

Kosz Katarzyna, Zielińska Martyna, Zarankiewicz Natalia, Kuchnicka Aleksandra, Cisel Bogumiła. Relationship between HPV and HIV. Prevalence, molecular mechanisms and screening of HPV among HIV infected women. *Journal of Education, Health and Sport*. 2020;10(7):127-137. eISSN 2391-8306. DOI <http://dx.doi.org/10.12775/JEHS.2020.10.07.013>
<https://apcz.umk.pl/czasopisma/index.php/JEHS/article/view/JEHS.2020.10.07.013>
<https://zenodo.org/record/3951124>

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.

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The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 25.06.2020. Revised: 01.07.2020. Accepted: 18.07.2020.

Relationship between HPV and HIV. Prevalence, molecular mechanisms and screening of HPV among HIV infected women

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Abstract

Introduction: Human papillomavirus (HPV) and human immunodeficiency virus (HIV) are the most common sexually transmitted infections (STI) globally. According to the World Health Organisation (WHO) there are around 17.4 million women living with HIV and over 290 million HPV infected women worldwide.

Purpose: This review is to summarize available data concerning the relationship between HIV and HPV infection among women. The analysis comprises molecular mechanisms of HPV infection among HIV(+) women as well as HIV infection among HPV(+) women, prevalence of HPV and cervical lesions among women living with HIV and screening of HPV and cervical cancer (CC) among HIV infected women.

Material and methods: The review includes publications from 2011 to 2020. The data has been collected by the use of the PubMed, Ovid, Up-To-Date and WHO website. Key words used to search for references include: HPV, HIV, prevalence, molecular mechanism, screening.

Results: HIV infection is a risk factor for HPV acquisition. On the one hand, prevalence of HPV, multiple HPV, high risk HPV (hrHPV) infections and cervical intraepithelial neoplasia (CIN) is higher among HIV(+) women. On the other hand, HPV infection can also predispose to HIV acquisition. Evidence on how these viruses influence each other can be a breakthrough in the range of prevention, detection and treatment of both HIV and HPV infection.

Conclusions: Relationship between HPV and HIV is an interest of nowadays medicine. Possibly, these viruses may cooperate and enable infection of each other. It has been showed that the prevalence of HPV, multiple HPV, hrHPV infections and cervical lesions is higher among HIV(+) in comparison to HIV(-) women. Further studies should be performed providing an insight into a molecular mechanism responsible for this cooperation.

Key words: HPV; HIV; prevalence; molecular mechanism; screening.

Introduction and purpose

HPV is a double-stranded DNA-virus which belongs to the *Papillomaviridae* family. This small non-enveloped virus forms a large and heterogenic group with new HPV types being constantly discovered [1]. Currently there are more than 200 identified HPV genotypes, which are classified into five genres with α -papillomavirus (Alpha PV) and β -papillomavirus, γ -papillomavirus, μ -papillomavirus and ν -papillomavirus [2,3]. The Alpha PV are divided into cutaneous and mucosal types, and further the mucosal types are subdivided into low- and high-risk groups depending on their oncogenic ability. The cutaneous Alpha types are also included as low-risk [4,5]. Low-risk HPV (lrHPV) usually cause benign hyperproliferative lesions and rarely lead to malignant lesions among the general population [6]. Most frequently detected lrHPV types are HPV-6 and HPV-11 which are the etiologic agents of over 90% of benign genital warts [6,7]. HrHPV account for almost 90% of all CC cases worldwide. Most common hrHPV include: HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52, HPV-58. Two HPV genotypes (16 and 18) account for the great majority (70-80%) of CC and pre-cancerous cervical lesions [8,9]. The determination of HPV genotypes is crucial for evaluation of a disease spectrum and severity. Although, HPV

genotypes are able cause either genital lesions or cutaneous, nongenital warts, particular attention was paid to genital lesions in this paper.

HPV is highly transmissible; it is estimated that there are more than 290 million HPV infected women worldwide [10]. Over 300 000 of them die on the grounds of CC each year [11]. Squamous cell carcinoma (SCC) and adenocarcinoma are the most common histological subtypes accounting respectively for approximately 70% and 25% of all CC [12]. In 2018, the total burden reached up to 311 000 of deaths due to CC worldwide [13]. HPV and HIV are considered as two of the most pathogenic sexually transmitted infections (STI) in the world. Nevertheless, both of them are incurable, their symptoms and disease caused by these viral infections, can be still reduced and modified through treatment [11].

The aim of this study is to review the actual knowledge concerning prevalence of HPV and cervical lesions as well as screening of HPV among HIV infected women. Moreover, it has been presented how HPV and HIV can cooperate enabling infection of each other. The review includes publications from 2011 to 2020. The data has been collected by the use of the PubMed, Up-To-Date and WHO website.

Description of the state of knowledge

HPV and carcinogenesis

Cervix is lower one third of uterus. It consists of endocervical mucosa lined with a single layer of columnar mucous cells and ectocervix covered with nonkeratinized stratified squamous epithelium [14]. Important for CC development is a transformation zone (TZ) which is described as the area where squamous metaplasia has occurred. TZ is crucial from the clinical point of view because it is a point of departure for 95% of SCC [15]. To have most plausible outcome of Pap smear test, both squamous cells and endocervical or squamous metaplastic cells should be present in a cytological sample and thus form a basis for the assumption that sample came from the TZ [16]. Even though, the entire anogenital epithelium can be infected by HPV, the cervical TZ is particularly susceptible to CC development. Possibly, it is because of the cell population in this area which can be an origin for most of the precancerous and cancer lesions [17].

It is widely acknowledged that the persistent cervical infection by oncogenic type of HPV is necessary for CC development and it is virtually impossible to develop CC in the absence of sexually transmitted HPV infection. Cervical carcinogenesis can be pictured as following stages: 1. HPV infection and its persistence 2. Development of precancerous lesions 3. Invasion leading to CC [17,18]. In order to classify cervical lesions, two systems based on either histological or cytological findings are used. First one, histological classification is described with the term - cervical intraepithelial neoplasia (CIN) with three degrees of severity: CIN 1 considered as a low-grade lesion referring to mildly atypical changes in the lower third of the epithelium, CIN 2 - high-grade lesion with moderately atypical cellular changes in the basal two-thirds of the epithelium and preservation of epithelial maturation and CIN 3 also high-grade lesion but with severely atypical cellular changes involving more than two-thirds of the epithelial thickness [19,20]. On the other hand, for describing cytological findings The Bethesda system (TBS) is used. Abnormalities of squamous cells can be described as: Atypical squamous cells of undetermined significance (ASCUS), Low grade squamous intraepithelial lesion (LSIL), High grade squamous intraepithelial lesion

(HSIL) or SCC. To simplify, all the neoplastic changes classified as CIN 1 or other lesions suggestive of HPV infections can be included to LSIL group, whereas CIN 2 and CIN 3 can be regarded as HSIL [16].

HPV and HIV transmission

HPV can be transmitted by sexual intercourse through vaginal, anal or oral sex. It needs to be noted that HPV may be also transmitted perinatally from mother-to-child resulting in recurrent respiratory papillomatosis in the baby [21]. HPV causing common warts can be spread and transmitted by the direct skin contact or by touching things which were touched by a person with warts [6]. HIV, the same as HPV can be transmitted via intact mucous membranes, injured skin or mucosa. Additionally, HIV is able to enter the body via parenteral inoculation, exchange of fluids such as blood, semen, vaginal secretions or breast milk. HIV may be also transmitted from mother-to-child during pregnancy and delivery. On the contrary, HIV cannot be passed via kissing or sharing personal objects [10, 21-23].

Correlation between HPV and HIV

HIV infection is generally characterized by the progressive loss of CD4(+) T cells through their destruction or reduced production. HIV-specific CD4(+) T cells are preferentially infected by HIV and their marked depletion leads to the acquired immune deficiency syndrome (AIDS) [24,25]. According to the latest Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV, two markers are recommended to monitor people with HIV: CD4(+) lymphocyte cell count and plasma HIV RNA [26]. Interestingly, in one of the studies it has been shown that plasma HIV RNA levels have a stronger association with HPV incidence than with HPV persistence [27]. Researchers are still looking for the molecular mechanism which could explain why patients with HIV are more liable to HPV infection in comparison to HIV-negative individuals. One of the molecular mechanisms through which HIV-induced immunosuppression increases HPV susceptibility is the CD4(+) level. Low CD4(+) amount (≤ 200 cells/ μ l) have been demonstrated as a principal and independent predictor of HPV infection. Moreover, in the HIV-infected individuals, the likelihood of HPV acquisition and the progression of intraepithelial neoplasia increases in the proportion to the loss of CD4(+) cells. Hence, this reduced CD4(+) count compromises T-cell function and favours HPV infection [28,29]. Another mechanism in which HIV can increase the HPV acquisition has been proposed. *Ex vivo* study consisted in the adjunction of HIV proteins (gp120 and tat) with cytokines produced by HIV-infected cells (TNF- α and IFN- γ) into the cervical epithelial cells in tissue explants from HIV-uninfected patients. This caused the separation of epithelial tight junction and enabled HPV penetration into basal epithelial cells. Possible mechanism in which HIV tat protein increased HPV penetration was probably through the enhancement of HPV transcription, HPV E oncogenes and L capsid proteins expression. It indicates that HIV can disturb the cohesion of epithelial tight junctions and thus facilitates HPV penetration into the targeted basal epithelial cells [29,30].

Prevalence of HPV

Meta-analysis performed by Forman et al. (2012) extracted data from 194 studies and provided an overview for the worldwide prevalence of HPV. According to this analysis, the prevalence of HPV accounts to 11.7% around the world. The highest incidence has been observed in The Caribbean (35.4%), Eastern Africa (33.6%) and Eastern Europe (21.4%). There was also a relationship between age and HPV prevalence with the maximum rates in women under 25 years and a monotonic decrease at older ages [31]. Not surprisingly, the prevalence of HPV among HIV-positive patients is higher in comparison to HIV-negative individuals. Study conducted in Central/Eastern Italy involved representative sample of 200 women aged 18-66 years. The overall prevalence of HPV was 33.0% with a higher prevalence among HIV-positive women (48.0%) in comparison to HIV-negative women (28.0%) [8]. The prevalence of HPV infection among HIV-positive patients was performed by Fusco et al. (2018). Researchers showed a high occurrence of HPV infection among HIV-patients (50.2%) in comparison to previous studies (23% in Konopnicki et al. 2016 or 19% in Delory et al. 2017) [32-34]. One of the highest rates was found in Southern India, where among 104 HIV-infected women, 57.7% of them had also HPV infection [35]. Interestingly, in Togo, Western Africa HPV occurrence among HIV-positive women amounted to 22.2% whereas for the general population it was 19.6% [31,36]. Although, this rate is one of the lowest in Western Africa, it needs to be considered that all of the women participating in this study were under combined antiretroviral therapy (cART). CART, as additional factor, could significantly influence and change the outcome of this study [37]. Not only the overall prevalence of HPV is higher among HIV-positive women, but also the prevalence of hrHPV or multiple HPV infections. According to current data, in one of the studies, 35% of HIV-positive and HPV-positive samples were found to be multiple HPV infections [32]. In Brussels, Belgium 116 of 508 HIV-positive women were carriers of hrHPV infection (23%) with the most frequent genotypes - HPV-52 (19.8%) and HPV-18 (14.6%) detected [37]. Higher rate has been observed in HIV infected women on cART in Thailand. It has been reported that among 214 HIV and HPV coinfecting women, 159 (74%) had ≥ 1 hr-HPV genotype infection. Most common genotypes were: HPV-52 (18%) and HPV-16 (10%). Low CD4+ count, younger age and low education were also found to be independently associated with hrHPV occurrence [34]. Another study compared hrHPV prevalence among HIV-negative and HIV-positive women in Central/Eastern Italy with a result: 18.67% vs. 40%. In the same study multiple HPV infections were found in 43.94% of HPV positive samples. Additionally, there was a statistically significant higher prevalence of HPV-11, HPV-16, HPV-18 and HPV-31 genotypes in the group of HIV-seropositive women [8]. Difference between hrHPV occurrence among HIV-positive and HIV-negative patients was also found in Ghana, West Africa (65.6% vs. 30.2%). Moreover, it has been reported that 60.6% of HIV(+) vs. 21.3% of HIV(-) had multiple hrHPV infections. [38]

Prevalence of precancerous lesions and cervical cancer

HPV infection is an indisputable contributor for LSIL, HSIL or CC development. The HPV genotype as well as immunodeficiency (e.g. HIV-seropositivity) are the only clear risk factors for the persistence and progression of HPV infection. HIV(+) women present a median 3-fold higher occurrence of cervical lesions in comparison to their HIV(-) counterparts. [40].

Performed studies showed that HIV can increase the prevalence of CIN, intensify LSIL to HSIL progression and most of all, increase possibility of developing CC [29,40,41]. Available data state that the incidence of CIN is four to five times higher among HIV(+) in comparison to HIV(-) women or juvenescent with high-risk sexual behaviours [42]. According to current knowledge, an increased prevalence of CIN is strongly associated with reduced CD4+ cell counts. Moreover, recurrence of CIN appears in approximately 90% women with CD4+ counts <200 cells/mm³ [40]. In one of the studies performed in Brazil, LSIL were observed in 7.8% of HIV(+) and 2.8% of HIV(-) women, while HSIL were present in 2.5% of HIV(+) and 0.8% of HIV(-). It clearly showed that HIV(+) women had a higher prevalence of cervical lesions in comparison to their HIV(-) counterparts [41]. A systematic review of 5,882 HIV(+) women from 15 studies also showed that LSIL to HSIL progression is higher among HIV(+) women and drew attention to the relevance of low CD4+ count in this progression. Taking into consideration the prevalence of invasive CC, it is also more common among HIV-infected women. Researchers found a relative risk of 5.4 for CC in HIV-infected women living in the United States, compared to the general population. However, this increased risk is not as high as in other AIDS-defining malignancies, such as non-Hodgkin lymphoma or Kaposi sarcoma. It has been also indicated that HIV-infected women develop invasive CC 10 to 15 years earlier in comparison to their HIV-negative counterparts. Moreover, they manifest more advanced disease stage and have less promising prognosis [40].

Screening of Cervical Cancer among HIV-positive women

Unfortunately, there is a lack or inconclusive evidence concerning suitable and effective CC screening tool for HIV-positive women [43]. According to Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV, currently a Pap smear is recommended for both groups of women with HIV infection aged <30 years and >30 years. However, for the second group a Pap smear can be also supported by HPV DNA co-testing. This screening should be done within the onset of sexual intercourse and no later than age 21 years. Provided that initial Pap smear is normal, the next one should be performed in 12 months and continued throughout a woman's life [44]. Bearing in mind that HIV is common among less developed countries, implementing any screening method is crucial. Inasmuch as there are some countries, that cannot afford to use Pap or HPV DNA test as a screening method, visual methods such as visual inspection with acetic acid (VIA) or visual inspection using Lugol's iodine (VILI) is a suitable alternative option. VIA/VILI-based screening should be implemented into HIV/AIDS care programmes in developing and least developed countries. It may also contribute to further introduction of low-cost HPV-based screening tests which has been already proposed as the primary screening method in Europe [45]. Knowing that a great majority of invasive CC are preventable thanks to refined access to high-functioning HPV testing, a routine targeted screening would significantly decrease the burden of CC among HIV(+) women. [46]

HPV presence and HIV acquisition

While it has been clearly showed that HIV presence is a risk factor for HPV acquisition, some researchers started to consider the opposite correlation, in which the HPV infection might have been the risk factor for HIV acquisition. It has been estimated that HIV acquisition rate is almost two times higher among HPV(+) individuals in comparison to HPV(-) counterparts. [47] The plausible mechanism through which HPV could facilitate HIV acquisition involve E7 protein. It has been demonstrated that the E7 protein downregulates an epithelial adhesion molecule – E-Cadherin and thus increases susceptibility to HIV acquisition. Downregulating proteins promote the infiltration of Langerhans cells, upregulate inflammatory cytokines and cause an increase of HIV replication [29,8]. Another possible mechanism is related to the T-lymphocytes level. Host immune response to HPV infection cause an increase in T-cell production and as T-lymphocytes are primary target cells for HIV, their enhanced number can facilitate HIV infection [29].

Summary:

Undoubtedly, there is a correlation between HIV and HPV infection. Infection of one, enables an acquisition of each other and possibly, these viruses have an opportunity to cooperate. However, there is a lot of uncertainty in the matter of molecular mechanism responsible for this appearance. Each of the molecular mechanisms seems to be plausible but there is still a need to explore it more deeply in order to get an undisputed answer. Evidence on how these viruses influence each other can be a breakthrough in the range of prevention, detection and treatment of HIV and HPV infection. It has been proven that prevalence of HPV is higher among HIV(+) women in comparison to their HIV(-) counterparts. Moreover, HIV (+) patients have a higher rate of hrHPV and develop multiple HPV infection more often. Aggressive cervical lesions, as well as CC are also more common among women living with HIV. HPV screening programmes should be implemented into HIV/AIDS programmes in order to minimize HPV occurrence among HIV(+) patients. Introducing HIV test among HPV(+) individuals can reduce an appearance of HPV and HIV coinfection. HPV prevention programmes have the potential to be an additional HIV control strategy, providing long-term benefits for both men and women.

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