Human Immunodeficiency Virus is a Driven Factor of Human Papilloma Virus among Women: Evidence from a Cross-sectional Analysis in Yaoundé, Cameroon

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Abstract

Background: Human papillomavirus (HPV) is the leading cause of cervical cancers, causing 270.000 deaths annually worldwide of which 85% occur in developing countries with an increasing risk associated to HIV infection. This study aimed at comparing HPV's positivity and genotype distribution in women according to their HIV status and determinants.

Methods: A comparative study was carried out in 2012 at the Chantal BIYA International Reference Centre (CIRCB) among 278 women enrolled consecutively at the General Hospital and the Gynaeco-Obstetric and Paediatric Hospital of the City of Yaoundé. HPV genotyping was performed by real-time PCR, HIV serological screening by serial algorithm, CD4 T cell phenotyping by flow cytometry and HIV viral load by Abbott m2000RT. Statistical analyses were performed using Microsoft Excel 2016 and Graph Pad version 6.0 software; with $P < 0.05$ considered statistically significant.

Results: Globally, mean age was 37 ± 3 years; median CD4-count for HIV+ was 414 cells/mm³ [IQR: 264.75-588] and median viremia was 50 RNA copies/mL [IQR: <40-8288]. Overall HPV rate was 38.49% (107/278); 58.88% for single women vs. others (28.97% married, 2.80% divorced, 9.34% for widows), OR: 2.164; $p = 0.0319$. Following HIV status, HPV rate was 43.48% (80/184) among HIV+ vs. 28.72% (27/94) among HIV- (OR: 1.937; $p < 0.0142$); HPV genotypes among HIV+ vs. HIV- were respectively distributed as follows: genotype 16 (3.75% vs. 0.00%, $p = 0.57$), genotype 18 (3.75% vs. 3.70%, $p = 1.00$), co-infection 16 and others (8.75% vs. 7.40%, $p = 1.00$), co-infection 18 and others (8.75% vs. 11.11%, $p = 0.71$), co-infection 16, 18 and others (2.50% vs. 0.00%, $p = 1.00$) and other genotypes (72.50% vs. 77.78%, $p = 0.80$). Among HIV+ participants, HPV rate following CD4 was 62.88% (61/97) for $CD4 < 500$ vs. 35.71% (20/56) for $CD4 \geq 500$ (OR: 3.05; $p = 0.0012$) while HPV rate following HIV viremia was 42.71% (41/96) with <1000 RNA copies/ml vs. 66.00% (33/50) with >1000 RNA copies/ml (OR= 0.384; $p = 0.009$).

Conclusion: In Yaoundé, HPV rate appear to be very high, with higher rates of genotypes other than 16 and 18. In the event of HIV infection, the risk of HPV positivity is two times higher, favoured essentially by immunodeficiency. Thus, HIV-infected women should be closely monitored to prevent the emergence of cervical cancer.

Keywords: HPV, HIV, Women, Yaoundé

Background

Human papilloma viruses (HPV) are non-enveloped DNA viruses that represent the most widespread sexually transmitted infection worldwide, with more than 200 species. HPV genotypes are responsible for 95% of the occurrence of cervical cancer in women [1]. Notably, HPV causes benign and malignant tumours in humans and viral genotypes that are oncogenic are classified as high-risk (HR-HPV) or low-risk oncogenic HPV (LR-HPV) [2]. Although all HR-HPV genotypes have oncogenic potential, some are more frequently involved in cancers than others. Thus, HPV 16 and 18 represent approximately 70% of all

cervical cancers worldwide, followed by HPV 31, 33, 45, 52, 58 and 68 which are among the ten most commonly isolated HR-HPV genotypes from cervical tumor biopsies [3, 4].

Indeed, cervical cancer is known to be a viro-induced neoplasm and that HPV is the causal agent in 99% of cases [4]. According to the World Health Organization (WHO), cervical cancer will kill more than 443 000 people worldwide each year by 2030, and 98% of these deaths will occur in developing countries, particularly in sub-Saharan Africa (SSA) where the HIV epidemic and other risk factors further increase the burden of this cancer [5, 6]. In SSA, HPV and HIV co-infection is commonly found and contributes to a rapid disease progression toward cervical cancer [4]. Importantly, HIV-positive women, especially those who are severely immunocompromised, are 5 times more likely to develop the cervical cancer than their HIV-negative peers.

Even though little is known on HPV genotypes circulating among HIV-infected women in SSA countries, recommendations for HPV vaccination in the population of people living with HIV (PLHIV) are still unclear [7]. Of note, people exposed to HPV are able to eliminate the virus and the viral clearance can last from 12 to 18 months. For 10% of HPV-infected individuals, there is viral persistence that remains at latency. In this frame, immunodeficiency may be the cause of viral persistence and reactivation subsequently [7, 8].

Factors that contribute to HPV infections include: early sexual activity, multiple sexual partners, immunocompromised (HIV essentially), smoking, and prolonged oral contraception [8]. Thus, the primary prevention of cervical cancer by vaccinating girls aged 9 to 14 years with one of the 3 available vaccines (Cervarix, Gardasil-4 or Gardasil-9) before they begin sexual intercourse would theoretically protect them against most HR-HPV infections [9, 10]. This primary prevention, combined with other prevention strategies (secondary and tertiary prevention) already in place in SSA, would be the ideal equation to overcome the high burden of cervical cancer on this continent [11, 12].

A recent study conducted in Chad during the year 2018 showed that the HPV types targeted by the Gardasil-9 prophylactic vaccine were detected in nearly 70% of the study population, and HR-HPV 58 genotype was the most common in the population (22.9%) [10]. In Cameroon, out of 14,000 new cases of cancer reported in 2016, among which cervical cancer occupied the second leading position of cancers among women (23.2%) [10, 13]. These observations are very concerning and suggest a high burden of HPV in these settings where HIV is also highly prevalent [14–16]. Thus, in the light of evidence generated from countries with similar programmatic challenges [17, 18], understanding the burden of HPV among women, its circulating genotypes and the effect of HIV-infection on HPV-positivity within the Cameroonian context, might help in shaping HPV preventive measures according to local realities.

Our study objective was to compare the rate of HPV-positivity according to HIV-serostatus, and to determine other predictors of HPV-positivity.

Methods

Study design and setting

A cross-sectional study was carried-out in 2012 from women attending the General Hospital and the Gyneco-obstetrical Hospital, both located in Yaoundé, the capital city of Cameroon. For all enrolled women, blood and cervical samples were collected. HIV screening tests, CD4 lymphocyte counts, HIV viral load, and HPV genotyping were performed at the Chantal BIYA International Reference Centre for research on HIV/AIDS prevention and management (CIRCB) in Yaoundé, Cameroon (http://circb.cm/btc_circb/web/). Briefly, CIRCB is a reference centre for HIV/AIDS, performing laboratory analysis with external quality controls and proficiency testing for HIV screening (CDC DTS), HIV early infant diagnosis (CDC PT program), CD4 and viral load (QASI, Canada).

Sampling strategy

Following a consecutive non-probabilistic sampling method, a minimum sample size of 272 was required to meet the study outcomes. Consenting women, sexually active, aged 18 years and above, were eligible for the study. However, women who had undergone a total hysterectomy were not considered for inclusion. After consenting, a standard questionnaire was administered to all participants, covering socio-demographic characteristics, gynaeco-obstetrical and reproductive history. Whole blood and cervical samples were collected; cervico-vaginal smear reading was done; HIV screening was performed following a serial algorithm as per the national guidelines, plasma HIV-1 viral load (solely for HIV + cases) was done using the Abbott m2000 RT-PCR platform, enumeration of CD4 T lymphocyte was performed by using the FACS Calibur of Becton Dickinson.

HPV genotyping

For HPV genotyping, the Abbott Real Time HR-HPV test was used. Briefly, viral DNA was extracted and amplified using the Abbott real-time polymerase chain reaction assay, with simultaneous detection and genotyping of HPV 16, HPV 18, and a pooled detection of 12 other HR-HPV genotypes (HPV 31, HPV 33, HPV 35, HPV 39, HPV 45, HPV 51, HPV 52, HPV 56, HPV 58, HPV 59, HPV 66 and HPV 68).

Statistical analysis

Data were collected using Excel 2016, and analyses were performed using Epi-info version 7 and Graph pad prism version 6. Odd ratio (OR) was calculated to determine whether the variable was a risk or protective factor. The confidence interval (CI) for the statistical tests was set at 95%, and the null hypothesis rejected at a 5% threshold. P-values ≤ 0.2 , obtained in uni- or bi-variate analysis, were considered in the multivariate analysis.

Ethics considerations

Ethical clearance was obtained from the CIRCB Ethics Committee (ref N⁰1810), and administrative authorization was provided by the facilities where the study was conducted. Written informed consent was provided by each participant, and results were delivered free of charge to participants for their clinical benefits.

Results

Sociodemographic and bioclinical characteristics of the study population

A total of 278 eligible women were enrolled as participants in this study, giving an enrollment rate of 103% (278/272) according to the required minimum sample size. According to HIV sero-status, 184 women were HIV-seropositive and 94 were HIV-seronegative. The mean age was 37 years $\pm$ 3 years, similar between HIV-seropositive women (36.7 years) as compared to HIV-seronegative women (37.3 years). The most represented age range was [30–39] years (44%). Single women were the most represented (58.88%), followed by married women (28.97%), widows (9.34%), and divorced (2.80%).

Immune status of HIV+/HIV- patients

Women with a normal immunity ($CD4 \geq 500$) were fewer (35.71%) as compared to those immunocompromised ($CD4 < 500$) representing 62.88% of the general population. The overall median [IQR] $CD4$ count was 399 cells/ mm^3 . According to HIV-serostatus, median $CD4$ was lower (354 [231–530 cells] cells/ mm^3) among HIV-seropositive women as compared to their sero-negative peers (414 [IQ 262–918 cells/ mm^3]).

HPV positivity rate and circulating genotypes

Overall, HPV positivity rate was 38.49% (107/278), indicating a high burden of HPV in the study population (Table 1). According to HIV sero-status, HPV prevalence was significantly higher in the group of HIV-seropositive women (43.47% vs. 28.42%, $p = 0.019$), indicating that HIV-infection increasing by about 8 folds more risks of acquiring HPV as compared to those free of HIV (OR: 8.609, 95% CI: 2.841–27,338).

Table 1
HPV positivity according to HIV serostatus

HPV HIV	HPV +	HPV -	Total	P-value
HIV+	80 (43.47%)	104	184	0.019
HIV-	27 (28.42%)	67	95	
Total	107 (38.48%)	171	278	

Diversity of HPV genotypes in infected women

Several HPV genotypes were identified in the study population. interestingly, 74% of women were infected by non-discriminated high-risk genotypes (31, 33, 35, 39, 45, 51, 52, 56, 56, 58 and 11 others) as per the genotyping assay. Surprisingly, only 3% and 4% of the study population were infected soleley with HPV 16 and HPV 18 respectively (Fig. 1).

Factors associated with HPV-infection

Effect of age on HPV-infection

The age range 20–29 years was the most infected by HPV (51.66%). This latter prevalence was significantly higher when compared with that obtained in those aged 40–49 years (25.00%); $p = 0.03$. Overall, HPV positivity decreased as participants grow older (Table 2).

Table 2
HPV positivity by age

HPV Age (years)	HPV+ n (%)	HPV-	Total	P-value
20–29	31 (51.66)	29	60	Ref
30–39	49 (41.52)	69	118	0.20
40–49	16 (25.00)	48	64	0.03
50–75	11 (30.55)	25	36	0.64
Total	107	171	278	

Table 3
HPV Association and Marital Status

HPV Marital status	HPV + n (%)	HPV -	Total	P-value
Single	63 (43.75)	81	144	Ref
Married	31(30.69)	70	101	0.36
divorced	3 (60.00)	2	5	0.04
Widow	10 (35.71)	18	28	0.55
Total	107	171	278	0.32

Effect of marital status on HPV-infection

According to marital status, the highest HPV positivity rate was recorded among divorced women (60%), and this latter prevalence was significantly higher when compared to those that were single ($p = 0.04$).

Effect of immunity on HPV-infection

Participants with poor immune status ($CD4 \leq 500$) had a significantly higher rate of HPV positivity as compared to those with a normal immunity (62.88% versus 35.71% respectively, $p = 0.046$). Interestingly,

the lower the CD4-count, the higher the rate of HPV positivity (Table 4).

Table 4
HPV-infection according to immune status

HPV CD4 (cells/mm ³)	HPV +	HPV -	Total	P-value
500–1600	20 (35.71%)	36	56	Ref
350–499	26 (55.31%)	21	47	0.046
200–350	15 (57.69%)	11	26	0.844
< 200	20 (83.33%)	4	24	0.048
Total	81	72	153	

Effect of HIV viremia on HPV-infection

Overall, HPV positivity seemingly increased with increasing values of viral loads. 42.71% (41/96) with < 1000 RNA copies/ml vs. 66.00% (33/50) with > 1000 RNA copies/ml (OR = 0.384; p = 0.009). However, these increments were not statically significant (Table 5).

Table 5
HPV positivity rates by HIV viremia

HPV Viremia (copies/mL)	HPV+ n (%)	HPV-	Total	P-value
Undetectable	25 (39.68)	38	63	Ref
1.60–2.99 log	25 (49.01)	26	51	0.34
> 3 log	38 (64.40)	21	59	0.12
Total	88	85	173	

Multi-variate analysis on HPV-infection

After adjusting for CD4, viral load and HIV status, only HIV-infection was 12 times more likely to increase the risk of acquiring HPV-infection (p = 0.0001), as shown in Table 6.

Table 6
Multi-variate analyses

Variable	Odds Ratio	Confidence interval 95%		P-value
CD4 : 500–1600	0.7323	0.2211	2.4260	0.6102
CD4 : 350–499	1.4735	0.4490	4.8361	0.5226
VL Undetectable	0.3839	0.1273	1.1580	0.0892
VL 1.60–2.99	0.5316	0.1109	2.5487	0.4295
HIV status	12.5000	4.0000	39.3000	< 0.0001

Discussion

The purpose of our study was to compare the rate of HPV positivity among HIV-positive women with that of HIV-negative women, and to determine predictors of HPV-infection. Out of a sample of 278 women enrolled, the mean age (37 years) mainly represents the most sexually active population and therefore having chronic exposure to sexually transmitted infections, including HPV. These results are similar to those obtained in Chad (mean age of 35 years) [10].

According to marital status, single women were the most represented (58%), a rate above the national proportion published in 2005 by the Central Bureau of Censuses and Population Studies in Cameroon where single women had a percentage of 41.46% [13]. the difference could be explained by changing overtime, as the social realities in the population could justify the increasing rate of single women [13].

The median CD4 count was lower in the frame of HIV-infection (354 versus 414 cells/mm³) in HIV-negative women. Median CD4 obtained in HIV-free population was surprising; however, this could be justified by the fact that these women attending the health facility (likely due to ill-health for some of them) [14–16]. Furthermore, a previous study had shown that CD4 cell levels can also vary in response to stress, smoking, the menstrual cycle, the contraceptive pill, recent physical activity or even the time of day [14].

The HR-HPV positivity rate was 38.48%, with very low rate of vaccine genotypes (3% for HPV mono-infection of genotype 16 and 4% for HPV mono-infection of genotype 18). This suggests that other genotypes are drivers of HPV-infection in the Cameroonian context and need to be depicted among cervical cancer cases, especially in the frame of HIV-infection [13, 17]. Our findings are comparable to those found in Central Africa Republic [18, 19], which suggest a predominance of non-vaccine HR-HPV different from those found in Western Europe and North America [20, 21]. Thus, for better vaccination coverage, the use of Gardasil 9 in SSA may offer optimal protection [9, 10]. Co-infections of several HR-HPV genotypes was also been recorded, similar to previous reports [22]. Multi-infections are often associated with viral persistence, especially if co-present with HPV 16.

HIV is confirmed as a contributing factor to HPV-infection ($p < 0.019$), also confirmed by multi-variate analysis. As expected, women infected with HIV have a weaker immune status [23], which henceforth increases risk of acquiring HPV [20, 24]. This calls for the need to regularly test people with HPV infection for HIV [20].

Younger age are at higher risk of acquiring HPV-infection, likely due to sexual habits [24]. Regarding marital status, divorced women stand at high risk of acquiring HR-HPV. The lack of statistical power limits the interpretation of this finding. Nonetheless, divorced women might be prone to multiple sexual partners, leading to HPV-infection [3, 25, 26]. The lack of synergistic effect between the HIV viral load and HPV-infection simply confirmed that HIV-infection interferes with HPV through immunodeficiency induced by HIV, and not via a direct viral-viral interaction [27–29].

After adjusting the different variables based on a multi-variate analysis, HIV status remains the independent factor associated with the risk of infection with this high-risk oncogenic HPV (12 times higher risk), as previously demonstrated [29, 31].

As study limitation, the reference molecular technique used for HPV detection made it possible to identify only vaccine genotypes 16 and 18. Given the high rate of other genotypes, it becomes essential to characterize this group. This therefore calls for sequencing for a better molecular characterization toward a rational selection of HPV vaccine candidate for the country.

Conclusion

In this sub-population of Cameroonian women, HPV burden appears to be very high, with higher rates of genotypes other than the commonly known 16 and 18. Interestingly, in the event of HIV infection, the risk of HPV-infection becomes higher, favoured essentially by immunodeficiency. The very high proportion of non-discriminative HPV genotypes calls for further studies to delineate the adequacy between the currently unknown genotypes and vaccine candidates (gardasil-4, gardasil-9, or cervarix). This measure is highly urgent to prevent risk of cervical cancer among HIV-infected women.

Abbreviations

AIDS
Acquired immunodeficiency syndrome;
CD4
Cluster of differentiation 4;
CIRCB
“Chantal BIYA” International Reference Centre for research on HIV/AIDS prevention and management
DNA
deoxyribonucleic acid
HIV

Human Immunodeficiency Virus;
HPV
human papilloma virus
HR-HPV
high risk oncogenic Human Immunodeficiency Virus;
LR-HPV
low risk non-Human Immunodeficiency Virus;
PLHIV
People living with HIV;
RT-PCR
real-time polymerase chain reaction
WHO
world health organization

Declarations

Ethics approval and consent to participate

This study obtained ethical clearance from the CIRCB Ethics Committee on the Project N^o 1810 and also authorization from CIRCB where the study was conducted. The participants freely signed informed consent forms, which were written in French and English (with respect to the first language of the participant), while the minor participants provided their assent.

Consent for publication:

Not applicable.

Disclosure statement

Authors declare that they have no financial, personal, or professional interests that could be construed to have influenced this manuscript.

Availability of data and materials

The dataset is available from the corresponding author.

Competing interests

The authors declared that, this study is without conflicts of interests.

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analysis of samples and data has been heavily involved.

Authors' contributions:

All authors read and approved the final manuscript. SMS, MCTT, JF, RK, JT, AN, GN, and AN designed the study. MCTT, ADN, TV, CC, ENJS, AA, AK, and BY analysed and interpreted the data. SMS, JF, RK and MCTT performed the HPV testing. VC and AN managed all aspects of the study in Yaoundé. SMS and JF supervised the performance of laboratory testing. MCTT, JF, and SMS drafted the manuscript.

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Some of these data were selected for a poster presentation at the 13th international Conference on HIV treatment pathogenesis (INTEREST 2019), Accra, Ghana (Reference number Poster 092).

The abstract of this work has been accepted for poster presentation at the 33rd International Papillomavirus Conference to be held in Barcelona, Spain.

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Figures

Figure 1

Distribution of HPV genotypes. HPV: human papillomavirus; others refer to oncogenic HPV other than the 16 and 18 genotypes identified by the molecular detection assay.