HIV/AIDS Programme

USE OF DEVICES FOR ADULT MALE CIRCUMCISION IN PUBLIC HEALTH HIV PREVENTION PROGRAMMES:

CONCLUSIONS OF THE *TECHNICAL ADVISORY GROUP ON INNOVATIONS IN MALE CIRCUMCISION*

MARCH 2012

World Health Organization

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Acknowledgments

WHO would like to acknowledge all the participants at the meeting of the WHO Technical Advisory Group on Innovations in Male Circumcision in January 2012 (see Annex 1), particularly the co-chairs, Timothy Hargreave and Peter Cherutich, and also the electronic contributions of those members unable to attend the meeting. We would also like to acknowledge the researchers from Rwanda, who have shared their confidential data. The principal writers of this report were Ying-Ru Lo and Julia Samuelson, WHO Department of HIV/AIDS, and Timothy Farley, Sigma3 Services, Nyon, Switzerland.

CONTENTS

ABBREVIATIONS AND ACRONYMS

GRADE	Grading of Recommendations Assessment, Development and Evaluation
PEPFAR	US President's Emergency Plan for AIDS Relief
PICO	Patient or Population under consideration, the Intervention of interest, the Comparison or Control, and the Outcome
TAG	Technical Advisory Group on Innovations in Male Circumcision
UNAIDS	Joint United Nations Programme on HIV/AIDS
VAS	Visual analogue scale
WHO	World Health Organization

EXECUTIVE SUMMARY

Background

The WHO Global Health Sector Strategy on HIV/AIDS, 2011–2015, strives to reduce new HIV infections. This goal will be achieved only by implementing existing effective prevention technologies with sufficient intensity and scale. In March 2007 WHO and UNAIDS recommended male circumcision as an efficacious intervention for the prevention of heterosexually acquired HIV infection in men. It is recommended that countries with generalized HIV epidemics and a low prevalence of male circumcision progressively expand access to safe voluntary medical male circumcision services *(1)*.

As countries have begun implementing this intervention, several challenges have become evident, including uncertain client demand and limited human and material resources. Specifically, the number of physicians and surgeons available to perform the procedure is low, and the time and equipment required for the currently recommended standard surgical methods are substantial. Therefore, research is underway to identify innovative methods that are simpler, less resource-intensive, usable by non-physician providers, acceptable to clients and providers, and as safe as standard surgical male circumcision. Research on specific devices for adult male circumcision as alternative methods to standard surgical male circumcision has evolved over the past year, and Member States and supporting partners have requested guidance regarding use of the new devices.

WHO, through expert consultations, has defined a pathway for the clinical evaluation of male circumcision devices for use in public health programmes for HIV prevention *(2)*. The pathway includes an initial efficacy and safety study in the country of intended use, followed by a series of clinical studies consisting of a comparative study and a field study. For WHO global recommendations on use of devices as alternative methods for male circumcision, two series of clinical studies from different countries are required. Once the clinical performance of the device has been established, it is not necessary for the same type of safety and efficacy clinical studies to be repeated. By the end of 2011, a series of clinical studies was completed in one low-resource country, Rwanda, on one device that causes necrosis of the foreskin over one week through controlled radial compression with an elastic ring, after which the device and necrotic foreskin are removed. Safety and efficacy and comparative studies had been completed on another device that achieves haemostasis by compression of the foreskin between two non-elastic locking rings. The foreskin can be excised immediately after the device has been placed correctly, and the device remains in place for one week. Field studies with this device are underway in 2012.

Objectives, target audience and development of conclusions and recommendations

This report provides the conclusions and recommendations of the WHO Technical Advisory Group on Innovations in Male Circumcision (TAG) on use of a device as an alternative method to standard adult surgical procedures. The TAG met in January 2012 and the report was developed to advise Member States implementing voluntary medical male circumcision as a HIV prevention intervention in national programmes and supporting partners. Given the data available, the conclusions and recommendations focus on an elastic ring controlled radial compression device. As noted, data on this device were available from one series of clinical studies conducted in Rwanda. Additional data on at least this device and another type of device are expected within the year. The exact timing of further guidance depends on availability of evidence from studies still in progress.

This report is intended for national public health officials in countries implementing male circumcision for HIV prevention and for policy- and decision-makers, including funders, interested in the potential use of devices as additional methods for male circumcision in resource-limited settings. It may also be of interest to health workers and non-governmental organizations.

To review the data and develop the conclusions, WHO applied the GRADE approach for the development and review of recommendations *(3).* The approach, in brief, includes stating clear questions to be answered and specifying primary outcomes of interest, reviewing the literature, and grading the quality of the evidence for each question and outcome *(4).* Moving "from evidence to recommendation" for each question requires consideration of the quality of evidence, the balance of benefits and harms, values and preferences, resource use and feasibility. A separate document with the GRADE tables and evidence summaries will be made available once the study data are in the public domain.

Each participant of the TAG and consultants submitted a Declaration of Interests to the WHO Secretariat. No significant conflicts or potential conflicts of interests were identified that required any invited participant not to attend. One participant had been involved as a clinical researcher on the initial safety research of the device studied in Rwanda. As requested by the Secretariat, he did not contribute to discussions on the implications of the evidence or the formulation of recommendations, but he did provide technical information on the study.

Key conclusions from the January 2012 meeting of the Technical Advisory Group

The key recommendations of the WHO TAG cover the use of the device as an alternative to standard adult surgical methods and its use by specific types of providers.

I. Use of an elastic ring controlled radial compression device for adult male circumcision

1.1 The elastic ring controlled radial compression device for which data were available from one safety, one comparative, and one field study in one country (Rwanda) by the end of 2011 can be used in that same country (Rwanda), subject to approval/endorsement by the national programme, for phased implementation among men 18 years and older with rigorous monitoring for adverse events and side-effects.

It was recommended that the phased implementation include:

a) active surveillance of the first 1000 clients to identify and record all adverse events and side-effects based on standardized definitions. The active surveillance may change to passive surveillance after the first 1000 clients if the incidence of events is reassuringly low, as determined by independent review.

b) appropriate counselling on sexual abstinence and condom use[1] after male circumcision and before complete healing is always crucial, but it is particularly crucial with use of this device because the healing time is at least one week longer than with standard surgery.

c) access to standard surgical male circumcision services for the approximately 10–15% of adult men not clinically eligible for this device due to phimosis or narrow opening of the foreskin. Alternative acceptable and efficient service delivery models for men who are not eligible for this device method should be identified, and these models should be pilot-tested for feasibility.

1.2 The elastic ring controlled radial compression device for which data were available from one safety, one comparative, and one field study in one country (Rwanda) in 2011 is not yet recommended for use as an alternative method for male circumcision in national programmes outside the country where the first series of studies was conducted.

1 Condom use is also advised after healing since male circumcision only partially reduces the risk of sexual transmission of HIV from women to men. Male circumcision should be considered as part of a combination prevention package.

II. Use of the elastic ring controlled radial compression device by mid-level providers

In Rwanda, where a field study with this device has been completed, physicians and mid-level providers (nurses) who are appropriately trained and deemed competent can perform the placement and removal of the device for men 18 years and older, with careful monitoring during phased implementation in actual practice in different types of settings, with active surveillance of the first 1000 clients as indicated above.

Information gaps

Since the device has not been evaluated in men under age 18 years, bridging studies must be conducted to establish its performance and safety in younger populations. In addition, no systematic follow-up of clients has been done beyond nine weeks and longer-term follow-up of selected clients must be completed to document wound healing and final cosmetic result one year after the procedure. Since there are limited data in men with HIV infection or those with other immuno-compromising co-morbidities such as diabetes, the performance and safety of the device in such clients must be documented. Service delivery models will need to be tested to identify efficient approaches to delivering the entire minimum service package and ensuring access to male circumcision for those men excluded for device-specific contraindications.

Data from independent studies in countries other than Rwanda are necessary before a recommendation can be generalized beyond the country where the initial three studies were conducted. A comparative and a field study to assess the safety, efficacy and acceptability of the device in another country are underway. The TAG encourages the studies to be completed so results would be available during 2012. The TAG recommended that national programmes interested in exploring the potential of devices within voluntary medical male circumcision for HIV prevention public health programmes, in advance of a global recommendation, should not conduct additional comparative studies but instead prepare in a stepwise manner for possible implementation, including discussing with key stakeholders and conducting preliminary research on acceptability and feasibility.

1. OVERVIEW

1.1 Background

The WHO Global Health Sector Strategy on HIV/AIDS, 2011–2015, seeks to reduce new HIV infections, moving towards achievement of the global vision of zero new infections. This vision will be achieved only by implementing existing effective prevention technologies with sufficient intensity and scale. In March 2007 the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) recommended male circumcision as an efficacious intervention for prevention of heterosexually acquired HIV infection in men. It is recommended that countries with generalized HIV epidemics and low prevalence of male circumcision should progressively expand access to safe voluntary medical male circumcision services *(1).* These recommendations were made following the review of evidence from three randomized controlled clinical trials, conducted in Kenya, Uganda and South Africa, that showed that male circumcision reduced the risk of heterosexually acquired HIV infection in men by about 60% *(5,6,7).*

Epidemiological and economic modelling commissioned by the US President's Emergency Plan for AIDS Relief (PEPFAR) and UNAIDS in 2011 determined that scale-up of voluntary medical male circumcision in appropriate settings constitutes a high-impact intervention with excellent value for money *(8).* Impact and costing estimates suggest that scaling up medical male circumcision to reach 80% coverage among males 15–49 years old in 14 priority countries of sub-Saharan Africa by 2015 would require the performance of 20.3 million circumcisions. The 80% level of coverage would avert 3.4 million, or 22%, of new HIV infections through 2025. In addition, while the model shows that this scale-up would cost US$1.5 billion by 2015, it would result in net savings amounting to US$16.5 billion due to treatment and care costs averted. The 14 countries have been identified as top priority for scale-up of voluntary medical male circumcision services for HIV prevention because of high prevalence of HIV and low prevalence of male circumcision. Achieving the 80% prevalence target is consistent with universal access targets and national targets for male circumcision for HIV prevention adopted in most of the priority countries.

The currently recommended standard surgical techniques for adolescent and adult male circumcision *(9)* require considerable time and skill, as they involve injectable anaesthesia, suturing for wound closure and diathermy and/or suturing for haemostasis. These techniques, as practised in the randomized controlled trials that demonstrated the protective effect of male circumcision *(5–7),* have been shown to be safe, effective and acceptable, with low rates of complications when delivered by trained doctors and surgeons in well-equipped and well-resourced settings.

Innovations in the surgical procedure, such as male circumcision devices, have the potential to reduce the time and resources required for male circumcision, to facilitate provision of the service by mid-level providers, to increase acceptance by providers and patients, to improve the safety of the procedure and, thus, potentially, to accelerate expansion of male circumcision programmes.

A number of device-based methods exist for adult male circumcision. The available data were not sufficient to support their inclusion in the WHO/UNAIDS/Jhpiego *Manual for male circumcision under local anaesthesia*, when published in 2008 *(9).* Adult male circumcision is more complex to perform than early infant male circumcision. While male circumcision devices have been safely and quite extensively used in infants and young boys in both developing and developed countries for many years, clinical experience with such devices in adults is very limited, and it is not possible to extrapolate the safety, acceptability and efficacy of devices from one population to another, particularly from infants and young boys to adults.

To support the generation of adequate performance data on devices used for adult male circumcision, WHO, in consultation with programme managers, implementing partners, surgeons and technical experts, developed the *Framework for clinical evaluation of devices for male circumcision (2)*, which addresses devices to be used for male circumcision and focuses on those devices to be used post-puberty, in adolescent and adult male circumcision (referred to in the remainder of this report as "adult" male circumcision), with which there is little clinical experience in resource-limited settings. This framework defines a progressive series of studies to establish the performance of a new device or of an existing device in new populations. The framework balances the importance of speed and innovation with the caution necessary when implementing male circumcision as a preventive public health intervention for men who would not otherwise be circumcised. Therefore, the clinical data requirements have been defined more stringently than national or regional public health regulatory authorities would normally require before giving marketing authorization for a medical device, particularly a device that is external and in contact with the body for a limited time.

The *Framework for clinical evaluation of devices for male circumcision* recommends that, after an initial efficacy and safety study in the country of intended use, at least two independent randomized controlled trials and two independent field studies from different settings or countries should be conducted before WHO considers a global decision on the suitability of a particular device for use in public health male circumcision programmes for HIV prevention. In the absence of a second series of studies (comparative study and field study), the decision to use a device should be restricted to the country or setting where the first series was conducted, provided the clinical data support such use and the national programme approves and endorses such use. However, it would not be possible to generalize the results to other settings or patient populations.

Over the past few years, research has been underway to identify innovative methods that are simpler than and as safe as the standard surgical methods. Research on specific devices as alternatives to standard surgical male circumcision has evolved so that, by the end of 2011, a series of clinical studies had been completed in one low-resource country, Rwanda. These studies involved a device that causes necrosis of the foreskin over one week through controlled radial compression with an elastic ring, after which the device and the necrotic foreskin are removed. Safety and efficacy studies and comparative studies have been completed on another device that achieves haemostasis by compression of the foreskin between two locking rings. The foreskin can be excised immediately after the device has been placed correctly and the device remains in place for one week. Field studies with this device are underway in 2012.

In view of these recent developments, Member States implementing male circumcision as a HIV prevention intervention in national programmes and supporting partners have requested guidance regarding use of devices.

1.2 Objectives

This report presents the conclusions and recommendations of the WHO Technical Advisory Group on Innovations in Male Circumcision (TAG) on use of a device as an alternative to standard surgical procedures. It focuses on the elastic ring controlled radial compression device for which data from one series of clinical studies in only one country were available by the end of 2011. Specifically, this report provides the results of assessments of available data regarding:

- the suitability of an elastic ring controlled radial compression device for use as an alternative to standard surgical methods for male circumcision in public health programmes;
- the use of the device by trained mid-level providers as an alternative to physicians in such programmes.

This report also indicates information gaps that were identified during the assessment—gaps that need to be filled to inform both decision-makers and the development of future guidance.

1.3 Target audience

This report is intended for national public health officials in countries implementing male circumcision for HIV prevention and policy- and decision-makers, including funders, interested in the potential use of devices as an additional method of male circumcision in national public health programmes in resource-limited settings. It also may be of interest to health workers and non-governmental organizations.

2. THE PROCESSES TO RETRIEVE AND REVIEW EVIDENCE AND DEVELOP THE REPORT

This report was prepared by WHO staff with external consultation and peer review. The WHO Department of HIV/AIDS led the external consultation with the Technical Advisory Group on Innovations in Male Circumcision (TAG) (see Annex 1 for list of participants) and the development of this report.

2.1 Retrieving, summarizing and presenting the evidence

WHO applied the GRADE (**G**rading of **R**ecommendations **A**ssessment, **D**evelopment and **E**valuation) approach *(10)* to the development and review of recommendations. The initial steps entailed identifying key topics, formulating the Population, Intervention, Comparison and Outcomes (PICO) questions, scoping the literature to determine whether evidence reviews existed or recent evidence could be assessed, and identification and retrieval of relevant evidence, including evidence of benefits and harms *(3).*

The focus of this report is male circumcision devices, in particular an elastic ring controlled radial compression device for which data were available by the end of 2011. The questions were stated in the standard PICO format for clinical questions, reflecting the **P**atient or **P**opulation under consideration, the **I**ntervention of interest, the **C**omparison or **C**ontrol, and the **O**utcome to be assessed. The WHO Male Circumcision Working Group developed the PICO questions in consultation with the co-chairs of the WHO TAG.

The PubMed database was searched using the term "male circumcision device". A total of 290 citations were retrieved, of which six *(11,12,13,14,15,16)* were in English and referred to clinical data on disposable devices used for adult male circumcision. Two of these report clinical data on the Shang Ring and one each reports on the PrePex, Tara KLamp and Ali's Clamp devices; one article is a commentary that accompanies one of the clinical reports.

Male circumcision programme managers, investigators known to be working on development or assessment of male circumcision devices, and manufacturers of male circumcision devices were contacted for technical and clinical information on devices either used or intended to be used in adults in resource-limited settings. Publications, conference abstracts and posters were retrieved where available.

In addition, the investigators made available prior to publication confidential study reports on the clinical research conducted in Rwanda with the elastic ring controlled radial compression device. (While a safety study on the same device had just been completed in Zimbabwe, the report was not available for review.) Key elements of each study that included clinically important outcomes were extracted from the available reports and summarized in a uniform manner for consideration by the TAG at their meeting in January 2012.

The GRADE framework was used to summarize this information. Draft GRADE Evidence Profiles and Summary of Evidence Tables were prepared for each PICO question. This entailed consideration of study limitations, inconsistency, indirectness, imprecision and other limitations *(17).*

PICO Questions

The PICO questions addressed in this report considered whether an elastic ring controlled radial compression device can be used as an alternative to standard surgery in adult male circumcision programmes for HIV prevention.

The two PICO questions reflect the clinical evaluation pathway defined in the Framework, in particular whether the device can be considered as an alternative to standard surgery when delivered by trained physicians, and whether trained mid-level providers, as an alternative to physicians, are able to deliver the device in resource-limited settings.

Therefore, the PICO questions were formulated as follows:

> Question 1: Among men age 15-49 years seeking male circumcision for HIV prevention, can the elastic ring controlled radial compression device be used as an alternative to surgical circumcision?
>
> Question 2: Can the elastic ring controlled radial compression device be used by trained mid-level providers, as an alternative to physicians, among men age 15-49 years seeking male circumcision for HIV prevention?

It is critical to note that these questions focus on the clinical performance of the device for adult male circumcision in the context of HIV prevention programmes in low-resource settings. Clinical trials have already established that medical male circumcision is highly efficacious in the prevention of heterosexually acquired HIV infection in men, thus, these questions focused on the efficacy of the device in ensuring the adequacy of the foreskin removed. WHO also has established a prequalification programme for male circumcision devices, which assesses additional aspects of male circumcision devices such as design and manufacturing, pre-clinical studies, labelling, commercial and regulatory history and the quality management system.

Outcomes that reflect key performance characteristics of male circumcision devices were selected to evaluate how well the device achieves its intended outcome and its safety and acceptability. These outcomes included client eligibility, efficacy in achieving a neat and complete result, acceptability by clients and providers, incidence of moderate and severe adverse effects and healing times.

2.2 Key principles

The TAG had previously considered principles and criteria in the clinical evaluation of devices. These underpinned the TAG's review of the evidence and the formulation of recommendations:

- Since male circumcision for HIV prevention is a public health intervention and involve large numbers of healthy men, more rigorous assessment of the clinical safety, efficacy and acceptability of male circumcision devices is necessary than typically required by standard device regulations.
- Innovations in methods for male circumcision are needed to support national programme efforts to reach full scale at an accelerated pace. There is a need, therefore, to balance the importance of speed and innovation, avoiding unnecessary barriers to entry of a new technology, with safety as a public health prevention intervention.
- Recommendations must be consistent with existing recommendations *(1)* for male circumcision for HIV prevention, which state that male circumcision must be part of a combination prevention package. The minimum service package for male circumcision (HIV testing and counselling, management of sexually transmitted infections, condom promotion and provision, safer sex information and education) must be made available regardless of the circumcision technique used.
- Cost per device needs to be reasonable in relation to manufacturing and distribution costs of the device itself and should consider the public health goals of male circumcision programmes and responsible use of public funds that are supporting such programmes.

2.3 Consensus, external review and updating

Prior to the TAG meeting, seven TAG members and WHO staff critically reviewed the data from the confidential reports and requested further information from the investigators. One key issue discussed was the classification of adverse events (one of the key outcomes to assess safety); there was consensus that the adverse events and side-effects would be classified according to the interpretation of the review group rather than the classifications assigned by the investigators. Prior to the TAG meeting in January 2012, all participants received the study reports. At the meeting, the evidence available from study reports was critically reviewed, and the evidence tables were presented to the full TAG for their review and deliberation. If consensus was not achieved, the minority view has been stated in the Summary of Evidence document (available for public review once currently confidential study data are in the public domain).

The TAG reviewed evidence relating to the two key PICO questions with regard to the elastic ring controlled radial compression device for which clinical data were available. The review included presentations on the summary of relevant evidence and the draft GRADE Evidence Profiles and Summary of Evidence Tables. Also, research gaps and information needs were noted during the meeting.

Using this information, the TAG deliberated on the evidence in order to formulate their conclusions and recommendations. The draft GRADE Evidence Profiles, Summary of Evidence Tables and initial conclusions and recommendations were revised following the meeting and circulated electronically to participants for final comment before publication. The WHO Secretariat also incorporated comments from an external peer reviewer (GRADE methodologist). The GRADE tables will be available once the study data are in the public domain.

Additional data on this device and other devices are expected within the year. It is anticipated that guidance will be developed once sufficient data are available.

3. DISSEMINATION

This report will be posted on-line and disseminated electronically to relevant policy-makers, WHO Regional and Country offices, programme managers, clinicians and researchers known to be working on male circumcision programmes for HIV prevention The report also will be disseminated through key stakeholders including appropriate WHO Regional and Country Offices.

4. DECLARATIONS OF INTERESTS

Each participant in the TAG and every consultant was asked to complete a Declaration of Interests and submit it to the WHO Secretariat in advance of the TAG meeting. Review of the declarations by the Secretariat and the TAG chairs identified no significant conflicts or potential conflicts of interest that would disqualify any invited participant. Ten participants indicated potential conflicts of interests. Four potential conflicts were due to the participant's involvement on a research team studying one or more devices, and one concerned involvement in modelling studies related to HIV prevention funded by the Bill and Melinda Gates Foundation. One participant had been previously employed by a company that worked on the development of male circumcision devices; two currently or previously worked on male circumcision device technologies, and one works with the Bill and Melinda Gates Foundation, which has supported device development and research. The WHO Secretariat determined that these interests were not sufficient to preclude participation in the development of the recommendations. One participant had been involved as a clinical researcher in the initial safety research on the device studied in Rwanda. At the request of the Secretariat, he did not contribute to discussions on the implications of the evidence or the formulation of recommendations, but he did provide technical information on the study. No other members were considered to have any current or potential conflicts of interest that might affect their impartiality, judgement or advice.

At the beginning of the meeting, the co-chairs explained the reasons for the written and verbal Declarations of Interests, summarized the relevant interests that had been declared and invited all participants to declare verbally to the group any other potential conflicts of interests.

5. COLLABORATION WITH EXTERNAL PARTNERS

Several external collaborators were involved in the development of this report, in particular, partners who serve as observers on the TAG: the Bill and Melinda Gates Foundation and the US President's Emergency Plan for AIDS Relief, through the Centers for Disease Control and Prevention and the United States Agency for International Development, and the US National Institutes of Health. Funds from the Bill and Melinda Gates Foundation supported the meeting and development of this report.

6. KEY RECOMMENDATIONS

The key recommendations of the WHO TAG cover the use of the device as an alternative to standard adult surgical methods and its use by specific types of providers.

Recommendation I

I. Use of an elastic ring controlled radial compression device for adult male circumcision

1.1 The elastic ring controlled radial compression device for which data were available from one safety, one comparative, and one field study in one country (Rwanda) by the end of 2011 can be used in that same country (Rwanda), subject to approval/endorsement by the national programme, for phased implementation among men 18 years and older, with rigorous monitoring for adverse events and side-effects.

It was recommended that phased implementation include:

a) active surveillance of the first 1000 clients, to identify and record all adverse events and side-effects based on standardized definitions. The active surveillance may change to passive surveillance after the first 1000 clients if the incidence of events is reassuringly low, as determined by independent review.

b) appropriate counselling on sexual abstinence and condom use[1] after male circumcision and before complete healing is always crucial, but it is particularly crucial with use of this device because the healing time is at least one week longer than with standard surgery.

c) access to standard surgical male circumcision services for the approximately 10–15% of adult men not clinically eligible for this device due to phimosis or narrow opening of the foreskin. Alternative acceptable and efficient service delivery models for men who are not eligible for this device method should be identified, and these models should be pilot-tested for feasibility.

1.2 The elastic ring controlled radial compression device for which data were available from one safety, one comparative, and one field study in one country (Rwanda) in 2011 is not yet recommended for use as an alternative method for male circumcision in national programmes outside the country where the first series of studies was conducted.

Remarks

Evidence retrieval and summary

All clinical data on the elastic ring controlled radial compression device have been generated by a team in Kigali, Rwanda, which submitted detailed study reports for review. The research included an initial safety and efficacy study involving 55 clients *(16)*, a randomized comparison between the device and surgery in 217 clients *(18)* and a field study with the device deployed on 590 clients by mid-level providers *(19)*. An additional study on use of the device in 49 clients when applied by mid-level providers had been conducted by the Rwanda team, but only a brief summary was available for review. While further studies of the device were underway in Zimbabwe at the time of the review, no data were available as of January 2012. These studies represent the full extent of clinical information on the device.

While there is considerable published clinical research and experience with implementation of male circumcision in programmes in resource-limited settings using a standard surgical approach, three key publications that present sufficient detail on the surgical methods, with systematic recording of adverse events and clinical findings,

1 Condom use is also advised after healing since male circumcision only partially reduces the risk of sexual transmission of HIV from women to men. Male circumcision should be considered as part of a combination prevention package.

provide the most relevant information with which to compare the clinical performance of the elastic ring controlled radial compression device. These studies were the three randomized controlled trials that demonstrated that male circumcision reduces the incidence of HIV infection (5–7). These three studies followed a similar design, randomizing men to immediate or delayed circumcision, with the procedure performed by experienced physicians, surgeons or clinical officers in facilities adequate for safe male circumcision. The published study reports include data on the performance and safety of circumcision in the men randomized to immediate surgery. Comparable safety information on those randomized to delayed circumcision has not been published, but there is no reason to expect any differences or systematic bias between the published and unpublished data.

Benefits and harms

The benefits of the elastic ring controlled radial compression device compared with surgery were assessed by three measures—the proportion of men in whom the device could be successfully applied (eligibility), the procedure times, and the efficacy with which the device achieved its intended purpose. Harms were assessed by the rates of adverse events associated with the device in comparison with surgery.

Eligibility: All men must be screened for contraindications to circumcision, in particular the presence of any penile abnormalities or genital infections. Since the elastic ring controlled radial compression device is placed under the foreskin just below the corona, men with phimosis, in whom the foreskin cannot be retracted, and men with a narrow foreskin opening are not eligible for circumcision with this device. In addition to the men ineligible for circumcision due to the standard contraindications that would rule out any male circumcision surgery, an additional 10–15% of men were found to be ineligible for circumcision with the controlled compression device because of phimosis or a narrow foreskin opening.

Procedure times: The procedure times with the elastic ring controlled radial compression device were substantially shorter than with standard surgery, even when the placement and removal times were added together and the time waiting for the injectable anaesthesia to become effective prior to standard surgery was excluded.

Efficacy: Among all men in whom it was possible to place the device, a neat and complete circumcision was achieved, similar to the high success rate with standard surgical circumcision. This assessment was made 42 to 63 days after device placement.

Adverse events: The harms associated with use of the elastic ring controlled radial compression device were assessed by two measures—the rate of moderate or severe adverse events and the rate of minor adverse events related to the procedure following device placement or surgery. The moderate and severe adverse events were considered more important than the mild adverse events. The TAG recognized that comparing adverse event rates between methods is difficult, as the mechanisms of action are different, but the reviewers considered that adverse events requiring the patient to return for an unplanned clinic visit or otherwise to consult clinical services was one relevant metric. Such adverse events would constitute a risk to the patient, a disruption of the patient's normal schedule and the consumption of health care resources, even if the event were managed successfully. The TAG considered adverse events to be related to the device or procedure if they occurred as a result of surgery or of device placement or removal or if they resulted from the patient's actions whether or not he had been advised against them. The TAG's categorization of adverse events resulting from the patient's actions differed from the categorization of such adverse events applied and reported by the investigators. The reviewers considered all adverse events meeting these criteria to be related or possibly related to the procedure or device.

The rates of moderate or severe adverse events with the device were low, and in fact, may be lower than the rates observed with standard surgical male circumcision, but further rigorous monitoring among a larger number of men would be necessary to detect a significant difference. Theoretical concerns remain about patient safety if the device becomes displaced during the process of necrosis, as well as about the safety of the device in men with compromised immune systems, such as men with HIV infection or diabetes.

Pain: Pain was assessed during placement, at various times after placement and during removal. The points in time retained for comparison were the time of placement, in the few hours after placement and during removal of the device. Pain was measured by asking clients to rate pain on a Visual Analogue Score (VAS) ranging from 0 (no pain) to 10 (excruciating pain).

Comparing the pain scores is extremely difficult because the pain control protocols evolved as the studies progressed and more information on pain became available. In the initial study no anaesthesia or analgesia was given for the first 25 men, but for the remaining 30 men 1 g of paracetamol was administered 30 minutes before device placement and again 30 minutes before removal. In the comparative study men were given ibuprofen 400 mg 30 minutes before device placement. In the study with limited data on 49 patients, 1 g topical anaesthesia (either the branded EMLA® cream or a cream containing 5% lidocaine prepared in the local pharmacy) was applied before placement. In the field study with nurse providers, lidocaine anaesthetic cream was applied at the start of the procedure, and two tablets of ibuprofen 400 mg were given to each client to take at home as needed.

Pain at the time of ring placement was minimal (Visual Analogue Scale (VAS) scores from the studies ranged from 0.5 to 1). The period of greatest discomfort and pain was in the 3–6 hours after placement, when the process of necrosis starts (VAS score: mean 2.3 with paracetamol or ibuprofen). In the field study the topical anaesthetic was applied just before device placement, which appeared to adequately reduce the pain at 30 minutes post placement (VAS score: mean 0.5; pain measurement was available only at 30 minutes). Topical anaesthetic is recommended to be used with the elastic ring controlled radial compression device. There was brief transient (2–5 seconds) pain (VAS score range 3–4.9) during device removal as the inner ring was detached from the healing wound.

Healing: Healing following male circumcision with the device is by secondary intention as opposed to primary intention as with conventional surgical circumcision. Healing as defined by epithelium covering the entire wound, takes at least one week longer with the device than with surgery (in the comparative study, a mean of 15 days longer, with a 95% confidence interval of 12 to 18 days). Thus, the device requires a longer period of post-circumcision sexual abstinence than do standard surgical methods. The TAG considered that theoretically there is a risk of HIV acquisition if men engage in sex before the wound is healed, but the magnitude of risk is unknown. Therefore, the group stressed the importance of good counselling about sexual activity and condom use. As full healing including remodelling of collagen in deep layers and maturation of the scar may take up to one year, the TAG also indicated that assessment of a group of men one year after circumcision with the device would further inform this outcome.

Values and preferences

Reviewers considered the benefits of the device—shorter procedure times, simpler procedure, absence of injectable anaesthesia and the potential for the device to be deployed by mid-level providers—and concluded that these benefits potentially outweighed the disadvantages of wearing the device for a week, the risks of complications during the necrosing process, and the longer healing time. Reviewers emphasized, however, that the available data, including reports from clients themselves, were limited. Information from another setting is essential to ascertain the acceptability of the device, compliance with instructions on care during the necrosing process while wearing the device, and its safety in other client populations including those that may have additional risks with device use such as working in hot, dusty settings or routinely riding a motorbike or bicycle. Also, the performance

of the device in men younger than 18 years has not been assessed. While the lower age limit in the comparative and field studies was 21 years due to local legal and ethical restrictions on participation in a research study, the initial study included a small number of men 18-20 years. The TAG noted that there was no apparent anatomical or developmental reason not to extrapolate a recommendation to men age 18–20 years.

Information gaps and needs

Key information gaps identified included the following:

- Data and experience are limited to just one country (Rwanda). More data are needed from other countries. A comparative study and a field study to assess safety, efficacy and acceptability of the device are underway in another country, Zimbabwe. The TAG encouraged the completion of these studies so that results would be available in 2012. The TAG recommended that national programmes interested in exploring the potential of devices within voluntary medical male circumcision for HIV prevention public health programmes, in advance of a global recommendation, should not conduct additional comparative studies but instead prepare in a stepwise manner for possible implementation, including discussions with key stakeholders and preliminary research on acceptability and feasibility.
- Data are limited to men age 18 years and older. More information is needed on the safety, acceptability and feasibility of using the device with younger men. While appropriate device sizes have not been determined for younger populations, it is possible that the proportion of clients who are eligible for use of the device may differ in a younger group because of lack of appropriately sized devices or a different proportion of males age 15–18 years with a narrow foreskin opening. It was noted that information is needed on the acceptability of device use among younger men, including on whether they are comfortable wearing it for a week, and whether they are able to avoid displacing or disturbing the device during the necrosis process.
- Since there are limited data in men with HIV infection or those with other immuno-compromising co-morbidities such as diabetes, it is important to document the performance and safety of the device in such clients.
- As adverse event data are limited to small numbers of clients, information is needed on safety in larger numbers of men.
- As not all men were eligible for use of the device, information is needed on suitable service delivery models to ensure access to male circumcision for those excluded for device-specific contraindications.
- More information is needed on the preferences of men for the device compared with standard surgical methods and on issues related to personal and wound care while wearing the device.
- No systematic follow-up of clients has been done beyond nine weeks. Longer follow-up of selected clients, e.g. one year after circumcision, is needed, particularly with regard to sexual function and the final cosmetic result, to be sure there is no late development of keloid or any other adverse consequence of healing by secondary intention.
- Given the theoretical concern about HIV transmission during wound healing, it was proposed that a modelling study be conducted to better inform the consideration of risks and benefits.
- Some pain occurs with use of this device. It is anticipated that the information from the studies underway in Zimbabwe will be sufficient to confirm the importance of pain control, however the optimal pain control protocol is unknown and further study may be needed.
- Certain occupational settings may influence acceptability, preferences and outcomes. For example, men working in hot, dusty environments or motorcycle riders may experience more discomfort and have a higher incidence of complications with device use than men with more sedentary occupations.

Recommendation 2

Use of the elastic ring controlled radial compression device by mid-level providers

In Rwanda, where a field study with this device has been completed, physicians and mid-level providers (nurses) who are appropriately trained and deemed competent can perform the placement and removal of the device for men 18 years and older, with careful monitoring during phased implementation in actual practice in different types of settings, with active surveillance of the first 1000 clients as indicated above.

Remarks

Evidence retrieval and summary

As noted, all available clinical data on the elastic ring controlled radial compression device have been generated by the team in Kigali, Rwanda, which provided detailed confidential reports for review. Three studies (16,18,19) provide data on the performance of the device when used by mid-level providers and by physicians—the field study of 590 clients with the device deployed by mid-level providers, and the initial safety and efficacy study in 55 clients and those randomized to the elastic ring controlled radial compression device in the randomized controlled trial, deployed primarily by physicians. A total of 10 nurses performed the procedures. These nurses were hospital-based and with two different qualification levels, A1 and A2. The findings of these studies constitute the full extent of information available on device use by specific types of providers.

The TAG considered that the field study demonstrated that, with careful training and supervision by a provider experienced in use of the device, mid-level providers could safely place and remove the device. The group indicated that generalization to settings outside Rwanda was not possible at this stage and evidence from field studies in other patient populations is needed.

Benefits and harms

The benefits of the elastic ring controlled radial compression device in the hands of mid-level providers compared with physicians was assessed by three measures—the proportion of men in whom the device could be successfully applied, the procedure time and the efficacy of the device in achieving its intended purpose. Harms were assessed in terms of the rates of adverse events. The study results indicated that the performance of mid-level providers was comparable to that of physicians.

Values and preferences

In light of the goal to provide circumcision to over 80% of men, the advantages in low-resource settings of a simple procedure delivered by mid-level providers are potentially large. Generalization to settings outside Rwanda is not possible at this stage, however, and evidence from field studies involving other provider and other patient populations is needed.

Information gaps and needs

The outcomes from additional field studies are needed to further inform the provision of the device by non-physician providers. In addition, further information is needed on efficient and safe models of service delivery that involve various combinations of non-physician providers for deployment and removal.

ANNEX 1. LIST OF PARTICIPANTS IN THE WHO TECHNICAL ADVISORY GROUP MEETING, JANUARY 2012

Meeting of WHO Technical Advisory Group on Innovations in Male Circumcision

World Health Organization, Geneva, 19–20 January 2012

List of Participants as Members, Observers and Secretariat

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REFERENCES

1. *New data on male circumcision and HIV prevention: policy and programme implications.* Geneva, World Health Organization and Joint United Nations Programme on HIV/AIDS, 2007.
2. *Framework for the clinical evaluation of adult devices for male circumcision*. Geneva, World Health Organization, 2012.
3. Guyatt GH et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *Journal of Clinical Epidemiology*, 2011, 64:395–400. http://www.ncbi.nlm.nih.gov/pubmed/21194891
4. Balshem H et al. GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology*, 2011, 64:401–406. http://www.ncbi.nlm.nih.gov/pubmed/21208779
5. Auvert B et al. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 trial. *PLoS Medicine*, 2005, 2:e298.
6. Bailey RC et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomized controlled trial. *Lancet*, 2007, 369:643–656.
7. Gray RH et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomized trial. *Lancet*, 2007, 369:657–666.
8. Njeuhmeli E et al. Voluntary medical male circumcision: modeling the impact and cost of expanding male circumcision for HIV prevention in eastern and southern Africa. *PLoS Medicine*, 2011, 8:e1001132. doi:10.1371/journal.pmed.1001132. http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001132
9. *Manual for male circumcision under local anaesthesia*. Geneva, World Health Organization, Joint United Nations Programme on HIV/AIDS and Jhpiego, 2008.
10. Schünemann H, Brożek J, Oxman A, eds. *GRADE handbook for grading quality of evidence and strength of recommendations*. Version 3.2 [updated March 2009]. GRADE Working Group, 2009. http://www.cc-ims.net/gradepro
11. McIntyre J. Can devices for adult male circumcision help bridge the implementation gap for HIV prevention services? *Journal of Acquired Immune Deficiency Syndromes*, 2011, 58:506–508.
12. Barone MA et al. The Shang Ring for adult male circumcision: a proof of concept study in Kenya. *Journal of Acquired Immune Deficiency Syndromes*, 2011, 57:e7–12.
13. Peng Y et al. No-needle local anesthesia for adult male circumcision. *Journal of Urology*, 2010, 184(3):978–983.
14. Senel FM, Demirelli M, Pekan H. Mass circumcision with a novel plastic clamp technique. *Urology*, 2011, 78:174–179.
15. Lagarde E et al. High rate of adverse events following circumcision of young male adults with the Tara KLamp technique: a randomized trial in South Africa. *South African Medical Journal,* 2009, 99:163–169.
16. Bitega JP et al. Safety and efficacy of the PrePex device for rapid scale-up of male circumcision for HIV prevention in resource-limited settings. *Journal of Acquired Immune Deficiency Syndromes*, 2011, 58(5):127–134.
17. Guyatt GH et al. GRADE guidelines: 4. Rating the quality of evidence––study limitations (risk of bias) and publication bias. *Journal of Clinical Epidemiology*, 2011, 64:407–415. http://www.ncbi.nlm.nih.gov/pubmed/21247734
18. Binagwaho A et al. *A prospective, randomized, open-label trial comparing the PrePex™ device to surgical circumcision for rapid scale-up of male circumcision in resource-limited settings (Protocol Number RMC-01)*. Kigali, Rwanda, 2011.
19. Mutabazi V et al. *One arm, open label, prospective, cohort field study to assess the safety and efficacy of the PrePex™ device for scale-up of non-surgical circumcision when performed by nurses in resource-limited settings for HIV prevention (Protocol RMC-03)*. Kigali, Rwanda, 2012.

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