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Factors associated with Ano-genital warts among Human Immunodeficiency Virus (HIV) infected patients at a Hillbrow clinic in Gauteng South Africa.

By

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

MASTER OF SCIENCE
IN EPIDEMIOLOGY
(EPIDEMIOLOGY AND BIOSTATISTICS)

UNIVERSITY OF THE WITWATERSRAND
May 2014

DECLARATION

I, Qinisile Sibanda declare that this research report is my own work, compiled under the supervision of Dr. E Musenge and Dr. B Muzah. The report is being submitted to the University of the Witwatersrand in partial fulfilment of a degree of Master of Epidemiology in the field of Epidemiology and Biostatistics. There are no prior submissions of this material to other institutions for academic purposes whatsoever.

Signature_____ Date_____

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ABSTRACT

Introduction

Ano-genital warts affect at least 30 million people worldwide. Ano-genital warts are caused by low risk Human Papilloma virus infections in 90% of cases. In African populations the ano-genital warts have not been adequately investigated thus our main goal was to highlight the factors associated with the occurrence of ano-genital warts among HIV infected individuals. Studies in both men and women have shown that the likelihood of getting ano-genital warts is significantly increased when one is infected with HIV hence the need to investigate in this population. More over data suggests that HPV infection occur more frequently among HIV infected individuals because of the HIV associated CD4+ T-cell immune-suppression.

Methods

We conducted an analytical cross sectional study of routinely collected secondary medical data from Ward 21 ART clinic at the Hillbrow community centre in Hillbrow Johannesburg central. Our study participants were all HIV infected patients 16 years and older who attended the ART clinic between 01 January 2009 and 31 December 2011 and were recorded in the therapy edge database. Our outcome was clinically diagnosed ano-genital warts. We analysed data using the Chi squared test or Fischers exact test to make comparisons in bivariate analysis. Logistic regression was used to assess factors associated with ano-genital warts. Factors assessed were other STIs namely syphilis, herpes simplex virus type 2 and

scabies as well as age, gender, first CD4 and employment status and ART status of a patient. The Models were assessed using the linktest and the Hosmer Lemeshow goodness of fit test.

Results

Ano-genital warts (AGWs) prevalence was 4% (251 out of 6634) among females and 3% (118 out 4116) among males. Prevalence of AGWs in both females and males decreased with increasing age. In females the prevalence was between 1% and 8% and in males it was between 1% and 4%. The odds of having ano-genital warts among females if one was above 25 years ranged from 1.6 to 18.3, showing an upward trend. Among females a CD4 count of less than 200 cells/ml^3 was also associated with ano-genital warts occurrence, OR 1.32(1.02 - 1.72). Among males the odds of having ano-genital warts if one was not on ART were 1.53 (1.01 ï 2.31) times when compared to those who were on ART.

Discussion and Conclusion

Prevalence of genital warts was highest among the younger age groups in both males and females and it decreased with increasing age consistent with literature. Age was strongly associated with ano-genital warts and the association became stronger with increasing age among females while no association was found among males. In line with findings from other studies we found low CD4 count of Ò 200 cells/m^3 to be associated with ano-genital warts in HIV positive females; however it was a weak association. Among males a weak association between ART status and ano-genital warts was established and none in females. This is consistent with the fact that in the post ART era there has been no substantial decline in HPV infections.

DEDICATION

To those who are infected and affected by HIV and AIDS, may you forever remain hopeful for a cure

ACKNOWLEDGEMENTS

I would like to extend my heartfelt gratitude to Nedbank for funding my studies. Without their financial support this research would have not been possible. I would also like to thank Wits RHI and Ward 21 clinic for allowing me to use the data from the Ward 21 clinic for my research. I do hope the results of this research contribute to improvement in management of the patients.

My sincere thanks goes to my supervisors Dr Eustasius Musenge and Dr Batanayi Muzah for their guidance and support throughout the compilation of this research report.

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A special mention goes to my husband Isaiah Sibanda who has been my pillar of strength when the going got rough and tough. You held my hand and showed me there was always light at the end of the tunnel. To my children Nontsikelelo and Anele, thank you for understanding when I could not attend to your needs fully.

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Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
AGWs	Ano-genital warts
ART	Antiretroviral therapy
CD4	Cluster of differentiation 4(a glycoprotein found on the surface of immune cells as T helper cells
HIV	Human Immune Virus
HPV	Human Papilloma virus
MSM	Men having sex with men
OR	Odds Ratio
STI	Sexually Transmitted Infection
WRHI	Wits RHI

Definition of terms

Aetiology: It refers to the study of the causes of a disease and the factors underlying their spread.

Baseline: A measurement used as a basis for comparison.

Condylomata acuminata: these are benign proliferation of the ano-genital skin and mucosa resulting from Human Papillomavirus (HPV) infection.

CD4 count: A measure of the number of helper T cells per cubic millimetre of blood, used to analyze the prognosis of patients infected with HIV.

Epidemiology: It is the study of the distribution and the determinants of health related states and events (including disease), and the application of the study to the control of diseases and other health problems.

Dichotomous: divided into two classifications or parts.

Genotype: The genetic constitution of an individual organism.

Incidence: The occurrence, rate of frequency of a disease. It is the number of new cases per population at risk that develop during a specific time period.

Prevalence: The total number of cases of a disease in a given population at a specific time and place.

Proxy: A variable that is used in place of the variable of interest (the inferred variable) that has a close correlation with the inferred variable.

Therapy Edge database: It is a web based decision support system used for the treatment of HIV.

1 INTRODUCTION

1.1 Background

Ano-genital warts which are also known as condylomata acuminata affects at least 30 million individuals worldwide (1). These are benign proliferation of the ano-genital skin and mucosa resulting from Human Papillomavirus (HPV) infection (1). HPV infection is the most common sexually transmitted infection (STI) (1-4). Infection is highest in the young sexually active population and declines significantly after age of reproduction (1, 5, 6). More than 100 HPV genotypes have been identified (7, 8). The genotypes are classified as either high risk or low risk depending on their association with malignant lesions of the cervix (7). Low risk HPV genotypes are associated with benign skin lesions and have been linked to 90% of ano-genital warts infections (7, 9).

According to a systematic review conducted by Banura et al, studies have found prevalence rates of AGWs among sex workers and women with STIs in Central and South African regions to range from 0.2% to 14% (10). The age range for these women lies between 14 and 65 years (10). Few studies have reported on the prevalence of AGWs among men in Africa (10, 11). In those studies where AGWs have been reported, the prevalence among sexually active men 18 years and older ,was found to range between 4.8% and 50.5% in central and south African regions (10).

Infections with HPV have been found to be prevalent among men attending sexual Health clinics in South Africa (12). HPV 6, 11, 16 and 18 have been found to be the most prevalent

either single or combined, with HPV 6 and 11 found to be significantly higher among those with AGWs (12). HPV/HIV co-infection is twofold higher and is associated with reduced HPV viral clearance due to impaired immunity (13). Ano-genital warts occur more frequently in women who are HIV infected especially those with low CD4 count (2), but some studies indicate that ano-genital warts affect both men and women equally (1, 14). This apparent higher incidence in women could be due to the fact that women tend to seek medical care more than men do (1). A study in Burkina Faso showed that genital warts were more prevalent among HIV infected women (7%) compared to uninfected women (1.6%). The association of other STIs with ano-genital warts is still poorly understood. The data available is uncertain and predominately from western populations (2).The impact of antiretroviral treatment on the occurrence of ano-genital warts remains uncertain with varying results on its incidence and persistence being obtained from different statistical designs (2).

1.2 Problem Statement

Literature shows that in African populations the incidence and prevalence of low risk-HPV and ano-genital warts are not well known, little is known about their epidemiology and natural history (3-5). Although ano-genital warts are the most common clinical lesions caused by HPV, they have not been adequately described (15). They have been overshadowed by the more life threatening cervical cancer. Previous and recurring ano-genital warts have been shown to be associated with multiple HPV-DNA infections leading

to the development of squamous intraepithelial lesions (16).Both HIV and HPV infections are prevalent in Sub- Saharan Africa. HIV infection when present is likely to increase transmission and acquisition of HPV as well as the development of clinically evident ano-genital warts (17). Those with ano-genital warts are likely to experience prolonged episodes exacerbated by a suppressed immune system (2). Current data suggest the need for better ano-genital warts data collection and surveillance especially in Africa (18).

The psycho-social and economic effects of ano-genital warts are quite substantial (19). They have a huge impact on health services and the individual patient (20). The presence of ano-genital warts impacts heavily on the quality of life of those with the disease causing extreme discomfort and embarrassment for most sufferers. The psychological stress associated with having the disease is often greater than the morbidity (21).

In this study we want to highlight the burden of ano-genital warts amongst HIV infected individuals at a Hillbrow clinic in Johannesburg, as well as the factors associated with their occurrence. The study will add to the body of knowledge on the occurrence of AGWs in the South African population.

1.3 Justification

In South Africa and the rest of Sub-Saharan Africa the incidence and prevalence of ano-genital warts is poorly described more so among males. Despite the paucity of data, ano-genital warts pose a substantial financial and medical burden on health services. In addition they also affect the quality of life of those infected, causing increased morbidity. Although

ano-genital warts are benign tumours caused by HPV type 6 and/or 11, co-infection with HIV has been found to result in multiple HPV infections (12).

1.4 Literature Review

1.4.1 Aetiology of Ano-genital warts

Ano-enital warts also known as condylomata acuminata affect at least 30 million individuals worldwide (1). These are benign proliferation of the ano-genital skin and mucosa resulting from Human Papillomavirus (HPV) infection (1). HPV is a highly contagious virus (9). Transmission of HPV is predominately through sexual contact with an infected person (9, 22). Additionally, sexual contact with an infected individual results in a 75% chance of contracting HPV (1, 9). In rare cases vertical transmission has been reported (9, 22). The Centre for disease control and prevention estimates that 50% of all sexually active individuals will acquire HPV infection at some point in their lives (9, 23) and at least 80% of women will have acquired it by the age of 50 (23). Infection is highest among young women of ages 20 to 24. (1, 22).

Genital warts are the most frequent of benign tumours occurring in the ano-genital region and approximately 90% of the genital warts are associated with low risk HPV type 6 and 11 (7, 9, 24). The lesions present as flesh coloured lesions on the external genitalia and are only clinically diagnosed, they usually develop 2-3 months after infection with HPV (typically 6 and 11) (25). However infection with HPV 6 and 11 does not always result in the occurrence of genital warts (25).

1.4.2 Risk Factors for Ano-genital Warts infection

Several studies have attributed the occurrence of ano-genital warts to the following risk factors; early age at first sex, increase in the total number of sexual partners, unprotected sexual intercourse, use of oral contraceptives, a history of sexually transmitted infections, smoking and immune-suppression (9, 21-22, 26). In addition to the factors already mentioned older age has been found be associated with the persistence and/or recurrence of ano-genital warts (18).

Other studies have found a history of other STIs to be associated with the occurrence of ano-genital warts (18, 22). It must be noted that the association of other STIs with ano-genital warts is still poorly understood. These data are uncertain and predominately from western populations (2).

The impact of antiretroviral treatment on the occurrence of ano-genital warts remains uncertain with varying results on its incidence and persistence being obtained from different statistical designs (2).

1.4.3 Ano-Genital Warts and HIV infection

Data suggests that HPV infection occur more frequently among HIV infected women because of the HIV associated CD4+ T-cell immune-suppression (27). In those who are co-infected with HIV and HPV, HIV infection may facilitate the development of clinically evident ano-genital warts (17). Studies in both men and women have shown that the likelihood of getting ano-genital warts is significantly increased when one is infected with

HIV (12, 17, 28). In HIV infected women the likelihood of developing ano-genital warts is 8 times greater than in HIV uninfected women (17).

A study in Burkina Faso showed that genital warts were more prevalent among HIV infected women (7%) compared to uninfected women (1.6%). High prevalence of genital warts is associated with low CD4 count (nadir CD4+ count Ò200 cells/ε L) (2).

Data on ano-genital warts is scarce from sub-Saharan Africa and South Africa, confirming the view that little is known on the epidemiology and natural history of ano-genital warts in this region. We believe this area of study has received inadequate attention. Many studies focus on HPV infection in association with the occurrence of cancerous tumours.

1.5 Study Objectives

1.5.1 Research Question

What are the factors associated with ano-genital warts among HIV infected patients at a Hillbrow clinic in Gauteng South Africa during the period 1 January 2009 to 31 December 2011**?**

1.5.2 Objectives

1. To describe the demographic distribution of HIV infected patients in a Wits Reproductive health Institute (WRHI) supported clinic in Gauteng South Africa from 1 January 2009 to 31 December 2011.

2. To determine the prevalence of ano-genital warts among HIV infected patients in a WRHI supported clinic in Gauteng South Africa from 1 January 2009 to 31 December 2011.

3. To determine the factors associated with ano-genital warts among male and female HIV infected patients in a WRHI supported clinic in Gauteng South Africa from 1 January 2009 to 31 December 2011.

2 MATERIALS AND METHODS

This chapter reviews the methods used in the study and includes procedures taken to ensure validity of results. A description of data analysis is given and it includes the statistical methods that were used for model assessment and validation.

2.1 Study Design

This study used an analytical cross-sectional design utilising secondary data collected routinely in the WRHI supported clinic. Only the first occurrence of a condition or disease within the study period for all study participants was used in analysis. The study period was from 1 January 2009 to 31 December 2011.

2.2 Study population and setting

The study population consisted of HIV infected patients attending Ward 21 clinic in Hillbrow which is a WRHI supported clinic in Gauteng from 1 January 2009 to 31 December 2011. This clinic is part of the Hillbrow Community Health Centre (29) situated in central Johannesburg. It is the largest non-hospital antiretroviral therapy initiation site in the world and sees over 4000 patients every month (29).

2.3 Study Sample

2.3.1 Inclusion criteria

All patients above the age of 16 who were entered into the Therapy Edge™ database during the study period were eligible for inclusion. (Therapy Edge™ database is a support system used for the treatment of HIV). It is used to capture a patientôs clinical information. The information captured typically included medical conditions, medications and treatment options.

Only those study participants with data on most of the exposures of interest which were other STIs namely syphilis, herpes simplex virus type 2 and scabies as well as age, gender, first CD4 and employment status and ART status of a patient under study were included.

2.3.2 Exclusion criteria

- Patients enrolled at the clinic outside of the study period were excluded.
- Study participants missing data on more than two exposures of interest were also excluded. The exposures of interest looked at were other STIs namely syphilis, herpes simplex virus type 2 and scabies as well as age, gender, first CD4 and employment status and ART status of a patient

2.3.3 Sample Size

Patients enrolled in the Therapy Edge™ database for the clinic during the study period were a total of 19 099. All these participants were eligible to form the study sample. However, all

those patients with missing data on more than two exposures of interest were dropped from further analysis as well as those younger than 16 years. Of the 19 099 patients 8 006 did not have any clinical conditions or infections recorded and 343 were younger than 16. The final sample size of the study participants who were included in analysis was 10 750, (4 116 males and 6 634 females).

2.4 Measurements

The outcome variable in the study was ano-genital warts clinically diagnosed as explained in the table below. The outcome was a dichotomous variable with patients either having ano-genital warts or not. Explanatory variables that were evaluated for association with the outcome variable are listed and explained in the table below.

Table2-1 Variables used in the study and their explanations.

Outcome variable	Ano-genital warts clinically diagnosed by a trained registered clinician.
Explanatory variables evaluate	ART treatment- stratified as being on ART or not. Generated using regimens of patients. All patients without a regimen were taken to be not on ART.
	Infection with herpes simplex 2- evidence of herpetic flare/occurrence during the study period
	Infection with syphilis - presentation of syphilitic lesion recorded during the study period
	Infection with scabies - taken to be the an episode of scabies recorded during the study period
	Concurrence with cervical cancer(females only)
	Age ï Categorised into age groups so that inferences can be made in group of individuals in each particular age group
	Employment status - as proxy for Income/socioeconomic status
	CD4 count- genital warts have been found to occur more frequently and persistently in individuals with low CD4 count. Low CD4 considered to be that below 200

2.5 Data management

2.5.1 Data Collection and processing

The data was routinely collected by the clinic for HIV management of patients. The clinic employs Therapy Edge^{TM} database to capture medical information of patients. Therapy Edge^{TM} was first introduced in the clinic in 2009. The data was transcribed into the Therapy Edge^{TM} database by trained data capturers. This data was then imported from Therapy Edge^{TM} database to Stata Statistical Software: Release 11. (StataCorp LP. 2007.College

Station, Texas) for analysis. Patient demographic information such as sex, age and nationality among others was collected when a patient first visited the clinic. A patientôs first CD4 count was also taken and recorded on their first visit to the clinic. A patient was then monitored and all conditions that a person suffered from recorded with each subsequent visit. Periodically the patients CD4 count was taken and recorded. Upon initiation on ART the last CD4 count that was taken before initiation was taken to be the baseline CD4 count of the patient. Data were cleaned and validated by the data capturers on a continuous basis.

2.5.2 Data Analysis

Individual datasets of clinical conditions, patient demographic information and clinical ART were merged to form one dataset. New variables for the different sexually transmitted illnesses were generated, including the outcome variable ano-genital warts. Age which is a continuous variable was recoded into age group categories. According to literature, HPV infection is highest in the young sexually active population of ages below 25, and above the age of 55 HPV infection drops significantly (1, 5, 6, 22). CD4 count was also recoded into a dichotomous variable with CD4 lower than or equal to 200 considered as low. A CD4 count of 200cells/mm^3 was the CD4 count at which a patient became eligible for ART initiation in South Africa during the data collection period (30). ART status of patients was determined using the current regimen of patients as a proxy. Approximately 50% of patients were missing data on their ART status hence regimen status was used as proxy. Those not on any regimens were taken as being not on treatment. The employment status of a patient was categorised as employed, unemployed, student and other (referring to all individuals on some

form of grant) and missing which referred to those with missing status. The level of significance used for all tests was 5%.

2.5.2.1 Descriptive Statistics

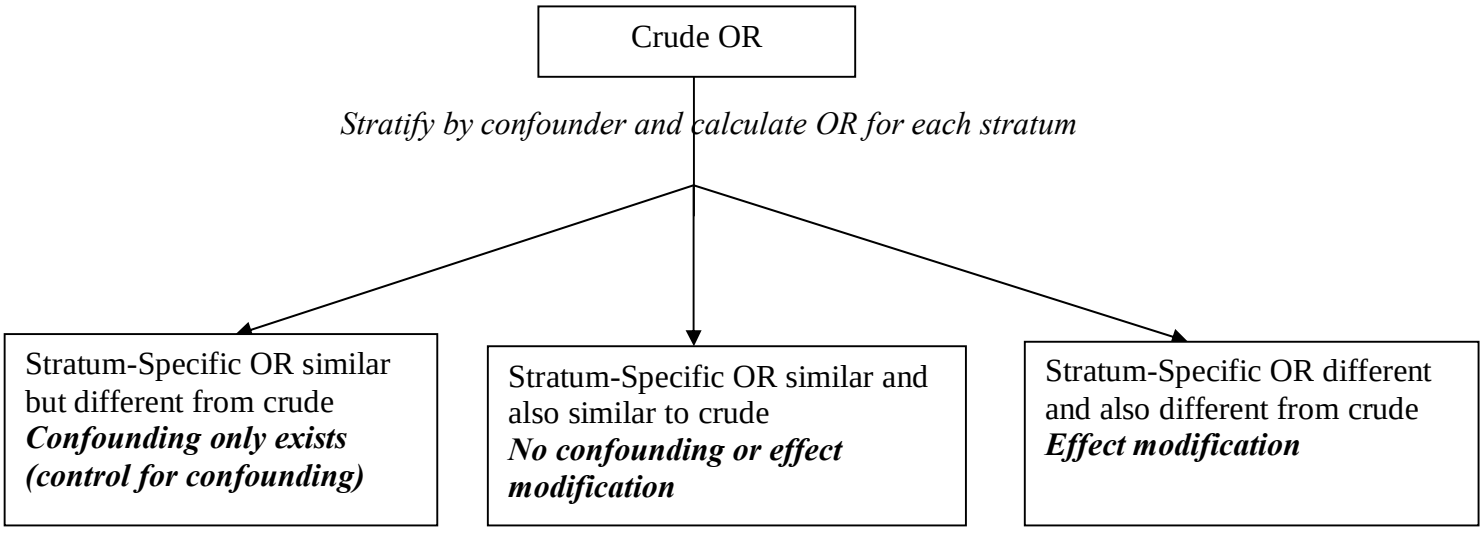
Frequency of socio-demographic and clinical factors across the study population was determined and presented using bar graphs and tables. All variables were described using proportions and percentages. The Chi squared test or Fisherôs Exact test where Chi-Square was invalid was used to make comparisons between those who have ano-genital warts and those without ano-genital warts.

2.5.2.2 Inferential statistics

The outcome variable in the study was dichotomous, being the presence or absence of ano-genital warts therefore logistic regression was used in analysis. Univariate Logistic Regression and multivariable logistic regression models were used to calculate crude (unadjusted) odds ratios and adjusted odds ratios respectively to determine factors associated with genital warts in the study.

2.5.2.3 Confounding and effect modification in the study

Epidemiology of genital warts has been found to differ significantly in males and females. Also other studies evaluated in the literature review were per each gender. As such confounding and effect modification by gender was independently assessed and gender stratified analysis was conducted. The algorithm below was used to determine if confounding and/or effect modification by gender exists.



Algorithm to determine confounding and effect modification

2.5.2.4 Model Assessment and Validation

The different models in multivariable analysis were compared using the likelihood ratio test and the model that best fit the data was accepted as the best model. All our models where assessed for validity using the linktest and the Hosmer and Lemeshowôs goodness of fit tests. The Linktest checks the model for any specification error. If a model is correctly specified we do not expect to have any additional predictors that are statistically significant except by chance (31). The linktest has its limits hence it was used in conjunction with another tool to check model validity, the Hosmer and Lemeshowôs goodness of fit test.

2.6 Ethical Considerations

The letter of permission to use the data was obtained from WRHI (appendix C). Ethical clearance was obtained from the university of Witwatersrand research ethics committee (Clearance Certificate number M120939). Study participants were identified using unique identifiers and no personal identifying information was on the dataset. The study was secondary analysis therefore informed consent from individuals was not sought.

3 RESULTS

This section outlines all the results of the analyses done in the study. The first section describes the study population in terms of gender and age. The second section describes the distribution of ano-genital warts in the study population. The third section gives the results of the evaluation of factors associated with genital warts with an assessment of confounding and effect modification by gender.

3.1 Description of the population under study

3.1.1 Distribution of gender in the study population

The final study sample consisted of a total of 10750 patients, of which 63% were females and 37% were males as shown in figure 3.1.

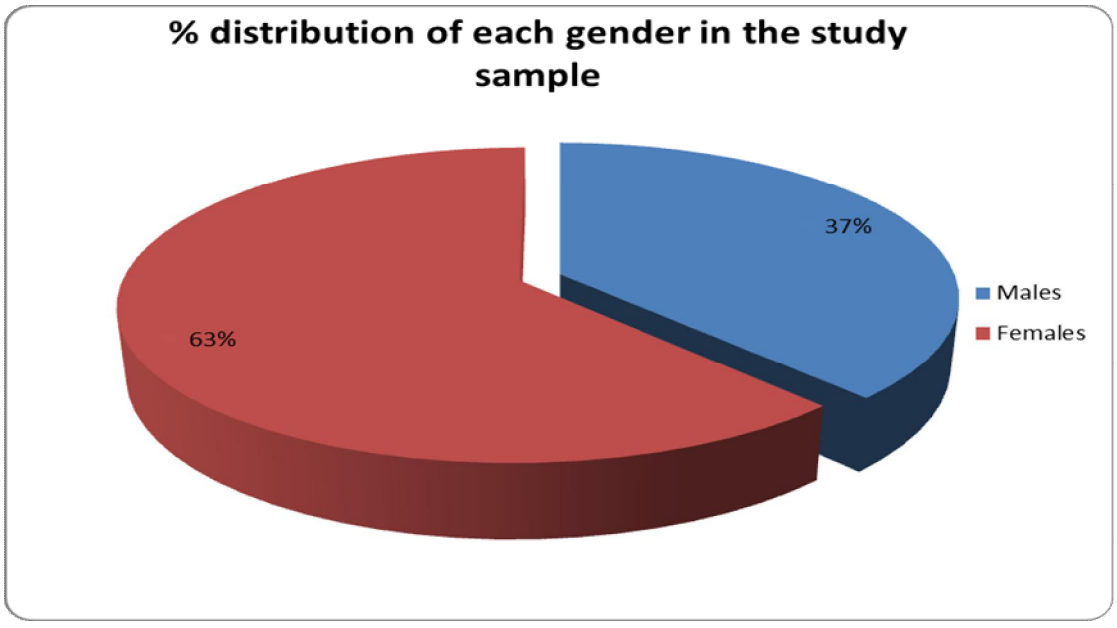


Figure 3.1 Percentage of each gender as a proportion of the whole study sample

3.1.2 Distribution of each gender in the study by age

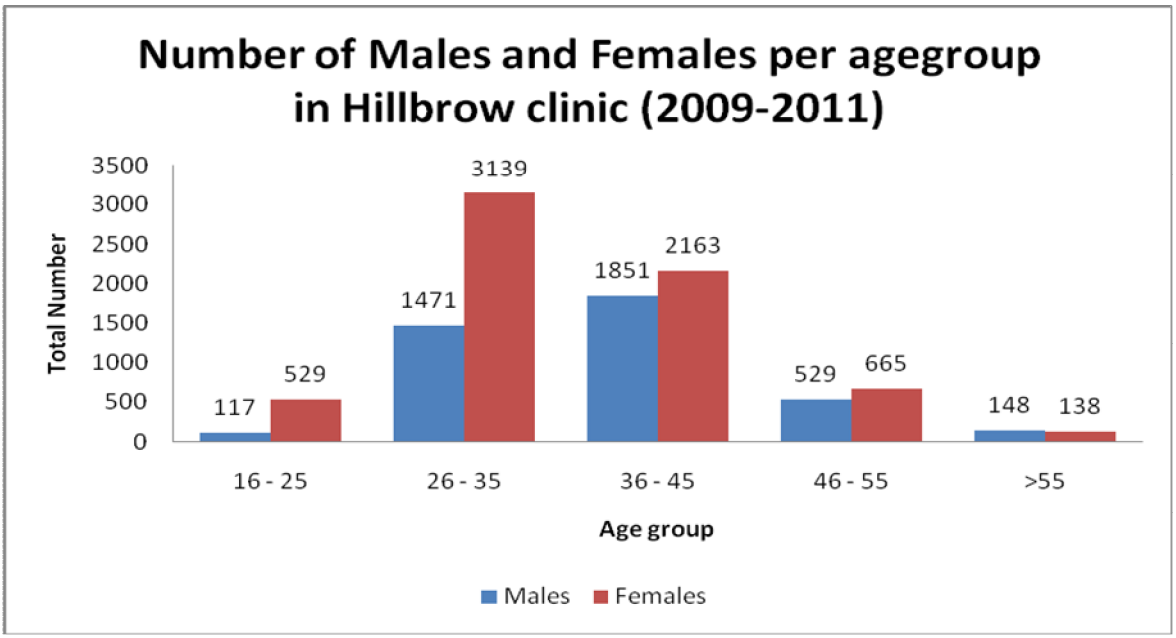


Figure 3.2. Description of gender by age group in the study sample

According to figure 3.2 above in all age groups except for those older than 55 years there were more females attending the clinic than males for ART care. In general more females patronized the clinic when compared to males during the period January 2009 to December 2011.

3.2 Description of the occurrence of ano-genital warts (Prevalence) in the study population

A total of 369 (3%) patients had at least one episode of ano-genital warts during the study period. Figure 3.3 shows that 68 % of these were females and 32% were males.

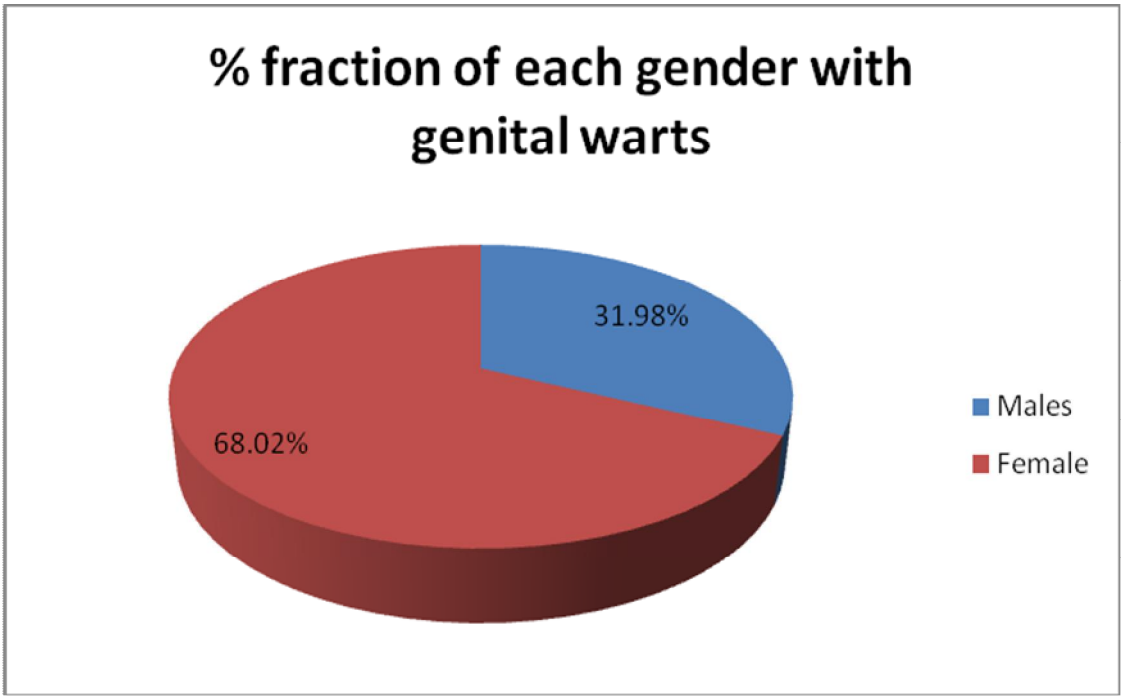


Figure 3.3. Distribution of genital warts among the study participants

3.2.1 Prevalence of ano-genital warts in the study population

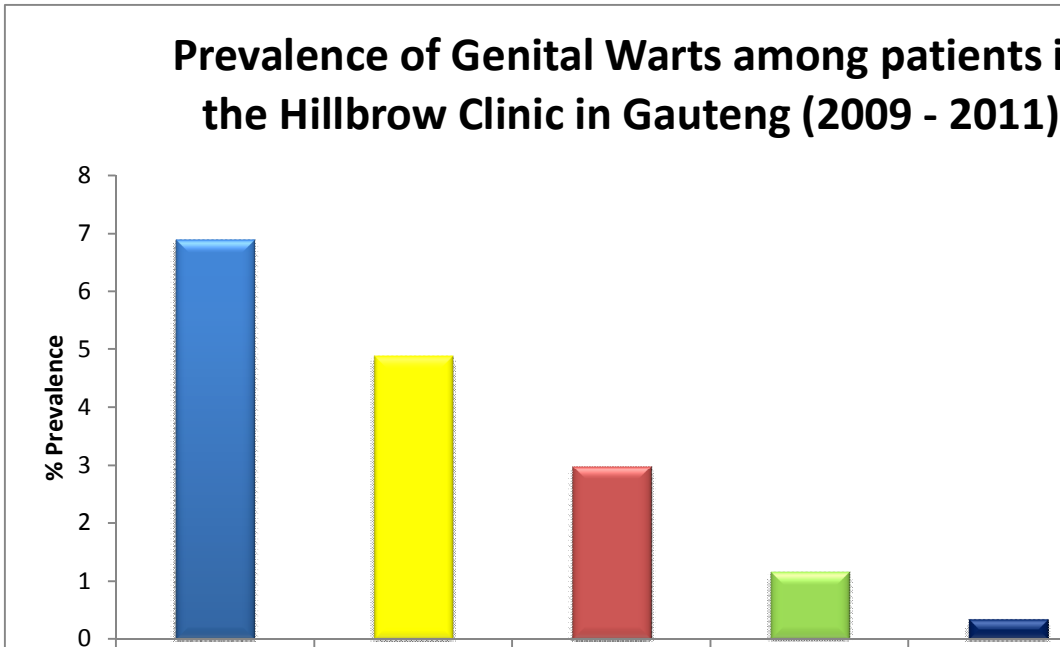


Figure3.4. Prevalence of ano-genital warts among the patients in the study sample.

The overall prevalence of genital warts in the study was 3%. Prevalence was 4% among females and 3% among males. Figure 3.4 above shows that the prevalence was highest in the 16 ï 25 year age group and decreased with increasing age. Table 3.1 below shows no significant differences between those with anogenital warts and those without ano-genital warts with regards to scabies, herpes simplex 2, syphilis, and ART status. Differences were detected with employment status (p-value 0.047), age (p-value <0.0001) and gender (p-value <0.011).

Table 3-1 Prevalence of ano-genital warts and tests for differences in the study sample

Explanatory variable	**No anogenital Warts (%)**	**Anogenital Warts (%)**	**p-values (0.05 level of significance)**
Gender : Male	97.13	2.87	0.011
Female	96.22	3.78	
Age categories:			< 0.001
16-25	93.03	6.97	
26- 35	95.90	4.10	
36- 45	97.01	2.99	
46- 55	98.83	1.17	
>55	99.65	0.35	
Scabies : yes	95.24	4.76	0.635
: no	96.57	3.43	
Herpes Simplex 2 : yes	96.19	3.81	0.682
: no	96.58	3.42	
Syphilis : yes	93.75	6.25	0.283
: no	96.58	3.42	
ART : yes	96.46	3.54	0.442
: no	96.73	3.27	
Employment status:			0.047
Employed	96.61	3.39	
Unemployed	96.19	3.81	
Student	92.31	7.69	
Other	100.00	0.00	
Missing	97.37	2.63	
CD4 count : <200 cells/ml^3	96.38	3.62	0.388
>200 cells/ml^3	96.69	3.31	

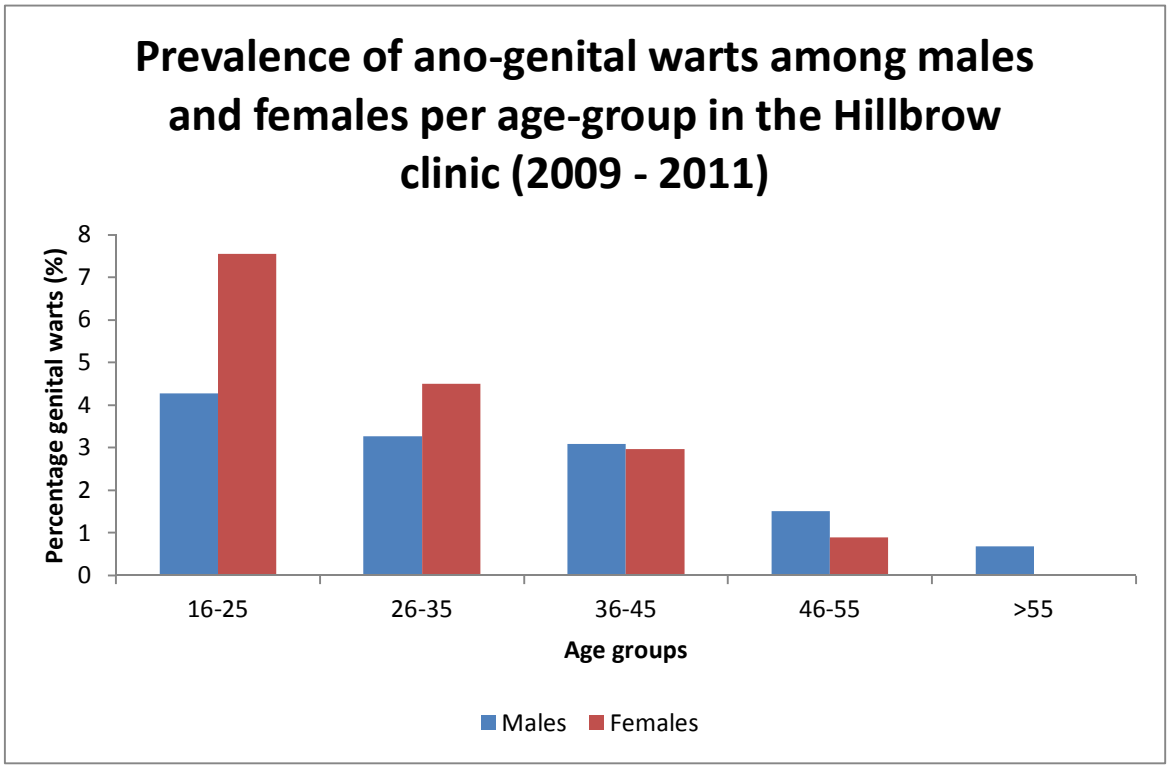


Figure 3.5. Prevalence of ano-genital warts in males and females by age group in the study sample

In figure 3.5 above, prevalence was highest among the 16 ï 25 year age group for both sexes and decreased with increasing age for both sexes. Between the ages of 16 and 25 as well as age group 26-35 prevalence was higher in females (8% and 5% respectively) than males (4% and 3% respectively). In the age group 36 to 45 the prevalence was similar between males (3%) and females (3%). Above the age of 46, prevalence was (0.7%) among males and among females it was (0%). (See also table 3.2 below).

Table 3-2 Prevalence of ano-genital warts and tests for differences between those who have genital warts and those without genital warts in each gender

	FEMALES Prevalence 3.78%			MALES Prevalence 2.87%		
Explanatory variable	**No Genital Warts (%)**	**Genital Warts (%)**	**p-values (0.05 level of significance)**	**No Genital Warts (%)**	**Genital Warts (%)**	**p-values (0.05 level of significance)**
Age categories:						
<=25	92.44	7.56	<0.001*	95.73	4.27	0.073*
26- 35	95.51	4.49		96.74	3.26	
36- 45	97.04	2.96		96.97	3.03	
46- 55	99.10	0.90		98.49	1.51	
>55	100	0		99.32	0.68	
Cervical Cancer: yes	100	0	1.00	-	-	
: no	96.21	3.79				
Scabies : yes	93.10	6.90	0.379	100	0	1.000
: no	96.23	3.77		97.12	2.88	
Herpes Simplex 2 : yes	97.10	2.90	0.498	95.00	5.00	0.099
: no	96.19	3.81		97.22	2.78	
Syphilis : yes	93.33	6.67	0.407	94.44	5.56	0.408
: no	96.23	3.77		97.14	2.86	
ART : yes	96.32	3.68	0.577	96.67	3.33	0.022*
: no	96.06	3.94		97.89	2.11	
Employment status						
Employed	96.31	3.69	0.097	3.01	96.99	0.49
Unemployed	95.88	4.12		3.18	96.82	
Student	90.00	10.00		0	100	
Other	100	0		0	100	
Missing	96.96	3.04		1.95	98.05	
CD4 count : >200	95.75	4.25	0.056	97.36	2.64	0.239
≤200	96.67	3.33		96.73	3.27	

Among females significant differences were detected between groups for age (p value of <0.0001) and CD4 count showed border line significance (p value 0.056). Employment status showed a p value of 0.097 therefore there was no significant association. There were no individuals among those with cervical cancer who had ano-genital warts. No significant differences were detected as well for scabies, herpes simplex 2, syphilis, and ART status.

Among males significant differences were detected for ART status (p value of 0.022).

Age and herpes simplex 2 had p values of 0.073 and 0.099 respectively and these were not significant. There were also no significant differences detected for scabies, syphilis, and CD4 count.

3.3 Univariate and Multivariate Analysis with assessment of confounding and effect modification by gender

3.3.1 Assessment of Confounding and effect modification by gender

Analysis was conducted to assess the effect of gender (table 3.3) on the relationships of other explanatory variables with the occurrence of ano-genital warts. For scabies, herpes simplex 2 and syphilis there was no confounding or effect modification by gender present. Univariate analysis before and after adjusting for gender as well as after stratification did not indicate a 10% difference which indicates the presence of confounding or effect modification. For the variables CD4 and ART status the assessment of the interaction with gender was significant. There was no difference in the crude and adjusted odds ratios indicating that there was no confounding by gender. After stratification the stratified odds ratios were significantly different from each other and from the crude. This indicated that gender was modifying the relationships of these variables with the occurrence of ano-genital warts. Therefore males and females were analysed separately.

Table 3-3 Results of the assessment of confounding and effect modification by gender

	Crude		Adjusted for Gender		Stratified by Gender				Interaction result	Decision
	OR	**95% CI**	**OR**	**95% CI**	**Males**	**95% CI**	**Females**	**95% CI**		
Scabies	1.41	0.34 ï 5.86	1.38	0.33 ï 5.74	-	-	1.89	0.45 - 8.0	Not significant	No effect
Syphilis	1.88	0.58 - 6.09	1.88	0.58 ï 6.08	2.00	0.26 ï 15.16	1.82	0.43 -7.10	Not significant	No effect
CD4	1.1	0.89 ï 1.36	1.1	0.89 ï 1.36	0.80	0.55 ï 1.16	1.29	0.00 ï 1.68	Significant	Effect modification
ART treatment	1.09	0.88 - 1.35	1.09	0.88 - 1.36	1.60	1.07 ï 2.41	0.93	0.72 ï 1.20	Significant	Effect modification
Age: **16-24**										
26 – 35	1.75	1.25 ï 2.45	1.71	1.22 ï 2.4	1.32	0.52 ï 3.39	1.74	1.21 ï 2.50		
36 – 45	2.43	1.71 - 3.46	2.32	1.62 ï 3.33	1.43	0.56 ï 3.64	2.68	1.79 ï 4.03		
46 – 55	6.31	3.44 - 11.59	6.06	3.29 ï 11.15	2.90	0.93 ï 9.05	8.98	3.78 ï 21.36	Not significant	Confounding
>55	21.34	2.93 ï 155.6	20.23	2.77 ï 147.7	6.56	0.76 ï 56.96	-	-		
Employment status: **Employed**										
Unemployed	0.88	0.71 ï 1.11	0.91	0.73 ï 1.14	0.94	0.63 ï 1.40	0.89	0.68 ï 1.18		
Student	0.42	0.17 ï 1.06	0.44	0.18 ï 1.12	-	-	0.34	0.13 ï 0.88		
Other	-	-	-		-	-	-	-		
Not indicated/Missing	1.29	0.94 ï 1.79	1.32	0.95 ï 1.82					Not significant	No effect

3.3.2 Univariate and Mutivariable Analysis to assess factors associated with ano-genital warts ocurrence

Univariate and multivariate analysis was done to assess factors associated with the occurrence of ano- genital warts for each gender and the results are presented below.

3.3.2.1 Univariate and multivariable analysis for females

In table 3.4 no associations with ano-genital warts occurrence was observed in both univariate and multivariate analysis for scabies, herpes simplex 2, syphilis, ART status and employment status amongst females in this study group. CD4 count was found to be weakly associated with ano-genital warts occurrence after adjusting for confounding, OR of 1.32(1.02 ï 1.72). Age was strongly associated with ano-genital warts occurrence before and after adjusting for confounding. The strength of the association increased with increasing age, OR of 1.65(1.13 - 2.41) for those aged between 26 and 35 years, 2.59(1.69 ï 3.59) for those aged 36 to 45 years, and 8.45(3.52 - 20.15) for those aged 46 to 55 years. A likelihood ratio testing the expanded age variable (categorical) model against the reduced age variable model was done to check for a linear trend. The null hypothesis in this instance was that the reduced model is equal to the expanded model. The p value of 0.24 was greater than 0.05 thus we did not reject the null hypothesis but concluded that there is a linear trend as the reduced model was not different from the expanded model.

Three models were compared using the likelihood ratio test to find the model that was the best fit for the data. A reduced model with variables CD4 count and age proved to be the best fit with a chi square statistic of 3.41 which was statistically insignificant (p value of 0.54). This model was tested for errors using the linktest and the Hosmer-Lemeshow test for goodness of fit. The Hosmer-Lemeshow test yielded a large p value of 0.92. Both tests indicated that the model fit the data well.

Table 3-4 Univariate and Multivariable analysis for females

Explanatory variable	**Crude OR**	**95% CI**	**Adjusted OR**	**95% CI**
Scabies	1.89	0.45 - 8.0		
Herpes Simplex 2	0.75	0.33 - 1.71		
Syphilis	1.82	0.43 - 7.10		
CD4 count	1.29	0.99 - 1.68	1.32	1.02 - 1.72
ART status	0.93	0.72 - 1.20		
Age categories:				
16 -25	1			
26- 35	1.74	1.21 - 2.50	1.65	1.13 - 2.41
36- 45	2.68	1.79 - 4.03	2.59	1.69 - 3.95
46- 55	8.98	3.78 - 21.36	8.42	3.52 - 20.15
>55	-	-		
Employment status:				
Employed	1			
Unemployed	0.89	0.68 - 1.18		
Student	0.34	0.13 - 0.88		
Other	-	-		
Missing	1.22	0.83 - 1.80		

3.3.2.2 Univariate and multivariable analysis for males

In table 3.5 there were no associations with ano-genital warts occurrence observed in both univariate and multivariate analysis for scabies, herpes simplex 2, syphilis, ART status, CD4 count, age and employment status amongst males in this study group. Significant associations were observed between ART status and ano-genital warts occurrence, OR 1.62(1.08 ï 2.45). Several models were used and compared to find the model that fit the data best using the likelihood ratio test. The model that was best was a reduced model with variables ART status and age. This model was tested for errors using the linktest and the Hosmer-Lemeshow test for goodness of fit. The yielded Hosmer-Lemeshow test a large p value of 0.74. Both test indicated the model fit the data well.

Table 3-5 Results of Univariate and Multivariable analysis for males

Explanatory variable	**Crude OR**	**95% CI**	**Adjusted OR**	**95% CI**
Viral herpes	1.84	0.88 - 3.84		
Syphilis	2.00	0.26 - 15.16		
CD4 count	0.80	0.55 - 1.16		
ART status	1.60	1.07 - 2.41	1.62	1.08 ï 2.45**
Age categories:				
16 - 25	1			
26- 35	1.32	0.52 - 3.39	1.4	0.55 - 3.66
36- 45	1.43	0.56 - 3.64	1.52	0.60 - 3.9
46- 55	2.90	0.93 - 9.05	3.08	0.99 - 9.6
>55	6.56	0.76 - 56.96	6.77	0.78 - 58.86
Employment status:				
Employed	1			
Unemployed	0.94	0.63 - 1.40		
Student	-	-		
Other	-	-		
Missing	1.56	0.87 - 2.80		

4 DISCUSSION

In this section the findings of this study and how they compare to existing literature as well as the limitations of the study are discussed.

4.1 Prevalence of Anogenital Warts

More women patronized the clinic during the study period when compared to men. This is in line with the fact that most women will seek treatment when not well. Most men generally do not seek treatment unless if they are very ill (1). This study found ano-genital warts to be more prevalent among females than among males. Prevalence was found to be 4% in women. This figure concurs with the findings of a study by Low et al, which found prevalence of ano-genital warts among women in Burkina Faso to be 3.5% (2). Banura et al found the prevalence of ano-genital warts among sex workers and women with STIs to range from 0.2 to 14% in Central and South African regions in a systematic review (10). Our findings fall within this range. According to the South African National Strategic Plan (2012 ï 2016) (32), sex workers are counted among high risk populations which refer to those at high risk of exposure as well as transmission of HIV. Risk of exposure to and transmission of other STIs is also higher because of multiple sex partners thus prevalence is expected to be higher in this group.

Our study showed prevalence among men to be 3%. In men the systematic review by Banura et al found the prevalence to range from 4.8% to 50.5%. Our prevalence of 3% falls below that generally found in central and South African regions for men. The studies evaluated in the systematic review reported on men attending sexual health clinics or having reported

STIs (10). Another recent study by Darwich et al found the prevalence of genital warts in HIV infected men having sex with men (MSM) to be 28% and 15% in heterosexual HIV positive men (33). This study was conducted on patients on the Can-Ruti HIV positive men cohort (33). These men were outpatients receiving HIV care and management in the University Hospital Germans Trias I Pujol, Badalona, Spain clinics. The vast difference in these findings could be explained in part by the differences in data collection, literature suggests that prevalence of ano-genital warts does depend in part on study methodology (11). In our study there was no active screening for the presence of ano-genital warts. Secondary data not collected for purposes of this study was used. However in the study by Darwich there was active screening for ano-genital warts presence and thus more patients could have been identified. Also the population studied consisted of a high percentage of men having sex with men (MSM), 74% (28). In this population the occurrence of ano-genital warts and other sexually transmitted illnesses is known to be high (34).

While prevalence was generally higher in females than males overall it was found to be higher in males above the age of 45 than in females of the same age group. This could be possibly because men remain sexually active longer into their old age than females. Also more males are found having sexual relations with younger women (<25) as they become older and this age group has the highest prevalence of ano-genital warts (1, 11, 22).

Prevalence of ano-genital warts decreased with increasing age in both men and women. It was highest in both men and women between the ages of 16 and 25. The prevalence in females in this age group was 7.56% and among males it was 4.27%. This is consistent with

what has been found in literature which states that prevalence is highest among sexually active women aged below 25 (1, 11, 22).

4.2 Factors associated with ano-genital warts

There was a strong association between age and the occurrence of ano-genital warts among females. This association became stronger with increasing age group at 95 % CI. Older age has been specifically found to be associated with recurrence of genital warts (16). However in this study it was not established whether this first occurrence during the study period was a recurrence or not.

In men, being on ART showed a weak association with the occurrence of ano-genital warts however among females ART status was not associated with the occurrence of ano-genital warts. The incidence of HPV related infections has not reduced substantially in the post ART era (35) and the effect of antiretroviral treatment on these infections still remains uncertain (2).

There was no association of CD4 count with ano-genital warts occurrence established among males. Consistent with our study findings, CD4 count was not found to be a risk factor in men in the systematic review by Banura et al. However among females there was an association between CD4 count and ano-genital warts occurrence. Low CD4 count Ò 200 cells/m^3 has been found to be a risk factor for ano-genital warts in HIV positive females by other studies (10, 17).

There were no association established between ano-genital warts and other STIs evaluated in this study. Other studies have reported associations of ano-genital warts with other STIs however these associations are still poorly understood and the data uncertain (2, 17, 22).

We could not establish any association of employment status with ano-genital warts occurrence and evaluated literature did not indicate employment status or education to be a risk factor (17).

4.3 Study Limitations

The data used for this study was collected for routine patient care for HIV infected patients and not for the purposes of this research. This data was therefore lacking in some important covariates which have been found to be associated with the occurrence of ano-genital warts. These factors include sexual history of a person, age at first sex, smoking and number of sexual partners among others. There was also a lot of missing data for some factors and they could not be used in analysis e.g. Only half of the study participants had baseline CD4 and the rest were missing.

Results of this study need also to be interpreted cautiously due to the very small number of study participants with the outcome of interest in the study sample, 369 out of 10 750. This could have compromised the results and introduced bias.

In our study we do not know which infection occurred first between HPV infection and HIV infection. Thus the prevalence found in our study does not therefore indicate if there is an elevation of genital warts due to HIV or not when comparing to the general uninfected population.

The study was a cross-sectional study and could only evaluate prevalent cases. Incident cases could not be evaluated in this study because in our participants we did not establish if the study participants were free from ano-genital warts at the beginning of the study. We therefore could not establish any new cases with certainty.

5 CONCLUSIONS AND FUTURE WORK

5.1 Conclusion

Prevalence of genital warts was highest among the younger age groups in both males and females and it decreased with increasing age. Prevalence was also higher in females than males up to the age of 35. Above the age of 35, prevalence was higher in males than in females. One of the strategic objectives of the South African government is to reduce STIs infection. Females between the ages of 16 to 24 are among key population in South Africa and there is therefore a lot of focus on them as part of managing the HIV epidemic as well as STIs. The South African population has seen a reduction in new HIV cases in the young population and more young people are delaying their sexual debut. This is a positive sign as it is likely to translate into the reduction of STIs including ano-genital warts among the young people. As things stand this prevalence indicates young people especially females are still getting exposed to HIV and STI infections in their teenage years.

There was a strong association between ano-genital warts and age among females but not among males. A weak association was found between ART status and the occurrence of genital warts among males. No association with ART status was established among females. Although the role out of ART in South Africa has increased in coverage we are still yet to see any meaningful impact of ART on ano-genital warts occurrence. There was no association found between any of the STIs with the occurrence of genital warts among both males and females. Among females a weak association between CD4 count and ano-genital warts was

found. Employment status of an individual was not significantly associated with ano-genital warts occurrence in both males and females.

5.2 Future work

The same research can be carried using a database from an STI clinic. These clinics are more likely to see more patients with ano-genital warts as well as being HIV infected.

A research into the prevalence of ano-genital warts amongst key populations in particular MSM, sex workers as well as females having sex with females is necessary as it has been established that prevalence of ano-genital warts is higher among some groups of the key populations (33).

A similar research can be done as a primary research to allow for collection of information on other relevant covariates like, sexual history, number of life partners and age at first sex.

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APPENDIX A: LETTER OF APPROVAL FROM WRHI

RHI
Policies and Procedures

Policy/SOP No:	XX-XXX

Title:	Access to data by external parties		
Prepared by:	Sinead Delany-Moretlwe		01-OCT-2010
	Name	Signature	Date
Authorized by:	Sinead Delany-Moretlwe on behalf of RLG		24-Nov-2010
	Name	Signature	Date

Background

RHI regularly receive requests from students or partners to conduct secondary analysis on existing datasets or to use data from existing cohorts. A process is required to clarify the relationship, expectations and deliverables from these collaborations.

Scope

All technical team heads or technical specialists or other staff that have investigator responsibilities.

Procedure

Requests from individuals wanting to make use of data from the RHI [project name] must follow the following procedure:

1. A written request to use the data set must be sent to [Principal Investigator Name] at the RHI. The request should include:
   1.1. Names of individuals who will be using the data set and their affiliations.
   1.2. A short proposal detailing the objectives of using the data, planned analysis, planned public distribution of results and date of finalization.
   1.3. The request will communicated with the relevant project team and/or senior research staff.

2. A consensus decision of this group, which includes the investigator and key technical staff on whether to grant permission for data use will be required in all cases. An RHI-based investigator to supervise the collaboration. This person will take responsibility for and manage all communication with the external party.
3. The applicant will be asked to write up a one page document outlining the objectives, analysis plan, individuals involved and purpose of the analysis (ie, dissertation, peer review publication, etc.) and which contains the following statements of assurance:
   3.1. All references to the data either in public/verbal presentation or print credit the RHIôs [Name] project as the source.
   3.2. Should the applicant wish to use the data for analysis beyond the originally submitted proposal, a further written request will be required and the procedures outlined above followed.
   3.3. Persons using the data set will submit a final draft of their work to the RHI for comment before it is submitted for publication or public presentation.
   3.4. The authorship of the paper will be decided using internationally recognized criteria, and must recognize the RHI researchers appropriately, as well as the international researcher/s involved in the data analysis. RHI will make the final decision about authorship.
   3.5. The applicant will also be required to submit a copy of the final product resulting from use of the data set to the identified RHI liaison person at RHI.
   3.6. The data set will not be shared, copied or provided to anyone other than the person/s outlined in the proposal
4. The proposal should be presented at RLG for information
5. Once approval has been agreed by the above group, a decision will be communicated to the applicant by RHI liaison.
6. A file will be maintained for all correspondence in this regard to the project. In particular:
   6.1. Correspondence documenting the approval process as out lined in Point 2 above
   6.2. The signed agreement of the applicant (this document).
   6.3. A copy of the final product resulting from use of the data.
7. Ideally, a paper for publication must have been produced within one year of receiving the data set (this means it must be submitted to a journal within one year of receipt of the

data). If the individual has not done so the applicant may forfeit the right to the data and to the topic of interest.

Agreement

In terms of this agreement Qinisile Sibanda will use the Ward 21 Clinic data for the completion of analysis and writing of a thesis entitled ñFactors associated with ano-genital warts among HIV infected patients at a Hillbrow clinic in Gauteng South Africaò which has been provisionally accepted by the University of Witwatersrand. The final version of the thesis will be reviewed and accepted by Dr Batanayi Muzah and Mr Eustasius Musenge before final submission. The data will not be used for any other publications before consultation with RHI.

I have read and accept these conditions.

Applicant:

Date:

03/09/2012

APPENDIX B: ETHICS CLEARANCE CERTIFICATE

Name: Qinisile Sibanda Student Number: 535739

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Ms Qinisile Sibanda

CLEARANCE CERTIFICATE	**M120939**
PROJECT	Factors Associated with Genital Warts among Human Immunodefiency Virus (HIV) Infected Patients at a Hillbrow Clinic in Gauteng, South Africa
INVESTIGATORS	Ms Qinisile Sibanda.
DEPARTMENT	School of Public Health
DATE CONSIDERED	28/09/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 28/09/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Mr E Musenge

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...