Prevalence and incidence of anogenital warts and their association with HIV status and other factors in Kenyan men reporting high-risk sexual behavior, including men who have sex with men (2005-2013)

Santiago Neme

A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Public Health

University of Washington

2014

Committee:

Susan M. Graham

Joanne D. Stekler

Anna Wald

Program Authorized to Offer Degree:

Epidemiology

University of Washington

Abstract

Prevalence and incidence of anogenital warts and their association with HIV status and other factors in Kenyan men reporting high-risk sexual behavior, including men who have sex with men (2005-2013)

Santiago Neme

Chair of the Supervisory Committee:
Assistant Professor Susan M. Graham
Medicine, Global Health, and Epidemiology

BACKGROUND: Human papillomavirus (HPV) causes a wide spectrum of disease ranging from warts to life-threatening cancers. Prevalence, incidence, and factors associated with anogenital warts in high-risk African men are largely unknown.

METHODS: Since 2005, men reporting high-risk sex behavior (having sex with men [MSM], transactional sex, recurrent sexually-transmitted infections [STI], serodiscordant or multiple sex partners) were followed at scheduled visits for collection of behavioral and clinical data (physical examination, HIV and STI testing). Visual inspection was used for detection of anogenital warts (AG) and genital ulcerations. Urethral and rectal samples were collected from symptomatic men to diagnose urethritis and proctitis. Logistic regression was used to identify associations between prevalent AG and predictors, adjusting for

confounders. Adjusted incidence rates were calculated. A Cox regression analysis was performed to analyze predictors of incident AG, adjusting for confounders.

RESULTS: AG prevalence was 2.9% (95% CI: 2.0% – 4.0%). HIV was associated with increased AG prevalence (OR 5.43; 95% CI: 2.03 – 11.29; P <0.001). Follow-up time was 1,639 person-years (PY), with a median of 1.4 years, and a median number of visits of 6. AG incidence was 5.3 per 100 PY (95% CI: 4.3 – 6.5). HIV and being diagnosed with a genital syndrome were associated with an increased risk of acquiring AG (HR 1.66; 95% CI: 1.01 – 2.72; P 0.04 and HR 4.78; 95% CI: 3.03 – 7.56; P <0.001, respectively).

CONCLUSIONS: We detected high prevalence and incidence of AG in a population of MSM and other high-risk men in Africa. AG prevalence is associated with HIV and that the risk of AG acquisition is associated with both having HIV and a genital syndrome. These findings motivate us to intensify our prevention efforts by expanding HPV vaccination in East Africa to include young men and by ensuring early diagnosis and treatment of STI (including HIV).

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

The author expresses sincere gratitude to Dr. Susan M. Graham, Dr. Joanne D. Stekler, and Dr. Anna Wald of the University of Washington for their invaluable contributions to this research.

Chapter 1

Introduction and Background

Infection with human papillomavirus (HPV) is responsible for significant morbidity and mortality worldwide.[1,2] HPV causes a wide spectrum of disease ranging from warts to life-threatening cancers.[3-6] Multiple risk factors for HPV infection or HPV-associated disease have been described in the literature.[7] Biological risk factors primarily affect the ability of the virus to cause cancer; these include characteristics of the virus itself as well as intrinsic host factors possibly impacting immune response (e.g., co-infection with HIV or other sexually transmitted infections, being uncircumcised, certain nutritional deficiencies, genetic polymorphisms in the human leukocyte antigen system).[8] Behavioral risk factors mainly affect the acquisition of HPV and include aspects related to sexual history (e.g., number of partners, characteristics of the partners, contraceptive use, post-coital genital washing, bathing frequency) and substance use (e.g., tobacco, alcohol, illicit drugs).[8-11] Although HPV infection is highly prevalent in East Africa, little is known about the prevalence, incidence, and risk factors associated with HPV infection in East African men reporting high-risk sexual behavior, including those who primarily but not exclusively have sex with men.[12]

Papillomaviruses are non-enveloped double-stranded DNA viruses that constitute the Papillomavirus genus of the Papillomaviridae family. There are more than 100 HPV types, affecting the skin or mucosa based on tissue tropism.[9,13] Low-risk HPV types tend to cause anogenital warts (types 6 and 11, mainly) while high-risk types (mainly 16 and 18) are the cause of several types of cancer (including cervical and anorectal). In a randomized controlled trial of an HPV vaccine, Vandepapeliere et al found that infection with multiple HPV types, including high-risk types, is common in anogenital wart disease.[14] In a large Danish cohort study, which included approximately 47,000 subjects (men and women), Blomberg et al found that individuals with anogenital warts have a long-term increased risk of anogenital cancers.[15]

The average worldwide incidence of anal cancer in the general population is estimated to be 1.0 per 100,000, with an estimated 27,000 new cases every year.[16,17] In 2011, the United States reported an incidence of anal cancer of 1.8 per 100,000 men and women per year.[18] Between 1973-1996 and 1997-

2009, the incidence rates for anal cancer in the United States increased threefold in men and 1.7-fold in women.[19] Anal cancer incidence among HIV-uninfected men who have sex with men (MSM) living in the United States is estimated to be as high as 37 per 100,000 person-years. HIV-infected MSM are estimated to have a two-fold increase in anal cancer risk compared to HIV-uninfected MSM.[20,21]

Several studies have shown that HPV infection incidence is higher among HIV-infected than uninfected men and women worldwide.[22,23] In a large cross-sectional study in Tanzania, the prevalence of high-risk HPV types in women of the general population was 20%, higher in HIV-infected women (47%) than in HIV-uninfected women (17%).[24] In a meta-analysis of 53 observational studies (mostly conducted in North America), the pooled prevalence for anal infection with any HPV type and any high-risk HPV type in HIV-uninfected men who have sex with men (MSM) was 64% and 37%, respectively.[23]

HPV vaccines have shown excellent efficacy in reducing the risk of cervical, vulvar and vaginal cancers, as well as genital warts in women. The quadrivalent HPV vaccine has been shown to reduce the rates of anal intraepithelial neoplasia (including grade 2 and 3) among MSM.[25,26] In the United States, the Advisory Committee on Immunization Practices (ACIP), recommends the routine use of quadrivalent vaccine in boys aged 11 or 12 years. The vaccine can be administered to individuals as young as nine years of age. ACIP also recommends the vaccine for male youth aged 13 to 21 years who have not been vaccinated previously or who have not completed the series. The vaccine is also recommended for MSM and men who are immunocompromised (including HIV infection) through age 26 (if not previously immunized).[27]

Approximately 40% of Kenyan women in the general population are estimated to have cervical infection with any HPV type at any given time.[28] Kavanaugh et al estimated the genital wart prevalence among high-risk women in Mombasa, Kenya to be 2.3%.[29] However, little is known about the prevalence or incidence of HPV infection or anogenital warts in Kenyan men reporting high-risk sexual behavior. To date, no study has been done to look at the potential association between anogenital warts and HIV status, hygiene practices, and other potential risk factors in this population with a high prevalence of HIV (estimated at 24.5%), homelessness, and poor access to bathing facilities.[30] Currently, there is no recommendation for HPV vaccination in men in East Africa.

Specific Aims

This research project sought to describe the prevalence, incidence, and factors associated with anogenital warts in a cohort of Kenyan men reporting high-risk sexual behavior (defined as having sex with men, sex in exchange for money, recurrent sexually-transmitted infections, serodiscordant sex partners or multiple sex partners). This work also addressed whether the presence of anogenital warts was associated with HIV serologic status and genital washing, among other potential risk factors.

Our study's specific aims were as follows:

SPECIFIC AIM 1: To determine the prevalence of anogenital warts in HIV-infected vs. uninfected Kenyan men reporting high-risk sexual behavior.

Hypotheses addressed by this aim:

a) The prevalence of anogenital warts will be higher in the HIV-infected men than in those who are HIV-uninfected.

SPECIFIC AIM 2: To estimate the incidence of anogenital warts in HIV-infected vs. uninfected Kenyan men reporting high-risk sexual behavior.

Hypotheses addressed by this aim:

a) The incidence of anogenital warts will be higher in the HIV-infected men than in those who are HIV-uninfected.

SPECIFIC AIM 3: To identify other factors associated with anogenital warts in Kenyan men reporting high-risk sexual behavior.

Hypotheses addressed by this aim:

a) The use of soap for genital washing will be associated with lower prevalence or incidence of anogenital warts.
b) Having sex with both men and women will be associated with higher prevalence or incidence of anogenital warts.
c) Being diagnosed with a genital syndrome other than warts (urethritis, proctitis or genital ulceration) will be associated with a higher prevalence or incidence of anogenital warts.

Chapter 2

Methods

Study Design

The study was designed to include a two-part analysis of existing data from both HIV seropositive and seronegative Kenyan MSM who enrolled and were followed prospectively in the Kenya Medical Research Institute (KEMRI) cohort.[30] Part one examined the prevalence of anogenital warts at enrollment and its association with HIV serologic status, genital washing and other factors. Part two looked at the incidence of anogenital warts and its association with HIV serologic status, genital washing, and other factors (Figure 1). The study period started on January 9, 2005 and ended on June 24, 2013, with inclusion of data from all 1,272 first exam visits and 1,639 person-years of follow-up during this period.

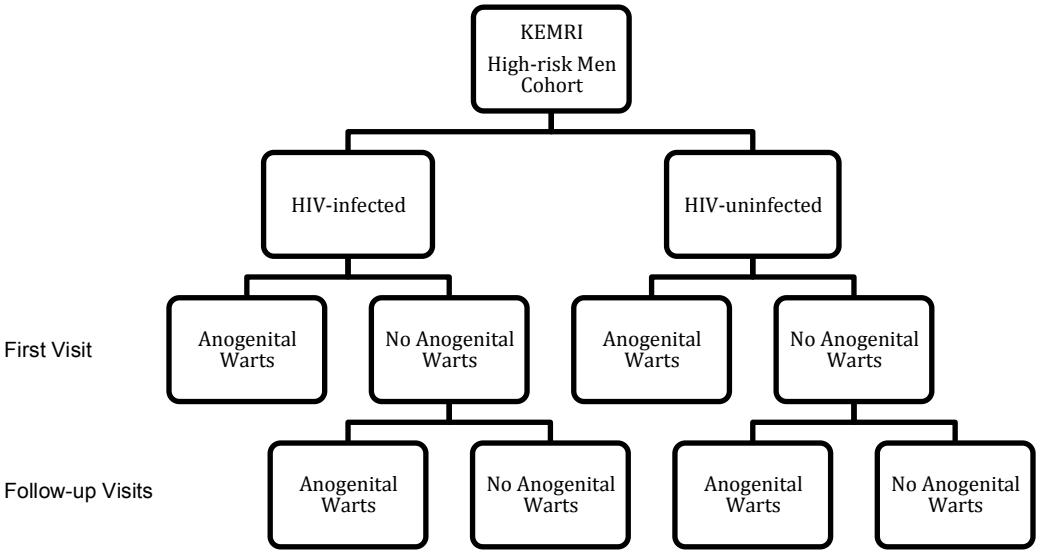

Figure 1: Study design schematic

Study Setting

In July 2005, the KEMRI HIV/STD clinic opened in Mtwapa, Kenya (approximately 13 miles north of the coastal city of Mombasa), as a collaborative research site supporting the work of investigators from KEMRI, the University of Oxford, and the University of Washington (UW). The International AIDS Vaccine Initiative (IAVI) funded the development of the site for a vaccine feasibility study in which high-risk, HIV-uninfected persons would be prospectively followed and monitored for HIV seroconversion.

Mtwapa was chosen due to its large population of female sex workers, high HIV prevalence, and poor access to HIV prevention services. After the clinic's opening, the research team identified an additional high-risk population of male sex workers who have sex with men.[30,31] Consequently, this high-risk population was included in outreach and prevention efforts.

Study Subjects

Potential study participants were identified and recruited by a team of 10-20 trained peer mobilizers, who approached them via personal networks and at venues at which MSM frequently met to establish contact with sexual partners (including clients). Men who self-reported any anal sex with another man within the last three months were enrolled as MSM. All men, regardless of reported sexual activity, orientation or preference, were included in the present study.

Data Collection

Prospective participants were invited to attend a drop-in center where they received information about participation in research, watched a video on informed consent, and met with a pre-enrollment counselor. Upon enrollment, a face-to-face interview was conducted by trained research staff to obtain a detailed socio-demographic history (including sexual behavior characteristics). After completing the risk assessment, blood was collected for HIV-1 screening. Study clinicians conducted and recorded a standardized medical history and physical examination, including genital examination. A rectal examination was also performed, if the patient reported receptive anal sex or anorectal symptoms. Starting in September 2006, participants who reportedly practiced receptive anal sex or experienced anal symptoms were offered proctoscopy to look for anal pathology (e.g., discharge, ulcerations, other benign conditions). The study participants were seen either every three months or monthly (when receptive anal intercourse was reported) at scheduled appointments. During weekdays, urgent medical care was also provided at the research clinic. At all visits, study staff provided participants with risk reduction counseling, performed repeat HIV counseling and testing, obtained a medical history, performed a physical examination and STI screening.

Genital warts were identified by visual inspection of the external genitalia by a trained healthcare provider at each clinic visit and included both verrucous and flat lesions. Genital and perianal warts were recorded separately. Lesions that appeared related to herpes simplex virus (e.g., ulcers, vesicles) or benign conditions (e.g., cysts or skin tags) were not counted as warts.

Urethritis was defined as having five or more polymorphonuclear cells (PMN's) per high power field on a Gram-stained urethral smear.[32] Due to limited resources, detection of Gram-negative, intracellular diplococci was used as a surrogate for gonococcal infection. A rectal Gram stain with five or more PMN's per high power field was used to diagnose proctitis. UW's Mombasa-based research laboratory trained our lab technicians, with periodic quality control of results.[30,31] In accordance with World Health Organization's guidelines, we administered syndromic STI treatment for symptomatic urethritis or proctitis.

For on-site HIV-1 testing, we used two rapid HIV-1 test kits (Determine, Abbott Laboratories, USA; Uni-gold Recombigen HIV, Trinity Biotech PLC, Ireland). We verified any discrepant result with a third enzyme-linked immunosorbent assay (ELISA) test (Genetic System HIV-1/2 plus O EIA, Bio-Rad Laboratories, Redmond, Washington, USA) performed at the Kenya AIDS Vaccine Initiative laboratories in Nairobi, Kenya. Participants who tested positive for HIV at screening were offered enrollment into a parallel HIV-infected cohort. The HIV-infected cohort provided participants with access to comprehensive HIV care (including antiretroviral therapy). We provided clinical care and referrals to all, irrespective of research study participation.

Data Storage and Management

Hard copies of all data collection forms were kept in locked cabinets in a secure office at the KEMRI clinic. At this office, data were entered into a secure database after each visit. Research staff assigned a study number to each participant, making sure no identifying information appeared on any data collection form, except for the consent form and a registration form used in the event that tracking was needed. Staff did not enter the consent and registration forms into the database. Instead, these were

kept in a separate, locked file cabinet. Periodic line listing was used to verify data accuracy, by checking the data against source documents.

Variable Definitions

Anogenital warts, our outcome of interest, was coded as a binary variable capturing the presence of any penile or perianal wart. Genital syndrome, one of our a priori predictors, was coded as a binary variable capturing the diagnosis of urethritis (five or more PMN's per high power field on a Gram-stained urethral smear), proctitis (five or more PMN's per high power field on a Gram-stained rectal smear) or genital ulceration (any ulceration, either penile or perianal, on physical exam) (Table 1).

Table 1. Variable Definitions

Variable Name	Variable Type	Coding
Anogenital warts (physical examination finding)	Outcome	No
		Yes (for any wart, either penile or anal - Refer to Variable Definition section for further details)
HIV status (serologic testing)	Predictor	Negative
		Positive
Use of any soap (self report)	Predictor	No
		Yes
Soap dose (self report)	Predictor	0 (did not use soap at all)
		1 (0-7 times/week)
		2 (7-14 times/week)
		3 (14-21 times/week)
Age group	Predictor	18-24 years
		25-34 years
		>34 years
Education	Predictor	Primary or lower
		Secondary
		Higher/Tertiary
Ever married	Predictor	No
		Yes
Employment	Predictor	None
		Self
		Formal
Circumcised (physical examination finding)	Predictor	No
		Yes
Number of sex partners in past month	Predictor	None
		1
		2-4
		>4
Condom use for anal sex	Predictor	No anal sex
		All protected
		Any unprotected
Condom use for all sexual activity	Predictor	No sexual activity
		All protected
		Any unprotected
Transactional sex in past 3 months	Predictor	No
		Yes
Sex partner's gender	Predictor	Men and women
		Only men
		Only women
Insertive anal sex	Predictor	No
		Yes
Receptive anal sex	Predictor	No
		Yes
Genital syndrome	Predictor	No
		Yes (for urethritis, proctitis or genital ulceration – Refer to Variable Definition section for further details)
Alcohol use	Predictor	None
		None with sex
		Yes with sex

Data Analysis

The primary analysis followed the steps outlined below:

A. Descriptive statistics were used to summarize baseline characteristics of the study population at cohort enrollment.

B. Analysis of Prevalence:

   i. The prevalence of anogenital warts in HIV-infected and HIV-uninfected was calculated, with 95% confidence intervals, using exact binomial methods.

   ii. Chi-square tests were used to evaluate the association between anogenital wart detection and HIV status, anogenital wart detection and use of soap for genital washing, as well as associations between anogenital wart detection and our list of predictors (refer to Table 1).

   iii. Logistic regression was used to identify independent associations between the a priori predictors HIV status and use of soap for genital washing and the primary outcome (i.e., prevalent anogenital warts), before and after adjustment for any potential confounders that were associated with anogenital warts in bivariate analysis at $p<0.10$.[34]

C. Incidence Analysis:

   i. Incidence rates were calculated in the entire population and by predictor categories (e.g., HIV status, use of soap for genital washing). The log-rank test was used to test for differences in risk of anogenital warts by HIV status and Kaplan-Meier estimates were obtained.

   ii. A Cox regression analysis was then performed on follow-up data to analyze predictors of incident warts during follow-up. Participant data was censored at the last clinic visit or end of study period, whichever came first. HIV-uninfected men were censored at HIV acquisition. This analysis was performed with and

without adjustment for potential confounders, using the same model-building approach as above.

Study Power

We looked at the prevalence of anogenital warts (outcome of interest) and HIV serologic status (primary predictor) in our dataset and calculated post-hoc study power based on these estimates. More specifically, we found 33 men with anogenital warts at enrollment and 1,104 controls. The HIV prevalence at enrollment was 12%. Based on these baseline estimates, we predicted detectable OR's for disease ≤0.09 or ≥2.91 in exposed (HIV-infected) subjects relative to unexposed (HIV-uninfected) with a power of 80%. Two-sided alpha = 0.05.

For incidence, we also performed a post-hoc power calculation. Based on study data, we estimated that the probability of wart-free survival in an HIV-uninfected subject for 1 year was approximately $m_1 = t \log_e(1/2)/\log_e(p)$, where t = 1 year and p = .95 (i.e., 1 - .05, based on our observed incidence rate). Application of this formula results in an estimate for median survival time among HIV-uninfected men of 12.7 years.

With 125 HIV-infected men and 979 HIV-uninfected men, and a median follow-up time of 1.4 years, we would be able to detect a relative risk of failure for HIV-infected subjects relative to HIV-uninfected subjects of 2.3 or greater with probability (power) 0.8. The Type I error probability associated with this test of the null hypothesis that the HIV-infected and HIV-uninfected survival curves are equal is 0.05.

Chapter 3

Results

Population

Between 2005 and 2012, 1,137 men were enrolled. Sixty percent of the men reported having sex with both men and women, 15% reported having sex only with men, and the remaining 25% reported having sex with women only (Table 2). The mean age was 28 years of age. Three-quarters of the men were single. Half had completed only primary school, while one third had completed secondary school and a small minority had additional training. Only one-quarter of the men reported formal employment. The majority reported having been paid for sex in the past three months. Overall, the HIV prevalence at baseline was 12.1% (95% CI, 10.3% – 14.2%).

Table 2. Baseline characteristics

Variable Name	Coding	n (%)
Anogenital warts (physical examination finding)	No	1,104 (97)
	Yes (for any wart, either penile or anal – Refer to Variable Definitions section for further details)	33 (3)
HIV status (serologic testing)	Negative	999 (88)
	Positive	138 (12)
Use of any soap (self report)	No	78 (7)
	Yes	1,056 (93)
Soap dose (self report)	0 (did not use soap at all)	78 (7)
	1 (0-7 times/week)	352 (31)
	2 (7-14 times/week)	554 (50)
	3 (14-21 times/week)	136 (12)
Age group	18-24 years	498 (44)
	25-34 years	464 (41)
	>34 years	175 (15)
Education	Primary or lower	577 (51)
	Secondary	438 (38)
	Higher/Tertiary	122 (11)
Ever married	No	842 (74)
	Yes	295 (26)
Employment	None	333 (29)
	Self	529 (47)
	Formal	275 (24)
Circumcised (physical examination finding)	No	99 (9)
	Yes	1,035 (91)
Number of sex partners in past month	None	73 (6)
	1	210 (19)
	2-4	482 (42)
	>4	372 (33)
Condom use for anal sex	No anal sex	436 (38)
	All protected	25 (2)
	Any unprotected	676 (60)
Condom use for any sexual activity	No sexual activity	245 (22)
	All protected	231 (20)
	Any unprotected	660 (58)
Transactional sex in past 3 months	No	473 (42)
	Yes	661 (58)
Sex partner's gender	Men and women	676 (60)
	Only men	176 (15)
	Only women	285 (25)
Insertive anal sex	No	608 (53)
	Yes	529 (47)
Receptive anal sex	No	587 (52)
	Yes	550 (48)
Genital syndrome	No	659 (58)
	Yes (for urethritis, proctitis or genital ulceration – Refer to Variable Definitions section for further details)	478 (42)
Alcohol use	None	81 (7)
	None with sex	460 (41)
	Yes with sex	593 (52)

Anogenital Wart Prevalence and Risk Factors

At enrollment, 33 of the 1,137 participants were diagnosed with an anogenital wart with a calculated prevalence of 2.9% (95% CI: 2.0% – 4.0%). Table 3 presents the logistic regression analysis of associations with prevalent anogenital warts at the first exam visit.

In bivariate analysis, HIV infection was the only variable associated with an increased prevalence of anogenital warts (OR 5.09; 95% CI: 2.47 – 10.49; *P* <0.001). Although the use of soap (both use of any soap as well as increasing soap dosage) for genital washing showed a reduced odds ratio, there was no statistically significant association. There was no association between prevalent anogenital warts and having sex with men exclusively compared to having sex with both men and women (OR 0.67; 95% CI: 0.23 - 1.93; *P* 0.48). We did not detect an association between prevalent anogenital warts and the presence of other genital syndromes (i.e., urethritis, proctitis or genital ulceration) (OR 1.68; 95% CI: 0.84 – 3.36; *P* 0.14).

In multivariate analysis, we included only HIV status and soap use as a priori predictors. HIV infection was associated with an increased prevalence of anogenital warts (OR 5.43; 95% CI: 2.03 – 11.29; *P* <0.001). Use of any soap for genital washing was not associated with a decrease in anogenital wart prevalence (OR 0.63; 95% CI: 0.19 – 2.16; P 0.47).

TABLE 3. Factors Associated with Prevalent Anogenital Warts at Enrollment Among 1,137 men

Characteristics and Behaviors	Anogenital Wart Proportion (%)	Bivariate Analysis		Multivariate Analysis	
		OR (95% CI)	Wald P	OR (95% CI)	Wald P
Age group			0.48		
18-24 years	11/498 (2.2)	Referent			
25-34 years	16/464 (3.4)	1.58 (0.73 - 3.44)			
>34 years	6/175 (3.4)	1.57 (0.57 – 4.32)			
Genital syndrome			0.14		
No	15/659 (2.3)	Referent			
Yes	18/478 (3.4)	1.68 (0.84 – 3.36)			
HIV status			**<0.001**		**<0.001**
Negative	20/999 (2.0)	Referent		Referent	
Positive	13/138 (9.42)	5.09 (2.47 – 10.49)		5.43 (2.03 – 11.29)	
Circumcised			0.61		
No	2/99 (2.0)	Referent			
Yes	30/1,035 (2.9)	1.45 (0.34 – 6.15)			
Education			0.13		
Primary or lower	21/577 (3.6)	Referent			
Secondary	7/438 (1.6)	0.43 (0.18 – 1.02)			
Higher/Tertiary	5/122 (4.1)	1.13 (0.42 – 3.06)			
Ever married			0.56		
No	23/842 (2.7)	Referent			
Yes	10/295 (3.4)	1.25 (0.59 – 2.66)			
Employment			0.96		
None	9/333 (2.7)	Referent			
Self	16/529 (3.0)	1.12 (0.49 – 2.57)			
Formal	8/275 (2.9)	1.08 (0.41 – 2.83)			
Any use of soap			**0.61**		**0.47**
No	3/78 (3.8)	Referent		Referent	
Yes	30/1,056 (2.8)	0.73 (0.21 – 2.45)		0.63 (0.19 – 2.16)	
Soap dose			0.49		
0 (did not use soap at all)	3/78 (3.8)	Referent			
1 (0-7 times/week)	12/352 (3.4)	0.88 (0.24 – 3.2)			
2 (7-14 times/week)	17/554 (3.0)	0.79 (0.23 – 2.77)			
3 (14-21 times/week)	1/136 (0.7)	0.19 (0.02 – 1.81)			
Sex partners in past month			0.49		
None	2/73 (2.7)	Referent			
1	6/210 (2.9)	1.04 (0.21 – 5.29)			
2-4	17/482 (3.5)	1.30 (0.29 – 5.74)			
>4	8/372 (2.1)	0.78 (0.16 – 3.75)			
Condom use for anal sex			0.61		
No anal sex	10/436 (2.3)	Referent			
All protected	1/25 (4.0)	1.78 (0.22 – 14.4)			
Any unprotected	22/676 (3.2)	1.43 (0.67 – 3.06)			
Condom use for any sexual activity			0.15		
No sexual activity	11/245 (4.5)	Referent			
All protected	8/231 (3.5)	0.76 (0.30 – 1.93)			
Any unprotected	14/660 (2.1)	0.46 (0.21 – 1.03)			
Transactional sex in the past 3 months			0.53		
No	12/473 (2.5)	Referent			
Yes	21/661 (3.2)	1.26 (0.61 – 2.59)			
Sex partner's gender			0.48		
Men and women	23/676 (3.4)	Referent			
Only men	4/176 (2.3)	0.67 (0.23-1.93)			
Only women	6/285(2.1)	0.61 (0.25-1.51)			
Alcohol use			0.67		
None	1/81 (1.2)	Referent			
None with sex	14/460 (3.0)	2.51 (0.32 – 19.36)			
Yes with sex	18/593 (3.0)	2.50 (0.33 – 19.01)			
Insertive anal sex			0.40		
No	20/608 (3.29)	Referent			
Yes	13/529 (2.46)	0.74 (0.37 – 1.50)			
Receptive anal sex			0.47		
No	15/587 (2.6)	Referent			
Yes	18/550 (3.3)	1.29 (0.64 – 2.59)			

Anogenital Wart Incidence and Risk Factors

The 33 men diagnosed with an anogenital wart on the initial exam were excluded from the analysis of wart incidence. Follow-up time was 1,639 person-years, with a median of 1.4 years (range: 0.03 - 7.59) and a median number of visits of 6. There were 87 incident cases of anogenital warts, with an incidence rate calculated at 5.3 per 100 PY (95% CI: 4.3 – 6.5) (Table 4). The log-rank test comparing the time to detection of anogenital warts by HIV status showed a p value equal to 0.009. Kaplan-Meier estimates are shown in Figure 2.

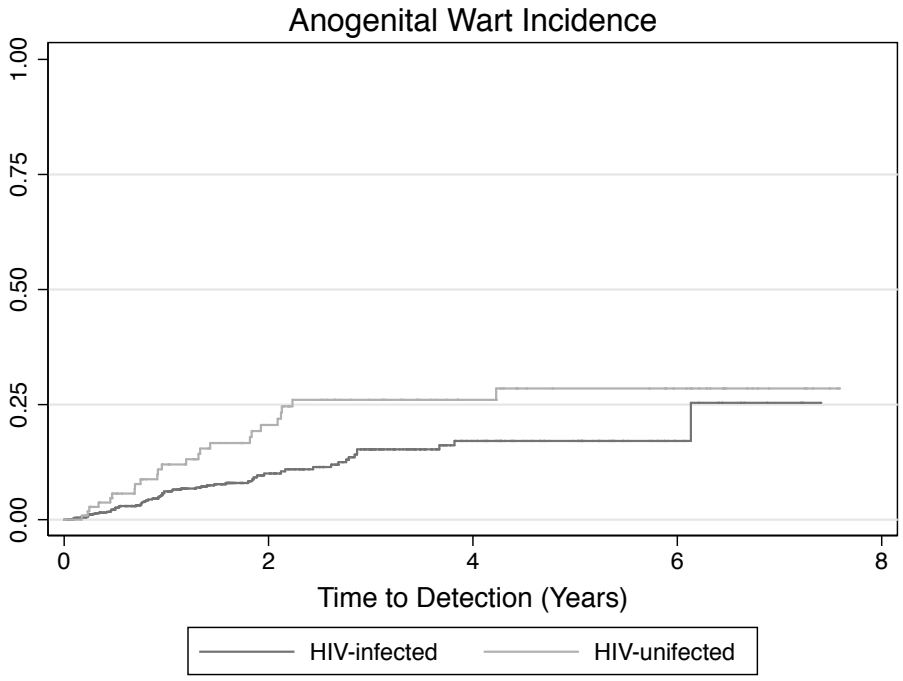

Figure 2: Kaplan-Meier Estimates

In bivariate analysis [Table 4], reporting being paid for sex in the past three months (HR 1.65; 95% CI: 1.06 – 2.57; *P* = 0.02) and being diagnosed with a genital syndrome (urethritis, proctitis or genital ulceration) (HR 5.10; 95% CI: 3.27 – 7.95; *P* <0.001) were associated with an increased risk of anogenital wart acquisition. HIV infection and having sex with other men exclusively were associated with a trend towards increased risk of anogenital wart acquisition (HR 1.50; 95% CI: 0.94 – 2.41; *P* 0.09 and HR 1.45; 95% CI: 0.79 – 2.64; *P* 0.053, respectively). Being married was associated with a trend towards decreased risk of anogenital wart acquisition (HR 0.62; 95% CI: 0.37 – 1.04; *P* 0.06). Although the use of

any soap for genital washing was not significantly associated with anogenital wart acquisition, the hazard ratio was reduced (HR 0.61; 95% CI: 0.26 – 1.40; *P* 0.28) (Table 4).

In our multivariate model, HIV infection and being diagnosed with a genital syndrome (urethritis, proctitis or genital ulceration) were associated with an increased risk of acquiring anogenital warts (HR 1.66; 95% CI: 1.01 – 2.72; *P* 0.04 and HR 4.78; 95% CI: 3.03 – 7.56; *P* <0.001, respectively). The use of any soap for genital washing was not associated with anogenital wart acquisition (HR 0.74; 95% CI: 0.32 – 1.74; *P* 0.49).

TABLE 4. Factors Associated with Incident Anogenital Warts Among 1,104 Men

Characteristics and Behaviors	Failures/ Per PY	Incidence/100 PY (95% CI)	Bivariate Analysis		Multivariate Analysis	
			HR (95% CI)	Wald P	HR (95% CI)	Wald P
Age group				0.10		
18-24 years	34/485.2	7.0 (5.0 – 9.8)	Referent			
25-34 years	40/803.5	5.0 (3.7 – 6.8)	0.71 (0.45-1.12)			
>34 years	13/358.4	3.6 (2.1 - 6.2)	0.52 (0.27– 0.99)			
Genital syndrome				**<0.001**		**<0.001**
No	47/1390.4	3.4 (2.5 – 4.5)	Referent		Referent	
Yes	40/256.7	15.6 (11.4 – 21.2)	5.10 (3.27 – 7.95)		4.78 (3.03 – 7.56)	
HIV status				**0.09**		**0.04**
Negative	63/1330.7	4.7 (3.7 – 6.1)	Referent		Referent	
Positive	24/316.4	7.6 (5.1 -11.3)	1.50 (0.94 – 2.41)		1.66 (1.01 – 2.72)	
Circumcised				0.15		
No	11/130.5	8.4 (4.7 – 15.2)	Referent			
Yes	76/1493.3	5.1 (4.1 – 6.4)	0.61 (0.32 – 1.14)			
Education				0.26		
Primary or lower	39/864.0	4.5 (3.3 – 6.2)	Referent			
Secondary	40/624.7	6.4 (4.7 – 8.7)	1.45 (0.93 – 2.26)			
Higher/Tertiary	8/158.4	5.1 (2.5 – 10.1)	1.20 (0.57 – 2.58)			
Ever married				**0.06**		0.23
No	68/1130.9	6.0 (4.7 – 7.6)	Referent		Referent	
Yes	19/516.2	3.7 (2.3 – 5.8)	0.62 (0.37 – 1.04)		0.71 (0.42 – 1.23)	
Employment				0.78		
None	21/413.3	5.1 (3.3 – 7.8)	Referent			
Self	42/797.4	5.3 (3.9 – 7.1)	1.12 (0.66 – 1.9)			
Formal	24/436.4	5.5 (3.7 – 8.2)	1.23 (0.68-2.22)			
Any use of soap				**0.28**		0.49
No	6/66.2	9.1 (4.1 – 20.2)	Referent		Referent	
Yes	79/1567.5	5.0 (4.0 – 6.3)	0.61 (0.26 – 1.40)		0.74 (0.32 – 1.74)	
Soap dose				0.58		
0 (did not use soap at all)	6/66.2	9.1 (4.1 – 20.2)	Referent			
1 (0-7 times/week)	16/335.9	4.8 (2.9 – 7.8)	0.57 (0.22 – 1.45)			
2 (7-14 times/week)	44/949.8	4.6 (3.4 – 6.2)	0.57 (0.24 – 1.34)			
3 (14-21 times/week)	17/270.6	6.3 (3.9 – 10.1)	0.71 (0.28 – 1.83)			
Sex partners in past month				0.23		
None	16/384	4.2 (2.6 – 6.8)	Referent			
1	18/473.7	3.8 (2.4 – 6.0)	0.85 (0.43 – 1.68)			
2-4	29/525.5	5.5 (3.8 – 7.9)	1.13 (0.60-2.11)			
>4	24/263.8	9.1 (6.1 – 13.6)	1.60 (0.83 – 3.13)			
Condom use for anal sex				0.21		
No anal sex	39/921.6	4.2 (3.1 – 5.8)	Referent			
All protected	11/100.8	10.9 (6.0 – 19.7)	1.90 (0.96 – 3.78)			
Any unprotected	37/624.7	5.9 (4.3 – 8.2)	1.07 (0.67 – 1.72)			
Condom use for any sexual activity				0.47		
No sexual activity	33/640.6	5.2 (3.7 – 7.2)	Referent			
All protected	20/454.8	4.4 (2.8 – 6.8)	0.81 (0.46 – 1.40)			
Any unprotected	34/549.1	6.2 (4.4 – 8.7)	1.13 (0.70 – 1.83)			
Transactional sex in the past 3 months				**0.025**		0.26
No	38/1003.2	3.8 (2.8 – 5.2)	Referent		Referent	
Yes	47/630.7	7.5 (5.6 – 9.9)	1.65 (1.06 – 2.57)		1.31 (0.82 – 2.11)	
Sex partner's gender				**0.053**		0.61
Men and women	65/1130.2	5.8 (4.5 – 7.3)	Referent		Referent	
Only men	13/158.8	8.2 (4.8 – 14.1)	1.45 (0.79 – 2.64)		0.88 (0.46 – 1.70)	
Only women	9/358.1	2.5 (1.3 – 4.8)	0.48 (0.21 – 1.06)		0.68 (0.30 – 1.53)	
Alcohol use				0.36		
None	8/209.5	3.8 (1.9 – 7.6)	Referent			
None with sex	38/805.6	4.7 (3.4 – 6.5)	0.74 (0.30 – 1.84)			
Yes with sex	39/618.7	6.3 (4.6 – 8.6)	1.02 (0.42 – 2.47)			
Insertive anal sex				0.65		
No	58/1133.3	5.1 (4.0 – 6.6)	Referent			
Yes	29/513.8	5.6 (3.9 – 8.1)	0.90 (0.57 – 1.42)			
Receptive anal sex				0.13		
No	49/1118.1	4.4 (3.3 – 5.8)	Referent			
Yes	38/529	7.2 (5.2 – 9.9)	1.40 (0.90 – 2.16)			

Chapter 4

Discussion and Conclusions

This is the first study, to our knowledge, that measured the prevalence and incidence of genital warts in a population of MSM and other high-risk men in Africa. We found a prevalence of 2.9% and incidence of 5.3%; both were substantially higher among HIV infected men than HIV uninfected men.

Men diagnosed with a genital syndrome such as urethritis, proctitis or genital ulceration also had an increased incidence of anogenital warts. Neither soap use nor having sex with both men and women was associated with anogenital prevalence or incidence, although our power to detect even fairly large risk estimates was limited.

Prevalence of genital warts in men reporting high-risk sexual behavior in other developing African countries has not been reported, preventing us from comparing our results with similar populations. However, a 2013 systematic review by Patel et estimated the global prevalence of anogenital warts to be between 0.1% and 5.1%; our data fall within this range.[35] Also noteworthy is the fact that the anogenital wart prevalence we found appears to be in alignment with urban North American data. In 2010, the prevalence of genital warts in several urban US cities (including Chicago, Birmingham, Richmond, Hartford/New Haven, Baltimore, Philadelphia, and New York City) ranged from 2.9% to 9.2% for MSM and from 2.6% to 7.2% for men who have sex with women.[36]

In our cohort, HIV-infected men had a higher prevalence of anogenital warts with minimal change in magnitude of risk after adjusting for potential confounders. These results are consistent with the findings of several studies describing higher rates of HPV infection in HIV-infected individuals in populations across the globe.[22-24,37] HIV-infected men may have a higher anogenital wart prevalence because HPV infection tends to persist and reactivate more frequently than in HIV-uninfected individuals.[38]

Although the use of soap for genital washing showed a reduced odds ratio, no statistically significant association was found. This is in contrast to the findings by Okuku et al in their work on HSV-2 incidence in the same cohort, where use of soap for genital washing was found to be associated with a

decreased risk of HSV-2 acquisition in Kenyan men reporting high-risk sexual behavior (aIRR 0.3; 95% CI 0.1–0.8).[39]

In contrast to our hypothesis, there was no association between prevalent anogenital warts and having sex with both men and women. No other Eastern African data on men with high-risk sexual behavior are available for comparison. Also, given that most US studies include both men who have sex with men exclusively and those who have sex with both men and women under "MSM", no comparison can be made to US risk sub-groups.

In terms of sexually transmitted infections, in our analysis of wart prevalence we did not detect any associations between prevalent anogenital warts and being diagnosed with a genital syndrome (urethritis, proctitis or genital ulceration). This is in contrast to what has been described in the literature.[40] Our findings could potentially be due to the relatively low sensitivity of the diagnostics used for STI testing in the present study, compared to the technology other studies may have used (e.g. nucleic acid amplification, polymerase chain reaction).

In this study, the anogenital wart incidence estimated in men (5.3 per 100 person-years) is almost four times higher than the anogenital wart incidence found in a cohort of male trucking company employees in Mombasa, Kenya (1.4 per 100 person-years) and 23 times higher than the incidence rate of genital warts found in a multinational (USA, Mexico, Brazil) cohort of men in the general population (0.23 per 100 person-years).[41,42] Our findings could potentially be due to the fact that our study population was much younger, was followed more closely, and more frequently reported high-risk sexual behavior than the general male population explored in the above-cited studies.

To our knowledge, this is the first prospective study to evaluate the prevalence and incidence of anogenital warts and their association with HIV status and other factors in Kenyan men reporting high-risk sexual behavior. Other strengths of this study include the longitudinal study design, the long duration of follow-up, close follow-up with monthly or quarterly visits, and a standardized physical exam including inspection for both genital and perianal warts.

This study has a number of limitations. First, our sample size was relatively small, especially for our analysis of wart prevalence; this potentially limited our power to detect potentially important

associations. Second, in order to increase power, we combined genital and perianal warts into "anogenital". In doing this, our ability to focus on anatomic site was reduced. Third, we used visual inspection as our method for anogenital wart detection. Without histologic testing, it is possible that other conditions (e.g., penile intraepithelial neoplasia) were misclassified as warts. We were unable to test for HPV DNA and subtypes, including HPV 6/11, an important predictor of the development of warts.

We have detected a moderate prevalence of anogenital warts and one of the highest rates of anogenital wart acquisition ever described. We have confirmed that anogenital wart prevalence is associated with HIV infection and that the risk of anogenital wart acquisition is associated with both having HIV and being diagnosed with a genital syndrome other than warts (urethritis, proctitis or genital ulceration). These findings are alarming and motivate us to intensify our prevention efforts by expanding HPV vaccination in East Africa to include young men and by ensuring early diagnosis and treatment of STI (including HIV).

References:

1. Carr J, Gyorfi T. Human papillomavirus. Epidemiology, transmission, and pathogenesis. Clinics in laboratory medicine. Jun 2000;20(2):235-255.
2. de Souza DL, Curado MP, Bernal MM, Jerez-Roig J, Boffetta P. Mortality trends and prediction of HPV-related cancers in Brazil. European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation. Jul 2013;22(4):380-387.
3. Franco EL, Duarte-Franco E, Ferenczy A. Cervical cancer: epidemiology, prevention and the role of human papillomavirus infection. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. Apr 3 2001;164(7):1017-1025.
4. Breese PL, Judson FN, Penley KA, Douglas JM, Jr. Anal human papillomavirus infection among homosexual and bisexual men: prevalence of type-specific infection and association with human immunodeficiency virus. Sexually transmitted diseases. Jan-Feb 1995;22(1):7-14.
5. Pierangeli A, Scagnolari C, Degener AM, et al. Type-specific human papillomavirus-DNA load in anal infection in HIV-positive men. AIDS (London, England). Oct 1 2008;22(15):1929-1935.
6. Wikstrom A, Vassilaki I, Hedblad MA, Syrjanen S. The spectrum of genital human papillomavirus infection among men attending a Swedish sexually-transmitted infections clinic: human papillomavirus typing and clinical presentation of histopathologically benign lesions. Acta dermato-venereologica. Mar 27 2013;93(2):223-227.
7. Nyitray A, Nielson CM, Harris RB, et al. Prevalence of and risk factors for anal human papillomavirus infection in heterosexual men. The Journal of infectious diseases. Jun 15 2008;197(12):1676-1684.
8. Dempsey AF. Human papillomavirus: the usefulness of risk factors in determining who should get vaccinated. Reviews in obstetrics and gynecology. Summer 2008;1(3):122-128.
9. Widdice LE, Breland DJ, Jonte J, et al. Human papillomavirus concordance in heterosexual couples. The Journal of adolescent health : official publication of the Society for Adolescent Medicine. Aug 2010;47(2):151-159.
10. Chin-Hong PV, Vittinghoff E, Cranston RD, et al. Age-Specific prevalence of anal human papillomavirus infection in HIV-negative sexually active men who have sex with men: the EXPLORE study. The Journal of infectious diseases. Dec 15 2004;190(12):2070-2076.
11. Backes DM, Snijders PJ, Hudgens MG, et al. Sexual behaviour and less frequent bathing are associated with higher human papillomavirus incidence in a cohort study of uncircumcised Kenyan men. Sexually transmitted infections. Mar 2013;89(2):148-155.
12. Vaccarella S, Bruni L, Seoud M. Burden of human papillomavirus infections and related diseases in the extended Middle East and North Africa region. Vaccine. Dec 30 2013;31 Suppl 6:G32-44.
13. Mandell D, and Bennett. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases.Chapter 144.
14. Vandepapeliere P, Barrasso R, Meijer CJ, et al. Randomized controlled trial of an adjuvanted human papillomavirus (HPV) type 6 L2E7 vaccine: infection of external anogenital warts with multiple HPV types and failure of therapeutic vaccination. The Journal of infectious diseases. Dec 15 2005;192(12):2099-2107.
15. Blomberg M, Friis S, Munk C, Bautz A, Kjaer SK. Genital warts and risk of cancer: a Danish study of nearly 50 000 patients with genital warts. The Journal of infectious diseases. May 15 2012;205(10):1544-1553.
16. Bruni L B-RL, Serrano B, Brotons M, Cosano R, Muñoz J, Bosch FX, de Sanjosé S, Castellsagué X. Human Papillomavirus and Related Diseases in Kenya. Summary Report 2014-03-17. ICO Information Centre on HPV and Cancer (HPV Information Centre). 2014.
17. de Martel C, Ferlay J, Franceschi S, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. The lancet oncology. Jun 2012;13(6):607-615.
18. Howlader N NA, Krapcho M, Garshell J, Neyman N, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2011. National Cancer Institute. 2014.

19. Nelson RA, Levine AM, Bernstein L, Smith DD, Lai LL. Changing patterns of anal canal carcinoma in the United States. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. Apr 20 2013;31(12):1569-1575.
20. Daling JR, Weiss NS, Klopfenstein LL, Cochran LE, Chow WH, Daifuku R. Correlates of homosexual behavior and the incidence of anal cancer. JAMA : the journal of the American Medical Association. Apr 9 1982;247(14):1988-1990.
21. Silverberg MJ, Lau B, Justice AC, et al. Risk of anal cancer in HIV-infected and HIV-uninfected individuals in North America. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. Apr 2012;54(7):1026-1034.
22. Mbulawa ZZ, Marais DJ, Johnson LF, Coetzee D, Williamson AL. Impact of human immunodeficiency virus on the natural history of human papillomavirus genital infection in South African men and women. The Journal of infectious diseases. Jul 1 2012;206(1):15-27.
23. Machalek DA, Poynten M, Jin F, et al. Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: a systematic review and meta-analysis. The lancet oncology. May 2012;13(5):487-500.
24. Dartell M, Rasch V, Kahesa C, et al. Human papillomavirus prevalence and type distribution in 3603 HIV-positive and HIV-negative women in the general population of Tanzania: the PROTECT study. Sexually transmitted diseases. Mar 2012;39(3):201-208.
25. Palefsky JM, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. The New England journal of medicine. Oct 27 2011;365(17):1576-1585.
26. Franco EL, Cuzick J, Hildesheim A, de Sanjose S. Chapter 20: Issues in planning cervical cancer screening in the era of HPV vaccination. Vaccine. Aug 31 2006;24 Suppl 3:S3/171-177.
27. CDC. Advisory Committee on Immunization Practices (ACIP) recommended immunization schedules for persons aged 0 through 18 years and adults aged 19 years and older--United States, 2013. MMWR Surveill Summ. 2013;62 Suppl 1:1. 2013.
28. Cancer IICoHa. Kenya: Human Papillomavirus and Related Cancers, Fact Sheet 2013. 2013.
29. Kavanaugh BE, Odem-Davis K, Jaoko W, et al. Prevalence and correlates of genital warts in Kenyan female sex workers. Sexually transmitted diseases. Nov 2012;39(11):902-905.
30. Sanders EJ, Graham SM, Okuku HS, et al. HIV-1 infection in high risk men who have sex with men in Mombasa, Kenya. AIDS (London, England). Nov 30 2007;21(18):2513-2520.
31. Grijsen ML, Graham SM, Mwangome M, et al. Screening for genital and anorectal sexually transmitted infections in HIV prevention trials in Africa. Sexually transmitted infections. Oct 2008;84(5):364-370.
32. Klausner JD, Kohn R, Kent C. Etiology of clinical proctitis among men who have sex with men. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. Jan 15 2004;38(2):300-302.
33. van Binsbergen J, Siebelink A, Jacobs A, et al. Improved performance of seroconversion with a 4th generation HIV antigen/antibody assay. Journal of virological methods. Sep 1999;82(1):77-84.
34. Bursac Z, Gauss CH, Williams DK, Hosmer D. Purposeful selection of variables in logistic regression. Source Code for Biology and Medicine. 2008;3(1):17.
35. Patel H, Wagner M, Singhal P, Kothari S. Systematic review of the incidence and prevalence of genital warts. BMC infectious diseases. 2013;13:39.
36. CDC. 2010 Sexually Transmitted Diseases Surveillance. 2010.
37. Remis RS, Liu J, Loutfy M, et al. The epidemiology of sexually transmitted co-infections in HIV-positive and HIV-negative African-Caribbean women in Toronto. BMC infectious diseases. 2013;13:550.
38. Phanuphak N, Teeratakulpisarn N, Pankam T, et al. Anal human papillomavirus infection among Thai men who have sex with men with and without HIV infection: prevalence, incidence, and persistence. Journal of acquired immune deficiency syndromes. Aug 1 2013;63(4):472-479.
39. Okuku HS, Sanders EJ, Nyiro J, et al. Factors associated with herpes simplex virus type 2 incidence in a cohort of human immunodeficiency virus type 1-seronegative Kenyan men and women reporting high-risk sexual behavior. Sexually transmitted diseases. Sep 2011;38(9):837-844.

40. Yanofsky VR, Patel RV, Goldenberg G. Genital warts: a comprehensive review. The Journal of clinical and aesthetic dermatology. Jun 2012;5(6):25-36.
41. Lavreys L, Rakwar JP, Thompson ML, et al. Effect of circumcision on incidence of human immunodeficiency virus type 1 and other sexually transmitted diseases: a prospective cohort study of trucking company employees in Kenya. The Journal of infectious diseases. Aug 1999;180(2):330-336.
42. Anic GM, Lee JH, Stockwell H, et al. Incidence and human papillomavirus (HPV) type distribution of genital warts in a multinational cohort of men: the HPV in men study. The Journal of infectious diseases. Dec 15 2011;204(12):1886-1892.