV services (FISH) in Mangochi, Malawi: Study protocol for a cluster randomized control trial.** *PLoS One.* 2022;17(1):e0262237.

Online at: <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0262237>.

BACKGROUND: Both HIV and schistosomiasis are major public health problems worldwide with 1.8 million new HIV infections, and up to 110 million untreated schistosomiasis cases globally. Although a causal link has not been established, there are strong suggestions that having schistosomiasis increases onward transmission of HIV from co-infected men to women. With both HIV and schistosomiasis treatment readily available in Malawi, there is a need to investigate the feasibility, acceptability and health impacts of joint management of these two hazards, with special focus on health education and demand-creation for fishermen. The aim of this project is to identify optimal models of delivering integrated HIV and schistosomiasis services for fishermen, particularly investigating the effect of using social networks, HIV self-test kits and beach clinic services in Mangochi, Malawi.

METHODS: We have mapped 45 boat teams or landing sites for a 3-arm cluster randomized trial using "boat team" as the unit of randomization. The three arms are: 1) Standard of care (SOC) with leaflets explaining the importance of receiving presumptive treatment for schistosomiasis (praziquantel) and HIV services for fishermen, and two intervention arms of 2) SOC + a peer explaining the leaflet to his fellow fishermen in a boat team; and 3) arm 2 with HIV self-test kits delivered to the boat team fishermen by the peer. The primary outcomes measured at 9 months of trial delivery will compare differences between arms in the proportions of boat-team fishermen: 1) who self-report starting antiretroviral therapy or undergoing voluntary medical male circumcision; and

2) who have ≥ 1 *S. haematobium* egg seen on light microscopy of the filtrate from 10mls urine ("egg-positive").

DISCUSSION: This is the first evaluation of an integrated HIV and schistosomiasis services intervention for fishermen, particularly investigating the effect of using social networks, HIVST kits and beach clinic services. The findings will support future efforts to integrate HIVST with other health services for fishermen in similar settings if found to be efficacious.

TRIAL REGISTRATION: This trial is registered in the ISRCTN registry: ISRCTN14354324; date of registration: 05 October 2020.

<https://www.isrctn.com/ISRCTN14354324?q=ISRCTN14354324&filters=&sort=&offset=1&totalResults=1&page=1&pageSize=10&searchType=basic-search>.

2. Santelli, J. S., et al. **HIV combination prevention and declining orphanhood among adolescents, Rakai, Uganda, 2001-18: an observational community cohort study.** *Lancet HIV*. 2022;9(1):e32–e41.

Online at: [https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018\(21\)00275-7/fulltext](https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(21)00275-7/fulltext).

BACKGROUND: Orphanhood increased markedly in the 1980s and 1990s in sub-Saharan Africa because of HIV-related mortality. Little is known about the contribution of HIV interventions, such as antiretroviral therapy (ART) and male medical circumcision, to more recent trends in orphanhood. In this study, we examined trends over time in maternal-only, paternal-only, and double orphanhood among adolescents before and after ART and male medical circumcision became widely available in the Rakai region of south-central Uganda. We sought to understand the association between adolescent orphanhood and HIV combination prevention (community-level ART use and prevalence of male medical circumcision). We hypothesised that increasing combination prevention, including greater use of ART and higher prevalence of male medical circumcision, would be associated with a lower probability of orphanhood.

METHODS: We examined the prevalence of orphanhood among adolescents aged 15-19 years, before and after roll-out of ART in mid-2004 and male medical circumcision in 2007, using data from 28 continuously followed communities within the Rakai Community Cohort Study. We used multinomial logistic regression with clustered SEs to estimate adjusted relative risk ratios (RRs) for maternal-only, paternal-only, and double orphanhood compared with non-orphanhood over 11 survey rounds between 2001 and 2018. Controlling for community HIV prevalence, household socioeconomic status, and adolescent age, we examined the association between community prevalence of ART

use among people living with HIV and prevalence of male circumcision, including traditional circumcision. The primary outcome was orphanhood among adolescents aged 15-19 years.

FINDINGS: Orphanhood declined from 52% (920 of 1768 participants) in 2001-02 to 23% (592 of 2609 participants) by 2016-18 ($p < 0.0001$), while double orphanhood declined from 20% (346 of 1768 participants) to 3% (86 of 2609 participants) ($p < 0.0001$). Community prevalence of ART use among people living with HIV increased from 11% (105 of 945 participants) in 2005-06 to 78% (1163 of 1485 participants) in 2016-18. Male circumcision rates rose from 19% (147 of 790 participants) in 2005-06 to 65% (3535 of 5433 participants) in 2016-18. In the multinomial logistic regression model, a 10% increase in community prevalence of ART use was associated with a decrease in maternal orphanhood (adjusted relative RR 0.90, 95% CI 0.85-0.95) and double orphanhood (0.80, 0.75-0.85). In the post-ART era, a 10% increase in the community prevalence of male circumcision was associated with a decrease in paternal orphanhood (2005-18, adjusted relative RR 0.92, 0.87-0.97) and double orphanhood (0.91, 0.85-0.98).

INTERPRETATION: Widespread availability and uptake of HIV combination prevention was associated with marked reductions in orphanhood among adolescents. Reductions in orphanhood promise improved health and social outcomes for young people.

FUNDING: Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Institute of Allergy and Infectious Diseases, the National Institute of Mental Health, and the Division of Intramural Research of the National Institute for Allergy and Infectious Diseases.

3. Pelletier, A. R., et al. **Impact of the DREAMS program on new HIV diagnoses in adolescent girls and young women attending antenatal care - Lesotho, 2015-2020.** *MMWR Morb Mortal Wkly Rep.* 2022;71(2):48–51.

Online at:

https://www.cdc.gov/mmwr/volumes/71/wr/mm7102a3.htm?s_cid=mm7102a3_w.

Lesotho is a small, landlocked country in southern Africa with a population of approximately 2 million persons, approximately two thirds of whom live in rural areas (1). Lesotho has the second highest prevalence of HIV infection in the world (2). In 2017, 25.6% of persons aged 15-59 years living in Lesotho were HIV-positive (3). Strategies implemented in recent years to control HIV include efforts to reduce mother-to-child transmission and improve coverage with antiretroviral therapy, as well as increasing testing for HIV. Among persons aged 15-24 years, the HIV prevalence among females in

2017 (11.1%) was approximately three times that among males (3.4%) (3). The Determined, Resilient, Empowered, AIDS-Free, Mentored, and Safe (DREAMS)* program in Lesotho was started during October 2016 in two districts. DREAMS comprises a package of biomedical, behavioral, and structural interventions to address factors that make adolescent girls and young women vulnerable to HIV acquisition (4). The goal of the DREAMS program was to decrease HIV incidence among adolescent girls and young women by 25% after 1 year and by 40% after 2 years (4). After 3.5 years of program implementation in Lesotho, new HIV diagnoses among adolescent girls and young women attending antenatal care (ANC) decreased 71.4% in the two districts that implemented DREAMS compared with a reduction of 48.4% in three comparison districts without the program ($p = 0.002$). During 2016-2020, reductions in new HIV diagnoses among adolescent girls and young women attending ANC in Lesotho have been substantial, both in districts that have and have not implemented the DREAMS program (DREAMS and non-DREAMS districts). Apart from the DREAMS program, the decrease in new HIV diagnoses might be a result of the reduction in viral load in the population because more persons living with HIV infection became virally suppressed while on antiviral therapy, as well as other interventions such as preexposure prophylaxis, voluntary medical male circumcision, behavior change, and increased HIV diagnostic coverage.

Cost and cost-effectiveness

1. Kripke, K., et al. **The case for prevention - primary HIV prevention in the era of universal test and treat: a mathematical modeling study.** *EClinicalMedicine*. 2022;46:101347.

Online at: [https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370\(22\)00077-3/fulltext](https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(22)00077-3/fulltext).

BACKGROUND: As antiretroviral therapy (ART) has scaled up and HIV incidence has declined, some have questioned the continued utility of HIV prevention. This study examines the role and cost-effectiveness of HIV prevention in the context of "universal test and treat" (UTT) in three sub-Saharan countries with generalized HIV epidemics.

METHODS: Scenarios were created in Spectrum/Goals models for Lesotho, Mozambique, and Uganda with various combinations of voluntary medical male circumcision (VMMC); pre-exposure prophylaxis; and a highly effective, durable, hypothetical vaccine layered onto three different ART scenarios. One ART scenario held coverage constant at 2008 levels to replicate prevention modeling studies that were conducted prior to UTT. One scenario assumed scale-up to the UNAIDS treatment goals of 90-90-90 by 2025 and 95-95-95 by 2030. An intermediate scenario held ART constant at 2019 coverage. HIV incidence was visualized over time, and cost per HIV infection averted was assessed over 5-, 15-, and 30-year time frames, with 3% annual discounting.

FINDINGS: Each prevention intervention reduced HIV incidence beyond what was achieved by ART scale-up alone to the 90-90-90/95-95-95 goals, with near-zero incidence achievable by combinations of interventions covering all segments of the population. Cost-effectiveness of HIV prevention may decrease as HIV incidence decreases, but one-time interventions like VMMC and a durable vaccine may remain cost-effective and even cost-saving as ART is scaled up.

INTERPRETATION: Primary HIV prevention is still needed in the era of UTT. Combination prevention is more impactful than a single, highly effective intervention. Broad population coverage of primary prevention, regardless of cost-effectiveness, will be required in generalized epidemic countries to eradicate HIV.

Enhancing uptake of VMMC

1. Bowa, K., et al. **Dissemination of the Spear & Shield Project using a training of trainers model: A reflection on challenges and successes (abstract).** *Transl Behav Med.* 2022 Mar 21;13(1):1-13. Online ahead of print.

Online at: <https://academic.oup.com/tbm/advance-article-abstract/doi/10.1093/tbm/ibac013/6551578?redirectedFrom=fulltext&login=false>.

Several large-scale clinical trials have conclusively demonstrated that voluntary medical male circumcision (VMMC) could provide a 50%-70% reduction in HIV acquisition, but willingness to undergo VMMC has been lowest in Zambia compared to other countries in eastern and southern Africa. This manuscript describes training for "task-shifting" among local healthcare workers at Community Health Centers (CHCs) applying state of the art strategies (e.g., Training of Trainers, i.e., ToT, and Training of Facilitators, ToF) to provide novel clinical services. Staff at 96 CHCs from four Provinces in Zambia were sequentially trained to provide the Spear & Shield intervention. A total of 45,630 men (n = 23,236) and women (n = 22,394) volunteered to participate in the S&S intervention service program when offered in the CHCs. Group sessions (total = 5313 sessions; 2,736 men's and 2,582 women's sessions) were conducted over 4.5 years. Remarkably, both men and women's groups achieved 97% retention. Of these, 256 sessions recorded from 128 group leaders were assessed and scored for intervention fidelity; fidelity was 80%-90% among the majority of clinics. S&S program sustainment exceeded expectations among 85% of clinics (82/96) in all provinces across the duration of the study. Of note, attendance in the S&S program was encouraged by CHC staff, but no financial incentives were provided to those attending S&S. This study examined the effectiveness of the ToT/ToF model in dissemination of the S&S program, which proved to be feasible even in resource-limited settings. Benefits and challenges are discussed.

2. Cristofari, N. V., et al. **Understanding barriers and facilitators to voluntary medical male circumcision and Spear and Shield uptake in Zambian community health centers (abstract)**. *Transl Behav Med*. 2022 Feb 23;ibac007. Online ahead of print.

Online at: <https://academic.oup.com/tbm/advance-article-abstract/doi/10.1093/tbm/ibac007/6534854?redirectedFrom=fulltext&login=false>.

Voluntary medical male circumcision (VMMC) has been an effective method for reducing the risk of HIV transmission by 50%-70% in Eastern and Southern Africa. The Spear and Shield (S&S) program is a community health center (CHC)-based biobehavioral VMMC HIV prevention intervention that increased VMMC uptake in male CHC attendees in Lusaka, Zambia. Qualitative data organized using the Consolidated Framework for Implementation Research (CFIR) has been used to characterize factors that may impact S&S/VMMC implementation. This manuscript uses the CFIR to examine S&S implementation across 96 CHCs in four Zambian provinces using a mixed-methods approach to (a) quantify successful S&S implementation; (b) understand how CFIR domains might provide insight into the degree of implemental success; (c) identify major themes among least and most successful CHCs; and (d) help guide future prevention efforts and policy related to VMMC promotion in the Zambian CHC context. In contrast with CFIR quantitative analyses, 12 major qualitative themes associated with the least and most successful CHCs provided unique insight into S&S and VMMC implementation and guidance for future implementation studies. Themes included lack of resources (staff, space, transportation) for the former and strong staff relationships and active community engagement for the latter. The CFIR framework appears extremely useful for the identification of qualitative themes related to intervention implementation, and reduction of qualitative data for quantitative analyses may sacrifice more nuanced information. Consideration of CFIR themes may be useful to inform HIV prevention strategies in Zambia and similar contexts.

3. Matoga, M. M., et al. **Uptake of voluntary medical male circumcision among men with sexually transmitted infections in Lilongwe, Malawi: a protocol for a pre-interventional and post-interventional study**. *BMJ Open*. 2022;12(1):e057507.

Online at: <https://bmjopen.bmj.com/content/12/1/e057507>.

INTRODUCTION: Voluntary medical male circumcision (VMMC) is one of the key interventions for HIV prevention. However, its uptake among men in Malawi is low. Implementation science strategies for demand creation of VMMC increase uptake. We designed an implementation science demand-creation intervention to increase the uptake of VMMC among men with sexually transmitted infections (STIs).

METHODS AND ANALYSIS: We designed a pragmatic pre-interventional and post-interventional quasi-experimental study combined with a prospective observational design to determine the uptake, acceptability, appropriateness and feasibility of a multifaceted intervention for scale up of uptake of VMMC among men with STIs at Bwaila STI clinic in Lilongwe, Malawi. The intervention includes transport reimbursement (R), intensified health education (I) and short messaging service (SMS)/telephonic tracing (Te) (RITe). The intervention will be implemented in phases: pre-implementation and implementation. Pre-implementation phase will be used for collecting baseline data, while the RITe intervention will be rolled-out in the implementation phase. The RITe intervention will be implemented in a sequential and incremental manner called implementation blocks: block 1: intensified health education; block 2: intensified health education and SMS/telephonic tracing; and block 3: intensified health education, SMS/telephonic tracing and transport reimbursement. The target sample size is 80 uncircumcised men for each intervention block, including the pre-implementation sample, making a total of 320 men (280 total, 70 per block will be surveyed). The primary outcome is uptake of VMMC during the implementation period. Mixed methods assessments will be conducted to evaluate the acceptability, appropriateness and feasibility of the RITe intervention.

ETHICS AND DISSEMINATION: The study protocol was approved by the Malawi's National Health Sciences Research Ethics Committee (approval number: 19/10/2412), University of North Carolina at Chapel Hill's Institutional Review Board (approval number: 19-2559) and University of the Witwatersrand's Health Research Ethics Committee (approval number: M200328). Results will be disseminated via publication in a peer-reviewed journal and presentations at relevant scientific conferences and meetings.

TRIAL REGISTRATION NUMBER: NCT04677374.

4. Hamidouche, M., et al. **Monitoring socioeconomic inequalities across HIV knowledge, attitudes, behaviours and prevention in 18 sub-Saharan African countries (abstract).** *AIDS*. 2022 Feb 21. Online ahead of print.

Online at: <https://www.ncbi.nlm.nih.gov/pubmed/35190511>.

OBJECTIVES: Socioeconomic inequalities in HIV prevention services coverage constitute important barriers to global prevention targets, especially in sub-Saharan Africa (SSA). We aimed at monitoring these inequalities from population-based survey data in 18 SSA countries between 2010 and 2018.

METHODS: We defined eight HIV indicators aimed at capturing uptake of HIV prevention services among adult participants. Country-specific wealth-related inequalities were measured using the Relative and Slope Index of Inequalities (RII and SII, respectively) and then pooled using random-effects meta-analyses. We compared inequalities between African regions using the Wilcoxon rank-sum test.

RESULTS: The sample consisted of 358 591 participants (66% women). Despite variability between countries and indicators, the meta-analysis revealed significant levels of relative and absolute inequalities in six out of eight indicators: HIV-related knowledge, positive attitudes toward people with HIV (PWH), condom use at last sexual intercourse, participation to prevention of mother-to-child transmission programs, medical male circumcision and recent HIV testing. The largest inequalities were reported in condom use, with condom use reported five times more among the richest versus the poorest [RII = 5.02, 95% confidence interval (CI) 2.79-9.05] and in positive attitudes toward PWH, with a 32-percentage point difference between the richest and poorest (SII = 0.32, 95% CI 0.26-0.39). Conversely, no significant inequalities were observed in multipartnership and HIV seropositivity among youth. Overall, inequalities tended to be larger in West and Central vs. East and Southern African countries.

CONCLUSION: Despite efforts to scale-up HIV-prevention programs, socioeconomic inequalities remain substantial over the continuum of HIV primary and secondary prevention in several SSA countries.

Epidemiological studies

1. Ruangtragool, L., et al. **Factors associated with active syphilis among men and women aged 15 years and older in the Zimbabwe Population-based HIV Impact Assessment (2015-2016)**. *PLoS One*. 2022;17(3):e0261057.

Online at: <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0261057>.

INTRODUCTION: Ulcerative STIs, including syphilis, increase the risk for HIV acquisition and transmission due to the presence of ulcers/chancres that serve as a point-of-entry and exit for HIV. In Zimbabwe, diagnosis of syphilis often occurs in pregnant women who seek ANC services where syphilis testing is offered, and among men and women who seek health care for STIs. Zimbabwe's national syphilis estimates are based on these diagnosed cases, with little information available about the prevalence of untreated syphilis among the general population. This analysis uses data from ZIMPHIA (2015-2016) to describe factors associated with active syphilis among men and women ages 15 years and older.

METHODS: ZIMPHIA collected blood specimens for HIV and syphilis testing from 22,501 consenting individuals (ages 15 years and older). Household HIV testing used the national HIV rapid-testing algorithm with HIV-positive results confirmed at satellite laboratories using Geenius HIV-1/2 rapid test (Bio-rad, Hercules, California, USA). Point-of-care non-Treponemal and Treponemal syphilis testing was performed using Chembio's Dual-Path Platform Syphilis Screen & Confirm Assay. Factors associated with active syphilis were explored using multiple variable, weighted logistic regression and were stratified by gender.

RESULTS: The likelihood of active syphilis in HIV-positive females was 3.7 times greater in HIV-positive females than HIV-negative females (aOR: 3.7, 95% CI 2.3-5.9). Among males odds of having active syphilis was 5 times higher among those that engaged in transactional sex than those who did not have sex or transactional sex (aOR: 5.3, 95% CI 1.9-14.7), and 6 times higher if HIV positive versus negative (aOR: 5.9, 95% CI 3.0-12.0). Urban residence, province, education (highest attended), marital status, number of sex partners, consistency of condom use, pregnancy status (females), and circumcision status (males) were not significant in the adjusted model for either females or males.

CONCLUSION: HIV status was found to be the only factor associated with active syphilis in both females and males. Given the persistent link between HIV and active syphilis, it is prudent to link individuals' diagnoses and treatments, as recommended by the WHO. Enhanced integration of STI and HIV services in health delivery points such as ANC, reproductive services, or male circumcision clinics, combined with consistent, targeted outreach to high-risk populations and their partners, may assist the MOHCC to eliminate active syphilis in Zimbabwe.

Impact and coverage

1. Johnson, L. F., et al. **The effect of HIV programmes in South Africa on national HIV incidence trends, 2000-2019.** *J Acquir Immune Defic Syndr.* 2022 Feb 3. Online ahead of print.

Online at:

https://journals.lww.com/jaids/Abstract/9000/The_effect_of_HIV_programmes_in_South_Africa_on.95697.aspx.

BACKGROUND: Recent studies have shown HIV incidence declines at a population level in several African countries. However, these studies have not directly quantified the extent to which incidence declines are attributable to different HIV programmes.

METHODS: We calibrated a mathematical model of the South African HIV epidemic to age- and sex-specific data from antenatal surveys, household surveys and death

registration, using a Bayesian approach. The model was also parameterized using data on self-reported condom use, voluntary medical male circumcision (VMMC), HIV testing and antiretroviral treatment (ART). Model estimates of HIV incidence were compared against the incidence rates that would have been expected had each programme not been implemented.

RESULTS: The model estimated incidence in 15-49 year olds of 0.84% (95% CI: 0.75-0.96%) at the start of 2019. This represents a 62% reduction (95% CI: 55-66%) relative to 2000, a 47% reduction (95% CI: 42-51%) relative to 2010, and a 73% reduction (95% CI: 68-77%) relative to the incidence that would have been expected in 2019 in the absence of any interventions. The reduction in incidence in 2019 due to interventions was greatest for ART and condom promotion, with VMMC and behaviour change after HIV testing having relatively modest impacts. HIV programme impacts differed significantly by age and sex, with condoms and VMMC having greatest impact in youth, and overall incidence reductions being greater in men than in women.

CONCLUSIONS: HIV incidence in South Africa has declined substantially since 2000, with ART and condom promotion contributing most significantly to this decline.

Infant male circumcision

1. Harper, L., et al. **Circumcision and risk of febrile urinary tract infection in boys with posterior urethral valves: result of the CIRCUP randomized trial.** *Eur Urol.* 2022;81(1):64–72.

Online at:

<https://www.sciencedirect.com/science/article/pii/S030228382101993X?via%3Dihub>.

BACKGROUND: Boys with posterior urethral valves (PUVs) have an increased risk of febrile urinary tract infections (fUTIs). Circumcision is believed to reduce the risk of fUTIs in boys, although there are no randomized trials demonstrating this.

OBJECTIVE: To determine the effect of circumcision on the risk of fUTIs in boys with PUVs.

DESIGN, SETTING, AND PARTICIPANTS: A clinical randomized trial that ran between August 2012 and July 2017 was conducted. The trial was multicentric, including 13 referral centers for pediatric urology. Male boys, aged 1-28 d, diagnosed with posterior urethral valves, confirmed by voiding cystogram, were included. The exclusion criteria included presence of a genital malformation contraindicating performing a circumcision.

INTERVENTION: Participants were randomized to neonatal circumcision + antibiotic prophylaxis (CATB) or antibiotic prophylaxis alone (ATB), and followed for 2 yr.

OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS: The primary outcome was a risk of presenting fUTIs in each group. An fUTI was defined as fever (>38.5 degrees C) with evidence of pyuria and culture-proven infection on urinalysis, obtained by urethral catheterization or suprapubic aspiration. A bivariate analysis of the primary outcome was performed using the Kaplan-Meier method.

RESULTS AND LIMITATIONS: In total, 91 patients were included: 49 in group CATB and 42 in group ATB. The probability of presenting an fUTI was 20% in group ATB versus 3% in group CATB. The hazard ratio of presenting an fUTI within 2 yr in the ATB group compared with that in the CATB group was 10.3 (95% confidence interval: 1.3-82.5). Sixty-four children (70.3%) had a complete follow-up at 2 yr of age.

CONCLUSIONS: Circumcision significantly decreases the risk of presenting an fUTI in boys with PUVs.

PATIENT SUMMARY: In this report, we compared, in a multicentric trial, the number of febrile urinary tract infections (UTIs) in boys with posterior urethral valves who had either antibiotic prophylaxis alone or antibiotic prophylaxis and circumcision. We found that those who had a circumcision had a significantly lower risk of febrile UTIs.

2. Bellieni, C. V. **Neonatal Infant Pain Scale in assessing pain and pain relief for newborn male circumcision (abstract)**. *Int J Impot Res*. 2022 Mar 29. Online ahead of print.

Online at: <https://www.nature.com/articles/s41443-022-00551-x>.

Circumcision-partial or total removal of the penile prepuce-requires cutting nerve-laden, sensitive genital tissue and is therefore liable to be painful. The aim of this review is to evaluate the evidence concerning pain felt by newborns during circumcision and to determine whether current analgesic methods can eliminate such pain. I performed a search in medical databases, selecting the trials published in the last 20 years that assessed pain in neonatal circumcision. Twenty-three trials have been retrieved. To get reliable findings, those trials that used validated pain scales were selected; then it was investigated which trials had comparable data for using the same pain scale. The only pain scale that was used in more than two trials was the modified Neonatal Infant Pain Scale (mNIPS) that ranges 0-6. The results of these trials show that none of the analgesic strategies used obtained the absence of pain. Some differences between circumcision techniques can be noticed, but most assessments exceed the score of 3, chosen as the clinically significant pain.

3. Palmer, E., et al. **Parental decision-making in infant and child male circumcision: a case study in two townships in Gauteng, South Africa (abstract)**. *Afr J AIDS Res*. 2022;21(1):32–40.

Online at: <https://www.tandfonline.com/doi/abs/10.2989/16085906.2022.2038645>.

Parental decision-making in infant and child male circumcision is influenced by complex, interrelated factors on many levels. Several studies have highlighted reasons for the acceptance and non-acceptance of child male circumcision. This study investigates the factors that influence parental decision-making in this matter and proposes a parental decision-making framework. The study was conducted in the townships of Diepsloot and Diepkloof in Gauteng, South Africa, using 48 in-depth interviews with parents, grandparents and uncles of the boys, as well as government officials and members of civil society as part of an explorative case study. Purposive and snowball sampling were used to select the participants. Thematic analysis was used to analyse the data by applying the conceptual framework of Bronfenbrenner's ecological systems theory. Three main themes emerged from the data: microsystem factors related to health and hygiene, the father's circumcision status, cultural expectations, pain, the child's autonomy and the extended family; mesosystem factors related to early childhood development centres; and exosystem factors related to circumcision policies and financial considerations.

Safety and quality

1. Murenje, V., et al. **Urethrocutaneous fistula following VMMC: a case series from March 2013 to October 2019 in ZAZIC's voluntary medical male circumcision program in Zimbabwe** *BMC Urol*. 2022;22(1):20.

Online at: <https://bmcurol.biomedcentral.com/articles/10.1186/s12894-022-00973-1>.

BACKGROUND: Urethrocutaneous fistula (subsequently, fistula) is a rare adverse event (AE) in voluntary medical male circumcision (VMMC) programs. Global fistula rates of 0.19 and 0.28 per 100,000 VMMCs were reported. Management of fistula can be complex and requires expert skills. We describe seven cases of fistula in our large-scale VMMC program in Zimbabwe. We present fistula rates; provide an overview of initial management, surgical interventions, and patient outcomes; discuss causes; and suggest future prevention efforts.

RESULTS: Case details are presented on fistulas identified between March 2013 and October 2019. Among the seven fistula clients, ages ranged from 10 to 22 years; 6 cases were among boys under 15 years of age. All clients received surgical VMMC by trained providers in an outreach setting. Clients presented with fistulae 2-42 days after VMMC.

Secondary infection was identified in 6 of 7 cases. Six cases were managed through surgical repair. The number of repair attempts ranged from 1 to 10. One case healed spontaneously with conservative management. Fistula rates are presented as cases/100,000 VMMCs.

CONCLUSION: Fistula is an uncommon but severe AE that requires clinical expertise for successful management and repair. High-quality AE surveillance should identify fistula promptly and include consultation with experienced urologists. Strengthening provider surgical skills and establishment of standard protocols for fistula management would aid future prevention efforts in VMMC programs.

Social and behavioural research

1. Yuan, T., et al. **Acceptability of male circumcision for HIV prevention among men who have sex with men in China: a short report (abstract).** *AIDS Care.* 2022;34(3):371–78.

Online at:

<https://www.tandfonline.com/doi/abs/10.1080/09540121.2021.1917759?journalCode=caic20>.

Recent evidence shows that circumcision is associated with lower HIV prevalence among MSM. We assessed the acceptability of circumcision for preventing HIV and that of Shang Ring circumcision (SRC) among men who have sex with men (MSM) in China. 538 adult MSM were recruited from six cities in China between January and March 2019. Participants were surveyed by an online, self-administered questionnaire. The acceptability of circumcision was assessed before and after the potential protective effect of circumcision against HIV was informed, and subsequently men's willingness to undergo SRC was assessed. The level of circumcision was 16.4%. Of 450 uncircumcised MSM, their willingness to be circumcised in the following six months increased significantly from 32.2% to 55.6% after the information session. Three quarters of men who were willing to undergo circumcision accepted SRC. MSM who perceived that circumcision could maintain genital hygiene were more likely to accept circumcision after the information session, whereas those who regarded circumcision as an embarrassing surgery were disinclined to be circumcised. The low circumcision rate, along with its high acceptability in Chinese MSM, suggests a great potential benefit of circumcision intervention if proved effective. SRC might be a popular circumcision procedure in this population.

2. Orel, E., et al. **Prediction of HIV status based on socio-behavioural characteristics in East and Southern Africa.** *PLoS One.* 2022;17(3):e0264429.

Online at: <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0264429>.

INTRODUCTION: High yield HIV testing strategies are critical to reach epidemic control in high prevalence and low-resource settings such as East and Southern Africa. In this study, we aimed to predict the HIV status of individuals living in Angola, Burundi, Ethiopia, Lesotho, Malawi, Mozambique, Namibia, Rwanda, Zambia and Zimbabwe with the highest precision and sensitivity for different policy targets and constraints based on a minimal set of socio-behavioural characteristics.

METHODS: We analysed the most recent Demographic and Health Survey from these 10 countries to predict individual's HIV status using four different algorithms (a penalized logistic regression, a generalized additive model, a support vector machine, and a gradient boosting trees). The algorithms were trained and validated on 80% of the data, and tested on the remaining 20%. We compared the predictions based on the F1 score, the harmonic mean of sensitivity and positive predictive value (PPV), and we assessed the generalization of our models by testing them against an independent left-out country. The best performing algorithm was trained on a minimal subset of variables which were identified as the most predictive, and used to 1) identify 95% of people living with HIV (PLHIV) while maximising precision and 2) identify groups of individuals by adjusting the probability threshold of being HIV positive (90% in our scenario) for achieving specific testing strategies.

RESULTS: Overall 55,151 males and 69,626 females were included in the analysis. The gradient boosting trees algorithm performed best in predicting HIV status with a mean F1 score of 76.8% [95% confidence interval (CI) 76.0%-77.6%] for males (vs [CI 67.8%-70.6%] for SVM) and 78.8% [CI 78.2%-79.4%] for females (vs [CI 73.4%-75.8%] for SVM). Among the ten most predictive variables for each sex, nine were identical: longitude, latitude and, altitude of place of residence, current age, age of most recent partner, total lifetime number of sexual partners, years lived in current place of residence, condom use during last intercourse and, wealth index. Only age at first sex for male (ranked 10th) and Rohrer's index for female (ranked 6th) were not similar for both sexes. Our large-scale scenario, which consisted in identifying 95% of all PLHIV, would have required testing 49.4% of males and 48.1% of females while achieving a precision of 15.4% for males and 22.7% for females. For the second scenario, only 4.6% of males and 6.0% of females would have had to be tested to find 55.7% of all males and 50.5% of all females living with HIV.

CONCLUSIONS: We trained a gradient boosting trees algorithm to find 95% of PLHIV with a precision twice higher than with general population testing by using only a limited number of socio-behavioural characteristics. We also successfully identified people at high risk of infection who may be offered pre-exposure prophylaxis or voluntary medical male circumcision. These findings can inform the implementation of new high-yield HIV tests and help develop very precise strategies based on low-resource settings constraints.