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Review

Effect of human papilloma virus in HIV infected person: A mini review

Solomon Sisay[1], Woldaregay Erku[2], Mulugeta Belay[3], Zufane Sisay[2], Moges Tiruneh[4], Desalegn Woldeyohannes[5]*

[1]Department of Biomedicine, School of Health Science, Dilla University, Dilla, Ethiopia
[2]Department of Medical Microbiology, Aklilu Lemma Institute of Pathobiology, Addis Ababa University, Addis Ababa, Ethiopia.
[3]Department of Tropical and Infectious Diseases, Aklilu Lemma Institute of Pathobiology, Addis Ababa University, Addis Ababa, Ethiopia.
[4]Department of Microbiology, School of Biomedical and Laboratory sciences, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia
[5]Department of Public Health, School of Medical and Health Sciences, Addis Ababa Science and Technology University, Addis Ababa, Ethiopia.

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Human immunodeficiency virus (HIV) infected person has greater frequency and severity of human papilloma virus (HPV)-associated cervical dysplasia than uninfected person. One of the risk factors for HPV infection and subsequent neoplasia of lower genital tract is impaired cell mediated immunity like in HIV patients. There is no clear information about infection of HPV and HIV in the same cell, but there is evidence which indicates role of HIV on HPV at molecular level. The impact of HPV on HIV is not also clearly understood. Currently, no data suggest that HPV acts differently in HIV positive person, but HPV persist in the lesion. Treatment for HPV in HIV patients involves both correction of immuno-suppression and combination of standard treatment use to clear HPV. HIV sero-positivity is known to be associated with an increased prevalence of ano-genital HPV infections in both sexes. Little is known whether HPV vaccine in HIV positive person can mount and maintain protective antibody titer against HPV infection. HIV positive women should undergo gynecological examination and vaccination against HPV genotypes to prevent the development of cervical cancer. The objective of this review is to indicate the interaction of HPV with HIV in modulating pathogenesis and disease progression in co-infected individuals.

Key words: Human immunodeficiency virus (HIV), human papilloma virus (HPV), HIV infected person, effect, risk factor

INTRODUCTION

Human papilloma virus (HPV) infection is the most common sexually transmitted viral diseases with prevalence rate ranging from 10 to 50% among sexually active women (Haganse et al., 2000). Besides, there are 70 types of known human papilloma virus. Out of which, 30 are further divided according to their oncogenic potential which infect ano-genital tract (Haganse et al., 2000).

*Corresponding author. E-mail:desalegn01@gmail.com

Abbreviations

AIDS -Acquired Immuno Deficiency Syndrome; AIN- Anal Intraepithelial Neoplasia; ATCD-Apoptotic T Cell Death; APC- Antigen Presenting Cells; CD- Cluster of Differentiation; CIN-Cervical Intraepithelial Neoplasia; CTL-Cyto Toxic Lymphocytes; DNA-Deoxyribo Nucleic Acid; g p-Glyco Protein; HIV-Human Immunodeficiency Virus; HPV-Human Papilloma Virus ; IFN-γ-Interferon gamma; IgG- Immunoglobulin G; IL-Inter Leuken; MSM - Men who have Sex with Men; nm-Nano Meter; pRb-

Protein Retino Blastoma; RNA; Ribo Nucleic Acid; SIL-Squamous Intraepithelial Neoplasia; Th-T helper cell; TNF-Tumor Necrosis Factor; µL-Micro Liter.

HPV associated lesions are usually transient and presumably regress as a result of cellular immune response specifically by T lymphocytes and have period of clinical latency, but it frequently reappears especially on human immunodeficiency virus (HIV) infected person (Gage et al., 2000). Additionally, HIV infected women have greater frequency and severity of HPV associated cervical dysplasia than uninfected women. Therefore, the presence of HIV exacerbates coexisting HPV infections (Gage et al., 2000).

Majority of ano-genital HPV infections appear to be transient and self limited in HIV sero-negative women while HIV sero-positive women are at risk for development of high-grade squamous intraepithelial lesion and cervical lesion with certain type of HPV infection like 16, 8, 31, 33, 35 and 45 (Sun et al., 1997).

Among HIV infected women, HPV disease manifest as cervical intraepithelial neoplasia on several studies, which is exacerbated by HIV induced immune suppression thereby reducing CD4 count. Moreover, women with high plasma HIV-RNA levels are at increased risk of cervical HPV infections and cytological abnormalities of cervix. However, cervical cancer without HIV infection has not shown such a dramatic relationship to lower CD4 cell counts (Clark et al., 2009).

HPV infections in most immune-competent individuals are transient, and the amount of persistent infections is relatively low when compared to immuno-suppressed individuals who exhibit high rates of persistent HPV infection. Consequently, these groups of individual have a high risk of HPV associated malignant disease (Kreuter et al., 2009). Among HIV infected individuals, men who have sex with men are especially at high risk of anal cancer and its potential precursor lesion like anal intraepithelial neoplasia (Kreuter et al., 2009).

Hence, infection with human papilloma virus poses the risk of cervical and anal cancer in women and anal cancer in men who are homosexuals. Consequently, there are high rates of cervical and anal HPV infection in HIV infected women and high rates of anal HPV infection in HIV infected men (Palefsky et al., 2007).

This review, therefore, tries to assess the interaction of HPV with HIV in modulating the pathogenesis and disease progression in co-infected individuals.

Virology of HPV

HPV is a member of the genus papilloma virus in the family of papovaviridae. HPV is a non-enveloped virus that measure from 50 to 55 nm in diameter, which have icosahedral capsid composed of 72 capsomer, and contain double standard circular deoxyribonucleic acid (DNA) genome. Genomic organization of all HPVs is similar which consists of an early (E) region, and late (L) region which comprise from L1 and L2 regions (Reichman et al., 1998).

Early region is divided into E1 and E2 regions, encode proteins, which are vital for DNA replication (Palefsky et al., 2007). E2 also encodes two proteins which inhibit transcription of early region and other deactivates transcription process. Additionally, early region is further classified into E6 and E7 which encode proteins for allowing the replication of the virus and transformation of host cell. L1 and L2 encode viral capsid protein during viral assembly (Motoyama et al., 2004).

Genomic classification of HPV

More than 80 types of HPV are known and classified according to their oncogenic properties (Motoyama et al., 2004). HPVs 16, 18, 31, 33, 35 and 39 are considered as high risk types which result in carcinoma and dysplasia [8]. HPVs 51 and 52 are considered as intermediate risks which result in mild dysplastic lesion (Motoyama et al., 2004). HPV types 16, 18, 31, 33 and 35 cause ano-genital infections which are responsible for 80% of high-grade squamous intraepithelial lesion and cervical cancer (Spinillo et al., 2001).

Clinical manifestation, pathogenesis and epidemiology of human papilloma virus

Clinical manifestation of human papilloma virus

Clinical manifestation of human papilloma virus depends on the location of lesion and types of virus. Common warts are usually occurring in the hands of flesh-colored to brown, exophytic, hyperkeratotic papule (Reichman et al., 1998). Plantar warts may be quite painful which contain thrombosed capillaries. Flat warts are common among the children and occur in the face, neck, chest and fore arms and legs (Reichman et al., 1998).

Ano-genital warts expressed as exophtic papulae which are seen on non-hair bearing skin involving vulva, cervix, perineum, penis and anal region which may progress to cauli flower like mass on penile shaft and vagina (Zanotti et al., 2002).

Pathogenesis of HPV

Replication of HPV begins with the infection of cell. HPV-DNA replicates and is transcribed when virus infected cells differentiates. Consequently, virus are assembled in the nucleus and released when host cells are shed. The

process is associated with proliferation of epidermal layers. Episomal HPV-DNA is present in the nuclei of infected cells in benign lesion, but in severe dysplasia, HPV is integrated with disruption of E1/E2 open reading frame which leads up regulation of E6 and E7 to interfere with cellular tumor suppressor protein (Motoyama et al., 2004).

E6 and E7 proteins are essentials for the maintenance of transformed state of host cells. E6 proteins are bind and degrade tumor suppressor gene P53 of host cells, on the other hand, E7 proteins inhibit retinoblastoma protein of host cell (Haganse et al., 2000). Binding of E6 with P53 helps to prevent the arrest of G1 phase which blocks DNA repair and activation of apoptosis of host cell (Bekker et al., 2004). E6 induces tolemerase activity thereby preventing the shortening of tolemere chromosome. Hence, the lengthening of telomere protects cell from apoptosis (Bekker et al., 2004). Binding of E7 to pRb releases host transcriptional factor (E2F) from pRb/E2F complex and E2F activates gene which is important for mitosis which cause hyper proliferation of host cell (Bekker et al., 2004).

Epidemiology of HPV

About 500,000 new cases of cervical cancer are annually recorded and reported in the world. Out of them, 26% are from China and India which contributes to 20% of the total reported new cases (Joshi et al., 2005). Epidemiological studies conducted in South Africa and Rwanda revealed that prevalence of cervical cancer was found to be 55% due to HPV (Clark et al., 2002). The same study in 1990 showed that 19% of asymptomatic HIV infection in young patients with cervical cancer, and 11% of sero-positivity among women attending clinic for the evaluation of pap smear.

Another study done in Rwanda showed that prevalence of all types of HPV was 47 % in HIV negative women as compared to 72% in HIV positive women. Besides, among HIV negative women, incidence of high risk types of HPV was 28% (Veldhuijzen et al., 2011). A similar study was done in Cameron to assess the prevalence and type of HPV infection in HIV infected women (Desruisseau et al., 2009). The study showed that 67% of women infected with HIV had HPV infection. Of those with high risk HPV infection, HIV positive women were more likely to have abnormal cytology than HIV negative women.

These and other similar studies showed that there was no increased association between cervical cancer and HIV infectivity in women in Africa due to short life span for untreated HIV positive women as compared from the average time required for CIN to progress into invasive cancer (Ferency et al., 2003).

Immunopathogenesis of HIV

Suggested immuno-pathogenic models of HIV encompass HIV specific CD8 CTL which can kill HIV infected CD4 cells, autoimmune reactions including auto antibodies that destroy the immune system, immune suppression induced by HIV protein (such as gp120, Tat and Nef), activation of APC and T cells which leads to replication of HIV and apoptotic T cell death (ATCD) suggested to contribute to pathology of HIV disease through reducing cellular immunity (Shearer et al., 1998).

HIV infection has an impact on human papilloma virus during co infection (Spinillo et al., 2001). HIV acts on HPV by increasing transactivational activity of early HPV gene such as E7. HIV activates HPV integration and induces synthesis of L1 protein and HIV gene interacts with HPV which results to the development of cervical cancer (Spinillo et al., 2001).

Host immune response to HPV

Humoral response

Human antibodies respond to HPV capsid antigen reaction with conformational epitopes (Haganse et al., 2000). Systemic HPV IgG level is high in persistent HPV infection, and IgA against HPV 16 level may be protective against local infection (Haganse et al., 2000). Local cervical HPV 16 DNA antibodies have been detected with specific immunoglobulin class like IgG after infection (Sheetym et al., 2005).

Cellular response

Cellular immune response to HPV shows that increase Th1 cytokines production like IL 2, IL 12, and IFN-γ which is commonly observed in control of intracellular infections by induction of cytolytic activity (Sheetym et al., 2005). Production of IL 2 by CD4 cell has been associated with viral persistence and diseases progression (Haganse et al., 2000).

Impact of HPV on HIV and vice versa

Infection with certain types of human papilloma virus has been identified as cause of cervical intraepithelial neoplasia and cervical cancer (Palefsky et al., 2006). One of the risk factors of HPV infection and subsequent neoplasia and cancer of lower genital tract is impaired cell mediated immunity. A study showed that HIV positive women have shown a strong and consistent relation between HPV co infection which predisposes to cervical

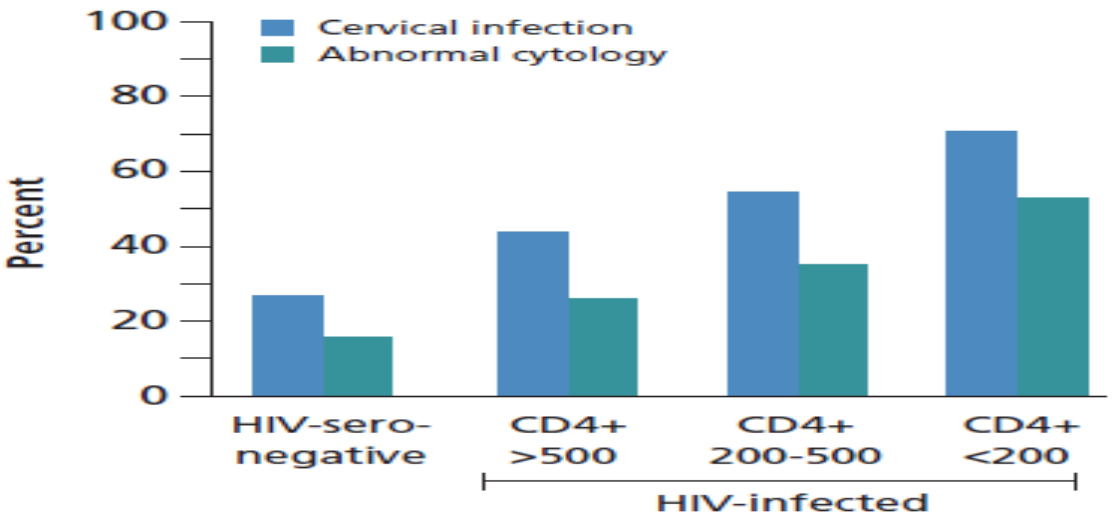

Figure 1. Rates of human papilloma virus cervical infection and abnormal cytology in HIV sero-negative women and HIV infected women according to CD4 count (cells/µL).

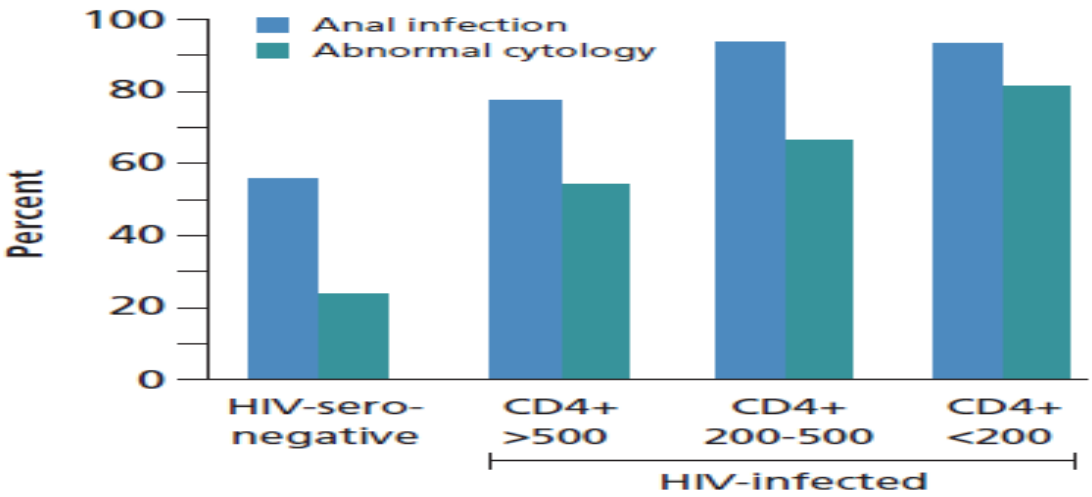

Figure 2. Rates of HPV anal infection and abnormal cytology in HIV sero-negative men who have sex with men and HIV infected MSM according to CD4 count (cells/µL)

intraepithelial neoplasia (Ferency et al., 2003).

Similar study revealed that prevalence of HPV infection was higher in HIV positive than among HIV negative women 87 and 73%, respectively. And, HPV infection was correlated with CD4 cell counts which was more likely to be detected in women with CD4 count below 500 cells/ µL (44%) than in those with higher counts (24%) (Ferency et al., 2003). HPV cause ano-genital neoplasia in infected male in condition where CD4 count is lower due to HIV related immuno-suppression. Therefore, incidence of anal cancer elevated in HIV infected male as compared from non-infected (Palefsky et al., 2006).

Figure 1, shows rate of HPV cervical infection and abnormal cervical cytology in HIV sero-negative women and HIV infected women according to CD4 cell count; rates of anal infection and abnormal cytology in homosexuals according to HIV status and CD4 cell count (Figure 2); and rates of cervical and anal human papilloma virus infection in HIV sero negative women and HIV infected women according to CD4 count (Figure 3). Rates of

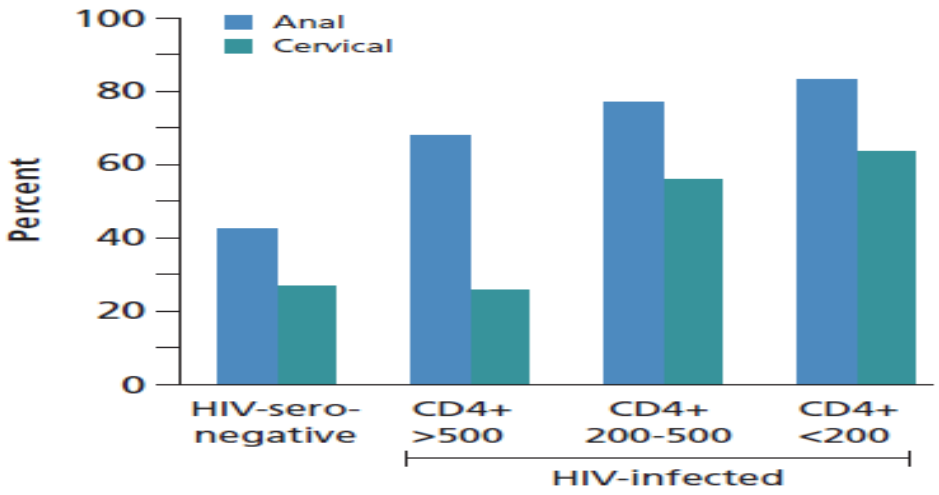

Figure 3. Rates of cervical and anal human papilloma virus infection in HIV sero negative women and HIV infected women according to CD4 count (cells/µL)

infection and abnormal cytology increase as CD4 cell count decreases, as do number of oncogenic HPV types involved in infection (Palefsky et al., 2007).

Impact of HPV on HIV

No physical evidence existed for infection of HIV in HPV infected the same host cell which signifies as co infection. HIV 1 tat protein may be secreted from HIV infected cells and taken up by HPV infected host cell. It is, therefore, unlikely that the two viruses interact directly (or physically) in a sustained manner which would be expected to modify the outcome of HPV associated disease (Palefsky et al., 2006).
However, other cell culture studies have shown increased positive regulation of HIV expression by HPV infected cells (Clark et al., 2002). Possible mediators of enhanced expression are HPV induced inflammatory cytokines particularly IL-6. IL-6 may induce HIV p24 expression in monocytes (Clark et al., 2002).

Impact of HIV on HPV

HIV 1 regulatory tat protein in combination of E2 protein of HPV 16 can transactivate HPV 16 P97 promoter in cervical carcinoma (Braun et al., 1994). HIV tat protein can also reverse E2 mediated repression of HPV 16 promoter which results in providing potential mechanism for enhanced HPV gene expression in cervical tissue (Braun et al., 1994).
Additionally, HIV tat protein can function when added exogenously to culture cells which also transactivate HPV in adjacent epithelial cells (Braun et al., 1994). However, indirect effects of HIV through aberrant expression of cytokines in cervical cells could influence the expression of HPV genes (Braun et al., 1994). Cytokines such as transforming growth factor have been shown to regulate expression of both HIV and HPV proteins (Braun et al., 1994).
Similar study showed that HIV is associated with an increase transactivational activity of HPV gene such as E7 which evidenced in vitro study showing that HIV 1 activates integration of HPV 18 and induce synthesis of L1 caspid protein. HIV 1 gene interacts with HPV 16 E6 which modifies cervical cell cancer (Spinillo et al., 2001).

Pathogenesis of HPV in HIV infected person

Pathogenic effect of HPV in HIV positive and HIV negative individuals is that lesions are likely to persist in former in a given attenuated immune response. Additionally, HPV plays major role through E6 mediated chromosomal instability (Palefsky et al., 2006). Moreover, inability of immune system in setting of HIV infection to clear HPV infected cells may serve further to facilitate pathology of HPV by providing HPV infected cells with ample time for changes to accumulate.
Beneficial effect of antiretroviral might be limited due to one of the two possibilities either due to damage which occurred to immune system which led to an irreversible loss of HPV specific immune response despite improvement in response to other agents or due to

antigens (or sufficient genetic) damage may have occurred in the epithelium in which cells continue to proliferate even if HPV specific immunity is restored (Palefsky et al., 2006).

Treatment of HPV in HIV infected person

Correction of immune-suppressed condition should be part and parcel of management approach. Antiretroviral therapy decreases incidence of genital warts by combining treatments which includes an ablative or excisional approach (Gage et al., 2000). Imiquimod drug has had mixed results in HIV infected individuals, but recent study has suggested that the responses to drug are similar in HIV infected and HIV uninfected individuals (Gage et al., 2000).

Hence, treatment for HPV in immune-suppressed patients involves both correction of the immune-suppression and standard treatment in terms of ablative and excisional approaches in combination with taking certain drugs like podophyllotoxin, trichloroacetic acid, cryotherapy and interferon (Zanotti et al., 2002).

HPV vaccine

Prophylactic and therapeutic vaccine is currently being implemented. The first clinical trials with prophylactic HPV16 vaccine appeared to be protective for the duration of trials (Bekker et al., 2004). Currently, HPV vaccine is available as quadrivalent vaccine against genotype 6, 11, 16 and 18 (Palefsky et al., 2007).

Efficacy of vaccine reaches 100% in woman without serologic and DNA evidence of HPV infection, while in woman who had previous exposure of HPV infection reaches 39% (Palefsky et al., 2007). Moreover, either several studies needed to indicate whether vaccine provides protection in HIV infected person or whether HIV positive person can mount and maintain protective antibody titer against HPV infection (Palefsky et al., 2007).

Conclusion and outlook

HIV sero-positive women have high rate of persistent HPV infections with certain types of HPV which are strongly associated with development of high-grade squamous intraepithelial lesions and invasive cervical cancer. Persistent infections may explain increased incidence of squamous intraepithelial lesions in HIV sero-positive women.

Antiretroviral therapy has limited positive effect on HPV related neoplasia. There is mounting evidence that incidence of anal cancer will continue to rise among HIV infected homosexuals even if antiretroviral therapy (ART) is provided for them. Incidence of anal intraepithelial neoplasia (AIN) and anal cancer is high among HIV infected women and homosexuals. Relation between HIV and HPV is still complex which requires observation from many perspectives. Beside, several studies are needed to indicate whether vaccine provides protection in HIV infected person or HIV positive person can mount and maintain protective antibody titer against HPV infection.

HIV positive women should undergo gynecological examination which incorporates thorough inspection of external ano-genital region, and all suspicious lesions should be removed for biopsy. Colposcopy should be performed in response to any abnormal cytological test results, including atypical squamous cells of undetermined significance.

Vaccination against HPV genotypes may prevent development of many CIN lesions, but the duration of protection and risk of cervical cancer in non-responders need to be evaluated before global introduction of the vaccine. Particularly, men and women at risk should be considered for screening, vaccination and treatment of AIN since real benefits accrue from early detection of cancer.

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