CLINICAL IMPLICATIONS OF THE INTERACTION BETWEEN HPV AND HIV INFECTIONS

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HIGHLIGHTS

- HIV associated immune depletion causes anogenital HPV related neoplasms
- Pre-pubertal HPV vaccination gains importance in HIV-prevalent nations
- Cervical cancer screening must accompany all ART programmes for women
- Screen positive women need standard treatment and follow-up
- Gynaecologic cancer in HIV-positive women is treated with total therapeutic doses
Abstract

HIV-related immunodeficiency has complex effects on female genital HPV which include increased risks of infection, multiple types, persistence, re-activation and the risk to develop pre-invasive and invasive disease.

Reconstitution of immunity with anti-viral drugs improves cellular immunity but the risk of HPV-related malignancy remains higher than background incidences and presents at younger ages. Early initiation of anti-retroviral therapy (ART) allows improved retention of immune memory via existing antibodies and T-cell clones and improves long-term outcomes.

Suggestions of a higher risk to contact HIV if there is existing genital HPV-infection are supported and explained by pathophysiological cervical changes including inflammation.

HIV-HPV interactions should influence public health decisions towards prioritising large-scale pre-pubertal HPV-vaccine roll-out, secondary cervical cancer prevention and early detection programmes for HIV-infected women as well as early initiation of ART.

This chapter will also focus on special considerations for the management of women with co-infection with these two viruses and genital HPV-related disease.

**Keywords:** cervical HPV; HIV; antiretroviral; vaccination; cervical pre-cancer; cervical cancer; immune-deficiency
INTERACTIONS BETWEEN HIV AND HPV

Viral acquisition and immune-response

Multiple ulcerative and inflammatory genital infections are generally accepted as risk factors to acquire HIV infection, including Neisseria gonorrhoea, Trichomonas vaginalis, syphilis, herpes simplex virus and Chlamydia trachomatis [1-3]. The relationship between HPV infection and the risk of HIV seroconversion remains unclear, currently suggesting an elevated risk of HIV acquisition with existing or new HPV infection. Two meta-analyses have demonstrated an increased acquisition risk (OR ~ 1.9) using data from eight observational studies [4,5] but these results may reflect residual confounding bias and is not supported by studies using different methodology [6].

HPV is highly transmissible and although it does not cause clinically recognisable inflammation, it recruits dendritic cells [7,8], T-cells and macrophages and inhibits Langerhans cells [9]. HPV infection also disrupts the mucosal integrity and immunity by down regulation of antimicrobial [10] and cell adhesion proteins [11]. All these mechanisms as well as the high prevalence of HPV infection provide a biological basis for a possible increase in HIV transmission ascribed to HPV.

Compromise to the immune system cause an increase in HPV acquisition, prevalence, persistence, and progression to disease. This association has long been observed among immunosuppressed transplant patients and now also confirmed among HIV positive vs. negative women and men [12].

Study of the host immune response to HPV was recently stimulated by the HIV and vaccine eras facilitated by HPV-diagnostic technologies. Even without immunodeficiency, initial infection of the basal layer keratinocyte by HPV effectively evades immune response by compromising innate defences and bridges between innate and adaptive immunity like interferon and cytokines [13].

The precise role of immune memory and recall after previous infection via naturally induced HPV neutralising antibodies is unclear; levels are generally low due to the exclusively intracellular location of the virus. Systemic vaccination, however, induces neutralising antibodies which prevent primary infection of basal layer cells. These abundant antibodies arrive via exudates from microscopic abrasions or secretions; they bind and present HPV antigens to phagocytes and immunocytes for the cellular immune system to neutralize the virus and create cellular memory [14].

After initial infection and latency of about three weeks, active viral replication follows and continues for a variable length of time. This phase is discontinued by poorly understood cell-mediated immune response and followed by regression [15]. When HPV DNA can no longer be detected by available technologies, it is called ‘clearance’, but the virus can be latent and reactivated when conditions are favourable. Among HIV-negative populations with normal immunity it was previously described that about 10-20% of infections become persistent; this is more likely after infection with oncogenic high-risk HPV types (hrHPV or
oncHPV) [15]. Host factors are important to determine viral suppression via cellular immunity; less oncogenic types may be more persistent and disease-causing. Differences in T-cell immunity best explain differences in epidemiology between healthy and HIV-prevalent populations [16].

**HIV and natural history of genital HPV**

Even among HIV-positive women high grade cervical lesions are very scarce without prior infection by hrHPV [17,18]. HPV DNA tests provide type-specific proof of replication, but must be repeated to study persistence; cytology detected intra-epithelial lesions are used as surrogate marker for integration into the genome and oncogenesis. Acquisition, re-acquisition, suppression, and re-activation are now being addressed in large longitudinal epidemiology studies among couples with and without HIV [19].

Research conducted among immune-depleted women without access to anti-retroviral therapy (ART), demonstrate almost universal infection and persistence. This includes high risk types (up to 95%) and multiple types (up to 75%) [20]. It is not known whether high prevalence rates are due to increased acquisition and persistence, or what role re-activation of previously cleared viral types plays.

Several cross-sectional and longitudinal studies have demonstrated that HIV viral suppression and higher CD4 T-cell counts help reduce HPV replication, persistence and multiple infections [18,21-24]. Individual differences (HLA-haplotype, smoking) influence HPV viral suppression after ART [6,25,26], but women clear HPV slower than men [12].

Non-cervical HPV follow the same pattern; peri-anal HPV is more persistent than oral [22] and more prevalent among women with cervical HPV [27]. Warts are caused by low risk HPV, are more prevalent among HIV-infected persons but size may not correlate well with immunity [28].

**EPIDEMIOLOGY OF HPV IN HIV-POSITIVE WOMEN**

**Prevalence and types**

Type specific HPV burden determines pre-invasive and invasive cancer burden and is important to interpret HPV data from lesions. Data from HIV-infected groups are complicated by differences in HIV disease stage or immunity. HPV prevalence among HIV-infected vary according to date, HIV control, region, social and sexual factors, age, etc [29,30]. HPV prevalence up to 89-98% (78-85% for hrHPV) has been reported in Gauteng, Southern Africa [12,31]. In the same region, women from the total population with normal cytology had HPV DNA in 67% and hrHPV in 34%, showing how changed HPV-epidemiology affects also HIV-negative women [32] By comparison, worldwide HPV prevalence is estimated at only 11.7% [33].

Initial reports suggested that HPV type distribution is unchanged among women with HIV, but in later reports non-16 high risk (and low risk) types are overrepresented. [29]. In Africa
HPV16 lost its place as commonest high-risk type [32,34]. Multiple types are more frequent among HIV-positive women which may be an independent oncogenic risk [35].

Cervical pre-cancer

Abnormal cytology rates differ between regions, populations and over time; seemingly following trends of the HIV epidemic and ART availability. Among populations with poor immunity and high HPV prevalence, abnormal cytology in 61% of HIV-infected women has been reported; HSIL becomes the most common abnormal finding [20,29,35-37].

Most studies reporting HPV types associated with cervical intra-epithelial neoplasia studied cellular or surface material rather than biopsies and show that multiple types are common among high grade lesions [35,36,38,39]. Molecular mapping, however, showed that each clonal lesion usually contains DNA of a single type [40]. Multiple clonal lesions may be confluent and even micro dissection may not be able to differentiate cellular material from two lesions. Multiple types were recently reported in 55% of CIN III tissue (83% of surface DNA) among HIV positive women [31]. Dominance of HPV 16 in CIN III is reported for HIV positive women [41]. Most reports based on surface material indicate an unchanged HPV16 rate but increased frequencies of all other oncogenic and lower risk types [38,39]. Differences exist between regions, countries, date and methodologies [35,36,39].

HIV therefore seems to have a weak effect on HPV 16-related cervical pre-invasive disease, decreasing the relative proportion of CIN III attributable to HPV16. Combined, HPV18, 45 and other non-alpha-9 types (39, 51, 56, 59) are linked to most CIN III. It remains uncertain whether 16-related alpha-9 types (31, 33, 35, 52, 58) have increased disease causing ability in HIV positive women as rates in pre-invasive disease follow population prevalence [39,42].

Cervical cancer

The epidemiology of cervical cancer among Sub-Saharan African (SSA) women provides a model to study the influence of HIV on cervical carcinogenesis. The burden of HPV, abnormal cervical cytology and cancer in SSA is uniquely high, partly due to HIV, but also to long term absence of screening, HPV control and many socio-economic factors [43]. HPV prevalence data generally run parallel to HIV-prevalence [17].

During early phases of the HIV pandemic, age at diagnosis was described as up to 15 years younger without increased incidence among women with AIDS [44]. Similarly, after ART introduction, no substantial decrease was found [45]. These anomalies may be due to initial poor life expectancy and postponed oncogenesis due to partial immune-reconstitution [46]. Best estimates from a current meta-analysis demonstrate standardised cervical cancer incidence rates (SIR) of 5.82 among HIV-positive women, mostly on ART [47].

HPV 16 is the most common oncogenic virus in cervical cancer among HIV-negative women [29,48]. It has retained that position among HIV positive women [42]. Similar to findings in pre-invasive lesions, HPV16 is, however, responsible for a smaller proportion of invasive cancers in HIV-infected women, demonstrating that immune-compromise does not further
increase its oncogenic potential. Proportionally the contribution of non-16 types, especially alpha-7 viruses HPV18 and HPV45, is increased among cervical cancer specimens [49]. HPV35 is more prevalent among all subgroups in SSA (normal cytology, precancer and cancer); it is an important oncogene in the region due to prevalence rather than association with HIV.

Another important and consistent finding is that multiple hrHPV types are more common within a single tumour even in biopsy material [21,49,50]. This finding complicates the attribution of cancer to HPV types. In a recent meta-analysis, it was concluded that due to multiple types, current data remain insufficient to confirm that types other than HPV18 gain oncogenic importance among immune compromised women [49]. Other authors have included type 45 in the list of types which may be linked to HIV [42, 50].

**Non-cervical disease**

Impaired immunity (CD4 < 500) may be needed before HIV-disease contribute to VIN II. Some researchers showed that prolonged immune suppression is needed before vulva cancer occurs [51]. ART may not prevent these lesions, but increased CD4 counts lower the risk [52,53].

Anal HPV prevalence, incidence and persistence is higher than oral HPV and is associated with anal sex. Anal HPV prevalence is around 80% among HIV positive men and women. It is unknown whether treatment impacts on subsequent risk for malignancy [22,25,28,52,54].

The interaction of HIV and non-oncogenic HPV is not well-studied, but genital warts are more common, can be large and problematic. Even marginal immune suppression may contribute to the development of warts, especially in tobacco smokers [53]. ART may reduce size and recurrence risk but this is not uniform and genetic factors may influence this interaction [28]. More HPV types are present in warts from immunosuppressed women but most will also have HPV6 and/or HPV11 [55]. Oncogenic types may increase progression to vulva cancer [53].

**CLINICAL IMPLICATIONS**

**Primary HPV-prevention**

Adult HIV-seroconversion demonstrates society’s failure to prevent sexually transmittable infection through behavioural interventions. Barrier protected sex can reduce HPV transmission about 2-fold, and carrageenan as vaginal microbicide is effective [56-58].

HPV-vaccination is an effective, cost-effective, but expensive primary prevention method with potential for large scale impact on HPV-induced disease [59]. Population effects via herd immunity are reported at female vaccination coverage of 50% [60].

Bivalent and quadrivalent HPV vaccines are safe in HIV-positive women, without impact on CD4 cell count, HIV viral load or stage [61]. Both vaccines are immunogenic in adults with high CD4-levels; antibody levels were higher after bivalent ASO4-adjuvanted vaccine
(significance was reached against HPV-18) [62]. Antibody levels are lower among HIV-infected populations, but serologic correlates for protection are unidentified and the significance of this finding remains unknown [62,63]. The efficacy of HPV-antibodies to contain viral replication, re-activation and neoplastic disease in women already infected by HPV is poorly understood. Adult HPV-vaccination of HIV-positive individuals seems to be an excellent idea, but efficacy remains unproven.

Currently population wide control of oncogenic HPV among HIV-prevalent populations relies on pre-pubertal vaccination. It is expected that induced anti-HPV antibodies will survive immune depletion. Coverage must be as wide as possible, therefore the affordability of the vaccine is the first and most important consideration.

Three other important factors need to be considered in the choice of vaccine for HIV-prevalent nations, namely oncogenic types prevented, antibody levels induced, and wart types prevented. Most of the proportional loss of HPV16 is gained by HPV18, so high antibody levels against both these viruses are paramount. Analysis of type contribution to invasive cancer suggests that 9-valent vaccine will have the largest benefit for HIV-prevalent countries, but cross-protection, antibody retention and levels are difficult to factor in. Highest antibody levels are expected from vaccination of pre-pubertal girls rather than older age groups; it remains unknown whether three doses are needed for HIV-positive girls. Large public health benefit (reduction of anogenital warts) is expected from vaccine cover against HPV6 and 11 [64].

**Detection of cervical cancer risk**

Improved cervical cancer screening is urgent to prevent the expected increase in invasive cervical cancer among HIV-positive women with improved life expectancies due to ART. Unfortunately, ideal screening, triage and treatment algorithm remains elusive and current strategies often depend upon affordability rather than efficacy [65]. Resources are scarcest in regions with the highest HIV- and HPV-burdens and health authorities seldom prioritise prevention.

Primary screening with visual inspection, cytology and HPV-tests all have high positive rates [66,67]. It is impractical to treat all screen-positives, so primary screening tests are preferred which have built-in triage. Women with the highest risk results can be treated, tests retain sensitivity because medium risk patients receive further triage with manageable numbers referred for treatment [68-70].

If cytology is chosen for primary screening, high grade squamous lesions are treated while lower grade abnormalities receive triage. Triage can be repeat cytology, immuno-cyto-staining, visual or colposcopic examination or HPV typing (as almost all are positive for HPV). Lesions which persist, extend to two or more quadrants, or have other high-risk features on colposcopy, biopsy or another triage test is treated [65,70,71].

HPV testing has demonstrated success as primary screening test for whole populations [72]. When HPV screening is used in HIV-positive women, it is recommended that partial
genotyping is included [73,74]. Treatment of alpha-7 taxon HPV types (18,45) as well as type 16 must be prioritised, other types can be followed or triaged.

Cervical cancer occurs between 10 and 15 years earlier in HIV-infected women, pointing to accelerated carcinogenesis [44]. This necessitates earlier initiation of screening and shorter intervals. Generally, programmes advise screening of all adult women from the time of HIV-diagnosis. Screen intervals between one and three years are proposed depending on the test and resources, but most SSA countries have not reached once-in-a-lifetime coverage. High risk HPV-negative women do not need increased screening as progression is minimal [17].

All available epidemiologic evidence suggests that (early initiation of) ART is essential as part of secondary cancer prevention. It must be coupled by cervical screening with vulva inspection to assist prevention, early diagnosis and effective treatment.

**Treatment of screen-positive women**

Many questions remain regarding optimal treatment of screen positive women. All treatment methods reduce of invasive cancer incidence provided enough women are treated [75,76]. Huge infrastructure and staff inputs are essential to provide cancer prevention treatment to all women who screen positive. Treatment facilities must be decentralised due to poverty and limited transport options.

Local destructive methods cannot cover large lesions or treat lesions within the cervical canal. Excision methods treat deeper and have lower recurrence risk, but cause more bleeding and traumatic injury. Excision is not safe near the transition to the vagina. Preferably local destruction methods should be available at primary or clinic level and performed by trained primary health care workers. Excision with or without colposcopy must be available at secondary or hospital level and is usually done by medical doctors. Scope of practise licencing must be considered when national treatment programmes are designed.

Follow up after treatment must include evaluation of histology (where available) as invasive cancer is more common [21,77]. Clearance of all hrHPV after treatment predicts less disease recurrence or progression but is unusual among immune depleted populations [77]. Cytology is recommended for follow-up after treatment with return to normal screening intervals once negative. Repeat lesions are best treated with excision to reach the endocervical canal better and have fewer recurrences. Repeated local destruction is also effective and safe. Vaginal cancer rates after hysterectomy, although increased, remain very low and screening is not recommended in resource restricted situations.

**Management of invasive cervical cancer**

Most data regarding the combination of cervical cancer and HIV originates from SSA and similar regions where both epidemics have been unchecked for many decades and poor population immunity increased the community circulation of HPV [19]. These are the areas worst-equipped to treat large numbers of increasingly young women, usually presenting at late stage. The loss of economically active women and mothers has devastating social and economic effects [44, 78].
During assessment, staging and treatment planning, usual protocols are followed but some factors deserve special consideration. Firstly, diagnosis must be made using histology to exclude other AIDS-related malignancies like Kaposi sarcoma and lymphoma and unusual infections [79]. The proportion of squamous carcinoma is increased in women with HIV-infection; the reason for this difference is unknown. Second, bone marrow and immune function deserves careful evaluation. Anaemia and low platelet counts are more common; more blood products are needed and it may complicate surgery, radiation and chemoradiation [80,81]. Thirdly, imaging gains importance, but loses specificity.

In poorly resourced countries, staging is done without advanced imaging. Ultrasound evaluation of the posterior bladder wall and kidneys as well as chest X-ray is essential to diagnose bladder invasion, ureteric obstruction and related or unrelated lung disease. Enlarged and metabolically active lymph nodes cause more false-positive PET/CT in HIV-positive patients; inflammation may reduce the accuracy of MRI [82,83]. If advanced imaging is chosen, care should be taken not to falsely upstage and undertreat.

Poor kidney function due to obstructive uropathy can usually not be salvaged by drainage procedures. Nephrostomy is limited by severe infectious morbidity and a short life span. It is not an option for severely immunocompromised women or when waiting times for radiation is long as it will increase morbidity without improving survival. Poor kidney function also limits the use of chemotherapy.

When surgery is planned, white cell count, absolute and %CD4 counts are especially important in newly diagnosed HIV-disease and in evaluating immune status [81]. White cell count >6 x 10^9 cells/l and %CD4 count >18% predict surgical complication rates equal to that of HIV-negative women, with lower counts associated with increased wound, pelvic, lung and urinary tract infections [84]. Surgery and post-operative care should be unchanged; adjuvant therapy recommendations follow generic protocols.

External beam radiotherapy with concurrent cisplatin followed by brachytherapy (or external boost if brachytherapy is unavailable) is the current recommended therapies in inoperable patients [85]. Most studies have reported worse treatment tolerability, increased toxicity and reduced survival [80,81,86,87]. Factors that reduce chemotherapy and radiation dosage or cause treatment interruptions have a negative effect on survival [80,85].

On the other hand, optimised treatment has outcomes similar to HIV-negative cohorts [87]. Treatment dosage must therefore be unchanged when curative intent is chosen. Highly active ART seems to reduce treatment toxicity and improves treatment completion [72,87]. Anaemia is an important cause of radiation interruption among HIV-positive women. The need for repeated blood transfusion must be minimised by optimal iron supplementation [80,88].

**Non-cervical genital HPV disease**

Vulva cancer also occurs at younger age and at increased standardised incidence rates (SIR 6.45) among HIV-infected women [47]. The clinical impression, from gynaecologic
oncology in an HIV-prevalent country, is that lesions and stage is more advanced, treatment is difficult, recurrences are common and outcomes poor. Data on this topic is scarce, but case reports support the impression [26,89,90].

Before, during and after treatment, local infection of the tumour, wounds, flaps, and skin defects as well as poor nutrition complicate healing. Many patients will require colostomy as large tumours often involve the posterior vulva and anal sphincter. Excision margins, inguinal node status and removal predict survival among HIV negative cohorts and probably among HIV-positive as well. This suggests that, like cervical cancer, treatment should not be reduced to limit complications and toxicity.

Radiation treatment with concurrent cisplatin-based chemotherapy is used as alternative or adjunct to surgery and may be sphincter sparing in large tumours. When multimodality treatment is needed for late stage disease, optimal sequencing remains unknown [91]. Few patients opt for completion surgery after radiation due to length and intensity of multimodality treatment [89].

Management of vulva warts in HIV-positive women is like treatment of HIV-negative women. Warts may be large and can cover the external genitalia. The tumours are frequently complicated by secondary infection and local hygiene including sitzbaths is helpful. Association with malignancy is relatively common thus histology must be obtained. Chemical or electrical destruction or imiquimod is used for small warts. Local destruction and shallow excision is used for large warts; sometimes it is necessary to perform the surgery in several sessions [53].
SUMMARY

HIV and HPV are both almost exclusively acquired through human sexual contact, cause disease after several years and have especially devastating effects on vulnerable women. Barrier protected intercourse, good immunity and intact mucous membranes are protective against diseases caused by these viruses. The acquisition of HIV and HPV are both increased by existing infection with the other virus and the clinical course of HPV-related disease is negatively influenced by poor immunity. Therefore HPV-related neoplasms, especially cervical cancer, cause significant morbidity and mortality among HIV infected groups.

The prevalence and incidence of any HPV, low risk, high risk and multiple type infections are increased by HIV and poor immunity. HPV16 remains the most common oncogenic type among HIV-positive women, but other types gain importance. In HIV-negative women, HPV16 is most common among those with normal cytology, pre-cancer lesions and invasive cancer. In HIV-positive women, non-16 types are more prevalent than HPV16 among those with normal cytology, while HPV16 remains the most prevalent type in women with pre-invasive and cancerous lesions. Non-16 types gain importance, however, and especially types 18 and 45 become proportionally more important oncogenes. Cervical cytological abnormalities (pre-cancer lesions) and cervical cancer are more common among women with HIV and management remains problematic.

HIV-HPV interactions should influence public health decisions towards prioritising large-scale pre-pubertal HPV-vaccination, secondary cervical cancer prevention by screening and early detection programmes for HIV-infected women to complement early initiation of ART. HIV co-infection influences response to treatment of neoplasms, both warty and cancerous. All these factors need to be considered when recommendations are formulated for population-based prevention and the treatment of the individual gynaecology patient.
CONFLICT OF INTEREST

The author is not aware of any conflict of interest related to this paper.
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