Contents available at **PubMed**
www.aidsreviews.com

PERMANYER

AIDS Rev. 2018;20:94-103

The Role of HIV in the Progression through the Stages of the Human Papillomavirus to Cervical Cancer Pathway

Kristopher O. Myers and Nasar U. Ahmed

Department of Epidemiology, Florida International University, Miami, Florida, United States

Abstract

Globally, an estimated 36.9 million persons are living with HIV/AIDS, and approximately 291 million women worldwide are carriers of human papillomavirus (HPV). A large number of women currently infected with either or both viruses constitute a large burden on the national health care system. Women with HIV have significantly higher rates of HPV infections than women without HIV. Approximately 77% of women with HIV are carriers of HPV. While research has established a linkage between HIV and progression to cervical cancer in general, there are currently no review articles exploring the role HIV has in the progression from HPV to each stage of carcinogenesis that leads to cervical cancer. The objective of this review is to examine the relationship between HIV and progression from HPV to each stage of carcinogenesis related to cervical cancer. The findings of the review support the conclusion that HIV infection increases the likelihood of progression to each stage of the HPV to cervical cancer pathway. **(AIDS Rev. 2018;20:94-103)**

Corresponding author: Kristopher O. Myers, kmyer016@fiu.edu

Key words

Uterine cervical neoplasms. HIV. Papillomaviridae. Review.

Introduction

Cervical cancer is a leading cause of death among women worldwide[1]. Globally, cervical cancer has been estimated to have been responsible for 265,700 deaths annually, and 86% of these deaths occurred in developing countries[1]. Women with HIV are particularly affected by the burden of cervical cancer. Population-based matched registry studies provide the best epidemiological estimates of the increased risk of cervical cancer as result of HIV. Recent studies have reported increased cervical cancer rate among HIV-positive women compared with the general population with standardized incidence ratio of 4.3 (95% confidence interval [CI]: 3.3-5.6, $p < 0.05$)[2]. This trend is exacerbated in low- to middle-income countries. For example, Côte d'Ivoire, where cervical cancer is the leading cause of cancer death, HIV-infected women were 3 times more likely than uninfected women to develop cervical cancer[3]. This trend persists in developed nations as well. Clifford et al. conducted a study using involving North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), in which they assessed the odds of incident cervical cancer among

Correspondence to:
Kristopher O. Myers,
Florida International University,
11200 SW 8th St, Miami, FL 33199, Florida, United States
E-mail: kmyer016@fiu.edu

Received in original form: 15/02/2018
Accepted in final form: 25/04/2018
DOI: 10.24875/AIDSRev.M18000021

HIV positive (13,690) and HIV negative women (12,021)[4]. The findings indicated that HIV-infected women with baseline CD4+ T-cells of ≥ 350, 200-349 and < 200 cells/uL had a 2.3 (95% CI: 1.3-4.1, $p < 0.05$) times, 3.0 (95% CI: 1.1-8.6, $p < 0.05$) – times, and 7.7 (95% CI: 4.7-12.6, $p < 0.05$) times increase in invasive cervical cancer (ICC) incidence, respectively, compared with HIV-uninfected women[4]. This study suggests that HIV-induced immunosuppression is a potential mechanism through which HIV increases progression from human papillomavirus (HPV) to cervical cancer. It is well established that HPV infection is the main contributor to cervical cancer and that it progresses to squamous intraepithelial neoplasia more frequently and rapidly in HIV-infected women than in the general population[5]. The prevailing hypothesis is that HIV-mediated immune dysfunction leads to longer and more persistent cervical HPV infections[6]. These infections then lead to oncogenic transformations that lead to cancer[7]. Supporting this hypothesis, a study conducted in Brazil of 151 women found HIV-positive women took a significantly longer time (7.0 ± 3.8 months) to clear HPV, compared to those not infected by HIV (5.9 ± 3.0 months) ($p < 0.05$)[8]. While both HIV and HPV are both considerable burdens on public health globally, they HIV and HPV interact causing a more rapid progression from HPV to cervical cancer[9-11]. In *ex vivo* models of cervical epithelial cells in tissue explants from HIV-uninfected patients, the adjunction of HIV proteins (tat and gp120) with cytokines produced by HIV-infected cells (tumor necrosis factor alpha [TNF-α] and interferon-gamma [IFN-γ]) has induced the separation of epithelial tight junctions and increased HPV penetration into the basal epithelial cells[11]. Basal epithelial cells are HPV targeted cells[11]. Immunology also plays an important role as HIV positive women with lower CD4 counts are more likely to harbor high-risk HPV types that increase progression from high-grade squamous intraepithelial lesions (HSIL) to cervical cancer[12]. The objective of this review is to examine the relationship between HIV and progression from HPV to each stage of carcinogenesis related to cervical cancer. The findings of the narrative review support the conclusion that HIV infection increases the likelihood of progression to each stage of the HPV to Cervical Cancer Pathway.

HIV and HPV acquisition

HIV is transmitted through sexual contact across mucosal surfaces, by maternal-infant exposure, and by percutaneous inoculation[13]. The most common transmission route identified worldwide is through the female genital tract[13]. The transmission probability per event varies from 1 in 200 to 1 in 2000[13]. Heterosexual transmission is responsible for nearly 70% of HIV-1 infections worldwide; the remainder is mainly attributable to male to male transmission, injection drug use, and maternal-infant infection[13]. Persons with HIV are considered to have progressed to AIDS if their CD4 count has been reduced to ≤ 200 cells/mL[14]. This is indicative of immunosuppression. Persons who are immunosuppressed most commonly die due to opportunistic infections[15]. Studies have suggested that females with HIV are particularly vulnerable to HPV infection as they have an increased likelihood of immunosuppression, and thus an increased probability of acquiring opportunistic infections such as HPV[11]. In a prospective study conducted by Konopnicki et al. involving 652 women, researchers determined through multivariate regression that a CD4 count > 500 cells per mL for 18 months among HIV positive women was significantly associated with reduced risk of HR-HPV acquisition (odds ratio [OR], 0.88; 95% CI: 82-0.94; $p = 0.0002$)[11].

The potential molecular mechanism through which HIV-induced immunosuppression can increase the likelihood of HPV acquisition is the CD4 level. Low CD4+ counts (≤ 200 cells/μL) have been shown to be the strongest independent predictor of infection with HPV[16]. Furthermore, in HIV-infected individuals, the probabilities of HPV acquisition and the development of intraepithelial neoplasia increase in proportion to the loss of CD4 T cells[17]. Persons with reduced CD4 counts are unable to produce effective CD4+ T cell responses or to make immunoglobulins in response to a potential infection[18]. This impaired T-cell function causes a greater susceptibility to HPV infection[18].

Another molecular mechanism regarding the method in which HIV increases HPV susceptibility has been proposed. In *ex vivo* models of cervical epithelial cells in tissue explants from HIV-uninfected patients, the adjunction of HIV proteins (tat and gp120) with cytokines produced by HIV-infected cells (TNF-α and IFN-γ) has induced the separation of epithelial tight junctions and increased HPV penetration into the basal epithelial cells[11]. Basal epithelial cells are HPV targeted cells[11]. During HPV replication, HIV tat protein was shown to significantly enhance HPV transcription and thus the expression of the HPV E oncogenes and L capsid proteins in cell cultures[11]. This suggests that HIV can reduce the cohesion of epithelial junctions and allow for penetration of HPV into the targeted basal epithelial cells.

HPV is the most common sexually transmitted virus and is often present in the cervical epithelia of women

who have no cytological abnormalities[19]. HPVs are generally recognized to be the central causative agent of cervical cancer[19]. HPV can be transmitted through vaginal, anal, or oral intercourse with someone who has the virus. It is most commonly spread during vaginal or anal sex[20]. HPV can be passed even when an infected person has no signs or symptoms[20]. If left untreated HPV can progress to lesions, which are major risk factor for cervical cancer[21,22].

HPV has been indicated to increase the likelihood of HIV acquisition. It has been demonstrated that the E7 protein of HPV type-16 downregulates an epithelial adhesion molecule called E-Cadherin which increases the susceptibility of the genital lining to HIV[23]. Another method in which HPV can increase the likelihood of HIV is through the T-cell response. The host immune response to HPV is conducted by T-lymphocytes, this increase in lymphocyte production may increase HIV susceptibility as T-lymphocytes is primary target cells for HIV[24,25]. An increased presence of these cells has been seen in HPV-infected cervical tissue.

Progression from HPV to cervical cancer

To understand the progression from HPV to cervical cancer, the nomenclature of the individual stages must first be understood. Over the past few decades, researchers have named the stages using histological and cytological methods of nomenclature. A previous literature review outlined the current understanding of cervical cancer precursors and the nomenclature of stages that progress to cervical cancer[21]. Histological nomenclature is based on the underlying neoplastic process and guides treatment[21]. Cytological nomenclature is used to assess the underlying histologic state[21]. The histological stages of progression are: negative, squamous atypia, cervical intraepithelial neoplasms 1 (CIN1), CIN2, and CIN 3[21]. The cytological stages of nomenclature are: negative for intraepithelial lesion or malignancy (NILM), atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL), and HSIL[21].

The literature has established a moderate correlation between histological and cytological detection of precursors to cervical cancer; however, these two systems of nomenclature are not equivalent in a definition or medical standard[26]. Histology is used to decide the treatment of cancer and precancer through categorization of the patterns of microscopic organization of cells in tissue sections from biopsy to surgical specimens[27]. In comparison, cytology assesses the exfoliated cells removed from the surface of the cervix[27]. Histology is the "gold standard" in modern medicine in determining the degree of progression in cervical disease[26]. These terms are often used interchangeably during assessments of progression from HPV to cervical cancer in the literature; therefore in this review, we begin with a description of the correspondence between the cytological and histological nomenclature.

Negative (NILM) is a cytological stage that is defined as having no cervical abnormalities or lesions. Squamous atypia is defined as microscopic abnormalities in cervical cells in which the significance of the abnormality is undetermined as it relates to cervical cancer[21]. This histological stage includes the cytological stage ASCUS[21]. For the purposes of this manuscript, ASCUS will not be included as a step in the pathway of HPV to cervical cancer as ASCUS is a cytological stage that is generally not the result of HPV, but rather inflammation caused by bacteria, fungi, or viruses other than HPV[28]. ASCUS will be included merely as a risk factor that is associated with prevalent HPV. CIN is the pre-malignant abnormal growth of squamous cells on the surface of the cervix[21]. CIN is a stage in which abnormal cells are found on the surface of the cervix. CIN has three substages stages: CIN1, CIN2, and CIN 3[21]. CIN 1 is defined as low-grade lesion. It refers to mildly atypical cellular changes in the lower third of the epithelium (basal 1/3), this stage includes the cytological stage LSIL[21,29]. CIN2 is considered a high-grade lesion; it refers to moderately atypical cellular changes confined to the basal two-thirds of the epithelium[21,29]. CIN3 is also considered a high-grade lesion and is used to identify severe dysplasia[21,29]. It refers to severely atypical cellular changes encompassing greater than two-thirds of the epithelial thickness and includes full-thickness lesions[21,29]. Both histological stages (CIN 2 and CIN 3) include the cytological stage HSIL[21,29]. Although none of the aforementioned stages constitute cervical cancer; each grade of lesion or neoplasm is a precursor to cervical cancer[21,29].

Prevalence of abnormal cytology among those with HPV

Few studies have assessed the association between HIV and HPV coinfection and abnormal cytology. However, some studies suggest that HIV positive women have a higher prevalence of HPV, and as a result, they have atypical cytology more often than HIV negative women with HPV only. In one study researchers

attempted to determine the association of HIV infection with the prevalence of HPV/DNA. This study also determined the association of HIV/HPV coinfection and prevalence ASCUS[30]. Researchers assessed a total of 333 (163 HIV-1 seropositive and 170 HIV seronegative) women who were recruited between July and December 2014[30]. Researchers determined that among the HIV positive women the HPV DNA prevalence was 75.0% versus 42.6% among HIV seronegative women ($p < 0.0001$)[30]. It was also determined that among the HIV positive group, with a significantly higher prevalence of HPV DNA, ASCUS was more common (7.4%). However, among the HIV negative group with a smaller prevalence of HPV DNA, ACSUS was less common (0.6%); the difference between the two percentages was significant, $p \leq 0.001$[30]. This study concluded that women with HIV have a higher prevalence of HPV and ACSUS.

Another study confirmed the findings of the Obiri-Yeboah et al. study. A study conducted by Luchters et al. assessed the association between HIV infection with distribution and viral load of HPV types among 803 Kenyan sex workers[31]. The researchers found that significantly more (73.3%) HIV-infected women were likely to have high-risk HPV as compared to HIV negative women (35.5%) ($p < 0.01$)[31]. The study also indicates that the HIV-infected group of women with a significantly higher prevalence of HPV have a significantly higher proportion of women with abnormal cervical cytology when compared to women without HIV and lower prevalence of HPV (27% vs. 8%, $p < 0.001$)[31]. The current research suggests that HIV increases the likelihood of HPV acquisition. This increase in HPV acquisition is accompanied by an increase in abnormal cytology[31].

The scientific basis for increased prevalence abnormal cytology among women with HIV/HPV coinfection as compared to HIV negative women with HPV has been well established in the literature[12]. The reason for this increased likelihood of prevalence is the persistence of HPV infection. The persistence of HPV infection is a crucial factor in the development of abnormal cytology and cancer[12]. HIV- and HPV-coinfected individuals are at an increased risk for persistent HPV infection mainly because of their reduced ability to clear HPV 17 and18, which are the two types largely responsible for the development of abnormal cytology and cancer[12]. While ASCUS is not a step in the HPV to cervical cancer pathway, ASCUS prevalence represents an increased likelihood of HPV infection and therefore must be discussed in this review[32].

Prevalence of lesions among those with abnormal cytology

Few recent studies exist that assess the prevalence of lesions among both HIV positive and negative women with ASCUS. One study was conducted by Duerr and colleagues, in which they utilized participants from the HIV Epidemiology Research Study. The study involved 1310 women (871 HIV infected and 439 at-risk, HIV-uninfected women) from 4 US cities[33]. The researchers found that among women with ASCUS, 60% of HIV infected and 25% of HIV-uninfected women developed squamous intraepithelial lesions (SILs) ($p \leq 0.01$)[33]. Visits in which HR-HPV was detected were more prevalent among HIV-positive women (23%) than among HIV negative women (14%) ($p < 0.05$)[33]. Visits in which intermediate risk HPV was detected were also significantly more prevalent among HIV positive women than among HIV negative women (24% vs. 12%, respectively, $p < 0.01$). The researchers subsequently conducted a multivariate logistic regression and found that among women with ASCUS at baseline, HIV-infected women had 2.4 times the risk of developing SIL, when compared with HIV-uninfected women (adjusted hazard ratio [AHR] = 2.4, 95% 1.2-4.9, $p < 0.05$). The researchers also determined that immunosuppressed HIV-infected women (CD4 < 200 cells/ml) were significantly more likely to develop SILs when compared to women with CD4 > 500 cells/ml (AHR = 1.9, 95% CI: 1.2-2.9, $p < 0.05$).

The immunosuppressive mechanism involved here are cytokines secreted by CD4 cells. They are divided into two types (Th1 and Th2). Th1 are inflammatory cytokines while Th2 are anti-inflammatory cytokines. As CD4 increases so do Th 1 secretion. Th2 secretion is inversely correlated with CD4 count[34]. At the beginning of HPV infection, there is an increase in the immunosuppressive cytokine interleukin (IL)-10 (Th2) at the cervical level, and this increases according with the grade of the lesion, being the highest concentration at cancer stage[35]. An increase in IL-10 is associated with progression in the severity of HPV-induced lesions[36]. Since HIV infection is associated with a reduction in the CD4 count, HIV-induced immunosuppression increases the likelihood of Th2 secretion and ultimately cervical lesions[37,34]. Not all HIV-infected women with ASCUS develop lesions, a likely factor reducing progressing from ASCUS to lesions among these women may be immunocompetence or immune health. Higher CD4 counts would mean that women could avoid the

cytokine imbalance and therefore avoid progression to lesions. As noted in the current study, the research also determined that HIV positive women with intermediate or high-risk HPV were more likely to develop SILs (AHR = 3.1, 95% CI: 2.2-4.3, $p < 0.05$) when compared to their HIV negative counterparts[33]. The biological mechanism by which the HIV virus increases the likelihood of progression of ASCUS to lesions occurs through the E6 and E7 proteins produced by high-risk HPV. The viral E6 and E7 oncoproteins are necessary for malignant conversion[38]. The abilities of oncogenic HPV E6 and E7 proteins to associate with the tumor suppressors p53 and pRB, respectively, have been suggested as a mechanism by which these viral proteins induce tumors and lesions among women with HPV[38,39]. Women infected with HIV have the highest risk for more rapid progression of HPV-induced CIN; this occurs as a result of HIV-induced immune suppression[40]. The HIV Epidemiology Research Study confirms this finding as among women with ASCUS at baseline who developed SIL during the follow-up period had a median time to SIL of 12 months among HIV-infected women and 18 months among HIV-uninfected women[33]. The immunosuppression that affects HIV-infected women results in the inability to control the expression of oncogenic types of HPV that are associated with the proliferation of atypical cellular formation[40]. These atypical cellular types are associated with a higher prevalence of HR-HPV[32]. A higher likelihood of high-risk HPV infection among women with HIV results in a higher prevalence of HPV-induced lesions.

Progression from LSILs to HSILs

The rate of progression from low-grade neoplastic lesions to higher grade neoplastic lesions is higher among HIV positive women than among HIV negative women. The frequency of progression from LSIL to HSIL is approximately 11%[41]. In the Women's Interagency HIV Study, the largest U.S. multicenter cohort study of women with HIV, researchers assessed the association of progression of LSIL to HSIL among HIV positive and HIV negative women[42]. All women included in the incidence calculation either had normal cytology, ASCUS or LSIL at baseline[42]. These women were observed over the course of 10 years. Among the 2477 women (1,931 HIV seropositive, 533 HIV seronegative, and 13 seroconverting), the incidence rate for HSIL was 5.3 per 1000 person-years among HIV positive women, (95% CI: 3.7-7.6, $p \leq 0.05$) and 1.3 per 1000 for HIV seronegative women, IR (95% CI: 1.2-9.5, $p \leq 0.05$)[42]. This study concluded that HIV positive women progress to HSIL at a significantly higher rate than do their HIV negative counterparts[42]. Later studies have consistently shown increased progression rates of LSIL to HSIL in HIV positive women compared with HIV negative women[12]. Researchers determined that a potential mechanism linked with this increased progression from LSIL to HSIL among patients with HIV is related to the fact that the inflammatory (e.g., cytotoxic) response to CIN lesions is suppressed in HIV-seropositive women, this would result in a reduced ability of the host to stop progression from HPV to advanced abnormal cytology (HSIL)[12]. Studies suggest that particular HR-HPV types are associated with progression from LSIL to HSIL. In a prospective cohort study in which researchers determined the natural history of HPV to cervical cancer, researchers determined that high-risk HPV types are associated with progression from LSIL to HSIL. In this study, 400 HIV-infected women underwent HPV DNA testing, cytology, histology, colposcopy, and CD4 count testing every 6 months for 3 years[43]. Researchers determined that 4% of cases progressed from LSIL to HSIL[43]. When progression of LSIL and HSIL was analyzed jointly, the only significant predictor of cytologic progression was positive high-risk HPV status at the start of the study interval (OR = 4.29; 95% CI: 2.51-7.33, $p < 0.05$), HR-HPV-positive women compared with HR-HPV-negative women. High-risk HPV types in this study included: HPV 16, 52, 53, 15, and 18. High-risk HPV is a major role in developing cervical cancer as high-risk types of HPV have specific oncoproteins (E6 and E7) that bind and to degrade p53 and pRb, proteins that regulate cells division and increase the likelihood of unregulated replication and tumor formation[44]. Low-risk HPV types have these proteins; however, proteins from low-risk HPV types weakly bind and do not degrade these regulatory proteins[44].

Immunology also plays an important role as HIV positive women with lower CD4 counts is more likely to harbor high-risk HPV types that increase progression from HSIL to cervical cancer[12]. HIV immune-suppressed women do not have an adequate CD4 response to lesions (which are infiltrated by CD4, CD8, and macrophages in an immunocompetent person)[45]. This reduced response allows the malignancies to progress[45].

HSIL to ICC

The final stage from HPV infection to cervical cancer is the progression from lesions to cervical cancer

among HIV positive women. Although most pre-cancerous lesions resolve without treatment, there is a risk for all women that HPV infection may progress to chronic and pre-cancerous lesions and subsequently lead to invasive cervical cancer[46]. It takes 15-20 years for HPV to progress to cervical cancer among women with normal immune systems[46]. This progression is reduced to 5-10 years among immunosuppressed women, such as those with untreated HIV/AIDS infection[46]. Although there is scarce literature relating progression from HSIL to cervical cancer, studies have been conducted to assess the association between HIV infection and progression to cervical cancer. Since the development of HSIL is necessary part of the natural progression of HPV to cervical cancer, we can assess the progression from HSIL to cervical cancer among women with HIV indirectly by reviewing the literature related to progression to cervical cancer among HIV positive women.

In a study conducted by Abraham et al., researchers assessed the risk of cervical cancer among both HIV positive and negative women using data from the NA-ACCORD study from 1996 to 2010[4]. Among the 25,711 women involved in the study, 13,690 were HIV-infected, and 12,021 were HIV-uninfected[4]. The regression analysis revealed that at every CD4 count category women with HIV progressed to cervical cancer at a higher rate than did women without HIV. The incidence rates from this study illustrated a trend indicating that incidence rates for cervical cancer increased with the decrease of the CD4 counts. The incidence rates for HIV-infected women were as follows: 47 (95% CI: 25-91, $p \leq 0.05$), 18 (95% CI: 6-57, $p \leq 0.05$), and 14 (95% CI: 6-33, $p \leq 0.05$) for the following CD4 groups: < 200, 200-349, and ≥ 350 cells/uL, respectively[4]. Among HIV negative women the incidence rate for cervical cancer was 6 (95% CI: 2-16, $p \leq 0.05$)[4]. All incidence rates were reported as cases per 1000 person-years. This research concluded that women with HIV have a higher rate of progression to cervical cancer than the rate in HIV negative women. These findings have been supported by later studies[19]. The scientific mechanism related to this association is reduced immune function as a result of HIV/AIDS, leading to a more persistent HPV infection. This persistence of HPV infection increases the likelihood of developing HSIL, and thus increases the likelihood of developing cervical cancer[47]. It is important to note that not all persons with HSIL will progress to cervical cancer[48]. One study conducted by Vink et al. conducted a cross-sectional study to estimate the time-span from detection of HSIL to cervical cancer. Although one cannot directly observe this time span, as the duration of longitudinal studies is not permitted, and CIN2/3 should be treated when detected, researchers developed a statistical model for estimating this duration. Researchers found that approximately 1.6% of lesions developed into cervical cancer over the span of 10 years overall[48]. However, when the results are stratified by HPV infection, 0.6% of HPV negative women develop cancer as compared to 2.4% with HPV infection.

Progression to cancer among women with HSIL developed through HPV is associated with high-risk HPV. The WHO has identified 12 high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59)[49]. Women with HIV are at an increased risk for high-risk HPV than women without HIV[49]. These high-risk types of HPV have specific oncoproteins (E6 and E7) that bind and to and degrade p53 and pRb, proteins that regulate cells division and increase the likelihood of unregulated replication and tumor formation[44]. As previously mentioned, low-risk HPV types have these proteins; however, these types weakly bind and do not degrade these regulatory proteins[44]. Immunology also plays an important role as HIV positive women with lower CD4 counts is more likely to harbor high-risk HPV types that increase progression from HSIL to cervical cancer[12].

A phenomenon known as spontaneous regression occurs in about 70% of HSIL lesions[50]. As previously mentioned, during the time of spontaneous regression of HPV-infected genital warts, the lesions are infiltrated with CD8+ cytotoxic T cells, CD4+ T cells, and macrophages in immunocompetent individuals[45]. One needs healthy T-cell reactivity for the occurrence of regression of HPV-induced premalignant lesions. HIV is associated with a loss of CD4 cells. This loss of CD4+ T-cells is associated with an increased prevalence of HPV infections, type-specific persistence and an increase of HPV-associated malignancies[45]. This would indicate that women with HIV, who are at a greater risk of immunosuppression, have a reduced chance of spontaneous regression.

While there is no study that directly assesses the role of immune-reconstitution with antiretroviral therapy on disease progression among women with HIV, there are articles that assess the association of ART use with the progression of lesions while assessing the impact of CD4 count. A prospective cohort study conducted by Adler et al. determined the impact of highly active antiretroviral therapy (HAART) on incidence, regression, and progression of cytopathological abnormalities in HIV-infected women. Researchers assessed the association between HAART use and likelihood of

regression/progression in consecutive smears using multivariate marginal models[51]. Researchers found that HIV positive women on HAART had a significant increase in the likelihood of regression of cervical lesions than did their untreated counterparts (OR = 2.61; CI: 1.75-3.89; $p < 0.0001$)[51]. Furthermore, researchers determined that immunosuppression is associated with progression of lesions to higher grade lesions (OR = 2.50, 95% CI: 1.67-3.73, $p < 0.05$), when compared to immunocompetent HIV positive women. These odds were reduced when assessing progression among women with higher CD4 counts: for CD4 between 201-350 cells/mL and 351-500, the odds for progression were (OR = 1.89, CI: 1.36-2.62, $p < 0.05$) and (OR = 1.84, CI: 1.31-2.59), respectively[51]. This suggests decreased odds of progression as the CD4 count increases and provides support for the importance of immune reconstitution among women coinfected with HIV and HPV. This study also suggests that women who develop improved CD4 counts (immune reconstitution) after HIV infection as a result of HAART may be at better odds of regression and a reduced odds of progression to a higher grade of neoplasia.

Another method in which HIV and HPV interact as it relates to the progression of lesions to cervical cancer is through superinfection or the infection of multiple HPV types at once. Women with HIV are at increased risk of superinfection with multiple HPV types[52]. In a study conducted by Maranga et al., researchers determined the range of HPV genotypes found in cervical smears and carcinomas from HIV positive to negative Kenyan women. Researchers determined that HIV infection was decidedly associated with multiple HPV infections and infection with high-risk genotypes ($p < 0.006$, $p < 0.01$)[52].

Furthermore, the odds of development of both HSIL and cervical cancer are increased among women with multiple HPV infections. In a study conducted by Murdiyarso et al., researchers evaluated the prevalence, age-adjusted distribution, and impact of single and multiple high- and low-risk HPV subtypes and their associations with cervical lesions. Researchers assessed cervical swabs from 11,224 women who had samples taken at a testing laboratory (Kalbe genomics laboratory). Researchers determined that among women with 1 high-risk HPV infection, the risk of HSIL was 63.9 (95% CI: 45.8-89.1, $p < 0.05$), and risk of SCC was 157.9 (95% CI: 46.7-534, $p < 0.05$) when compared cells from women with no HPV infection. Among women with multiple HPV infections risk of HSIL was 79.9 (95% CI: 49.2-129.7, $p < 0.05$) and risk of cervical cancer was 40.4 (95% CI: 4.2-392, $p < 0.05$)[53]. This indicates that women with multiple HPV infections have higher rates of HSIL, however lower rates of cervical cancer. It should be noted that the "multiple infection" category included low-risk types of HPV as well; therefore, further research should assess the association between multiple high-risk types and progression to cervical cancer as compared to women with only one high-risk type HPV[53]. Table 1 summarizes the findings of key studies related to the progression from HPV to cervical cancer.

Discussion

In the literature, we find that a large majority of women with HIV are also carriers of HPV DNA[20]. An explanation for the high percentage of HIV positive women with HPV DNA is immunosuppression and interaction between HIV and HPV. Women with HIV-induced immunosuppression lack the ability to develop effective CD4+ T cell responses or to make immunoglobulins in response to a potential infection. This impaired T-cell function causes greater susceptibility to HPV infection[18]. HIV also affects HPV acquisition through the molecular interaction of the two viruses. HIV proteins (tat and gp120) interact with cytokines produced by HIV-infected cells (TNF-α and IFN-γ) and induces the separation of epithelial tight junctions and increased HPV penetration into the basal epithelial cells. A possible clinical implication for this finding would be to ensure women with HIV maintain a CD4 cell count adequate to respond to the exposure of HPV. Another implication related to the interaction of HPV and HIV would be further research related to increasing the cohesion of epithelial junctions among women with HIV to reduce the likelihood of HPV infections.

We also determined that groups of women with HIV were more likely to acquire ASCUS[30]. An explanation for this higher prevalence of ASCUS among HIV-infected women is that HIV-infected women are at increased risk for persistent HPV infection[12]. A clinical implication resulting from this knowledge should lead to an increase in mandatory screening among HIV- and HPV-coinfected women. The literature indicates that women with HIV are more likely to progress from ASCUS to lesions of various severity[40]. The scientific explanation for the pattern is that immunosuppression is associated with an inability to control the expression of oncogenic types of HPV that are associated with the proliferation of atypical cellular formation. Immunosuppression is also associated with an increase in (IL-10) secretion at the cervical level[35] An increase in IL-10 is associated with progression in the severity of HPV-induced

Table 1. Selected studies that examined the progression of HPV cervical infection to cancer

Stage in HPV to cervical cancer	Author Name, Year	Finding
Lesions among women with ASCUS	Duerr et al. 2006	Among women with ASCUS, 60% of HIV infected and 25% of HIV-uninfected women developed SILs (squamous intraepithelial lesions) ($p \leq 0.01$)[33]
LSIL to HSIL	Massad et al. 2008	Among the 2477 women (1931 HIV seropositive, 533 HIV seronegative, and 13 seroconverting), the incidence rate for HSIL was 5.3 per 1000 person-years among HIV positive women, (95% CI: 3.7-7.6, $P \leq 0.05$) and 1.3 per 1,000 for HIV seronegative women, IR (95% CI: 1.2-9.5, $P \leq 0.05$)[42]
	Denny et al. 2008	When progression of LSIL and HSIL was analyzed jointly, the only significant predictor of cytologic progression was positive high-risk HPV status at the start of the study interval (OR = 4.29; 95% CI: 2.51-7.33, $P < 0.05$), HR-HPV-positive women compared with HR-HPV-negative women
HSIL to cervical cancer	Abraham et al. 2013	The incidence rates for cervical cancer were HIV-infected women were as follows: 47 (95% CI: 25-91, $P \leq 0.05$), 18 (95% CI: 6-57, $P \leq 0.05$), and 14 (95%CI: 6-33, $P \leq 0.05$) for the following CD4 groups: < 200, 200-349, and ≥ 350 cells/uL, respectively[4]. Among HIV negative women the incidence rate for cervical cancer was 6 (95% CI: 2-16, $P \leq 0.05$)[4].
	Vink et al. 2013	Researchers found that approximately 1.6% of lesions developed into cervical cancer over the span of 10 years overall[48]. However, when the results are stratified by HPV infection, 0.6% of HPV negative women develop cancer as compared to 2.4% with HPV infection
	Adler et al., 2012	Researchers found that HIV positive women on HAART had a significant increase in the likelihood of regression of cervical lesions than did their untreated counterparts (OR = 2.61; CI: 1.75-3.89; $P < 0.0001$)
	Maranga et al., 2013	Researchers determined that HIV infection was decidedly associated with multiple HPV infections and infection with high-risk genotypes ($p < 0.006$, $P < 0.01$)[52]
	Murdiyarso et al. 2016	Among women with multiple HPV infections risk of HSIL were 79.9 (95% CI: 49.2-129.7, $P < 0.05$) and risk of cervical cancer was 40.4 (95% CI: 4.2-392, $P < 0.05$)[53]
	Adler et al., 2012	Researchers determined that immunosuppression is associated with progression of lesions to higher grade lesions (OR = 2.50, 95% CI: 1.67-3.73, $P < 0.05$), when compared to immunocompetent HIV positive women. Odds were reduced when assessing progression among women with higher CD4 counts: for CD4 between 201-350 cells/mL and 351-500, the odds for progression were (OR = 1.89, CI: 1.36-2.62, $P < 0.05$) and (OR = 1.84, CI: 1.31-2.59), respectively[51]

HPV: human papillomavirus, ASCUS: atypical squamous cells of undetermined significance, SILs: squamous intraepithelial lesions, HSIL: high-grade squamous intraepithelial lesions, CI: confidence interval, LSIL: low-grade squamous intraepithelial lesions, OR: odds ratio, HAART: highly active antiretroviral therapy

lesions[36]. IL-10 increases according to the grade of lesion, being the highest concentration at cancer stage. A clinical recommendation would be to ensure that with women with HPV-induced ASCUS are maintaining a healthy CD4 cell count to reduce the likelihood of ASCUS progression to a cervical lesion.

The literature also provided evidence that women with HIV are more likely to progress from low-grade lesions to lesions of increased severity[42]. A potential reason for this increase in progression to higher grade cervical lesions is the inflammatory (e.g., cytotoxic) response to CIN lesions is suppressed in HIV-seropositive

women; this would result in a reduced ability of the host to stop progression from HPV to advanced abnormal cytology (HSIL)[12]. A clinical improvement would be to assess HIV- and HPV-coinfected women's immunological status more regularly as a timely cytotoxic response is dependent on the presence of functioning T-cells[54]. The literature also provided evidence that progression from LSIL to HSIL among women with HIV is related to HIV-infected women having a greater likelihood of HR-HPV infection[49]. High-risk types of HPV have specific oncoproteins (E6 and E7) that bind and to degrade p53 and pRb, proteins that regulate cells division and increase the likelihood of unregulated replication and tumor formation[44].

Finally, HPV is more likely to develop into cervical cancer among HIV-infected women as a result of HPV persistence[4]. A clinical improvement, in this case, would be to ensure any HIV-infected women maintain a healthy CD4 level so that they are immunocompetent. Immunocompetent women or women with normal immunological responses have the ability to clear infections or avoid being infected with a persistent strain of HPV.

Conclusion

HIV increases the likelihood of progression to multiple stages of cytology that results in cervical cancer. Women who were infected with HIV were more likely to have acquired an HPV infection. HIV positive women with a higher prevalence of HPV had a greater occurrence of ASCUS. Women with HIV had a higher risk for rapid progression of HPV-induced CIN and invasive cervical cancer, which occurs because of HIV-induced immune suppression. The hypothesis that we developed from this review is that HIV is a significant driving force in the rapid progression of HPV to cervical cancer. Vaccines to combat the progression of HPV among HIV positive women have been determined to be safe[55]. Recent studies have suggested that the HPV vaccine provides significant increases in CD4 cell count and anti-HPV 16 and 18 antibodies[55]. This suggests that the progression of HPV to cervical cancer among women with HIV can be moderated through vaccine.

Conflict of interest

The authors declared that they have no conflicts of interest.

Funding

This study was not funded by any institution.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65:87-108.
2. Chaturvedi AK, Madeleine MM, Biggar RJ, Engels EA. Risk of human papillomavirus-associated cancers among persons with AIDS. JNCI J Natl Cancer Inst. 2009;101:1120-30.
3. Adjorlolo-Johnson G, Unger ER, Boni-Ouattara E, et al. Assessing the relationship between HIV infection and cervical cancer in Cote d'Ivoire: A case-control study. BMC Infect Dis. 2010;10:242.
4. Abraham AG, Strickler HD, Jing Y, et al. Invasive cervical cancer risk among HIV-infected women: A North American multi-cohort collaboration prospective study. J Acquir Immune Defic Syndr. 2013;62:405-413.
5. Isaakidis P, Pimple S, Varghese B, et al. HPV infection, cervical abnormalities, and cancer in HIV-infected women in Mumbai, India: 12-month follow-up. Int J Womens Health. 2013;5:487-94.
6. Dryden-Peterson S, Bvochora-Nsingo M, Suneja G, et al. HIV infection and survival among women with cervical cancer. J Clin Oncol. 2016; 34:3749-57.
7. Petry KU. HPV and cervical cancer. Scand J Clin Lab Invest. 2014;74:59-62.
8. Jalil EM, Bastos FI, Melli PP, et al. HPV clearance in postpartum period of HIV-positive and negative women: A prospective follow-up study. BMC Infect Dis. 2013;13:564.
9. United States Department of Health and Human Services. Global Statistics; 2017. Available from: https://www.aids.gov/hiv-aids-basics/hiv-aids-101/global-statistics. [Last cited on 2018 Jan 30].
10. de Sanjosé S, Diaz M, Castellsagué X, et al. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: A meta-analysis. Lancet Infect Dis. 2007; 7:453-9.
11. Konopnicki D, De Wit S, Clumeck N. HPV and HIV coinfection: A complex interaction resulting in epidemiological, clinical and therapeutic implications. Future Virol. 2013;8:903-15.
12. Pantanowitz L, Michelow P. Review of human immunodeficiency virus (HIV) and squamous lesions of the uterine cervix. Diagn Cytopathol. 2011;39:65-72.
13. Shaw GM, Hunter E. HIV transmission. Cold Spring Harb Perspect Med. 2012;2:a006965.
14. Center for Disease Control and Prevention. Terms, Definitions, and Calculations Used in CDC HIV Surveillance Publications; 2016. Available from: https://www.cdc.gov/hiv/statistics/surveillance/terms.html. [Last cited on 2017 Aug 30].
15. Ghate M, Deshpande S, Tripathy S, et al. Incidence of common opportunistic infections in HIV-infected individuals in Pune, India: Analysis by stages of immunosuppression represented by CD4 counts. Int J Infect Dis. 2009;13:e1-8.
16. Denny LA, Franceschi S, de Sanjose S, Heard I, Moscicki AB, Palefsky J. Human papillomavirus, human immunodeficiency virus and immunosuppression. Vaccine. 2012;30:F174.
17. Lisco A, Vanpouille C, Margolis L. War and peace between microbes: HIV-1 interactions with coinfecting viruses. Cell Host Microbe. 2009; 6:403-8.
18. Collin M, Bigley V, Haniffa M, Hambleton S. Human dendritic cell deficiency: The missing ID? Nat Rev Immunol. 2011;11:575-83.
19. Chaturvedi AK. Beyond cervical cancer: Burden of other HPV-related cancers among men and women. J Adolesc Health. 2010;46:S20-6.
20. Center for Disease Control and Prevention. Genital HPV Infection-Fact Sheet; 2017. Available from: https://www.cdc.gov/std/hpv/stdfact-hpv.htm. [Last cited on 2017 Aug 30].
21. Schiffman M, Wentzensen N. Human papillomavirus infection and the multistage carcinogenesis of cervical cancer. Cancer Epidemiol Biomarkers Prev. 2013;22:553-60.
22. Maucort-Boulch D, Plummer M, Castle PE, et al. Predictors of human papillomavirus persistence among women with equivocal or mildly abnormal cytology. Int J Cancer. 2010;126:684-91.
23. Laurson J, Khan S, Chung R, Cross K, Raj K. Epigenetic repression of E-cadherin by human papillomavirus 16 E7 protein. Carcinogenesis. 2010;31:918-26.
24. Houlihan CF, Larke NL, Watson-Jones D, et al. HPV infection and increased risk of HIV acquisition. A systematic review and meta-analysis. Acquir Immunodefic Syndr. 2012;26:2211-22.
25. McKinnon LR, Nyanga B, Chege D, et al. Characterization of a human cervical CD4+ T cell subset coexpressing multiple markers of HIV susceptibility. J Immunol. 2011;187:6032-42.

26. Anschau F, Guimarães Gonçalves MA. Discordance between cytology and biopsy histology of the cervix: What to consider and what to do. Acta Cytol. 2011;55:158-62.
27. Jenkins D. Histopathology and cytopathology of cervical cancer. Dis Markers. 2007;23:199-212.
28. University of Richmond. Abnormal Pap test results; 2018. Available from: https://www.wellness.richmond.edu/common/pdfs/factsheets/abnormal-paptest.pdf. [Last cited on 2018 Apr 24].
29. Adekunle OO. Cervical Intraepithelial Neoplasia (CIN)(Squamous Dysplasia). Intraepithelial Neoplasia. Rijeka, Croatia: InTech; 2012.
30. Obiri-Yeboah D, Akakpo PK, Mutocheluh M, et al. Epidemiology of cervical human papillomavirus (HPV) infection and squamous intraepithelial lesions (SIL) among a cohort of HIV-infected and uninfected Ghanaian women. BMC Cancer. 2017;17:688.
31. Luchters SM, Broeck DV, Chersich MF, et al. Association of HIV infection with distribution and viral load of HPV types in Kenya: A survey with 820 female sex workers BMC Infect Dis. 2010;10:18.
32. Kajaer, SK, Munk C, Junge J, Iftner T. Carcinogenic HPV prevalence and age-specific type distribution in 40,382 women with normal cervical cytology, ASCUS/LSIL, HSIL, or cervical cancer: What is the potential for prevention? Cancer Causes Control. 2014;25:179-89.
33. Duerr A, Paramsothy P, Jamieson DJ, et al. Effect of HIV infection on atypical squamous cells of undetermined significance. Clin Infect Dis. 2006;42:855-61.
34. Bajaj JS, Singh A, Aggarwal SK, Chattopadhya D, Baveja UK. Synergistic immunosuppression by candida in HIV infection: A cytokine based analysis. J Commun Dis. 2000;32:1-9.
35. Torres-Poveda K, Bahena-Román M, Madrid-González C, et al. Role of IL-10 and TGF-β1 in local immunosuppression in HPV-associated cervical neoplasia. World J Clin Oncol. 2014;5:753.
36. Bermudez-Morales VH, Gutierrez LX, Alcocer-Gonzalez JM, Burguete A, Madrid-Marina V. Correlation between IL-10 gene expression and HPV infection in cervical cancer: A mechanism for immune response escape. Cancer Invest. 2008;26:1037-43.
37. Duro R, Rocha-Pereira N, Figueiredo C, et al. Routine CD4 monitoring in HIV patients with viral suppression: Is it really necessary? A Portuguese cohort. J Microbiol Immunol Infect. 2017.
38. Yim EK, Park JS. The role of HPV E6 and E7 oncoproteins in HPV-associated cervical carcinogenesis. Cancer Res Treat. 2005;37:319-24.
39. Ghittoni R, Accardi R, Hasan U, et al. The biological properties of E6 and E7 oncoproteins from human papillomaviruses. Virus Genes. 2010;40:1-3.
40. Chakravarty J, Chourasia A, Thakur M, Singh AK, Sundar S, Agrawal NR. Prevalence of human papillomavirus infection and cervical abnormalities in HIV-positive women in eastern India. Indian J Med Res. 2016;143:79-86.
41. Chen EY, Tran A, Raho CJ, Birch CM, Crum CP, Hirsch MS. Histological 'progression'from low (LSIL) to high (HSIL) squamous intraepithelial lesion is an uncommon event and an indication for quality assurance review. Mod Pathol. 2010;23:1045.
42. Massad LS, Seaberg EC, Wright RL, et al. Squamous cervical lesions in women with human immunodeficiency virus: Long-term follow-up. Obstet Gynecol 2008;111:1388-93.
43. Denny L, Boa R, Williamson A, et al. Human papillomavirus infection and cervical disease in human immunodeficiency virus-1-infected women. Obstet Gynecol. 2008;111:1380-7.
44. Doorbar J, Quint W, Banks L, et al. The biology and life-cycle of human papillomaviruses. Vaccine. 2012;30 Suppl 5:F55-70.
45. van der Burg SH, Palefsky JM. Human immunodeficiency virus and human papilloma virus - why HPV-induced lesions do not spontaneously resolve and why therapeutic vaccination can be successful. J Transl Med. 2009;7:108.
46. World Health Organization. Human Papillomavirus (HPV) and Cervical Cancer; 2016. Available from: http://www.who.int/mediacentre/factsheets/fs380/en. [Last cited on 2018 Jan 15].
47. Ghebre RG, Grover S, Xu MJ, Chuang LT, Simonds H. Cervical cancer control in HIV-infected women: Past, present and future. Gynecol Oncol Rep. 2017;21:101-8.
48. Vink MA, Bogaards JA, van Kemenade FJ, et al. Clinical progression of high-grade cervical intraepithelial neoplasia: Estimating the time to preclinical cervical cancer from doubly censored national registry data. Am J Epidemiol. 2013;178:1161-9.
49. Borruto F, De Ridder M. HPV and cervical cancer: achievements in prevention and future prospects. Berlin, Germany. Springer Science & Business Media; 2012.
50. Origoni M, Salvatore S, Perino A, Cucinella G, Candiani M. Cervical intraepithelial neoplasia (CIN) in pregnancy: The state of the art. Eur Rev Med Pharmacol Sci. 2014;18:851-60.
51. Adler DH, Kakinami L, Modisenyane T, et al. Increased regression and decreased incidence of human papillomavirus-related cervical lesions among HIV-infected women on HAART. AIDS. 2012;26:1645-52.
52. Maranga IO, Hampson L, Oliver AW, et al. HIV infection alters the spectrum of HPV subtypes found in cervical smears and carcinomas from Kenyan women. Open Virol J. 2013;7:19-27.
53. Murdiyarso LS, Kartawinata M, Jenie I, et al. Single and multiple high-risk and low-risk human papillomavirus association with cervical lesions of 11,224 women in Jakarta. Cancer Causes Control. 2016;27:1371-9.
54. Andersen MH, Schrama D, Straten PT, Becker JC. Cytotoxic T cells. J Invest Dermatol. 2006;126:32-41.
55. Denny L, Hendricks B, Gordon C, et al. Safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine in HIV-positive women in South Africa: A partially-blind randomised placebo-controlled study. Vaccine. 2013;31:5745-53.