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High Prevalence of High-Risk Human Papillomavirus Genotypes Other Than HPV-16 and HPV-18 in Congolese Women Living With HIV: Implication for Cervical Cancer Prevention in a Resource Limited Setting

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ABSTRACT

Background: Despite the undeniable benefits provided by antiretroviral therapy (ART) in drastically reducing AIDS-related mortality, women living with HIV (WLWH) are disproportionately affected by high-risk Human Papillomavirus (HR-HPV) infection and cervical cancer. We herein assessed the distribution of HR-HPV genotypes according to HIV immunovirological prognostic parameters and their implications for the prevention of cervical cancer.

Methods: Among 276 screened WLWH on ART attending the HIV outpatient treatment clinic in Brazzaville, in the Republic of Congo, 122 tested positive for HR-HPV (mean age: 43.92 ± 9.98 years) were included in a cross-sectional study. Sociodemographic and clinical information were collected and CD4+ T cells count and HIV RNA load were determined. HR-HPV genotypes distribution was determined from cervicovaginal samples using the ABBOTT Real Time High Risk HPV kit (Abbott, Chicago, USA).

Results: A total of 122 (44.4%) WLWH were tested positive for any-HR-HPV, including 73.8% of HR-HPV genotypes other than HPV-16/HPV-18, while HPV-16 (14.7%) and HPV-18 (11.5%) were less frequently detected. Overall, nor CD4+ T cells count, HIV-1 RNA load or the duration of HIV diagnosis did have a significant impact in the distribution of HR-HPV genotypes in WLWH positive for cervical HR-HPV infection. However, around half of all HPV-16 infections occurred in women with the highest CD4+ T cells count (≥500 CD4+ T cells/µL). On the other hand, women with lower CD4+ T cells count (200 to 349 cells/µL) were more likely to carry HPV-18 DNA and HR-HPV genotypes other than HPV-16.

Conclusion: WLWH in Brazzaville in the Republic of Congo are largely infected by HR-HPV genotypes other than HPV-16 and HPV-18, suggesting a possible reduced predictive efficacy of HPV vaccine in this population. A secondary prevention with a regular screening for cervical pre-cancerous lesions should be prioritized in WLWH living in Brazzaville, in the Republic of Congo.

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Introduction

Cervical cancer is the most frequently detected cancer in women living with HIV (WLWH) and is classified as an AIDS-related disease [1]. Thanks to the accelerated access to antiretroviral therapy (ART) in the last decades AIDS-related mortality has declined considerably, and life expectancy of people living with HIV (PLWH) now approaches that of those without HIV [2]. As a result, the number of WLWH has increased up to 6 times in the last 30 years to reach 20 million in 2022, and around 60% of these women are living in sub-Saharan Africa (SSA) [3]. As their life expectancy increase, the risk of developing cervical cancer also rise in WLWH [1,2]. Nearly 5% of all cases of cervical cancer worldwide are attributable to HIV, and the large majority of WLWH that also suffer from cervical cancer are living in SSA,

pointing out the major contribution of HIV to the cervical cancer burden in SSA [4-6].

Indeed, HIV infection had been associated in promoting the persistence of high-risk carcinogenic Human Papillomavirus (HR-HPV) infection which is the main cause of cervical cancer [5, 6]. The severe immunodeficiency induced by HIV infection in people experiencing AIDS or those without AIDS but not optimally responding to ART, has been linked to HR-HPV infection and cervical cancer [7-9]. For instance, in a recent study conducted in a large cohort of WLWH recruited from several countries in SSA, Chachage et al have shown that low CD4+ T cells count (below 200 cells/µl) substantially increased the risk of having HR-HPV in WLWH [9]. In addition, other studies also pointed out high HIV RNA load in virological non-responders as an independent risk factor associated with persistent HR-HPV infection and cervical cancer [7,8]. Although the perturbed immune response induced by HIV is globally linked to HR-HPV infection and the progression to cervical cancer, less is known about the possible relationship between the status of the immune system (as reflected by the immunovirological parameters including the CD4 T cells counts and HIV RNA load) and the distribution of specific HR-HPV genotypes in WLWH. In most sub-Saharan African setting, HPV-16 and HPV-18 are the genotypes the most frequently detected in cervical cancer cases in WLWH [9-11]. These findings would roughly suggest that WLWH carrying HPV-16 and HPV-18 might have a more increased risk for progressing to cervical cancer compared to WLWH carrying other high-risk genotypes. However, several studies have also highlighted the high prevalence of HR-HPV other than HPV-16 and HPV-18 in African WLWH with or without cervical cancers [10-14]. But it is still unclear if the differential distribution of these HR-HPV genotypes would be associated to the HIV-related perturbed immune system of these African WLWH. HIV infection had been reported to selectively affected CD4 T cells immune response specific to HR-HPV genotypes such as HPV-16 in women with cervical abnormalities [15, 16]. Such findings might explained, at least partially why HPV-16 is commonly detected in cervical cancers in WLWH compared to other HR-HPV [9]. It would also be interesting to see if these HIV immunovirological parameters, easy to measure in resource limited settings, could provide information on the risk of infection by specific HR-HPV genotypes in WLWH attending HIV healthcare facilities.

In the Republic of Congo, very few data exist on the HR-HPV genotypes distribution in WLWH [13]. In a sample of WLWH never screened and vaccinated against HR-HPV, attending the HIV outpatient clinic of Brazzaville, the Capital City of the Republic of Congo, we have assessed the relationship between HIV-1 immunovirological prognostic parameters including the CD4+ T cells count, HIV RNA load and the duration of HIV diagnosis, and the distribution of HR-HPV genotypes.

Methods

Study Design and Population

From April 2021 to March 2022, a total of 276 adult (18 years and older) WLWH not-vaccinated and never having being tested for HPV infection, and seeking for ART at the HIV Outpatient Treatment Clinic (OTC) of Brazzaville, the Capital City of the Republic of Congo, were approached to be screened for cervical HR-HPV infection, and signed a consent form. The OTC is the main health care facility specialized in prevention and treatment of HIV infection and AIDS-related illnesses. The flow chart of the Figure 1 depicts the recruitment procedure of the women in the study.

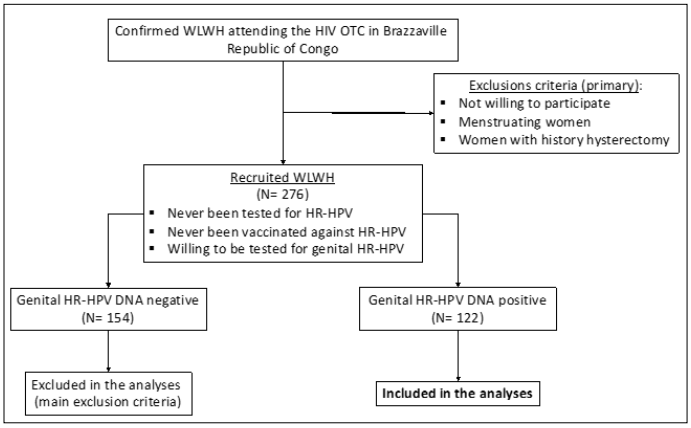

Figure 1: Flow Chart of The Recruitment Procedure of Women Living with HIV with Positive HR-HPV Test Attending the HIV Outpatient Treatment Clinic of Brazzaville, The Capital City of The Republic of Congo

Briefly, among the 276 screened WLWH, those tested positive for HR-HPV infection were included in the cross-sectional study. Inclusion criteria were having a confirmed HIV infection status, aged 18 years or older, having a positive HR-HPV genotyping test result, having a patient record at the HIV OTC with well documented follow-up of HIV parameters including CD4+ T cells counts, HIV RNA load, and the duration since HIV diagnosis, and willing to participate to the study. Menstruating women and those with a history of total hysterectomy were not included in the study.

Data Collection and Biological Sampling and Processing

After signing the consent form, a standardized questionnaire was administrated by a clinician to WLWH to collect sociodemographic and clinical information. Then the recruited women underwent a blood draw to determine the CD4+ T cells counts using BD FACS PrestoTM (BD Biosciences, NJ, USA) and plasma HIV-1 RNA load using the GeneXpert viral-Load HIV-1 system (Cepheid, CA, USA), with a limit of detection of 40 copies/ml [17].

On the other hand, the screened women also had a cervical sampling using the Cervi-Collect specimen kit® (Abbot, Chicago, USA) according to the manufacturer instructions. Briefly, the sterile cytobrush included in the kit® was rotated 3 times on the layers of the endocervical mucosa before being discharged onto the collection tube containing the conservation and transport medium. The collected cervical specimens were then store at -20°C before being transferred using ice packs to the National Laboratory for Public Health (NLPH) for HR-HPV testing and genotyping.

High-Risk Human Papillomavirus Detection and Genotyping

HR-HPV DNA was detected from cervical samples using the real-time PCR system from the ABBOTT RealTime High Risk HPV kit m2000sp, m2000rt, m24sp (Abbott, Chicago, USA) [18]. From extracted total DNA, the Abbott RealTime High Risk HPV kit allows the simultaneous detection and genotyping of HPV-16, HPV-18, and pooled detection of 12 other HPV genotypes including HPV-31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68). Therefore, a HR-HPV infection was defined as the presence of at least one HR-HPV genotype in the tested samples.

Statistical Analyses

The data collected was reported on the Microsoft Excel 2016© spreadsheet (Microsoft, Redmond, Washington, USA). Data processing and statistical analyses were carried out with IBM

SPSS Statistics 25 software (IBM, SPSS Inc., Armonk, New York, USA). Quantitative variables were expressed as mean with standard deviation and median with inter quartiles. Qualitative variables were expressed in absolute and relative frequencies. The Pearson Chi-square test or Fisher Exact test were used for comparison of proportions. The significance threshold was set at a *p-value* less than 0.05.

Ethical Consideration

This study was conducted in accordance with the Declaration of Helsinki for studies involving human subjects, and approved by the Ethics Committee for Research in Health Sciences (CERSSA) issued under the number 228/MRSIT/IRSSA/CERSSA of September 20, 2019. Written informed consent was obtained for all women included in the study.

Results

Sociodemographic and Clinical Characteristics of the Study Population

From the 276 women screened for HR-HPV DNA, 44.2% [n=122; mean age: 43.92 ± 9.98 years (range: 19-71 years)] were tested positive for genital HR-HPV infection and included in the study. The sociodemographic and clinical characteristics of the included WLWH are summarized in the Table 1. Globally, the included women tested positive for genital HR-HPV DNA were mostly aged above 40, with around half of them (46.7%) aged 40-49 years old, and 20.5% belonging to the 50-59 age range. More than half of these women (59.8%) were single or in cohabitation relationship (30.3%), and none of them were married at the time of the inclusion. Less than one quarter (16.4%) of the study participants reached the university education level, while the majority of them reached only the high school education level (62.3%), and 20.5% had only elementary education level.

Table 1: Sociodemographic and Clinical Characteristics of the 122 Women Living With HIV and Positive for Genital HR-HPV Infection.

N=122 WLWH	n (%)
Age range (years)	
<20	1 (0.8)
20-29	9 (7.4)
30-39	23 (18.9)
40-49	57 (46.7)
50-59	25 (20.5)
>60	7 (5.7)
Marital status	
Single	73 (59.8)
Divorced	5 (4.1)
Bride	5 (4.1)
Cohabitation	37 (30.3)
Widow	7 (5.7)
Level of education	
None	1 (0.8)
Elementary	25 (20.5)
High school	76 (62.3)
University	20 (16.4)
Duration of antiretroviral therapy (years)	
<11	60 (49.2)
≥ 11	62 (50.8)
Antiretroviral regimen	
First line	83 (68.0)
Second and third line	39 (32.0)
Duration of HIV (years)	
≤ 10	50 (41.0)
>10	72 (59.0)

Human Papillomavirus Detection and Genotyping

Overall, 44.2% (n=122) of the screened WLWH were diagnosed positive for HR-HPV DNA. The Figure 2 depicts the distribution of HR-HPV genotypes within the study population. The three-quarter (73.8%) of WLWH positive for HR-HPV DNA carried exclusively non-HPV16/HPV-18 genotypes. The genotype HPV-16 was detected in 14.7% (18/122) of women, corresponding to 8.6% of HPV-16 mono-infection and 6.6% of infection containing HPV-16 and other HR-HPV genotypes. The genotype HPV-18 accounted for 11.5% (14/122) of all HR-HPV, 6.6% corresponding to HPV-18 mono-infection and 4.9% of infection containing HPV-18 and other HR-HPV genotypes (Figure 2).

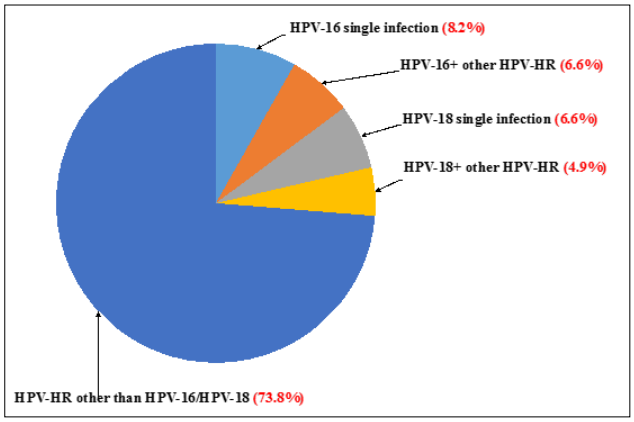

Figure 2: Distribution of HR-HPV Genotypes in 122 WLWH Tested Positive for HR-HPV DNA

Human Papillomavirus Genotypes Distribution and HIV-1 Immunovirological Prognostic Parameters

The distribution of HR-HPV genotypes was then assessed according to HIV-1 immunological and virological prognostic parameters including CD4+ T cells counts, HIV-1 RNA load as well as the duration of HIV diagnosis, and the results are presented in the Table 2.

Table 2: High-risk Human Papillomavirus Genotypes Distribution According to Immunovirological Parameters of WLWH

	HPV-16 (n=10)	HPV-16 +other HR-HPV (n=8)	HPV-18 (n=8)	HPV-18 +other HR-HPV (n=6)	Non-HPV16/ HPV-18 (n=82)	*P-value*
CD4 T cells counts (cells/ml) [n (%)]						
<200	0 (0.0)	1 (12.5)	1 (12.5)	1 (16.7)	8 (9.0)	0.969
200-349	4 (40.0)	2 (25.0)	3 (37.5)	3 (50.0)	36 (40.4)	
350-499	2 (20.0)	1 (12.5)	1 (12.5)	1 (16.7)	19 (21.3)	
≥500	4 (40.0)	4 (40.0)	3 (37.5)	1 (16.7)	19 (21.3)	
HIV RNA load [n (%)]						
Detectable	1 (10)	3 (37.5)	2 (25.0)	0 (0.0)	18 (20.2)	0.476
Indetectable*	9 (90.0)	5 (62.5)	6 (75.0)	6 (100.0)	71 (79.8)	
HIV duration in years [n (%)]						
2-7	2 (20.0)	1 (12.5)	1 (12.5)	3 (50.0)	24 (26.7)	0.692
8-12	1 (10.0)	2 (25.0)	3 (37.5)	2 (33.5)	29 (32.2)	
13-17	5 (50.0)	4 (50.0)	2 (25.0)	1 (16.7)	27 (30.0)	
>17	2 (20.0)	1 (12.5)	2 (25.0)	0 (0.0)	10 (11.1)	

*A woman was considered undetectable when her plasma HIV RNA load was below the detection limit of the quantification method (<40 copies/ml) [17].

HIV: Human Immunodeficiency Virus; HPV: Human Papillomavirus; RNA: Ribonucleic Acid

Overall, nor CD4+ T cells count, HIV-1 RNA load or the duration of HIV diagnosis did have a significant impact in the distribution of HR-HPV genotypes in WLWH positive for cervical HR-HPV infection. When regarding the distribution of HPV-16, while around half (44.4%; 8/18) of all women positive for HPV-16 DNA had a CD4+ T cells count above 500 cells/μL, only one woman with a CD4+ T cells count below 200 cells/μL was positive for HPV-16. One-third (33.3%; 6/18) of HPV-16 infection were detected in women with a CD4+ T cells count ranging between 200 and 349 cells/µL. In addition, the majority of women positive for HPV-16 (77.7%; 16/18) had indetectable HIV-1 RNA load, and half of all HPV-16 infection occurred in women with a HIV infection lasting between at least 13 and 17 years old. Regarding HPV-18 distribution, the group of women with a CD4+ T cells count between 200 and 349 cells/µL (42.8%; 6/14) were the most infected. While severe immunocompromised women (<200 CD4+ T cells/μL) accounted for one-quarter (14.3%; 2/14) of all HPV-18 infection, 28.6% (4/14) of HPV-18 infection occurred in women with the highest CD4+ T cells counts (≥500 CD4+ T cells/μL). Similar to what was observed for HPV-16, the majority (85.7%; 12/14) of all HPV-18 infections occurred in women with indetectable HIV-1 RNA load, only two women harbored a HPV-18 mono-infection. While, HPV-18 infection was relatively well distributed in all the sub-groups of HIV duration, the group of women with at least 8 to 12 years of HIV infection was the most infected by HPV-18 (35.7%; 5/14). For infections caused by HR-HPV genotypes other than HPV-16 or HPV-18, around half (40.4%; 36/82) of these infections occurred in women with a CD4+ T cells count ranging in 200-349 cells/µL. Severe immunocompromised women had the lowest infection rate (9.0%; 8/82), and around one-quarter (21.3%; 19/82) of women with the highest CD4+ T cells count (≥500 CD4+ T cells/µL) carried exclusively non-HPV16/

HPV-18 HR-HPV genotypes. Similar to what observed for HPV-16 and HPV-18, the majority (79.8%; 71/82) of non-HPV16/HPV-18 HR-HPV infections occurred in women with indetectable HIV-1 RNA load. Finally, although relatively well distributed in all the sub-groups of HIV duration, the group of women with at least 8 to 12 years of HIV infection was the most infected by non-HPV16/HPV-18 HR-HPV (32.2%; 29/82).

Discussion

We herein report on the distribution of HR-HPV genotypes according to the HIV immunovirological prognostic parameters in a series of adult WLWH non-vaccinated and never screened for HPV infection and living in Brazzaville, the Capital city of the Republic of Congo. Overall, almost half (44.4%) of WLWH screened were positive for cervical HR-HPV DNA, with the large majority (73.8%) corresponding exclusively to HR-HPV genotypes other than HPV-16 and HPV-18. Cervical infections with HPV-16 (14.7%) and HPV-18 (11.5%), were less frequent in WLWH living in Brazzaville. In that cross-sectional series, we were not able to uncover any significant association between a specific HR-HPV infectious profile and the HIV-1 prognostics parameters, especially HIV-1 RNA load or HIV infection duration. However, we found a trend of a pattern in the distribution of HR-HPV genotypes according to the status of the immune system of these women. Indeed, around half of all genital HPV-16 infections occurred in women with the highest CD4 T cells count (≥500 CD4+ T cells/μL), while in women with the most severe immunosuppression (<200 CD4+ T cells/μL), only one carried genital HPV-16 DNA. On the other hand, it was mostly women with very low to medium CD4+ T cells count (200 to 349 cells/μL) who were more likely to carry HPV-18 DNA and also genital infection with HR-HPV genotypes other than HPV-16. These results could suggest that despite HIV infection, a relatively competent immune system (≥500 CD4+ T cells/μL) could protect against infections by non-HPV-16 HR-HPV genotypes, and this immune protection against non-HPV-16 genotypes would decline with CD4+ T cells depletion. Unlike non-HPV-16 genotypes, during HIV infection, the immune protection against HPV-16 would not be optimal, even at relatively high CD4+ T cells count (≥500 CD4+ T cells/μL). In other words, while the immune protection against non-HPV-16 genotypes appeared to be strong, requiring a strong depletion of CD4+ T cells to be lost, the immune protection against HPV-16 appeared to be more labile and overwhelmed very early, despite relatively good CD4+ T cells counts. Additional studies are required to be able to better identify the specific components of the immune response involved in the protection against these HR-HPV genotypes. Restoring this specific immune response could pave the way towards the establishment of a therapeutic vaccine against HR-HPV infection and cervical cancers.

In this series of adult WLWH in Brazzaville, in the Republic of Congo, we found a high prevalence (44.4%) of genital HR-HPV infection, with HR-HPV genotypes other than HPV-16 and HPV-18 predominantly represented (73.8%), while HPV-16 (14.7%) and HPV-18 (11.5%) were less frequently detected. In a recent study conducted in Brazzaville and the Plateaux department in the Republic of Congo in which 18% of the included women were HIV-positive, 83.1% of WLWH were positive for HR-HPV infection (84.4% and 80.9% for Brazzaville and the Plateaux department, respectively). This difference in the prevalence of HR-HPV infection within the same area might be explained, at least partially by the fact that our study population was older (mean age: 44.7 years, with almost 40% aged above 45 years) than women from the report of Tsimba Lemba et al (mean age: 37.8 years; range, 18–63) [13]. Indeed, younger age is well-known to be associated to high frequency of HR-HPV infection [19]. In line with our findings, Tsimba Lemba et al. have also reported high frequency of HR-HPV genotypes other than HPV-16/HPV-18 in HIV-positive women, with HPV-56 (22.6%) being the most frequently detected genotype, followed by HPV-16, HPV-45, HPV-51, HPV-52, HPV-56, and HPV-68 (20.7%) HPV-18 (11.3%) was less frequent [13]. A study conducted in Cameroon, a neighboring country, Tagne Simo et al. also reported a similar HR-HPV distribution profile with HPV-33 (75.5%) being the most detected, even though HPV-16 (22.5%) was still well represented, while few women were positive for HPV-18 (5.8%) [20]. In Ghana, in west Africa, Akakpo et al. found that around half (42.7%) of tested WLWH were positive for HR-HPV DNA, with HPV-59 representing more than half (50.4%) of the HR-HPV positive women, HPV-16/and or HPV-18 (37.5%) and other HR-HPV genotypes such as HPV-35 (26.2%), HPV-58 (17.0%) and HPV-45 (14.9%), were also well represented, but at lower levels [14]. The high frequency of HR-HPV genotypes in WLWH attending the HIV OTC of Brazzaville support the need for joining screening for cervical pre-cancerous lesions to the current regular HIV care service provided to WLWH living in Brazzaville, in the Republic of Congo.

In our analysis, according to the status of the immune system, we found that the distribution of HR-HPV genotypes tended to define a pattern, with women with low CD4+ T cells counts (200 to 349 cells/μL) tending to be more infected with HR-HPV other than HPV-16/HPV-18, while most of HPV-DNA positive women had the highest CD4+ T cells counts (≥500 CD4+ T cells/μL). Even though these associations were not significant, our findings are globally in line with what is commonly known about the influence of HIV on the pathogenesis of HR-HPV [5-16]. Globally, HIV-induced CD4+ T cells depletion had been well documented to be associated with increase proportion of HR-HPV infection compared to HIV negative women [7-16]. Cervical HR-HPV specific CD4+ T cells response has also been shown to mirror the CD4+ T cells depletion occurring in peripheral blood during HIV, suggesting globally that locally, mucosal CD4+ T cells might have a pivotal role in the protection against genital infection by HR-HPV genotypes [15]. More specifically, our results suggest that HIV could have a selective impact on the specific immune response, depending on HR-HPV genotypes. HPV-16 specific immune protection would be more labile, as good immunological responders (≥500 CD4+ T cells/μL) were more likely to carry HPV-16 DNA, while cervical immune protection against HR-HPV other than HPV-16/HPV-18 might be more robust and requiring a strong immune depletion to be lost, as immunological non- or weak-responders (200 to 349 cells/μL) carried preferentially HR-HPV other than HPV-16. Similar findings in favor of a selective effect of HIV on the HR-HPV specific immune response according to the HR-HPV genotypes have also been reported [15,16]. Indeed, in line with our assumptions, Mbuya et al. highlighted in a series of WLWH a low immune response against HPV-16 oncoproteins compared to oncoproteins from other HR-HPV genotypes, indicating a more pronounced loss or dysfunctional response toward HPV-16 [16]. However, as in their study, our observations are also based on systemic CD4+ T cells rather than mucosal locally resident HR-HPV specific CD4+ T cells. Therefore, further studies focused on mucosal HR-HPV specific cervical resident T cells in WLWH would improve our understanding on the effect of HIV on the pathogenesis of HR-HPV. By identifying components (T cells or innate immune cells) of the

immune response, specific to the various HR-HPV genotypes, which is lost or perturbed during HIV infection, could guide us designing a vaccine able to induce a more targeted immune response, more suitable for people living with HIV.

Our study has limitations, in particular its cross-sectional design did not allow us to better evaluate the impact of HIV infection on the persistence of HR-HPV infection. Furthermore, the Abbott Real Time High Risk HPV kit did not allow us to better discriminate between genital infection caused by HR-HPV genotypes other than HPV-16 and HPV-18. This limitation would have hide the preponderance of a particular HR-HPV genotype. On the other hand, it may also have overestimated the frequency of HR-HPV genotypes other than HPV-16 and HPV-18, making these two genotypes appeared less frequent.

In conclusion, our study showed that WLWH in Brazzaville in the Republic of Congo are largely infected by HR-HPV genotypes other than HPV-16 and HPV-18. These findings would suggest a possible reduced predictive efficacy of HPV vaccine in this population. Therefore, secondary prevention with a regular screening for cervical pre-cancerous lesions should be prioritized in WLWH living in Brazzaville, in the Republic of Congo.

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