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Original Article

Human papillomavirus infection in women with the human immunodeficiency virus type-1

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ABSTRACT

Human Papillomavirus (HPV) is the most common sexually transmitted infection. The prevalence rates of HPV among women living with HIV can range from 36.3% to 97.1%; according to specific samples' risk behaviours, location, and sample size. The aim of the study is to evaluate the risk factors and to evaluate the prevalence of HPV infection among women infected with HIV in Tanzania. This is a cross-sectional study with a sample size of 1286 consecutive women attending the AIDS and cancer diagnostic centre. Data was collected on HPV positivity, cervical cytology, HPV risk/co-factors, and HIV information through assisted self-administered questionnaires, gynaecological examination, HPV-PCR linear array genotyping, CD4 count and viral load was done. 868 subjects were positive for HIV-1. Prevalence of HPV was 67.2% among HIV positive individuals. The age range of the women was 18 to 65 years with a mean age of 43 years. 70.5% of women of age group 18-35 y were positive for HPV and 64.7% of the women had education less than high school. 34.3% of women were engaged in stable relationship (marriage/consensual union) and 8.4% were widows. 82% of women were non smokers. HPV genotyping was done for total 868 samples. Among of them 583 were HPV positive. Out of which HPV 16 was the most prevalent type detected 236 (40.5%). Non HPV 16 was detected in 347 (59.5%) . Among HPV-16 positive women, 83.9% had abnormal PAP smear and 16.1% normal PAP smear. 40% showed high grade cervical squamous intraepithelial lesions. Similarly among non HPV-16 positive women, 87.9 had abnormal PAP smear, out of which 5.8% showed high grade cervical squamous intraepithelial lesions. There was a high prevalence of HPV/HIV coinfections among the study population and the presence of HPV correlated with some risk behaviors as well as with markers of immune function such as CD4 and RNA HIV viral load. Although an abnormal Pap smear was more frequently associated to the presence of HPV, there were women with HPV expression had a normal Pap smear. Vaccinations will be key to decreasing the high burden of disease and deaths attributable to the dual epidemics of cervical cancer and HIV infection in medically under-served women worldwide.

1. Introduction

It is now generally accepted that certain types of human papillomavirus (HPV) play an important role in the genesis of cervical carcinoma [1]. Human papillomavirus (HPV), a common sexually transmitted DNA virus, is the central cause of cervical cancer2. Most HPV infections resolve or become latent and undetectable, whereas persistent infection with an oncogenic HPV type is required for cancer development [2]. Of more than 100 HPV types, more than 40 can infect the cervix, and at least 13 of these are considered oncogenic types including HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66. Cervical cancer is the second most common worldwide cause of cancer in women, with almost two-fold higher incidence in developing countries than in industrialized countries [3]. In the Tanzania, women with HIV/AIDS have several-fold higher rates of cervical cancer

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compared with the general population. Studies shown that the estimated average prevalence for cervical HPV infection in HIV positive women is between 40%-70%, and negatively correlated to CD4 counts. HAART has improved the survival of people living with HIV, but its impact on HPV-related manifestations is less clear. Some have reported on reduced persistence or progression of HPV while others have not [4].

Although there is a clinical test available to detect 13 types of oncogenic HPV infections, there are currently no recommendations for use of this test in HIV-seropositive women [5,6]. There is no information on HPV co-infection (rates and types) among women living with HIV in Tanzania.

2. Materials and Method

2.1.Study design and population

This is a cross-sectional study. The study population consists 1286 of women attending AIDS and cancer diagnostic centre. Study subjected has not been documented diagnosis of HIV infection, with no prior history of cervical cancer; and who are scheduled for their routine clinical visit.

2.2.Data collection procedures

Upon completing the informed consent process, participants complete two self-administered questionnaires that collect information on their previous exposures or risk factors associated with HPV infections, as well as socio-demographics. The participant is then seen by the study clinician who performs a pelvic exam for Pap test and HPV samples using a Digene's cervico-vaginal sampler. A blood sample is also collected to determine HIV viral load. CD4 cell counts. A CD4 cell count was accepted for the study purpose if it had been performed within 3 months of the visit date. Otherwise, a blood sample for CD4 determination was also obtained at the visit date [7,8].

2.3.Cytology and histology

Pap smears were examined and classified according to the Pap classification. All patients showing cytologically abnormal smears were referred for colposcopy-directed biopsy [9,10].

2.4.HPV typing

All HPV samples are being evaluated using a Linear Array PCR-DNA to identify each participants HPV positivity and genotypes (HPV-16, other than HPV-16) [11-13].

2.5. Statistical analysis

For this preliminary analysis, descriptive statistics were used to describe the prevalence of HPV infection (overall and type specific) and of related co-morbidities in the study population. Contingency table analysis and chi-square statistics were used to determine factors associated to HPV cervical infection [14]. All data was evaluated using SAS 9.0.

3.Results

A total of 1286 specimens were tested for HIV. Among of them 868 specimens were HIV-1 positive. HIV- 2 positive cases were not found. The age range of the women was 18 to 65 years with a mean age of 43 years. The majority of women attending for AIDS and cancer diagnosis and treatment are of low socioeconomic status. The specific details regarding the socio-economic or demographic status were collected from individual women participating in the invasive cancer study. 70.5 of women of age group 18-35 y were positive for HPV, 64.7% of the women had education less than high school, 34.3% of women were engaged in stable relationship (marriage/consensual union) and 8.4% were widows. 75.5% of women were non smokers

Table 1. Prevalence of Hpv 16 In Study Cases

Contents	Total Numbers	Percentage (%)
Total case study	1286	
HIV Positive	868	67.5 %
HIV Negative	418	32.5 %
HPV Positive	583	67.2 %
HPV Negative	285	32.8 %
HPV 16 Positive	236	40.5 %
Non HPV 16	347	59.5 %

HPV genotyping was done for total 868 samples. Among of them 583 were HPV positive. Out of which HPV 16 236 (40.5%) was the most prevalent type detected. Non HPV 16 was detected in 347 (59.5%)

Table 2. Age Wise Distribution Of Hpv- 16 Type In Aids Women

Age Group	HPV Sample size (Total No - 583)	HPV 16 Positive samples (Total No - 236)	Percentage of HPV 16 Positive (%)
18 – 29	266	119	50.4 %
30 – 35	128	56	23.7 %
36 – 40	98	37	15.7 %
41 – 49	54	18	7.6 %
50 – 60	37	06	2.5 %
60 – 65	0	0	0 %

Among HPV-16 positive women, 83.9% had abnormal PAP smear and 16.1% normal PAP smear. 16.1 % showed atypical cells of undermined significance, 44.9% showed low grade cervical squamous intraepithelial lesions and 40% showed high grade cervical squamous intraepithelial lesions. Similarly among non HPV-16 positive women, 87.9 had abnormal PAP smear, out of which 12.1% showed atypical cells of undermined significance, 82.1% showed low grade cervical squamous intraepithelial lesions and 5.8% showed high grade cervical squamous intraepithelial lesions.

58% of HPV-16 positive women showed history of dysplasia and 16.7% of non HPV-16 positive women showed history of dysplasia. Genital warts on baseline examination were seen in 83% among HPV-16 positive women and 14.1% among the women who were positive for other HPV types.

Table 3. Socio-demographics features of HPV positive women

Socio – Demographics	non HPV 16 (n - 347)	%	HPV16 Positive (n -236)	%
Socio - Demographics				
Age				
Less than 35 years	236	68.01	175	74.15
Above 35 years	111	31.98	61	25.8
Education				
Less than high school	192	55.33	185	78.38
High school or more	155	44.66	51	21.61
Marital status	194	55.9	140	59.3
Single	128	36.85	72	31
Married / consensual union	25	7.2	24	10.2
Widow				
Life style				
# sex partners (past 12 months)				
< 3 partners	334	96.25	220	93.2
Sex partners (Life time)				
< 10 partners	347	100	236	100
10 partners				
Cigarette smoking				
Non smokers	294	84.72	184	78
Former smokers	27	7.78	37	16
Current smokers	26	7.49	15	6
Health status				
Pap smear results at baseline				
Normal	42	12.1	38	16.1
Abnormal	305	87.9	198	83.9
Type of abnormal pap results				
ASCUS and atypical endocervical cells	42	69.45	38	11.9
ASCH, HSIL and carcinoma	20	6.05	92	39.0
LSIL	285	24.5	106	44.9
History of dysplasia				
No	289	83.3	99	42
Yes	58	16.7	137	58
Warts - active lesions (Baseline)				
No	298	85.9	40	17
Yes	49	14.1	196	83
CD4 cell counts				
200 cell count (cells/mm3)	259	74.6	42	18
201 - 499 cell count (cells/mm3)	65	18.7	77	32.5
500 cell count (cells/mm3)	23	6.6	117	49.5
Viral load (HIV)				
Less than 75 copies	240	69.2	140	59.3
75 - 1000 copies	46	13.3	38	16.1
1000-100000 copies	37	10.7	33	14.0
>100000 copies	24	6.9	25	10.6

CD4 cell count was evaluated in all HPV positive individuals. 74.6% individuals had CD4 cell counts less than 200 cells/mm3 among the women who were positive for HPV other than HPV type 16 and 18% of women had CD4 cell counts less than 200 cells/mm3 in HPV 16 positive individuals.

Evaluation of HIV viral load, indicated that, 69.2% of women who were positive for non HPV 16 had < 75 copies of HIV and 59.3% HPV -16 positive women had < 75 copies of HIV. Similarly 6.9% of non HPV -16 positive women and 10.6% of HPV-16 positive women had HIV viral load greater than 100000 copies.

4. Discussion

More than one-third of the 8 million persons infected with the HIV virus worldwide are women15 , and AIDS is rapidly becoming a leading cause of death in women, especially in developing countries 16 . Likewise, worldwide, cervical cancer is a leading cancer cause of death in women, particularly in developing countries [17] .

This present study showed that women with cervical cancer more likely to be infected with HIV-1 than women without cervical cancer. Furthermore, the risk of cervical cancer increased with age, higher parity, and among those who had ever smoked. Few studies have established an association between HIV and invasive cancer of the cervix in Africa [3,15].To explain this situation; there are a number of plausible reasons.

First, though cancer of the cervix is the commonest malignancy in women in Africa, it is rare when compared to many other diseases. The invasive cancer of the cervix is less frequent than pre invasive cervical cancer. Second, it has been suggested that the combination of cancer of the cervix and HIV is usually lethal and many women with these two diseases die before they seek health care [18].

The results of this study suggest that HIV is a cofactor in the association between HPV and CN; this effect seems to vary by level of immune function. These hypotheses are biologically credible and are supported by the general consistency of findings across studies and similar types of neoplasia and the dose-response-like relationship for level of immunosuppression. Although the precise biological mechanism underlying the interaction between HIV and HPV has yet to be determined, there are two potential mechanisms for the interaction: (a) HIV and its resultant effects on immune function affect the susceptibility to, severity of, and/or potential oncogenicity of HPV; and/or (b) there is a molecular interaction between HIV and HPV. In the present study18% of individuals had CD4 counts less than 200 cells/mm3 and all these individuals had grade III pap smear results and all these individuals had warts.

Biological mechanisms through which cellular immunosuppression could facilitate the oncogenic effects of HPV include prolonging the length of time of an HPV infection [19,21], increasing HPV viral load [19,20], allowing for more rapid HPV replication [18] , persistence [17], or progression [18] , or impacting on Langerhans' cells [19] . Increased oncogenicity of HPV in HIV-infected women is also supported by clinical observations of more rapidly progressive disease [15] and higher rates of recurrence among HIV-positive compared with HIV-negative women with HPV [22,23] .

Sexual behavior is also associated with risk of human papillomavirus infection. The decrease of human papillomavirus prevalence in older women agrees with other studies that argue in favor of a biological effect, such as increased immunity to human papillomavirus with age. In the present study 70.5% of HPV positive women were below the age of 35 years.

HIV-1 infection is associated with invasive cancer of the cervix. Under developing countries with a high burden of HIV-1 and cervical cancer should adopt a high-risk approach that targets HIV-1 positive women for screening of cervical cancer initially by utilizing HIV/AIDS resources.

5. Conclusion

There was a high prevalence of HPV/HIV co-infections among the study population The presence of HPV correlated with some of the well known risk behaviors such as lifetime number of sexual partners. This was statistically significant. The presence of HPV correlated with markers of immune function such as CD4 and RNA HIV viral load. These were statistically significant. Although an abnormal Pap smear was more frequently associated to the presence of HPV, half of the women with HPV expression had a normal Pap smear.

The results confirm the earlier studies on the role of high risk HPV infection as a major risk factor for development of cancer in the cervix. Further, the distribution of high risk HPV type 16 is similar to those reported conducted in other part of Africa. The prevalence of HPV-16 in the AIDS women samples suggests that effective vaccination against HPV 16 can considerably bring down the cancer burden in Africa. However early detection of the virus by diagnostic and screening methods would be much useful for detection and treatment of this virus as early as possible.

The clarification of the associations between immune function, HPV, and cervical carcinogenesis will be decisive to efforts to defensive efforts, including HIV and HPV vaccinations. Such efforts will be key to decreasing the high burden of disease and deaths attributable to the dual epidemics of cervical cancer and HIV infection in medically under-served women worldwide.

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