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The Similarities and Differences of Anal High-Risk HPV Infection in HIV-Positive Women and Men

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Abstract

The incidence of HPV-related anal cancer keeps increasing in the Post-Antiretroviral Therapy (ART) era. It preferentially affects women, and most of the new cases come from certain high-risk groups, including Men who have Sex with Men (MSM) and HIV-positive (HIV+) individuals, especially HIV+ women. We recently conducted a single-institutional retrospective study focusing specifically on the similarities and differences in high-risk HPV (hrHPV) infection and their clinicopathologic correlation between HIV+ women and HIV+ men. We found that both HIV+ women and HIV+ men have a significantly higher rate of hrHPV infection than their HIV-negative (HIV-) counterparts do, suggesting a synergistic relationship between HIV and hrHPV. Infection with other high-risk HPVs (ohrHPV) is much more common than the infection with HPV16 or 18. In addition, the hrHPV infection in HIV+ women and men possesses genotype profiles of greater complexity and a significantly higher rate of coinfecting with hrHPVs of multiple genotypes than their HIV- counterparts do. Our data strongly suggest that HPV16 is the most oncogenic subtype. Coinfection with more than one genotype of hrHPV, especially when one of them is HPV16, significantly increases the risk of developing a High-grade Squamous Intraepithelial Lesion (HSIL). In comparison with HIV+ men, HIV+ women have different hrHPV genotype profiles and higher rates of high-grade lesions. In this review, we summarized our findings and compared them with other recently published studies. We believe these results have important implications for developing more effective vaccination and surveillance guidelines.

Keywords: Anal cancer; HIV; Human papillomavirus

Introduction

The incidence of anal cancer has been steadily increasing over the past four decades, especially in developed countries. Most of the new cases come from certain high-risk groups such as HIV positive (HIV+) individuals, Men who have Sex with Men (MSM), and individuals with HPV-related cervical lesions. There are over 37.7 million HIV/AIDs patients globally, including 1.2 million in the United States. The introduction of Antiretroviral Therapy (ART) has significantly decreased the risk of infection-related deaths in individuals with HIV/AIDS; however, the morbidity and mortality of HIV-related malignancies remain elevated. Because HIV infection can cause persistent HPV infection, it is associated with a 40- to 80-fold higher risk of developing anal cancer [1,2]. Without treatment; the overall five-year survival rate is only ~69%.

Because MSM is one of the strongest risk factors for HPV-related anal cancer, most studies on HPV-related anal squamous lesions have focused on MSM or HIV+ men. Nonetheless, anal cancer still preferentially affects women. From 1999 to 2015, the prevalence of anal cancer increased 2.1% per year for men and 2.9% per year for women [3]. In 2022, ~67% (6,290 of 9,440) of newly diagnosed anal cancers and ~56% (930 of 1670) of all anal cancer-related deaths have been women. Women with HPV-induced cervical, vaginal or vulvar cancers have a 3 to 22 times increased risk of developing anal cancer [4]. In 2013, HPV-related non-cervical cancer cases surpassed cervical cancer cases [5]. Thus, more studies focusing on HPV-related anal squamous lesions in women are urgently needed.

To address this issue, we conducted a large-scale, U.S., single-institutional study to investigate the similarities and differences in high-risk HPV (hrHPV) infection between HIV+ women and HIV+ men [1]. We compared the hrHPV genotyping results of 323 HIV+ women and 1,931 HIV+ men and correlated with their anal Papanicolaou test and anal biopsy. The goal of this review is to summarize our findings and compare them with other recently published data. We believe a comprehensive understanding of this information is essential for developing more effective vaccine and screening guidelines for the prevention of anal cancer.

The Synergism between HIV and hrHPV

HIV and HPV are both sexually transmitted viruses and thus influenced by similar risk factors. Both translational and clinical researches have shown a direct biological and immunological synergism between HIV and HPV. Epidemiological data have shown that HPV infection is associated with a 1.9 times increased risk of HIV infection [6] A recent meta-analysis of 11 independent studies also showed that HPV infection was associated with a doubling of HIV infection incidence [7]. Multiple mechanisms contribute to this synergism, including HPV-induced disruption of the mucosal integrity, degradation of cell adhesion proteins, down regulation of antimicrobial immunity, and generation of a pro-inflammatory local immune milieus. By the same token, HIV infection is associated with a significantly higher infection rate for both low-risk and high-risk HPVs. The same meta-analysis performed by Looker, et al. estimated that the hrHPV infection rate was doubled in HIV+ patients, and the hrHPV clearance rate was halved [7]. The main mechanisms for this effect include HIV-induced immunity compromise and decreased HPV clearance.

In our study, the overall hrHPV infection rate was 67.5% for HIV+ women and 78.5% for HIV+ men, both significantly higher than their HIV-counterparts, estimated to be 38.4% for HIV-women and 41.8% for HIV-men [8]. These results confirmed that there was a similarly strong synergism between HIV and hrHPV in both HIV+ women and HIV+ men. In a recent meta-analysis, Wei, et al. summarized 64 papers that studied ~29,900 MSM and found that the hrHPV infection rate was 6.9% in HIV-men who have sex with women (MSW) and 26.9% in HIV+ MSM [9]. The hrHPV infection rate increased to 41.2% in HIV-MSM and 74.3% in HIV+ MSM [9]. Most of the HIV+ men in

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our cohort are MSM. As expected, our result is very close to that of this large-scale meta-analysis. There are much fewer studies on the hrHPV infection rate in HIV+ women. A meta-analysis showed that the hrHPV infection rate was 22.0% in HIV+ women [10]. In our study, the hrHPV infection rate in HIV+ women was almost 3 times higher, and similar to the hrHPV infection rate reported for HIV+ men. Many reasons can cause the higher hrHPV infection rate in our study, such as the age and ethnicity of the HIV+ women in our cohort and the sensitivity of the hrHPV genotyping platform. We used the Cobas 4800 platform, which is highly sensitive and can simultaneously detect 14 subtypes of the most common hrHPVs.

A More Complex hrHPV Infection Genotype Profile in HIV+ Patients

More than 200 genotypes of HPVs have been identified so far, categorized into low-risk and high-risk groups based on their oncogenic potential. Most of the low-risk HPVs can be spontaneously cleared; thus, they are mostly asymptomatic or cause only benign warts. The most common low-risk HPVs include HPV 6,11,42,43, 44,54,61,70,72 and 81. By contrast, high-risk HPVs can integrate into the host genome and lead to squamous dysplasia. The most common hrHPVs include HPV 16,18,31,33,35,39,45,51,52,56,58,59,66 and 68. The hrHPV infection genotype profile varies in different anatomic sites or among different patient populations.

It is generally believed that HPV16 is the most common genotype of hrHPV causing anal cancer, followed by HPV18. Choi, et al. demonstrated that the most frequent hrHPV genotype in MSM is HPV16 (33.7%), followed by HPV18 (16.3%). Other common genotypes of hrHPV in MSM include HPV45,33,58,31 and 52 [2]. In our study, HPV16 and 18 infection rates were 28.1% and 15.6%, respectively, in HIV+ men, and 18.0% and 18.6%, respectively, in HIV+ women. These results align with those of previous studies. These data also suggest that even though HPV16 and 18 are the most common genotypes associated with HIV infection, they account for only a minority of hrHPV genotypes seen in HIV+ patients. The majority of HIV+ women and men are infected with non-HPV16 and non-HPV18 hrHPVs, such as HPV 31,33,35,39, 45,51,52,56,58,59,66 and 68. One limitation of our study is that we could only genotype these non-HPV16 or 18 hrHPVs as a group, which we included together as other-high-risk HPVs (ohrHPVs). Nonetheless, these results suggest that vaccination and surveillance targeting only HPV16 or 18 may not provide adequate protection for HIV+ women and men. A more complete coverage of more genotypes of hrHPVs should be considered for HIV+ women and men.

More interestingly, our data also showed that HIV+ patients were associated with a higher rate of coinfection with multiple genotypes of hrHPV. In our cohort, infection with either HPV16 or HPV18 alone accounts for only a small minority, while most of the HIV+ individuals tested positive for two or more genotypes. The rates of infection with multiple genotypes of hrHPVs were 26% in HIV+ women and 33% in HIV+ men. In comparison, Palefsky, et al. reported that 23% of HIV-MSM and 73% of HIV+ MSM individuals were infected with multiple genotypes of hrHPV [11]. In our cohort, most of the individuals infected with either HPV16 or HPV18 were also positive for ohrHPV. Among all HIV+ individuals who tested positive for HPV16, only 10.8% tested positive for HPV16 alone; the remaining 89.2% tested additionally positive for HPV18 and/or at least one ohrHPV. Similarly, among all HIV+ individuals who tested positive for HPV18, only 11.8% tested positive for HPV18 alone, while the remaining 88.2% tested positive for coinfection with HPV16 and/or at least one ohrHPV. Most importantly, our data also showed that the individuals infected with multiple genotypes of hrHPVs, especially those coinfected with HPV16, were at a higher risk of developing high-grade lesions (HSIL in anal Pap test). These data suggest that a synergism exists among different genotypes of hrHPVs and further support the importance of covering more hrHPV genotypes in vaccination and detection for HIV+ individuals.

HPV16 is the Most Oncogenic Genotype in HIV+ Women and Men

Our results strongly support that HPV16 is the most oncogenic subtype. In our cohort, 14.3 % of HIV+ women and 5.5% of HIV+ men infected with HPV16 showed an HSIL in anal Pap test. Both rates are significantly higher than the rates of those infected with non-HPV16 hrHPV (3.8% in HIV+ women and 1.9% in HIV+ men, Figure 1A). The analysis of anal biopsy results further supports this conclusion. In our cohort, 65.6% of the HIV+ women and 64.0% of HIV+ men infected with HPV16 showed AIN2-3 in anal biopsy. Both of these rates are significantly higher than the rates of those infected with non-HPV16 hrHPV (31.3% in HIV+ women and 39.9% in HIV+ men, Figure 1B). When there is coinfection of ohrHPV with HPV16, the risk of developing an HSIL is increased significantly (from 3.6% to 14.3% in HIV+ women and 1.7% to 5.9% in HIV+ men). In comparison, when there is coinfection of ohrHPV with HPV18, the risk of developing an HSIL is increased (from 3.6% to 5.9% in HIV+ women and 1.7% to 3.8% in HIV+ men, Figure 2A), but the finding is not statistically significant. The same conclusion is true for the anal biopsy result as well. When there is coinfection of ohrHPV with HPV16, the risk of developing AIN2-3 is significantly increased (from 31.1% to 70.6% in HIV+ women and 38.8% to 61.0% in HIV+ men). In comparison, when there is coinfection of ohrHPV with HPV18, the risk of developing AIN2-3 is increased (from 31.1% to 40.0% in HIV+ women and 38.8% to 49.5% in HIV+ men, Figure 2B), but the finding is not statistically significant. Similar findings were also reported by a recently published large-scale meta-analysis of 95 studies between 1992 to 2017, which included 18,646 individuals, showed that HPV16 is enriched in high-grade lesions and suggested that HPV is the most carcinogenic Subtype [12]. Their data also suggested that HPV16 was less frequent in HIV+ women and men than it was in those negative for HIV. Overall, these results suggest that HPV16 carries the highest oncogenic potential and should be a priority target for vaccination and early screening, especially for individuals living with HIV or MSM.

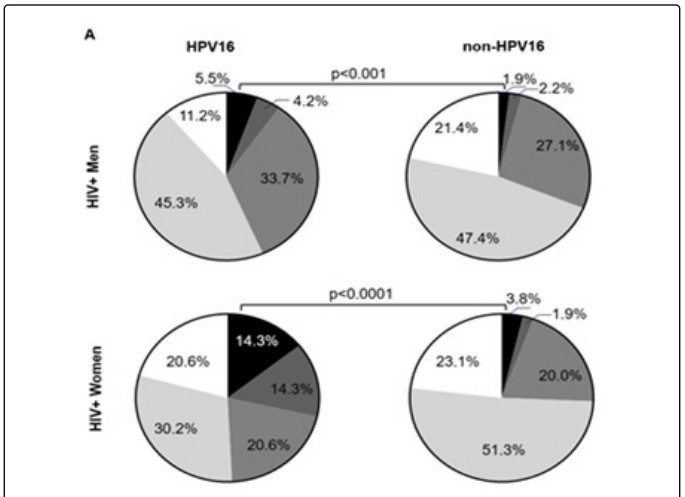

Figure 1A: HPV16 is the most oncogenic subtype of hrHPV. HPV16 infection is associated with a significantly higher rate of HSIL in anal Pap test (5.5% of the HIV+ men infected with HPV16 vs. 1.9% in HIV+ men infected with non-HPV16 hrHPV, p<0.001; 14.3% in HIV+ women infected with HPV16 vs. 3.8% in HIV+ women infected with non-HPV16 hrHPV, p<0.0001). **Note:** (▬) HSIL, (▬) ASCH, (▬) LSIL, (▭) ASCUS, (▭) Normal

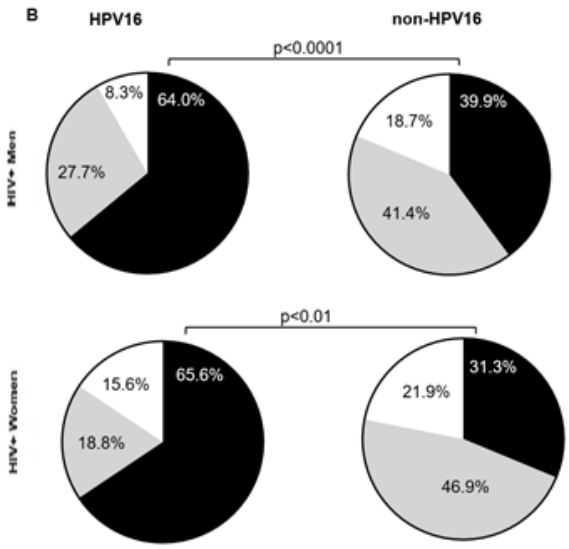

Figure 1B: HPV16 is the most oncogenic subtype of hrHPV. HPV16 infection is associated with a significantly higher rate of AIN 2-3 in anal biopsy (64.0% of the HIV+ men infected with HPV16 vs. 39.9% in HIV+ men infected with non-HPV16 hrHPV, p<0.0001; 65.6% in HIV+ women infected with HPV16 vs. 31.3% in HIV+ women infected with non-HPV16 hrHPV, p<0.01.). **Note:** (▬) AIN2-3, (▭) AIN1, (▭) Normal

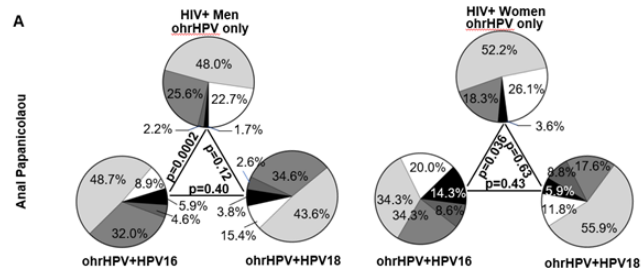

Figure 2A: Coinfection with HPV16 significantly increases the risk of high-grade anal squamous lesion. In HIV+ men, The rate of HSIL in HIV+ men increased from 1.7% in ohrHPV-only infection to 5.9% to ohrHPV-HPV16 coinfection (p=0.0002). The rate of HSIL increased from 1.7% in ohrHPV-only infection to 3.8% in ohrHPV-HPV18 coinfection, but this finding was not statistically significant (p=0.12). Similarly in HIV+ women, the rate of HSIL increased from 3.6% -14.3% ohrHPV-HPV16 coinfection (p=0.036). The rate of HSIL increased from 3.6% in ohrHPV-infection only to 5.9% in ohrHPV-HPV18 co-infection, but this finding was not statistically significant (p=0.63).

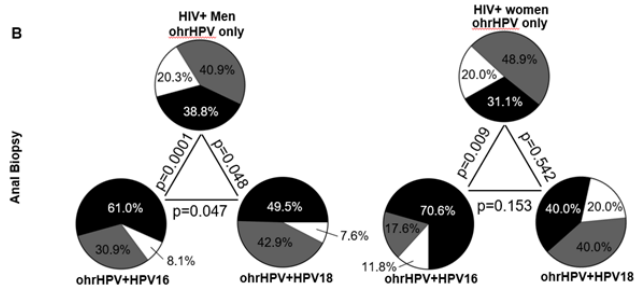

Figure 2B: Coinfection with HPV16 significantly increases the risk of high-grade anal squamous lesion. In HIV+ men, the rate of AIN2-3 increased from 38.5% in ohrHPV only infection to 61.0% to ohrHPV-HPV16 coinfection (p=0.0001). The rate of AIN2-3 increased from 38.5% in ohrHPV-only infection to 49.5% (p=0.048) ohrHPV-HPV18 coinfection. Similarly, in HIV+ women, the rate of AIN2-3 increased from 30.1% in ohrHPV-only infection to 70.6% in ohrHPV-HPV16 co-infection (p=0.009). The rate of AIN2-3 increased from 30.1% in ohrHPV-only infection to 40.0% in ohrHPV-HPV18 co-infection, but this finding was not statistically significant (p=0.542). **Note:** (▬) AIN2-3, (▭) AIN1, (▭) Normal

The Important Differences in hvHPV Infection between Women and Men Living with HIV

In addition to the similarities discussed above, our study also found important differences in hrHPV infection between HIV+ women and HIV+ men. For example, although both groups showed significantly higher hrHPV infection rates than their HIV-counterparts did, HIV+ women exhibited a significantly lower overall hrHPV infection rate than did HIV+ men (67.5% vs. 78.5%, p<0.0001). In addition, the rate of being simultaneously infected by multiple genotypes of hrHPVs was also significantly lower in HIV+ women (26% vs. 33%, p<0.01). Because most of the HIV+ men in our cohort are MSM, we hypothesize that the overall higher hrHPV infection rate and more diverse genotype profiles in HIV+ men were most likely due to the higher frequency of anal receptive intercourse in the HIV+ MSM individuals in our cohort. Regarding the hrHPV infection genotype profiles, while the HPV16 and ohrHPV infection rates were significantly lower in HIV+ women, the HPV18 infection rates were similar between HIV+ women and men. The reason for this relative HPV18 enrichment in HIV+ women is unclear. Nonetheless, these results suggest that the assumption that HIV+ women and men have similar hrHPV genotype profiles may be over-simplified. More comparative studies are warranted to characterize the gender differences in more detail.

Another important difference is that despite the overall lower hrHPV infection rate, HIV+ women seem to have a higher risk of high-grade lesions as determined by the anal Papanicolaou test. In our cohort, 4.6% of HIV+ women were found to have an HSIL in anal Papanicolaou tests, a rate that was significantly higher than it was for HIV+ men, of which only 2.5% were found to have an HSIL. The mechanism for this increased susceptibility of developing HSIL in HIV+ women is unclear. In our cohort, the proportion of individuals older than 30 years of age was significantly greater in HIV+ women than it was in HIV+ men (92% vs. 81%, p<0.01). This suggests that HIV+ women tend to start their anal Papanicolaou screening later than HIV+ men do in our current practice, which may contribute to the higher incidence rate of HSILs. Providers should consider starting vaccination and anal Pap screening for HIV+ women earlier.

Discussion and Conclusion

By comparing the hrHPV genotype profile and their correlation with anal cytology and biopsy in a large cohort of HIV+ women and men, we showed that both groups exhibit significantly higher hrHPV infection rates and more complex genotype profiles than their HIV-counterparts do. Consequently, the risk of developing high-grade lesions is significantly higher in both groups. These results support the strong synergism between HIV and hrHPV. HPV16 is the most oncogenic genotype and should be a priority target for vaccination and screening. In comparison with HIV+ men, HIV+ women are associated with a lower hrHPV infection rate and lower rate of being infected with multiple genotypes of hrHPV but a higher rate of developing high-grade lesions. Overall, our results suggest that earlier surveillance and intervention are warranted for HIV+ individuals, especially HIV+ women. Further studies are warranted to investigate the gender differences of hrHPV infection. A comprehensive understanding of this information is important for the development of more effective vaccination and surveillance guidelines.

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