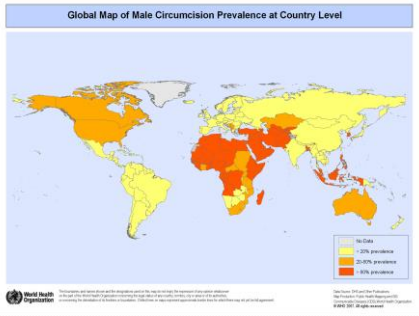
MALE CIRCUMCISION FOR STI PREVENTION: HOW WELL DOES IT WORK AND HOW IS IT DONE?

Kawango Agot
Impact Research & Development Organization
Kisumu, Kenya

World STI & HIV Congress 2015
September 13-16, 2015.
Brisbane Convention and Exhibition Centre
Brisbane, Australia.

Presentation Outline



PART 1:
MALE CIRCUMCISION & SEXUALLY TRANSMITTED INFECTIONS

INTRODUCTION TO PART 1
1855: Review of venereal disease patients

	Jews (n=58)	Non-Jews (n=272)
Syphilis	11 (19%)	165 (61%)
Gonorrhoea	47 (81%)	107 (39%)

Author's interpretation: *"The circumcised Jew is, then, very much less likely to contract syphilis than an uncircumcised person"*

Hutchinson, J. BMJ & Medical Times and Gazette, Vol. II Dec 1855, pp. 542-3
(Slide courtesy of Helen Weiss, LSHTM)

MC/STI Association Revisited

- In the 1980s and 1990s, observational studies indicated that male circumcision (MC) was potentially effective against HIV acquisition [1-3]
  - Evidence also emerged that MC could confer protection to non-HIV STIs [4-5]
- In 2005-2006, three randomized controlled trials (RCTs) demonstrated that MMC reduces by 51-60% the risk of acquiring HIV in African men [6-8]
  - The RCTs also evaluated the effect of MMC on other non-HIV STIs
- Since the RCTs, additional studies, systematic reviews and meta-analyses have explored the association between MMC and various STIs

[1-3] *Cameron et al, Lancet 1989; 2(8660):403-7); Urassa et al, 1997; 11(3):73-80; Weiss et al. 2000; 14(15):2361-70;* [4-5] *Simonsen et al, NEJM 1988; 319(5):274-8; Jessamine et al, Scand J Infect Dis Suppl. 1990; 69:181-6;* [6-8] *Auvert et al, PLoS Med 2005; Bailey et al Lancet 2007, Gray et al, Lancet 2007*

Human Papillomavirus

Association between MC and HPV: Non-RCT Data

Study Title	Author	Population	Effect size (95% CI)	Other Info
MC and STI Acquisition	Homfray et al, *PLoS One*, 2015	Men age 16-44yrs in Britain (n=1859)	AOR 0.26 (0.13-0.50) AOR 0.14 (0.05-0.40)	Any HPV type High risk
Prevalence, incidence, and risk factors for HPV 16 seropositivity in Australian homosexual men	Poynten et al, *Sex Transm Dis* 2012	Insertive MSM in Australia n=1,772	HR 0.43 (0.21-0.88)*	HPV-16
MC and the incidence and clearance of genital HPV infection in men	Albero et al, *BMC Infect.* Dis., 2014	Healthy Men in USA (n= 4033)	aHR 1.08 (0.91-1.27) aHR 0.95 (0.88-1.02)	HPV incidence Clearance for any HPV
MC and prevalence of genital HPV: A systematic review and meta-analysis	Albero et al, *Sex Transm Dis* 2012	Meta-analysis of 21 studies 1971-2010 (n=14,382)	OR 0.57 (0.42-0.77) RR 1.01 (0.66 –1.53) HR 1.57 (0.51–4.89)	HPV prevalence HPV incidence HPV clearance
MC and HPV infection in men: A systematic review and meta-analysis	Larke et al, *J Infect Dis* 2011	Systematic review of 23 papers	OR 0.57 (0.45-0.71) RR 0.75 (0.57-0.99) OR 0.47 (0.37-0.60) OR 0.35 (0.12-1.05)	Overall prevalent HPV Overall incident HPV Samples from glans/corona Samples from Urethra

* Association may be spurious given relationship between MMC and HIV in MSM not clear-cut

Association between MC and HPV: S. Africa & Kenya RCTs

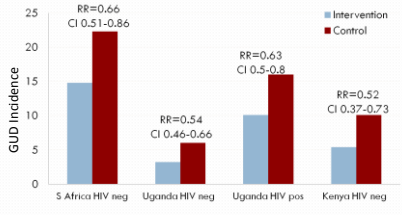
Study Title	Author	Population	Effect size (95% CI)	Other Info
Effect of MC on the prevalence of high-risk HPV in young men: results of a RCT in Orange Farm, South Africa	Auvert et al *J Infect Dis* 2009	South Africa: Young men (n=3274)	PRR 0.66 (0.51-0.86)	Incidence in high risk HPV
Association of Low-Risk HPV Infection with MC in Young Men: Results from a Longitudinal Study Conducted in Orange Farm, South Africa	Tarnaud et al *Infect Dis Obstet Gynecol* 2011	South Africa: Young men (n=1,264)	aPRR 0.53 (0.40-0.70)	Incidence in low risk HPV
Acquisition and persistence of HPV-16 and HPV-18 among men with high-HPV viral load infections in a circumcision trial in Kisumu, Kenya	Senkomago et al, *J Infect Dis* 2015; Backers et al, *Int J Cancer*, 2012	Kenya: Young men (n=2,290)	HR 0.32 (0.20-0.49) HR 0.34 (0.21-0.54) RR 0.36 (0.18-0.72) RR 0.34 (0.13-0.86)	Incidence of HPV 16 Incidence of HPV 18 Persistence of HPV 16 Persistence of HPV 18

Association between MC and HPV: Uganda RCT

Article	Author	Population	Effect Size (95% CI)	Other Info
MC decreases acquisition and increases clearance of high-risk HPV in HIV-negative men	Gray et al, *J Infect Dis* 2010	Uncircumcised HIV-negative men 15-49yrs (n=840)	RR 0.45 (0.28-0.73) RR 1.39 (1.17-1.64)	Incidence of multiple high risk HPV Clearance of pre-existing HPV increased with MC
MC of HIV-infected men: Effects on High Risk HPV Infections	Serwadda et al, *J Infect Dis* 2010	Uncircumcised HIV-positive men 15-49yrs (n=210)	RR, 0.53 (0.33-0.83) RR, 1.09 (0.94-1.27)	Incidence of multiple high-risk HPV Clearance of new HPV
HPV incidence and clearance among HIV+ and HIV-men	Tobian et al; *AIDS* 2012	HIV-neg. & HIV-pos. men 15-49yrs (n=999)	aIRR=0.70 (0.55-0.89) aRR 1.48 (1.26-1.74)	HPV incidence HR- HPV clearance increased with MC
Effect of MC of HIV-neg. men on transmission of HPV to HIV-neg women	Wawer et al, *Lancet* 2011	Concordant HIV-negative couples (n=1245) (women)	RR 0.77 (0.63-0.93)	Incidence of high-risk HPV in women

Genital Ulcer Disease

Circumcision Reduces GUD: Results from the 3 RTCs



Auvert B *JID* 2009; Gray RH *Lancet* 2007; Mehta SD *AIDS* 2012 (Slide courtesy of Supriya Mehta, UIC)

Herpes Simplex Virus Type 2

Evidence from the 3 RCTs: South Africa and Uganda Trials

- **Orange Farm Trial**
  - Circumcision had borderline impact on incident HSV-2 in intention to treat analysis (IRR 0.66; CI 0.39-1.12) but was significantly protective in as treated analysis (IRR 0.55; CI 0.32-0.94) [1]
- **Rakai Trial**
  - At 24 months follow up, incident HSV-2 was lower in circumcision group (aHR 0.72; CI 0.56-0.92) [2]
  - Contrary to findings in men, circumcision of partner did not affect HSV-2 acquisition among females with HSV 2-positive partners (RR 0.85; CI 0.44-1.67)[3]

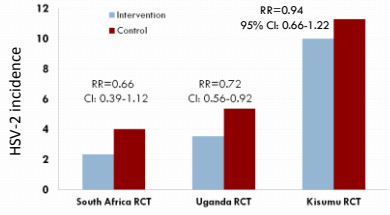
[1] *Sobngwi-Tambekou et al., JID 2009; 199:958-64;* [2] *Tobian et al NEJM 2009; 360(13):1298-309;* [3] *Tobian et al, J Infect Dis 2012; 205(3):486-90*

Evidence from the 3 RCTs: The Kenya Trial

- **Kisumu Trial:**
  - Overall, the incidence of HSV-2 did not differ by MC status (RR 0.94; CI 0.7-1.25) [1]
  - Blood samples from HIV seronegative men were tested for HSV-2 using HerpeSelect HSV-2 ELISA (n=120), Kalon HSV-2 ELISA (n=120), U of Washington Western blot (n=101) and a recombinant inhibition test (n=90) [2]
    - Compared to Western blot: HerpeSelect had 100% specificity but only 40% sensitivity; while Kalon had 92% sensitivity and 79% specificity
    - Relative to recombinant inhibition test, Kalon test had 80% sensitivity and 82% specificity
    - Using the recombinant inhibition test, sensitivity of Western blot was low, at 49%
    - Overall, the Kalon HSV-2 ELISA performed better than HerpeSelect

[1] *Mehta et al, AIDS 2012; 26(9):1141-9;* [2] *Smith et al., Sex Transm Infect; 85(2):92-6*

Mixed results on association between MC and HSV-2



Auvert B *PloS Med* 2005 Tobian AR *NEJM* 2009 Mehta SD *AIDS* 2012 (Slide courtesy of Supriya Mehta, UIC)

Syphilis

Evidence from a Systematic Review/Meta-analysis and RCTs

- In 2006, a systematic review and meta-analysis of 26 published articles indicated significant reduction in syphilis in circumcised men (RR 0.67; CI 0.54-0.83) [1]
- **Kisumu Trial:**
  - Incident syphilis did not differ by MC status (RR 1.23; CI 0.41-3.65) [2]
- **Rakai Trial:**
  - Incident syphilis did not differ by MC status (aHR 1.10; CI 0.75-1.65) [3]

[1] Weiss et al, *Sex Transm Infect.* 2006 (82(2):101-9; [2] Mehta at al., *AIDS* 2012; 26(9):1141-49; [3] Tobian et al., *NEJM* 2009; 360:1298-309

Recent Evidence

Association between Male Circumcision and the Incidence of Syphilis among Men and Women: A Prospective Study in HIV-1 Serodiscordant Heterosexual African Couples

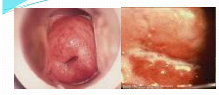
Pintye J, Baeten J, Manhart L, et al., *Lancet Glob Health* 2014; 2(11):e664-71

Rationale, Objectives and Methods

- **Objectives**: Assess the association between MC and incident syphilis among HIV-infected and -uninfected men and women enrolled in the Partners PrEP Study
- **Population:** Participants in Kenya and Uganda HIV-1 serodiscordant heterosexual couples in the Partners PrEP Study
- **Methods**: Analysis of prospective data covering 2.75 years of follow-up

Results

- Data obtained from 4,716 HIV-1 heterosexual serodiscordant couples
- 221 incident syphilis infections were identified (122 men and 99 women)
- Circumcised men had a **42%** overall reduction in risk of acquiring syphilis overall (aHR 0.58; CI 0.37-0.91), and:
  - A **62%** significant reduction among HIV-infected men (aHR 0.38; CI 0.18-0.81)
  - A **36%** non-significant reduction among HIV-uninfected men (aHR 0.64; CI 0.36-1.11)
- Partners of circumcised men had a **59%** reduction in risk of acquiring syphilis overall (aHR 0.41; CI 0.25-0.69), and:
  - A **48%** reduction among HIV-infected women (aHR 0.52; CI 0.27-0.97)
  - A **75%** reduction among HIV-uninfected women (aHR 0.25; CI 0.08-0.76)



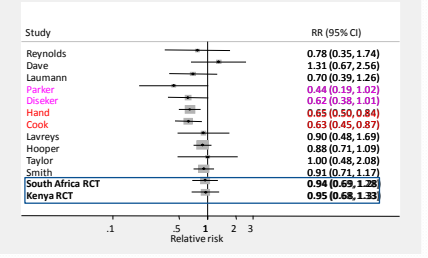

Neisseria Gonorrhoeae, Chlamydia Trachomatis and Trichomonas Vaginalis


Does MC protect against Ng, Ct and Tv?

- Kenya Trial:
  - The incidence of N. gonorrhoeae, C. trachomatis and T. vaginalis, combined or individually, did not differ by circumcision status [1]
- Uganda Trial:
  - MC did not protect against genital discharge (PRR 0.84; CI 0.63-1.11) or Dysuria (PRR 0.97; CI 0.77-1.21) [2]
  - Among female partners circumcision reduced symptoms of Tv (aPRR 0.52; CI 0.05-0.98), any Bv (aPRR 0.60; CI 0.38-0.94) and severe Bv (aPRR 0.39; CI 0.24-0.64) [3]
- South Africa Trial:
  - The prevalence of Ng, Ct and Tv did not vary by MC status in intention-to-treat analysis (Ng= OR 0.97; p = 0.84; Ct= OR 0.58; p = 0.065; Tv= OR 0.54; p = 0.06); however, in the as-treated analysis, circumcision protected men against Tv (AOR 0.41, p = 0.03) [4]

[1] Mehta et al., *J Infect Dis* 2009; 200(3):270-8; [2] Gray et al., *Lancet* 2007; 369:657-66; [3] Gray et al, *Am J Obstet Gynecol* 2009; 200(1):42.e1-7; [4] Sobngwi-Tambekouet al, *Sex Transm Infect* 2009; 85(2):116-20

Circumcision does not protect against Gonorrhea



Observational studies and RCTs

Slide, courtesy of Supriya Mehta, UIC

Summary of MC and non-HIV STIs in the RCTs: Men

Infection	Outcome	Trial	RR	95%CI
Penile HPV	Incidence	S Africa	0.66	0.51-0.86
		Uganda	0.67	0.50-0.91
		Kenya	0.40	0.30-0.50
HSV2	Incidence	S Africa	0.68	0.38-1.22
		Uganda	0.72	0.56-0.92
		Kenya	0.94	0.7-1.25
N. Gonorrhoea	Prevalence	S Africa	0.94	0.69-1.29
	Incidence	Kenya	0.95	0.68-1.34
Chlamydia trachomatis	Prevalence	S Africa	0.56	0.32-1.00
	Incidence	Kenya	0.87	0.65-1.16
Syphilis	Prevalence	Uganda	1.14	0.75-1.65
	Prevalence	Kenya	1.23	0.41-3.65
Genital Ulcer Disease	Incidence	Kenya	0.66	0.51-0.86
		Uganda	0.54	0.46-0.66
		South Africa	0.52	0.37-0.73

Slide courtesy of Helen Weiss, LSHTM (modified)

Conclusions (1/2)

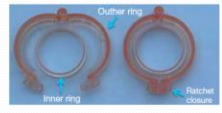
- Interest in the association between MC and STIs has spanned over 160 years
- HPV prevalence, incidence and clearance lower in HIV-uninfected circumcised men
  - Site of sample collection matters!
- Incidence of high risk HPV also lower in female partners of circumcised men
- MC reduces genital ulcer disease in both HIV-uninfected and HIV–infected men
- Mixed RCT results on effect of MC on incident HSV-2: significant reduction in Uganda, borderline reduction in South Africa, and no effect in Kenya.
  - Testing method matters!
- In the Uganda trial, MC lowered HPV risk in female partners but had no effect on their acquisition of HSV-2

Conclusions (2/2)

- MC had no effect on syphilis in the Uganda and Kenya trials, but:
  - A recent analysis of among PrEP participants, MC reduced incident syphilis among HIV infected men and female partners of both infected and uninfected men
- MC had no effect on Ng, CT and Tv among men in the trials, except in as treated analysis in South Africa
  - Ugandan women with circumcised partners has lower symptoms of Tv and Bv

PART 2:

MALE CIRCUMCISION DEVICES



Introduction to Part 2

- Long term follow up of circumcised men in the randomized controlled trials showed sustained reduction in HIV acquisition: 73% in Uganda after 5 years [1] and 58% in Kenya after 7 years [2]
- In South Africa, VMMC rollout led to significant reduction in HIV incidence by 57-61% [3]
- WHO/UNAIDS estimate that 20.8m circumcisions are needed to achieve 80% coverage in 14 priority countries in Africa and avert 3.4m infections by 2025
- About 9.1m circumcisions were performed in these countries between 2008 and 2014
- A key obstacle to rapid rollout of VMMC is the technical difficulty of surgical techniques recommended by WHO/UNAIDS: forceps guided, sleeve resection and dorsal slit
  - These techniques take around 15-30 minutes, and require highly trained providers (physicians in a number of counties) and relatively sterile environments
- Simplified VMMC methods, such as devices, could greatly facilitate rollout.
- Two adult VMMC devices have been prequalified by WHO: PrePex, in 2013 and Shang Ring, in 2015.

[1] Gray et al., AIDS 2012; 26(5)609-15; [2] Mehta et al., AIDS 2013: 27(18)2890-907; [3] Auvert et al., PLoS MED 2013: 10(9):e1001509

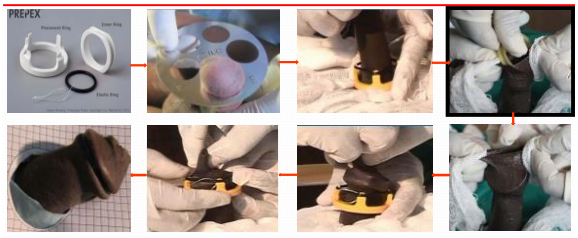
PREPEX MALE CIRCUMCISION SYSTEM

(Circ MedTech Ltd, Tartola, British Virgin Islands)

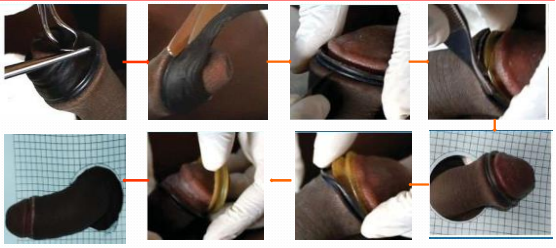
PrePex™ – Background

- PrePex™ is a single use, disposable device consisting of an inner ring, elastic outer ring, placement ring, verification thread and sizing accessory
- Works by compressing the foreskin and cutting off circulation, leading to necrotic foreskin which is then removed after 7 days
- Requires no sutures, no injectable anesthesia (uses anesthetic cream), no sterile (but clean) settings, and no bleeding during placement or removal
- Easily used by trained lower cadre health care providers
- Prequalified by WHO on 13/May/2013 following 8 studies of 2,417 men in Rwanda, Uganda and Zimbabwe

How does PrePex work: Placement



How does PrePex work: Removal



Pre-Pex Studies, and counting……

Study (Type)	Location	Clients	Type of providers
Safety study	Rwanda	55 healthy, HIV-negative clients	Physicians and Nurses
Randomized comparison with surgery	Rwanda	144 PrePex, 73 surgery (dorsal slit)	Physicians and Nurses
Pilot study	Rwanda	49 healthy, HIV-negative men	Nurses
Field study	Rwanda	666 generally healthy men (5 positive)	Lower cadre Nurses
Safety Study	Zimbabwe	53 HIV-negative men	Physicians and Nurse Assistants
Randomized comparison with surgery	Zimbabwe	240 HIV-negative men	Physicians and Nurse Assistants
Field Study	Zimbabwe	641 HIV-negative men	Nurses, with physician back-up
Two field studies	Uganda (IHK) Uganda (Rakai)	634 healthy men 187 HIV-negative men	Surgeons, Medical Officers, Clinical Officers, Nurses Not stated
Safety/acceptability study	Kenya	477 HIV-negative men	Clinical Officers and Nurses
Safety/acceptability	Kenya	HIV-positive men (ongoing)	Clinical Officers and Nurses
Active surveillance study	Kenya	≥1,000 HIV-negative men (ongoing)	Clinical Officers and Nurses

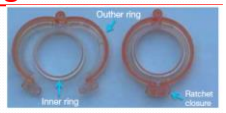
Results from Comparative Trials: Pre-Pex & Conventional Surgical Methods

	Nine studies (n=2,477)		Notes
	PrePex	Surgery	
Total placement and removal time	5.7 min.	19.2 min.	After application of anesthesia
Adverse events: Moderate/Serious	Serious: 0.4% Moderate: 0.7%	<1%	**Serious**: Device displacement (sex, masturbation, erection, spontaneous dislodging); early self removal; wound disruption; meatal injury at removal)
Satisfaction with cosmetic result	99%	"similar"	≈90% would recommend procedure to someone
Pain (on Visual Analog Scale of 1-10) (Kenya Safety and Acceptability Study)	Placement: 0.5 Removal: 5.3 Erection: 3.2	"comparable"	Intense at removal, but fleeting and returns to 1.5 soon after
Preference	60% Uganda 84.6% Moz.	40% Uganda 15.4% Moz.	79% of men concerned with offending odor from nectrotic skin
Successful placement / Removal	92.6% / 99.5%	N/A	• 5-7% not suitable for circumcised with device • 99% returned for device removal 5-7 as recommended

SHANG RING MALE CIRCUMCISION DEVICE

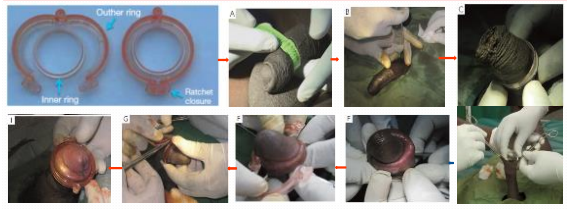
(Wu Hu SNNDA Medical Treatment Appliance Technology Co. Ltd, Wu Hu City, China)

Shang Ring – Background

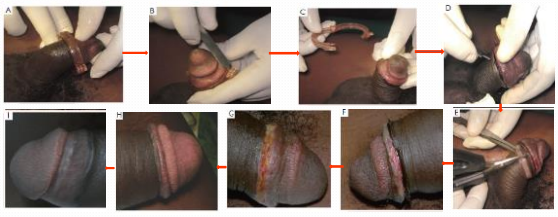


- Shang Ring is a sterile, single use, disposable device consisting of 2 concentric plastic rings – inner and outer rings – that interlock; remains in place for 5-7 days and requires no suturing
- Comes in 32 sizes (for all ages, from neonates to adults); approved for sale and use in EU & USA
- Over 600,000 circumcisions have been performed in China since 2005 using Shang Ring
- 3 studies in China showed that Shang Ring is safe, acceptable and easy to use
- 5 studies have been conducted in Kenya, Uganda and Zambia and confirmed safety, ease of use and acceptability profiles observed in China
- Following these studies, the device was prequalification by WHO in May 2015

How does Shang Ring Work: Placement



How does Shang Ring Work: Removal



Clinical Evaluation of Shang Ring in Adult African Men

Study [type of study]	Reference	Location	Year	Number and type of participants
Safety Study [case series]	Barone M, Ndede F, Li PS et al. JAIDS. 57:e7-e12. 2011	Kenya (1 site)	2009	40 healthy HIV-negative men ≥18 years old
Spontaneous Detachment Study [comparative trial]	Barone M, Awori Q, Li PS et al. JAIDS. 60(3):e82-9. 2012	Kenya (1 site)	2010/11	50 healthy HIV-negative Men ≥18 years old
RCT Conventional vs Shang Ring [comparative trial]	Sokal D, Awori Q, Barone M, et al. AIDS 2012. 2012	Kenya (1 site) Zambia (1 site)	2011	400 healthy HIV-negative men ≥18 years old 200 allocated to Shang Ring circumcision and 200 to conventional circumcision
Field Study [field study]	Sokal D, Li PS, Zulu R, et al. JAIDS, epub ahead of print. 2014	Kenya (7 sites) Zambia (3 sites)	2012	1211 healthy men ≥18 years old HIV-negative and HIV positive
Acceptability & Safety [field study]	Kigozi G, Musoke R, Watya S, et al. JAIDS. 63:617-621. 2013	Uganda (1 site)	2011/12	621 healthy HIV-negative men ≥18 years old 508 chose Shang Ring circumcision 113 chose conventional surgical circumcision

Results from Comparative Trials: Shang Ring & Conventional Surgical Methods

	Kenya & Zambia		Uganda	
	Shang Ring (n=200)	Surgery* (n=200)	Shang Ring (n=508)	Surgery* (n=113)
Mean duration of procedure	7 min.	20 min.	6 min.	18 min.
Adverse events	7.6%	5.0%	1.0%	0.9%
Pain 1 hour post-op**	3.8	3.4	Not reported	Not reported
Very satisfied or satisfied with appearance	92.4%	75.6%	99.8%	98.2%
Complete healing	Mean days		At 4 weeks	
	44.1 days	38.9 days	84.0%	98.2%
Men's preference			81.8%	18.2

*Kenya - forceps guided, Uganda & Zambia – dorsal slit
**Pain using Visual Analog Scale of 1-10: 0 = none; 10 = worst possible
Significant differences are in red

Observations with programmatic implications

Shang Ring ongoing studies:

- Spontaneous detachment; use of topical cream instead of injectable lidocaine (Kenya)
- Using every other size so that the number of sizes that one could need to stock can be reduced (Zambia)
- ShangRing has received registration for use in clinical practice in Kenya (June 2015)

PrePex – new developments with programmatic implications:

- Many adolescents ineligible – due to phimosis and adhesions
  - WHO lists 53% for 13 year olds, 40% for 14 year olds, and 29% for 15 year olds ineligible
- Risk of tetanus infections in PrePex – need for TT vaccination prior to placement.
- ??? Use in remote settings: Early displacements / self-removals after the onset of necrosis and before all circulation to the distal foreskin has stopped

Conclusions

- VMMC devices are safe and highly acceptable among African adults, hence a viable option for scaling up of MMC in sub-Saharan Africa
  - Shang Ring most suitable for adolescents
- Both clients and providers preferred devices to conventional surgical methods
- Performed efficiently by non-clinicians thus can address human resource shortfalls
- No need for sterile setting hence availability of theater space not huge limitation
  - However,
    - Train service providers on surgical procedures as well to serve those ineligible for device placement or address AEs.

Acknowledgements

Reviewed the presentation and gave useful feedback:

- Allan Ronald, University of Manitoba
- Helen Weiss, London School of Hygiene & Tropical Medicine
- Tim Farley, Sigma3 Services, Nyon, Switzerland; formerly WHO Technical Advisor on VMMC Devices
- Mark Barone, Engenderhealth
- Supriya Mehta, Department of Epidemiology and Biostatistics, University of Chicago, Illinois
- Benard Ayieko, Head, VMMC Program at Impact Research and Development Organization

Provided administrative support:

- Rosemary Onayngo, Impact Research and Development Organization, Kisumu, Kenya
- Gift-Noelle Wango, Afya Bora Fellow, Centers for Disease Control and Prevention, Kisumu, Kenya
- Virginia Akach, Impact Research and Development Organization, Kisumu, Kenya

Thank You!