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Full Length Research Paper

Prevalence, Risk and High Human Papilloma Virus IgM and IgG Concentration in Human Immune Deficiency positive individuals in Southwest Nigeria

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Background Human papillomavirus (HPV) are a major public health concerns among immune-compromised individuals. There is paucity of reports in Nigeria as to their prevalence and risk among HIV positive individuals and the antibody concentration to determine the level of infection. Methods and Findings. This study examined 797 individuals confirmed to be living with HIV using the competitive ELISA technique were screened for HPV and the concentration of IgG and IgM determined using ELISA among which 282 (37%) males were positive to HPV and 470 (63%) females. There was a high prevalence of HPV infection with overall of 76% and 0.6183 for the minimum and were 0.8004 for the maximum (CL=2.5%-97.5%) using the Bayesian estimate of true prevalence. The risk factors evaluated included alcohol intake, smoking, habit, comorbidity, sexual habit, HAART administration, other STIs, men having sex with men (MSM) and ages. The young and mid ages has the highest prevalence of HPV infection as well as have highest number of individuals with high concentration of IgM and IgG. Conclusions. The high level of IgM is an indication of recent infection and the subjects may still be actively sexually involved. High smoking index, alcohol consumption, multiple sexual partners and

infection with more than 1 STI, hepatitis B virus (HBV) infection were implicated as risk or predisposing factors to HPV infection in HIV patients. The high prevalence of HPV and identified risk factors among immunocompromised individuals has serious implications for healthcare.

Keywords: IgG, IgM, Concentration, HPV, HIV

INTRODUCTION

Human Papillomaviruses (HPVs) are DNA viruses that belong to the papilloma virus family with specialized capability of infecting humans. Decades of studies have revealed that the papilloma viruses are highly diverse and occur mostly in humans, mammals and birds (Villiers *et. al.,* 2004). Generally, the papilloma viruses are reputable for their ability to induce benign tumors, warts and papillomas in different hosts, most especially among humans (Clifford *et. al.,* 2003). The HPVs have special affinity only for the keratinocytes of the skin and mucous membranes in humans and this characteristic enable them to establish a long term infection in susceptible humans. Prolonged infections with HPV may lead to cancers of the cervix, vulva, vagina, penis and increased risk of cardiovascular infections (CDC, 2008; Kuo and Fujitse, 2011). The transmission of HPV infections are generally considered sexual but non sexual transmission may occur in extremely rare cases (Kjear *et. al.*, 2001; D'Souza *et. al.,* 2014). Persistent infection with "high-risk" HPV types different from the ones that cause skin warts may progress to precancerous lesions and invasive cancer (Schiffman and Castle, 2003).

There are currently a huge body of evidence indicating that the HPV has a vast epidemiology; fueled by globalization and increased speed of air travel across all continents with the highest prevalence in Sub-Sahara Africa, Eastern Europe and Latin America (Bruni *et. al.,* 2010: De Sanjose *et. al.,* 2007). In addition, the geographical distribution of genital HPVs among men also spans across different continents with the highest prevalence reported in Europe and North America especially in Men sleeping with men (MSM) (Smith *et. al*., 2011). Clinical evidences are also available that HPV infections are relatively common in Nigeria. A study by (Thomas *et. al.,* 2004) confirmed a relatively high prevalence of the human papillomavirus infection among women in Ibadan, Nigeria. Studies have similarly explored the relationship between HIV positive individuals and HPV infections (Ezechi *et. al.,* 2014). A similar study by (Ogoina *et. al.,* 2013) presented evidence of strong association between HPV and HIV infections among adult patients. The overriding hypothesis therefore, is that individuals with HIV and other immune-compromised individuals have a significant risk of infection with HPV and carriage of the virus (Akorolo-Anthony *et. al.,* 2013). Despite this reports, there is still paucity of information regarding the risk factors that could predispose HPV infection in HIV infected individuals. This study therefore examines not only the prevalence of HPV infection in HIV patients but as well as the risk of acquiring HPV in HIV infected individuals. (Naoyoshi Nagata *et. al.,* 2015) examine the risk of anal HPV infection among HIV positive individuals in Japan and found several genotype associated with anal infection of HPV. The risk they observed included MSM, heavy smoking, younger ages and coinfection with other STI. Such a study in Southwest Nigeria will help inform policy makers and clinicians in general on predisposing risk of HPV in HIV positive individuals towards reducing the public health burden in this part of Nigeria.

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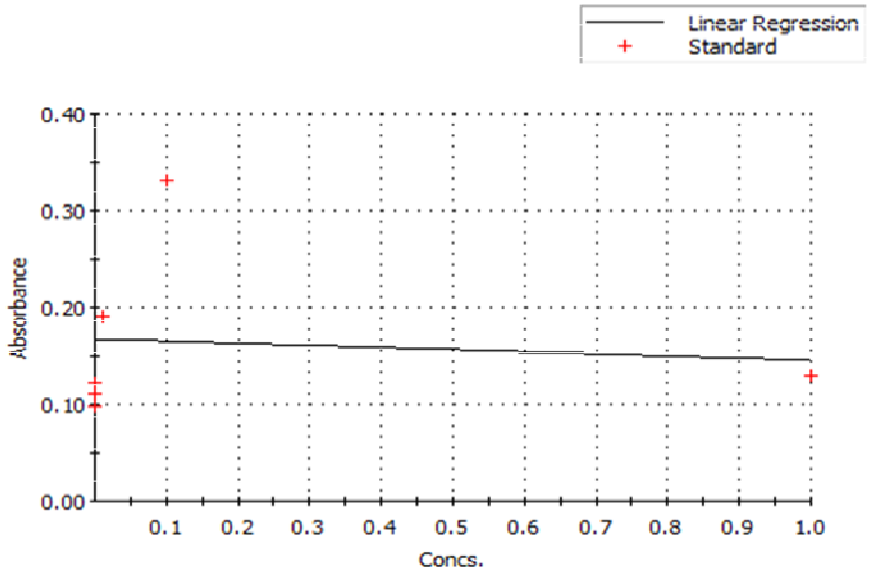

Figure I: Linear regression of IgG and IgM concentration in sera samples tested using their absorbance.

This study also aims at establishing the effect of antibody concentration (IgG and IgM) on HPV infection in HIV patients which is likely the first of such study in Nigeria.

METHODS

Collection of blood samples for HPV screening

Blood samples were collected from 797 consenting HIV patients visiting clinics in Southwest Nigeria. Blood samples were collected using EDTA bottles and were centrifuged for 5 minutes at 3000 rpm after which the serum was separated. The sera were stored in -20◦C refrigerator until used. A well-structured questionnaire were administered on the patients with the following information, alcohol drinking habit, smoking, habit, health related status like hypertension, diabetes, sexual habit (number of sexual partners), current status of STI, Length of period of administration of HAART, MSM, likely route of HIV infection.

Sample screening

Sera were brought out of the -20◦C refrigerator and allowed to attain room temperature, the sera were tested for Human Papilloma IgM and IgG using ELISA research kits (WKEA medical supplies China) which also determine the concentration of both antibodies. The antibody concentration for HIV IgG and IgM was also determined using the same ELISA kits. All the ELISA kits were brought out of the refrigerator and allowed to attain room temperature and test carried out as described by the manufacturer (WKEA medical supplies, China). Absorbance and optical density of the samples after test was determine on ELISA plate reader (Thermomax, Molecular devices, UK), and assay results was analysed and antibody (IgM and IgG for both HPV and HIV) determined using online ELISA assay software Myassays. The standard curve from the analysis is shown in figure 1. Diagnostic ELISA kit (WKEA medical supplies China) was used to screen for syphilis, Hepatitis B virus (HBV) and *Chlamydia trachomatis.*

Table 1: Age and sex distribution of HPV positive individuals among individuals living with HIV/AIDS

Age group	Number of Males		Number of Females		% positive
	Positive	Negative	Positive	Negative	
1-10	5	0	6	9	55
11-20	15	0	35	11	82
21-30	53	0	109	0	100
31-40	79	0	196	15	94
41-50	70	0	94	0	100
51-60	60	15	30	15	75
Total	282(37.5%)	15	470 (59%0	30	76

Statistical analysis

HIV patients with HPV were compared with those without HPV using baseline their set characteristics using $\chi 2$ test and Fisher's exact test, analysis of variance was also done for both continuous and categorical variables. Logistic regression analysis was used to compute odd ratio (OR) at 95% confidence interval (CI). Univariate analysis and multiple regression model were used to include all factors with $p<0.05$ on univariate analysis. It was not possible to do regression analysis for MSM because it was limited to only males. Relationship between HPV infections and IgG and IgM concentration was determine using the $\chi 2$ test. All analysis was done with online R statistical software (Rosner, 2000) and Microsoft excel 2013 version.

RESULTS

Of the total of 797 samples collected from individuals living with HIV/AIDS and tested for HPV IgM and IgG using the ELISA techniques 297 (37%) were males and 500 (63%) were females. A total of 752 (76%) with a prevalence of HIV positive individuals were positive to HPV infection, of which 282 (37.5%) were males and 470 (62.5%) were females. The prevalence was 0.7605 and mean 0.7227 (CI: 0.6183-0.8004) (Table 1 and 3). Age distribution shows that the younger and mid age groups have the highest prevalence as compared to the extreme ages. Analysis of variance shows significant difference within the age groups ($\alpha=0.8203$).

Antibody concentration (IgG and IgM for HIV and HPV) were independent of HPV infection among HIV positive individuals ($\chi 2=196.8$, **p=**0.0000001) (table 2).

Table 3 shows the risk and prevalence of predisposing factors for HPV infection and their odds of responsible for HPV infection among HIV positive individuals. Distribution of HPV IgG and IgM shows that the number of HIV positive person with high concentration were more in age group 21-30 and 31-40 with IgM having higher number of individuals with high antibody concentration (figure. 2). Figure. 3 and 4 shows the sexual distribution of high concentration of HPV IgM and IgG in HIV positive individuals with more females having significant concentration, more females had IgM as compared to males

DISCUSSION

Of the 797 HIV patients tested for HPV antibodies in this study, 76% were positive to HPV antibodies which included both IgM and IgG, the high prevalence of HPV in HIV

Table 2: Distribution of HPV and HIV IgG and IgM concentration in individuals living with HIV/AIDS

Concentration of Antibodies	Number for IgM		Number for IgG		χ2
	HIV	HPV	HIV	HPV	
1-10	11	9	10	12	
11-20	10	10	9	11	
21-30	10	15	10	8	
31-40	18	22	22	18	
41-50	18	35	25	8	
51-60	41	62	24	3	
61-70	50	72	22	23	
71-80	56	69	30	18	
81-90	80	101	41	27	
91-100	52	63	13	11	
101-110	50	61	12	3	
111-120	60	72	27	15	
121-130	15	15	36	39	
Total	**471**	**606**	**281**	**196**	**196.8 (p=**0.0000001)

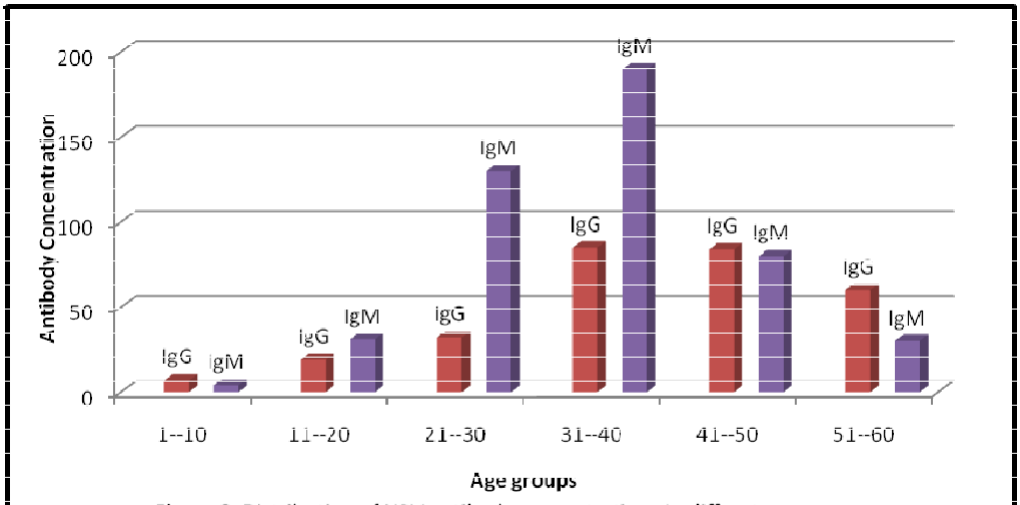

Figure 2: Distribution of HPV antibody concentrations in diffrent age groups among HIV positive individuals

Table 3: Characteristics of HIV infected persons and risk factors associated with HPV infection among HIV infected individuals

Variables	Number males	Number females	Prevalence (Median)	Upper limit	Lower limit	Mean (SD)
Age in years						
1-10	**5**	**6**				
11-20	**15**	**35**				
21-30	**53**	**109**				
31-40	**79**	**196**				
41-50	**70**	**94**				
51-60	**60**	**30**	0.7605 (0.724)	0.6183	0.8004	0.7227 (0.0211)
			OR	**Upper limit**	**Lower limit**	**p**
Alcohol consumption						**0.0000001**
None	76	71	1.012	0.77	1.332	
Light	96	200	3.193	2.465	4.147	
Heavy	119	110	2.593	2.032		
Smoking index						0.07846
Never Smoked	99	50	0.8938	0.6843	1.168	
Light Smoker	153	131	1.368	1.089	1.721	
Heavy smoker	30	289	1.174	0.9424	1.463	
Comorbidity and drug use						
Hypertension	81	163	1.853	1.443	2.385	0.000000343
Diabetes	85	151	1.654	1.299	2.107	0.00002501
Dyslipidemia	34	47	2.499	1.621	3.852	0.00001077
Chronic Kidney disease	43	41	0.9374	0.6748	1.302	0.3810
Use of Corticosteroid	39	68	1.09	0.7942	1.499	0.3180
HIV related factors						
MSM	34	NA	2.522	1.26	5.393	0.003358
Heterosexual						
≤ 5 sex partners	39	184	1.372	1.08	1.743	0.005550
≥ 5 sex partners	143	276	6.121	4.768	7.859	0.0000001
Injecting drug use	45	111	3.216	2.268	4.617	0.0000001
Unknown	21	52	1.099	0.7538	1.609	0.3377
Administration of HAART	97	279				
Duration in years						
≥5 years	20	89				
≤5 years	65	131				
≥10 years	12	59				
STI						
Syphilis	48	81	11.03	6.013	22.09	0.0000001
Hepatitis B virus	99	156	1.656	1.3	2.112	0.00001503
Chlamydia	135	233	2.823	2.249	3.543	0.0000001
Number of infection						
≥2 infections	261	389	6.551	5.056	8.489	0.0000001

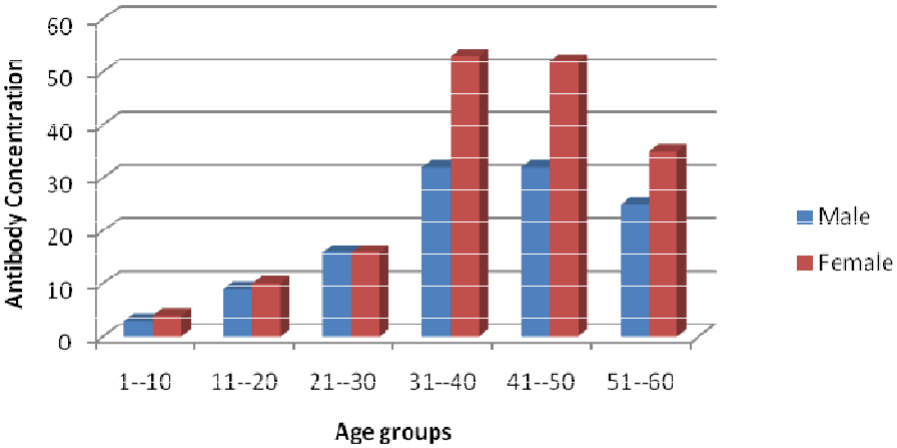

Figure. 3: Sex distribution of HPV IgG concentration among HIV positive Individuals

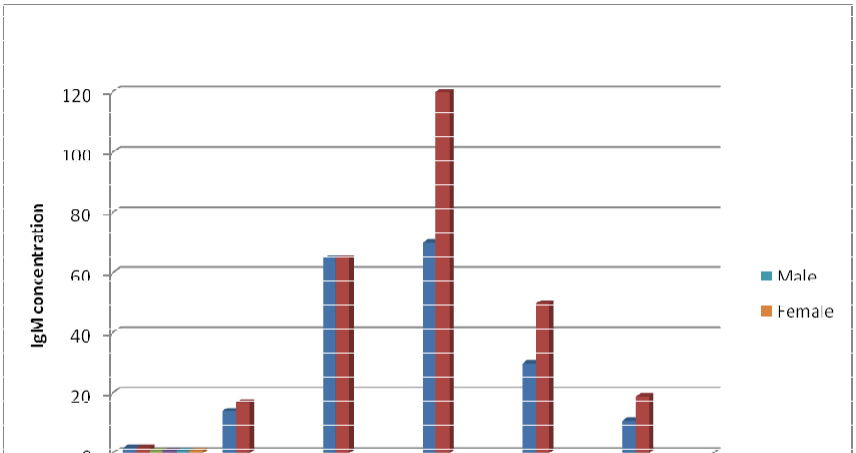

Figure. 4: Sex distribution of HPV IgM concentration among HIV positive individuals

positive individuals obtained in this study supports several studies in different parts of the world. (Naoyoshi Nagata, *et. al.,* 2015) also reported a 76% prevalence of HPV in HIV patients although they were more interested in Men Sleeping with Men (MSM) and anorectal infection in heterosexual HIV patients in Japan. Similar results were also obtained in Shenzhen, China where 71% of HIV positive MSM were positive for HPV (Hu *et. al.,* 2013). (Naoyoshi Nagata, *et. al.,* 2015) also reported a 21% of HPV positivity among heterosexual men; this is similar to

the 28% positive from men obtained from this study. (Piketty *et. al.,* 2003) investigated 50 HIV positive individuals who are injecting drug users and found a 44% positivity to HPV among these males who were also heterosexual, their result was higher that what was obtained in this study and also what was reported by (Naoyoshi Nagata, *et. al.,* 2015) which may due to the fact that they work on injecting drug users which is a very vulnerable population, In another report that investigated HIV positive African women living in Europe, 43% of them were positive to HPV (Konopnicki Deborah *et. al.,* 2013) which was similar to the 48% result obtained in this study. In Zaria, Nigeria (Ogoina *et. al.,* 2013) reported 41.3% positivity to HPV IgG among 63 HIV patients. This report was lower than the 76% HPV positive results in this study which may be firstly because of their small sample size and also largely due to the use of IgM and IgG in this current study. (Nweke *et. al.,* 2013) reported that the prevalence of HPV among HIV positive women that reported at the Lagos University Teaching Hospital was 44% of 98 individuals. (Akorolo-Anthony *et. al*., 2013), also reported a relatively high prevalence of HPV among women, with higher prevalence reported among HIV positive women that HIV negative women. In a study by (Ojiyi *et. al.,* 2012), pap smears of 450 randomly selected sexually active women were examined and the prevalence rate was established at 10.7%. Despite the consistency in these findings, the prevalence rate observed in this present study was high compared to other studies is this is a cause for serious public health concern. Such high prevalence may have been as a result of increasing prevalence of HIV/AIDS in Nigeria which is the cause of high morbidity and mortality, it also led to the infected individuals being immunocompromised and as such exposed to a variety of infections like high risk HPV which is responsible for lots of reported cervical cancers in females and anorectal cancers both in male and female. UNFPA has put the HIV prevalence in Nigeria at 4.6%, a prevalence which is suspected to be higher unofficially. In South Africa, (Adler David *et. al.,* 2015) reported that more HIV positive women are exposed to the risk of acquiring HPV than their male counterparts, a result which is largely consistence with this study; this may not be unconnected with high rate of vertical transmission than horizontal transmission as seen in the case of HIV transmission.

The distribution of HPV in HIV positive individuals in this study shows that prevalence was higher among age groups 11-20 and 21-30 which is suggested to be due to high sexual activities in this age groups. We also find evidence of mother to child transmission in this study as there was HPV positivity among HIV positive individuals within age bracket 1-10, though the mechanism of this transmission is of HPV in the absence of sexual intercourse has not been reported but there are reports of infection being from transiently infected fingers and toys (Piketty *et. al.,* 2003) which may be a route of infection from mother to child especially in anorectal infections. Though age group 41-50 has not being reported as a very sexually active age group, the high prevalence in this age group might be as a result of persistence infection since they also have high levels of HPV IgG concentration. Persistence infection has earlier being reported in older women in South Africa (Adler David *et. al.,* 2015). Another important observation in this study is the prevalence of the HPV was highest among the women within the age group of 31-40 years. Studies have confirmed that infection with the HPV and the high prevalence of HPV is always associated with high level of sexual activity and such infections can coexist with other sexually transmitted infections (Wilkin *et. al.,* 2010). Naturally, sexual activity among humans attains its peak within this age group and this facilitates easy spread of the HPV among such individuals. This important finding in this present study strongly suggests that the HIV positive individuals captured in this study may have repeatedly had some sexual intercourse for some time prior to this study which is evident in their high concentrations of HPV IgM. There were 50 HIV positive individuals who were positive to both HPV IgM and IgG in high concentration suggesting that they must have had persistent infection an observation which is in agreement with a South African report by (Adler

David *et. al.,* 2015). The high IgM concentration seen in the mid ages shows that these population are still very sexually active which account for why IgM concentration was higher across these ages than IgG. This is a serious public health concern because of likely high transmission rate of HPV and HIV, hence more community engagement and awareness campaign must continue if this has to be curbed. There was however no significant difference between the concentration of HPV IgG, IgM and HIV IgG and IgM, showing that the two infection occur side by side of each other or were co-transmitted or the HIV patients may have acquired HPV shortly after the infection with HIV. This may also mean that some of the HIV cases may have recently occurred (Caussy *et. al*., 1990).

Alcohol intake was observed to be a likely factor in the transmission of HPV among HIV positive individuals in this study, though very few reports have it that alcohol intake could be implicated in the transmission of HPV in HIV positive individuals, however, alcohol intake have been reported to increase sexual activities which is a factor for transmission of HPV. Smoking was found to influence the HPV infection as heavy smokers and light smoker has high OR of contacting HPV a finding which supports early report by (Nishijima *et. al.,* 2015) where they showed that was associated with anorectal condyloma in HIV infected persons. Comorbidity with other diseases do not seem to be a high risk for HPV infection in HIV positive individuals though their OR was a little above 1, except for dyslipidemia with OR above two but the mechanism of this effect has not been reported. Men having sex with men (MSM) possess a serious challenge in the transmission of HPV as the was high in this study and was consistent with other studies where it has been implicated as a major source of transmission and cancers that has been described of which anorectal cancer was clearly seen (Naoyoshi Nagata *et. al.,* 2015). Multivariate analysis of the data from this study shows that the younger and mid ages, alcohol intake, more than 2 STI , MSM and more than 5 sexual partners were independently associated with HPV infection. It was also found that an increase in HPV IgM was associated with most of the risk factors in this study. This is however, consistence with previous studies that have implicated specific risk factors including younger age though this study observed both younger (Law *et. al.,* 1991; Breese *et. al.,* 1995; Nakashim *et. al.,* 2014) and mid ages, HBV infections (38) and positive to *Chlamydia trachomatis* IgM thereby suggesting strong implication of sexual transmission of HPV infection. Possible administration of HAART was not associated with HPV infection in this study though report from (Naoyoshi Nagata *et. al.,* 2015) has shown an independent association between long term administration of HAART and HPV infection. This study further confirms that immunosuppression remains a major factor for acquiring HPV infection in HIV positive persons.

Limitations to this study are that data from certain other infections and characters that may predispose to HPV infection was not collected. The relatively high amount of individuals screened in this study though the study population allowed timely collection of samples from patients. This study could not confirm if the high concentration of IgG and IgM from this study were protective. This study could not confirm the type of HPV infecting HIV patients in the study population.

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