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Molecular Genotyping of Human Papillomaviruses (HPV) in HIV+ and HIV− Women in Senegal

Babacar Faye[1,2,3*], Serigne A. A. M. Gueye[1], Jean A. D. Tine[4], Hameth Sarr[1], Alioune Dièye[3]

[1]Laboratory of Molecular Biology, Military Hospital of Ouakam (HMO), Dakar, Senegal
[2]AIDS Program of the Senegalese Armed Forces, Dakar, Senegal
[3]Service of Immunology, Department of Pharmacy, Faculty of Medicine, Pharmacy and Odonto-Stomatology of Cheikh Anta Diop University, Dakar, Senegal
[4]Public Health Unit, Faculty of Medecine, Pharmacy and Odonto-Stomatology of Cheikh Anta Diop University, Dakar, Senegal
Email: *bab_faye@yahoo.fr, *babacar6.faye@ucad.edu.sn

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Abstract

Background: Different studies have demonstrated high prevalence of HPV infection and dysplastic lesions of the cervix in immunocompromised patient such as women living with HIV. Is this high prevalence due to a greater susceptibility to HPV infection, which is known to be frequent in its latent form in women? **Objective:** This study aims to identify HPV genotypes in HIV+ and HIV− women to understand HPV molecular epidemiology in Senegal. **Material and Method:** Endocervical samples from 331 HIV+ and HIV− women, sexually active, were collected. The molecular identification of the 28 genotypes studied (19 HPV-HR and 9 HPV-LR) was carried out after DNA extraction, by multiplex PCR with the Anyplex™ II HPV28 detection kit from Seegene on CFX96™ Bio-Rad machine. The comparisons were made by calculating the p-value and odds ratio with R Studio software (version 4.1.0). The results were considered significant if $p < 0.05$. **Results:** The general prevalence of HPV was significantly higher in HIV+ women with 78.95% vs 64.65% for HPV; 72.18% vs 57.07% for HPV-HR; 57.14% vs 34.34% for HPV-BR ($p < 0.05$). Among the 28 genotypes studied, all were more frequent in HIV+ patients except HPV59, HPV66, HPV68, HPV69, HPV11 and HPV26. The most frequently found genotype was HPV56 and non-vaccine genotypes were among the most frequent. Co-infection was also more frequent in HIV+ women ($p < 0.001$). The study of socio-demographic factors revealed that HIV+ women aged between 35 and 50, married and using contraception were significantly more infected with HPV than the same strata of HIV− women. **Conclusion:** Our results showed that the prevalence of HPV,

HPV-HR and HPV-BR was significantly higher in HIV+ women. Non-vaccine genotypes were among the most found genotypes. Groups of HIV+ women aged between 35 and 50, married and using contraception were significantly more infected with HPV than the same groups of HIV-women.

Keywords

HPV, Prevalence, Genotypes, HIV, PCR

1. Introduction

Human papillomavirus (HPV) infections are caused by a small, non-enveloped, circular DNA virus. Worldwide, HPV is known to be one of the most common sexually transmitted infections (STIs) [1]. Today, more than 200 HPV genotypes are identified based on the nucleotide sequence of the L1 gene, coding for the major capsid protein [2]. These genotypes can be classified according to their cutaneous or mucosal tropism. Mucosotropic HPVs that infect the genital tract are divided into 2 groups, high-risk HPVs (HR-HPVs) including HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and Low-risk HPV (HPV-BR) including HPV6, 11, 13, 40, 42, 43, 44, 54, 61, 70, 72, 81, 89, depending on their association with the development of cervical cancer [3]. Most sexually active women will be infected at some point in their lives, and some are at risk of infection multiple times. The critical contamination period for women is at the very beginning of sexual activity [4].

For about three decades, HPVs have been shown to be the most important agents for the development of cervical intraepithelial neoplasia (CIN) and invasive cervical cancer (ICC) [5] [6]. Cervical cancer is the fourth most common cancer in women worldwide, with approximately 570,000 cases and 311,000 deaths reported in 2018 [7]. Indeed, it is the second cancer on the African continent, and it is on this continent that we find 19 of the 20 countries most affected by the disease in the world [8]. In Senegal, cancer of the cervix is the leading gynecological cancer and accounts for 34% of cancer cases that occur and 30% of cancer-related death cases [9].

HIV-induced immunosuppression may limit the ability of the immune system to effectively clear or control the HPV infection, increasing the risk of developing CIN or cancer in a woman co-infected with HIV and HPV [10]. However, the exact mechanism between HIV-induced immunosuppression, HPV infection and its clinical sequelae has not yet been clearly established.

Many studies suggest that women infected with the human immunodeficiency virus (HIV) have higher rates of HPV infection than non-HIV-infected women and are also at greater risk for persistent infection and progression to malignancy [11] [12].

Approximately 70% of HPV infections clear spontaneously within 1 year and

90% within 2 years; the infection persists in the remaining cases [13]. Although persistent infection with HPV-HR genotypes is not sufficient to cause cancer, it does increase the risk of progression to cancer. Elimination of HPV requires an effective cell-mediated immune response [14]. Therefore, HIV/HPV co-infected individuals may be less likely to clear HPV infections compared to HIV-negative women with HPV and, therefore, will have an increased risk of developing benign warts and malignant tumors.

HPV genotypes, however, differ considerably in their geographical distribution. In sub-Saharan Africa, for example, where two-thirds of the world's HIV-infected population live, HPV genotypes vary by country and HIV status and differ significantly from HPV genotypes seen in other regions of the world [15].

HPV detection and genotyping techniques are essentially based on molecular biology given the difficulty of cultivating HPV routinely. There are many variations on HPV detection formats. Thus, HPVs can be detected in combination without specifying the high-risk genotypes present using generic tests; other partial genotyping techniques detect HPVs in a combined way for the main HR-HPVs with specific identification of HPV16, 18 and sometimes 45. The latest techniques developed are specific, we then speak of complete genotyping. In the latter case, the number of genotypes identified varies from one kit to another. These different detection and genotyping techniques can lead to variations in the predominance of revealed HPV genotypes [16].

To date, there is limited data on the epidemiology of HPV genotypes circulating in Senegal. In the current context of type-specific HPV vaccination and mass screening for cervical cancer, information on prevalence, HPV genotypes, the relationship between HIV and HPV, and their relative contribution to development of the CIN and ICC are of great importance in assisting in the planning of vaccines, the implementation of cervical cancer screening and an effective eradication policy. It is in this context that we proposed to carry out this work with the general objective of participating in the molecular epidemiology of HPV in Senegal by identifying the genotypes in circulation in HIV+ and HIV− women.

2. Material and Method

2.1. Study Type and Population

This prospective, descriptive and comparative study was carried out at the Molecular Biology Laboratory of the Armed Forces AIDS Program at the Ouakam Military Hospital (HMO) Dakar, Senegal from February 2019 to May 2021. The target population consisted of 198 HIV-negative women came to be screened for cervical cancer on the basis of a medical prescription in various health establishments and 133 HIV-positive women followed in the armed forces' program to fight HIV/AIDS. Each woman responded to a survey sheet collecting information on her identity, socio-demographic parameters such as age, marital status, contraception and abortion. To be eligible, women had to be sexually active

and able to undergo a vaginal speculum examination.

2.2. Samples

Endocervical samples were taken using a cytobrush, swabbing the endocervix of 331 women (133 HIV+ and 198 HIV−).

The cytobrush is then introduced into a transport tube of the Abbott multi-sample collection kit (Abbott GmbH Co. KG Max Plank, Germany) and the sample is stored at −80˚C until testing.

2.3. DNA Extraction and Nanodrop Lite Assay

The extraction of viral DNA was done using the Zymo DNA kit™ Research, USA, (https://www.zymoresearch.com) according to the manufacturer's protocol. 200 µl of endocervical sample was used for the extraction. Viral DNA extracts were analyzed using NanoDrop™ Lite [17] to assess its quality and quantity and then stored at −20˚C until the PCR was performed.

2.4. Molecular Genotyping

The molecular analysis was carried out by multiplex PCR with the Seegene Anyplex II HPV28 Detection kit on the CFX96 real-time Biorad machine according to the manufacturer's protocol. The Anyplex II HPV28 Detection method makes it possible to detect 28 HPV genotypes in vitro in cytological fluids or cervical samples. This technique makes it possible to detect genotyping and quantify individually 19 HPV-HR (16, 18, 26, 31, 33, 35, 39, 45, 51, 52,53, 56, 58, 59, 66, 68, 69, 73, 82) and 9 HPV-LR (6, 11, 40, 42, 43,44, 54, 61, 70) by using DPO (double priming oligonucleotide) and TOCE™ (Tagging Oligonucleotide Cleavage and Extension) technology [18], a fragment of the β-globin gene was co-amplified as an internal control.

2.5. Statistical Analysis

Data analysis was performed using the R studio software (version 4.1.0).

The qualitative variables were described with an absolute frequency and a relative frequency in percentage. For the quantitative variables, the means and their standard deviations were calculated.

The chi-square test was used to compare statistical differences with a significance level set at $p < 0.05$. Stratified analyzes made it possible to search for possible confounding factors.

The odds ratios with their 95% confidence intervals made it possible to measure the associated risks.

3. Results

3.1. HPV, HPV-HR, HPV-BR Infection Prevalence and HIV Status

Our study population consisted of 331 women including 133 HIV+ and 198 HIV−.

The HPV infection rate was significantly higher among WLHIV (women living with HIV) compared to HIV− women with 78.95% vs. 64.65% (p = 0.005; OR = 2.05).

HPV-HR prevalence was higher in WLHIV with 72.18% vs. 57.07% in HIV-negative patients. This difference is statistically significant (p = 0.005; OR = 1.95; Table 1).

HPV-BR prevalence among WLHIV was 57.14% versus 34.34% among HIV-negative women. This difference is statistically significant (p < 0.001; OR = 2.54; Table 1).

68.42% of WLHIV against 37.37% of HIV-negative women had multiple infections, *i.e.* harbored at least two HPV genotypes. Multiple infection was correlated with HIV in our study (p < 0.001; OR = 3.63; (Table 1).

3.2. HPV Infection by Age Group and HIV Status

HPV infection was more frequent in WLHIV in all age groups compared to HIV− women. But it is only in the age group [35 - 50 years], that the difference is significant; 75% in WLHIV versus 51.8% in the group of HIV− women (p = 0.003; OR = 2.79; Table 2).

3.3. HPV Infection by Marital Status and HIV Status

HPV carriage was higher among unmarried than married.

However, it is at the level of the married group that HIV+ infection is linked to the level of HPV infection, with a prevalence of 75% among married WLHIV against 60.1% among HIV-married women (p = 0.026; OR = 1.98).

In unmarried women, HPV carriage was higher in HIV+ patients, but there was no correlation with HIV (Table 2).

3.4. HPV Infection According to Contraception and HIV Status

Overall, the frequency of HPV infection was higher in women not using contraception than in women using contraception.

In the group of women under contraception, HIV infection favored HPV carriage, 73.08% of WVVIH against 47.06% in HIV− women carried HPV infection (p = 0.023; OR = 3.05; Table 2).

In the group of women who did not use contraception, HPV infection was slightly higher in HIV+ patients with no correlation with HIV (Table 2).

3.5. HPV Infection According to Abortion and HIV Status

The frequency of HPV infection was substantially identical in the two groups of women who had not had or had undergone at least an abortion.

HIV infection had no influence on HPV carriage regardless of the group. (p > 0.05; Table 2).

3.6. Distribution of HPV Genotypes in the Study Population

The multiplex PCR used is a technique using DPO (double priming oligonucleo-

tide) and TOCETM (Tagging Oligonucleotide Cleavage and Extension) technology which makes it possible to individually detect 28 HPV genotypes. Among the 28 genotypes studied, all were more frequent in WLHIV except HPV59, HPV66, HPV68, HPV69, HPV11 and HPV26. HPV56 was the most common genotype in both groups with 46.62% in FVVIH versus 27.78% in HIV− women.

Table 1. Prevalence and distribution of HPV genotypes according to HIV status.

HPV prevalence		HIV+ patients N = 133 n (%)	HIV− patients N = 198 n (%)	P-value	Odds Ratio
HPV		105 (78.95)	128 (64.65)	0.005	2.05 [1.23 - 3.41]
HPV-HR		96 (72.18)	113 (57.07)	0.005	1.95 [1.21 - 3.12]
HPV-BR		76 (57.14)	68 (34.34)	<0.001	2.54 [1.62 - 4.00]
IM-HPV		91(68.42)	74 (37.37)	<0.001	3.63 [2.27 - 5.78]
HPV-HR genotypes	**HPV16**	27 (20.30)	14 (7.07)		
	HPV18	11 (8.27)	10 (5.05)		
	HPV26	0 (0.00)	0 (0.00)		
	HPV31	11 (8.27)	16 (8.08)		
	HPV33	19 (14.29)	10 (5.05)		
	HPV35	8 (6.02)	3 (1.52)		
	HPV39	9 (6.77)	2 (1.01)		
	HPV45	5 (3.76)	4 (2.02)		
	HPV51	21 (15.79)	4 (2.02)		
	HPV52	12 (9.02)	17 (8.59)		
	HPV53	20 (15.04)	8 (4.04)		
	HPV56	62 (46.62)	55 (27.78)		
	HPV58	17 (12.78)	14 (7.07)		
	HPV59	2 (1.50)	4 (2.02)		
	HPV66	9 (6.77)	24 (12.12)		
	HPV68	15 (11.28)	24 (12.12)		
	HPV69	0 (0.00)	7 (3.54)		
	HPV73	13 (9.77)	9 (4.55)		
	HPV82	24 (18.05)	14 (7.07)		
HPV-BR genotypes	**HPV6**	15 (11.28)	9 (4.54)		
	HPV11	0 (0.00)	1 (0.50)		
	HPV40	4 (3.01)	2 (1.01)		
	HPV42	42 (31.58)	28 (14.14)		
	HPV43	21 (15.79)	10 (5.05)		
	HPV44	11 (8.27)	10 (5.05)		
	HPV54	15 (11.28)	16 (8.08)		
	HPV61	6 (4.51)	5 (2.53)		
	HPV70	13 (9.77)	7 (3.54)		

Table 2. Prevalence of HPV infection according to socio-demographic characteristics and HIV status.

Socio-demographic characteristics		HIV+ patients n (%)	HIV− patients n (%)	P-value	Odds Ratio
Age	[20 - 35[	24/31 (77.42)	38/56 (67.86)	0.345	-
	[35 - 50]	51/68 (75.00)	43/83 (51.8)	0.003	2.79 [1.38 - 5.60]
	≥50	30/34 (88.24)	47/59 (79.7)	0.291	-
Marital status	Not married	47/56 (83.93)	36/45 (80)	0.608	-
	Married	57/76 (75.00)	92/153 (60.1)	0.026	1.98 [1.07 - 3.66]
	Missing data	1	-	-	-
Contraception	Yes	19/26 (73.08)	32/68 (47.06)	0.023	3.05 [1.13 - 8.20]
	No	83/104 (79.81)	96/130 (73.8)	0.285	-
	Missing data	3	-	-	-
Abortion	Yes	49/63 (77.78)	61/96 (63.5)	0.057	-
	No	54/69 (78.26)	67/102 (65.7)	0.076	-
	Missing data	1	-	-	-

HPV26 was not found and HPV69 and HPV11 were only present in HIV-seronegative women (Table 1).

Among HR-HPV, apart from HPV56, HPV16, HPV82, HPV51, HPV53 and HPV33 were the most frequent in WLHIV. In HIV-negative patients, HPV66, HPV68, HPV52, and HPV31 were more common (Table 1).

Among HPV-BR, HPV42, HPV43, HPV6, and HPV54 were more common among WLHIV and among HIV-negative women, HPV42, HPV54, HPV43, and HPV44.

HPV16 and HPV18 had respective prevalence of 20.30% and 8.27% among WLHIV and 7.07% and 5.05% among HIV-women (Table 1).

4. Discussion

The frequency of HPV as well as high-risk genotypes (HPV-HR) and low-risk genotypes (HPV-BR) were significantly higher among HIV-positive women in our study population ($p = 0.005$ for HPV, $p = 0.005$ for HPV-HR and $p < 0.001$ for HPV-BR). Our results are consistent with many previous studies reported in the literature. Indeed, a study conducted in Senegal in 2013 by Hanisch *et al.* described similar results [19]. The same trends were found in a study conducted among 630 Nigerian women in 2018 [20]. Similarly, in the meta-analysis conducted by Gui Liu *et al.*, HIV was also associated with a HPV infection [21].

This higher frequency of HPV infection in HIV-positive women is thought to be due to HIV-induced immunosuppression and the potential for latent virus reactivation due to HIV-associated immunosuppression. HIV+ women carrying HPV would be more susceptible to the persistence of HPV and to a risk of adverse cervical events, in particular those who are immunocompromised. Indeed,

HIV-positive women have been shown to have both higher rates of CIN frequency and persistence of low-grade lesions [22] [23].

Regarding multiple HPV infections, we found an association between multiple infections and HIV ($p < 0.001$). In our study population, HIV+ women had a 3.63 risk of being infected with multiple HPV genotypes compared to HIV-negative women. Another conducted in Senegal in 2019, among sex workers had described similar results [24]. Moreover, *Rousseau et al*., in their study conducted among women in Burkina Faso, also found multiple infections more frequent in HIV-positive women with a risk of 2.45 [25]. Also, in a systematic review conducted in sub-Saharan Africa, multiple infections were also more frequent in HIV-positive women ($p < 0.001$) [26].

These multiple HPV infections, which are more frequent in HIV-positive women, are thought to be caused by the reduction in HPV clearance following HIV-induced immunosuppression. This decrease in the elimination of HPV viruses would favor the accumulation of different HPV genotypes, hence a more frequent multiplicity of infections in HIV-seropositive women.

Of all the genotypes studied, HPV56 was the most common genotype in both groups. Among HR-HPV, this genotype was followed in decreasing order of frequency by HPV16, HPV82, HPV51, HPV53, and HPV33 in HIV-infected women and by HPV66, HPV68, HPV52, HPV31, and HPV16 in HIV-negative women.

Consistent with our findings, HPV56 was also the most prevalent genotype among HIV-positive and HIV-negative Kenyan women in the study by Maranga *et al.* in 2013 [27]. In 2 other studies in HIV-positive women, conducted in Brazil by Badial *et al.* and in New York by Luque *et al*., HPV56 was also the most common genotype [28] [29]. However, our results differ from those of other studies conducted in Senegal. Indeed, Diop *et al*., found HPV52 as the most prevalent genotype in a study conducted on Senegalese sex workers [24]. Moreover, in another study conducted in Senegal, HPV58 was the most common [19].

In our study population, we found that HPV16 and HPV18 vaccine genotypes had a high prevalence; these two genotypes hold the attention of because of their strong implication in cervical cancers. Hanisch *et al.* in Senegal found relatively lower prevalence for HPV16 (sixth position) and HPV18 (ninth position) [19]. This observation is also found by another study conducted in Senegal [30]. Our results are not different from those of other studies in Africa which note that HPV-HR non-16 and non-18 genotypes were the most frequent in HIV-infected women [31] [32]. However, they contrast with results from other studies of HIV-infected women and HIV-negative women, in whom HPV16 and HPV18 generally predominate [33] [34].

Regarding HPV-BR, HPV42 was most prevalent in both groups followed by HPV43, HPV54, HPV6 and HPV70 in HIV positive women and HPV54, HPV43, HPV44 and HPV6 in HIV negative women. In another study conducted in Senegal, the most common HPV-BRs in HIV-positive women were HPV61, HPV62, and HPV54, and in HIV-negative women, the most common were

HPV54, HPV61, and HPV62 [19]. Another study conducted in Kenya among HIV-positive and HIV-negative women showed HPV44, HPV43, and HPV42 to be most prevalent among HIV-positive women and HPV42, HPV11, and HPV40 were most common among HIV-negative women [27]. These data are consistent with the results obtained in our study. Like HPV-HR, we also found that the most frequent HPV-BR were different genotypes from HPV6 and HPV11.

These differences described in the distribution of HPV genotypes can be explained by a geographical variation of genotypes according to the zones. In the same area, these differences can be explained by the diversity of the population subgroups targeted in the studies [15] [16]. Finally, and above all, they can be explained by the difference in the molecular genotyping techniques (panels of genotypes sought, sensitivity, specificity) used in the studies. Indeed, our detection technique with the Seegene Anyplex II HPV28 kit is highly sensitive and allows the detection and identification of 28 HPV genotypes.

Since current vaccines primarily target HPV16, HPV18, HPV6, and HPV11, a high frequency of other high-risk and low-risk genotypes could infer additional risk of non-16 and non-18 cervical carcinogenesis and benign lesions due to different genotypes of HPV6 and HPV11. Therefore, the results of our study could provide additional information on HPV molecular epidemiology for the development of HPV vaccines targeting circulating genotypes.

The study of socio-demographic factors allowed us to find that HIV-positive women with an age between 35 and 50 years old, married HIV-positive women and HIV-positive women using contraception were significantly more infected with HPV compared to the same strata of HIV-negative women. Abortion was not associated with a higher frequency of HPV infection among HIV-positive women in our study.

Our results are similar to those found by Dols *et al.* with an average age of HIV-positive women infected with HPV of 35.4 years in South Africa and 40.5 years in Tanzania [35]. In another study involving 282 HIV-positive women in Cameroon, those aged 26 - 59 tended to have a higher prevalence of precancerous lesions than other women [36]. However, in another study conducted in Senegal, HPV infection was more common in HIV-positive women under 35 years of age [19].

According to Delfraissy, the passage from primary HIV infection to the stage of AIDS, corresponding to the most profound state of immunosuppression, can last between 10 and 15 years [37]. This could explain the significant exposure to HPV infections found in this advanced age group, which would correspond to a more in-depth immunosuppression of these HIV-positive women. The level of HPV infection is higher in unmarried women (single, widowed and divorced) than in married women. The hypothesis would be that the higher multipartnership in the group of women living alone would favor sexually transmitted infections.

With regard to contraception, other studies found confirm our results. A study in Brazilian women infected with HIV associated the use of oral contraceptives with HPV infection [38]. Jamieson *et al.* have also associated contraceptive use with HPV infection among HIV-positive women in the United States [31]. Contraceptives can cause changes in the genital area. These modifications could lead to a facilitation of HPV infections or a reactivation of latent infections, especially in immunocompromised women. This could explain the high frequency of HPV infections in this group of women.

In our study, HIV-positive women with a history of abortion were not significantly more infected. The same observation is found with the study by *Musa et al.* in HIV-infected women in Nigeria [39].

An increase in our sampling would strengthen our results in both groups and epidemiological surveillance of HPV would take this aspect into account.

5. Conclusion

Our results showed that seropositive women were more infected by total HPV, high-risk HPV and low-risk HPV. HIV-positive women aged between 35 and 50 years old, married and using contraception were significantly more infected with HPV than the same strata of HIV-negative women. They were also more likely to harbor multiple HPV genotypes. High-risk, non-16 and non-18 HPV genotypes have been detected in HIV-infected women and even in HIV-negative women.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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