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HPV-related neoplasias in HIV-infected individuals

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Abstract

Human papillomavirus (HPV) infection of the lower genital tract is now considered the most important factor in the initiation of neoplasia. Human immunodeficiency virus (HIV) infection appears to alter the natural history of HPV-associated oncogenesis, but its impact on gynaecology has only recently been defined; the Centers for Disease Control (CDC) designated moderate and severe cervical dysplasia as a category B defining condition, and invasive cervical cancer as a category C defining condition of AIDS in 1993. Anal HPV infection and anal squamous intra-epithelial lesions have been found to be highly prevalent among HIV-positive homosexual men, and recent preliminary data suggest a relatively high prevalence among HIV-positive women as well. Moreover, HPV infection and associated lesions are also observed in body sites other than the anogenital area, particularly the skin and the oral cavity.

Keywords: Human papillomavirus; Squamous intra-epithelial lesions; Cervix; Vagina; Vulva; Anus; Penis; Skin; Immunodeficiency

1. Introduction

Human papillomaviruses (HPVs) are small DNA viruses that cause benign and malignant epithelial proliferations. Because HPVs complete their life cycle only in fully differentiated epithelial cells, they are difficult to propagate in cell culture and, as a consequence, unlike most other viruses, their taxonomy is based on DNA homology rather than antigenic diversity. To date, 84 different genotypes have been fully cloned and sequenced, and the existence of at least 70 additional genotypes is suggested by polymerase chain reaction (PCR) analysis with degenerate consensus primers and subsequent sequencing [1].

HPVs are strictly epitheliotropic and tissue-specific, with cutaneous and mucosal types forming two distinct groups. Approximately 30–40 types infect the anogenital area; this group includes the most extensively studied HPVs, and is associated with a large spectrum of diseases, from benign proliferations to invasive cancers (Table 1).

It is now firmly established that HPVs play a central role in the pathogenesis of cervical cancer. Indeed, viral sequences are found in more than 99% of cervical cancers worldwide, with type 16 present in 50%, and types 18, 31 and 45 in another 30% [2,3]. High grade cervical intra-epithelial neoplasia precursor lesions (CIN 2 and 3) have similarly high rates of the same HPV types [4,5]. Laboratory studies have demonstrated that cancer-associated types contain genomic sequences with oncogenic activity, *E6* and *E7*, which are consistently retained and expressed in cancers, and able to interact with cell cycle regulators [6]. Based on the strength of their association with cervical cancer, genital HPVs fall into different risk categories, as follows: high risk: types 16, 18, 31 and 45 (each found in at least 5% of invasive cancers); intermediate risk: types 33, 35, 39, 51, 52, 56, 58, 59 and 68 (each found in 1–5% of invasive cancers); low risk: types 6, 11, 42, 43 and 44 and many others (rarely found in invasive cancers). The International Agency for Research on Cancer (France) and the National Institutes of Health (USA), both concluded that high risk and most intermediate risk genital HPV types act as carcinogens in the development of cervical cancer [4,7].

While the data supporting the role of HPV in other anogenital cancers are more limited, a large proportion

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Table 1
Spectrum of HPV-associated lesions[a]

HPV group	HPV type(s)	Lesions
Mucosal		
	6, 11	**Genital warts, laryngeal papillomatosis**
	13, 32	Oral focal epithelial hyperplasia
	16	**Anogenital intra-epithelial neoplasia and carcinoma, oropharyngeal cancer**
	18, 31, 33, 35, 39, 45, 56, 58 and others	**Anogenital intra-epithelial neoplasia and carcinoma**
	30	Anogenital, oral, laryngeal carcinoma
	34, 40, 42	Anogenital warts, intra-epithelial neoplasia
	61, 62	Anogenital intra-epithelial neoplasia
	72, 73	Oral papillomas (ISP)
	72 and 73 variants	Cervical intra-epithelial neoplasia
Cutaneous		
	1	Plantar warts
	2, 4	Common warts
	3	Flat warts
	5, 8, 20 and many others	Benign and malignant EV lesions
	41, 48 and others	Squamous cell carcinoma (mainly ISP)
	75, 76, 77	Common warts (ISP)

ISP, immunosuppressed patients; EV, epidermodysplasia verruciformis; HPV, human papillomavirus.
[a] Bold face indicates the most frequently detected types.

of anal, as well as a subset of vulvar, vaginal and penile cancers is also associated with high-risk HPVs [8].

2. Host reaction to HPV

Infection initiates when a viral particle gains entry into a basal cell of the epithelium. The virus multiplies exclusively in the nuclei of infected cells in a differentiation-specific manner; mature virions can form only in fully differentiated cells, and escape from the infected epithelial surface within desquamating keratinocytes; there is no lytic phase. HPV infection in the genital tract is common in young, sexually active individuals, the majority of which clear the infection without overt clinical disease. Persons who develop lesions in most cases also mount an effective cell-mediated immune response regulated by CD4 T-cell dependent mechanisms, with subsequent regression of the lesion. The nature of the effector response, however, remains unclear. There is increasing evidence that both natural killer cells and antigen-specific cytotoxic T lymphocytes (CTL) are important effectors, but these responses are still poorly understood. Antibody responses to the major virus capsid protein L1 accompany the induction of successful cell-mediated immunity, which, in animals, is protective against subsequent viral challenge [9]. It appears that antibodies to viral capsid proteins are lost fairly rapidly after resolution of productive infection. If the cell-mediated response fails to induce lesion regression and viral clearance, then a persistent viral infection results [9]. In a productive viral infection, the viral genome replicates as an episome in the differentiated cells. The infection instead becomes non-permissive after viral integration into the host cellular genome, which usually occurs upon disruption of the viral *E1* or *E2* open reading frames, and is a hallmark of malignant progression. As a consequence, the expression of the *E6* and *E7* viral oncoproteins is dysregulated [6].

Antibodies to early viral proteins have also been detected, but they appear to be poor immunogens during natural infection [9]. Cell-mediated immunity to E6 and E7 proteins, instead, is of interest as a potential basis of immunotherapy for HPV-associated cervical cancers. Indeed, the results obtained in various animal models have stimulated the development of HPV vaccines. Phase I–II clinical trials are under way to assess the safety and immunogenicity of various prophylactic vaccines, based on the use of virus-like particles (VLP), and preliminary results are promising; although trials with therapeutic vaccines have given less encouraging results, the development of a vaccine that both protects from infection and eliminates persistent HPV infections appears possible and imminent [10–12].

3. Cofactors in the development of HPV-associated cancers

While infection with high-risk HPVs appears to be 'necessary' for the development of cervical cancer, it is not 'sufficient' because cancer does not develop in the vast majority of infected women, and thus raises the issue of possible cofactors, that include both virus-specific factors and host immune reactivity. The relative oncogenic potential of the HPV type is a well established viral factor, and some data suggest that genotypic variants within a high-risk type may affect the potential

for progression [4,13]. The viral load appears to have some influence, and has been mainly investigated in HPV type 16-associated lesions [14,15]. Persistence of viral infection is associated with progression [16,17]. Indeed, most HPV infections are transient in nature; the median duration of incident infection in young women is 8 months (range: 95% CI: 7–10 months), with rates of persistence of only 30% after 1 year and 9% after 2 years [16]. Integration of the viral DNA into the cellular genome occurs in most cervical cancers, and marks lesion progression.

The host immune response, and particularly cellular immunity, represents a critical determinant in the incidence of infection, and the outcome (regression, persistence or progression) of HPV-associated lesions. Individuals with altered cellular immunity show an increased incidence of HPV infections, and malignant conversion of associated lesions. In particular, the genodermatosis epidermodysplasia verruciformis (EV), which is characterised by a defect in T-cell-mediated immunity, is associated with a high frequency of malignant conversion of cutaneous HPV-related lesions [18]; organ-transplant recipients receiving immunosuppressive therapy show very high incidences of HPV infections and cutaneous malignancies that are directly related to the extent and duration of immunosuppression [19].

4. HPV–HIV interactions

An increased incidence of genital HPV infections in HIV-infected individuals was observed since the mid-1980s [20]. The development of cervical intra-epithelial neoplasia (CIN) defines a stage B condition (Centers for Disease Control (CDC) Classification System); invasive cervical cancer became an AIDS-defining condition on 1 January 1993, based on a higher prevalence of cervical dysplasia among HIV-infected women, particularly those with greater immunosuppression, and the possible adverse effect of HIV infection on the clinical course and treatment of cervical dysplasia and cancer [21]. While HIV's major role is related to the decrease in both circulating CD4 cell number and function, similar to what has been observed in other immunosuppressed patients, the possibility of a more direct interaction has also been addressed. Indeed, HIV and HPV may both be found in cervical lesions, but they do not infect the same cells (HPV infects the epithelium, and HIV the infiltrating lymphocytes) [22]; interactions, therefore, are mediated through soluble factors such as cytokines or growth factors, or through soluble viral transactivators such as tat, as demonstrated *in vitro* [23,24], that possibly alter HPV transcription, HIV replication and local immunity [25,26] (Fig. 1).

Following the introduction of highly active antiretroviral therapy (HAART), HIV-related mortality and most major opportunistic infections have dramatically decreased, as have Kaposi's sarcoma (KS) and primary brain lymphomas [27]. The influence of HAART on HPV-associated lesions is less clear. However, the definition of its effects (or lack of) is of utmost importance. In fact, while in the case of HAART efficacy, incidence and lesion progression might decrease, in case of no influence, a higher number and severity of HPV lesions might be expected, as a consequence of longer survival of (moderately) immunodepressed individuals. Preliminary data seem to favour this second scenario, but further studies are needed to highlight the long-term consequences of HAART use, also because, besides genital infections, an increase in oral and cutaneous HPV infections has been documented.

5. Genital HPV-associated lesions in HIV-infected women

5.1. Cervix

Compared with HIV-uninfected women, HIV-infected women are approximately 4 times more likely to be infected with HPV, and the infection is more likely to persist [28]. Indeed, depending on the sensitivity of the detection method and the woman's characteristics, prevalences range from 50 to 70%. Among the published studies, one of the most important is the Women's Interagency HIV Study (WISH), a large prospective cohort study initiated in October 1994 and conducted in six different centres in the USA. Its results have shown that women with less than 200 CD4+ cells/mm^3 are at the highest risk of HPV infection, irrespective of HIV viral load; the viral load comes second as a risk factor, only for women with a CD4 count greater than 200 cells/mm^3. African–American women are at higher risk than Caucasians, while current smoking and younger age (<30 years) are other important risk factors [29]. A higher prevalence of high-risk HPV types and multiple infections have been reported in HIV-positive versus HIV-negative women (Fig. 2) [29,30].

The higher prevalence of HPV infection is paralleled by a higher prevalence and a higher incidence of cervical squamous cell neoplasia (SIL) (Table 2) [30–36]. SIL prevalences range from 11 to 49% (and even higher according to other authors), figures which are 5 times higher than those for HIV-negative women. The degree of immunosuppression influences both SIL prevalence and severity; the lower the CD4+ lymphocyte count, the higher the prevalence of high-grade SIL. A meta-analysis of data pooled from published studies found that the pool summary odds ratio (OR) for the association between HPV and cervical neoplasia was 8.8 (95% CI: 6.3–12.5) for HIV-positive subjects, and 5.0 (95% CI: 3.7–6.8) for HIV-negative subjects [37], suggestive of

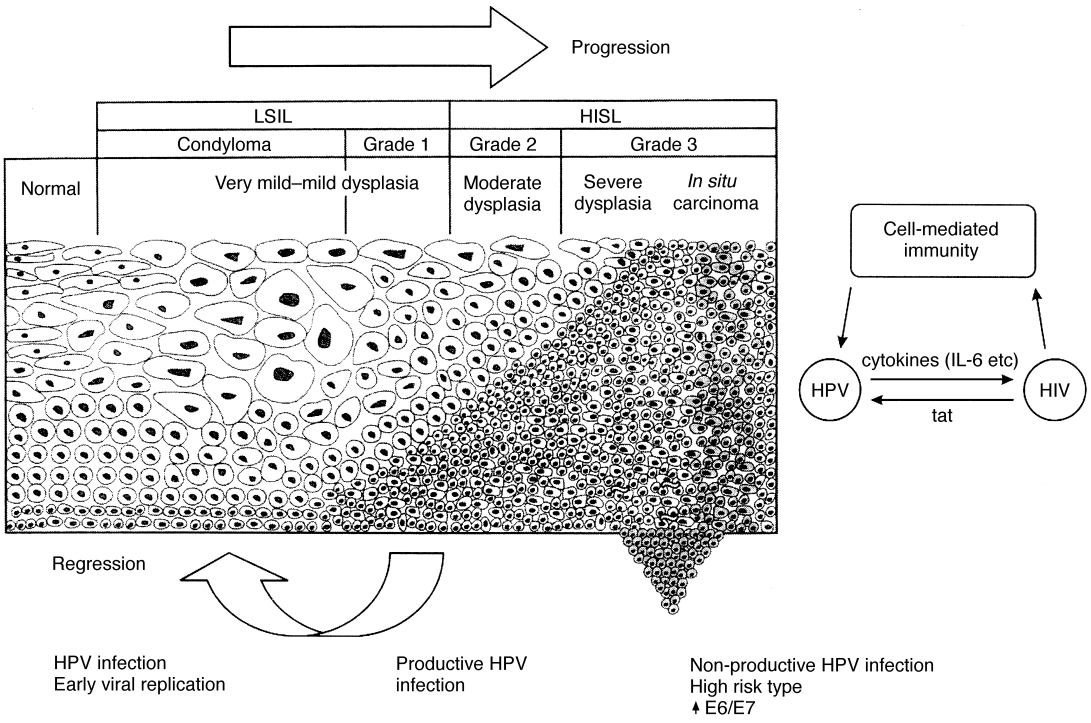

Fig. 1. Schematic representation of HPV-associated oncogenesis and the possible interactions between HPV and HIV on HPV-associated lesions. The clinical outcome of a HPV infection is influenced by viral and host factors; persistent infection with high-risk HPV types and impaired immune function are both linked with a higher risk for progression. HIV increases the rate of HPV infection, persistence and progression, indirectly by decreasing systemic and local cell-mediated immunity and perhaps directly by enhancing HPV early gene expression through tat. Conversely, HPV-infected cells might be able to activate HIV replication (as demonstrated in monocytes) through the production of cytokines, such as interleukin-6 (IL-6). HPV, human papilloma virus; LSIL, low-grade squamous intra-epithelial lesions; HISL, high-grade squamous intra-epithelial lesions.

an interaction between HIV and HPV. A prospective cohort study conducted in USA [35] among 328 HIV-infected and 325 uninfected women with no evidence of SIL by Papanicolaou (Pap) test or colposcopy at study entry, disclosed that 20% of the HIV-infected women developed biopsy-confirmed CIN within 3 years, compared with only 5% of the uninfected ones; by multivariate analysis, the most significant factors for incident SILs were persistent HPV infection (relative risk (RR) = 11.6 (95% CI: 2.7–50.7) for types 16 and 18, RR = 7.6 (95% CI: 1.9–30.3) for other types); transient HPV infection (RR = 5.5; 95% CI: 1.4–21.9), and HIV infection (RR = 3.2; 95% CI: 1.7–6.1); the incidence of SILs in HIV-infected women taking antiretroviral therapy (one- and two-drug regimens not including protease inhibitors) was not significantly different from that in women not receiving antiretroviral therapy. In another study [36], HPV detection and low CD4 cell count were

Table 2
Squamous intra-epithelial lesions (SIL) among HIV-infected women

Ref.	Location	Total women evaluated	SIL prevalence (%)	SIL severity	
				LSIL (%)	HSIL (%)
[31]	Italy	273	42	20	22
[32]	USA	248	32	24	8
[33][a]	USA	67	38	27	11
		185	11	10	1
[34]	USA	1713	17.5	15	2.5
[35]	USA	328	22	19	3
[36]	Europe	485	24	21	3
[30]	Italy	249	49	32	17

LSIL, low-grade squamous intra-epithelial lesion; HSIL, high-grade squamous intra-epithelial lesion.

[a] Women enrolled in two different protocols; ACTG 175, an antiretroviral trial (CD4+ counts 200–500 cells/mm^3), and ACTG 196, a Mycobacterium avium complex prophylaxis trial (CD4+ counts <100 cells/mm^3).

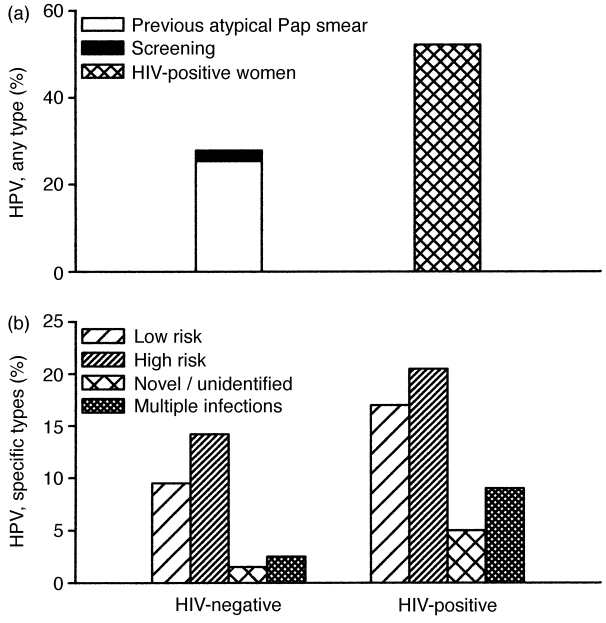

Fig. 2. Panel (a): overall cervical human papilloma virus (HPV) infection rates in HIV-negative (193/694, 27.8%) and HIV-infected women (130/249, 52.2%) ($P<0.0001$). HIV-infected women show a prevalence rate much higher than that observed in HIV-negative screening-attending women (17/235, 7.2%), but also higher than that observed in women referred for a previous atypical Papanicolaou (Pap) smear (176/459, 38.3%). Panel (b): distribution of the different HPV types (see [30] for details).

independently associated with incident SIL. In HIV-infected women, CIN lesions are also more difficult to treat, with much higher percentages of persistence and relapse than uninfected women [38,39] using standard treatment protocols, and highly influenced by the degree of immunodeficiency (>60% relapsed among in severely immunocompromised women). Regression from untreated low grade SIL at 1 year was observed in only 30% of the women. Our preliminary data show that immune function reconstitution by antiretroviral therapy can improve the response to surgical treatment (manuscript in preparation), even though carcinoma *in situ* can develop also in women undergoing HAART therapy [30].

Unlike the precursor lesions, invasive cervical cancer (ICC) has not shown a dramatic increase in the wake of the epidemic. After its introduction as an AIDS-defining illness, ICC was the most common malignancy among women with AIDS in both Europe (2.7%, 393/14 348) and the USA (2.1%, 580/28 024) [40], and its frequency was shown to be approximately 3-fold higher among the intravenous (i.v.) drug users than in other HIV-infected women [41]. Indeed, until recently, it was debated whether the rate of ICC was increased in women with AIDS. Linkage studies in the USA and Italy found clearly increased rates of cervical cancer in women with HIV [42,43]. From a broader perspective, while no increase in RR for ICC has been registered in Africa and Australia, a nearly 15-fold increase has been reported in Italy and France, and a less pronounced, more conflicting figure of 3–5-fold in the USA [44].

5.2. Vulva and vagina

Less data are available on the impact of HIV infection on HPV infections and associated lesions in the vulva and vagina. Penn [45] reported a 100-fold increase in the number of vulvar and vaginal carcinomas in transplant recipients, compared with the general population. Increased numbers of condylomata and vulvar intraepithelial neoplasia (VIN) have been reported in HIV-infected women [46,47]. Estimates for VIN prevalence range from 5.6 to 37% [48]. To date, 5 cases of invasive vulvar carcinoma in HIV-positive patients have been described [49–52]: patient ages ranged from 12 to 59 years; 3 had a history of previous condyloma/VIN; CD4+ cell counts at diagnosis ranged from 300 to 735 cells/mm^3; histologically 4 were squamous and 1 verrucous; 3 had nodal metastases at diagnosis; all underwent surgical excision; 2 (both with positive nodes) died from tumour progression at 9 and 11 months after diagnosis, respectively, while the other 3 were alive 16–48 months post-diagnosis. The development of invasive vulvar carcinoma in a 12-year-old girl is of particular concern, and stresses the need for periodical gynaecological examination of HIV-infected girls. In 2 patients, the vagina and the perineal/perianal regions, respectively, were also involved; multifocal genital neoplasia secondary to a HPV infection involving the entire genital tract has indeed been reported in a subgroup of patients with vulvar carcinoma, who developed additional lesions some time during their life [53]. We are aware of an HIV-infected patient with a cervical HPV-16 infection since 1989 [38], who developed cervical *in situ* carcinoma; she was initially treated with local excision, and was hysterectomised 5 years later, and 3 years post-hysterectomy she developed an invasive vulvar carcinoma. These data suggest the occurrence of a 'field effect' in some immunodepressed women. A case of rapidly progressing squamous cell carcinoma of the vagina in a 40-year-old HIV-infected woman has recently been reported [54].

6. Genital HPV-associated lesions in HIV-infected men

6.1. Anus

Anal HPV infection, most commonly with HPV 16, has been reported to occur in nearly all HIV-infected, as well as in a substantial proportion of HIV-negative, homosexual men [55,56]. HIV-infected homosexual and bisexual men are at increased risk for persistent HPV infection, and HPV-associated anal squamous intra-

epithelial lesions (ASIL), with prevalence rates ranging from 25 to 45%. Risk factors for ASIL include a lower CD4 cell count, and HPV infection [57]. A significant proportion of ASIL is of high grade; moreover, it was observed that high grade SIL developed in 15% of HIV-infected men who initially had no evidence of ASIL over a 21-month period. These studies were conducted in the pre-HAART era, but early data suggest that at least 75% of patients with HSIL lesions do not regress while receiving HAART [57]. ASIL as a distinct entity was only recently introduced, but screening HIV-positive homosexual and bisexual men with an anal Pap test has been advocated and claimed to be cost-effective [57]. Unfortunately, there exist structural impediments to the introduction of anal screening, such as the training of physicians and cytologists. A very high prevalence of anal HPV infection has been recently demonstrated also in women; 76% among HIV-infected, and 42% among HIV-negatives [58].

Invasive anal cancer was reported to be increased in persons with AIDS; AIDS–cancer linkage studies in Australia have shown a standardised incidence ratio of 36.5 [59], and similar figures are emerging in the USA. A combined chemoradiation protocol is actually the standard treatment for anal cancer in the non-HIV population; the same treatment was shown to be safe and effective also in 12 HIV-positive homosexual men, with an actuarial 2-year survival of 60% [60].

6.2. Penis

Genital HPV infections and associated lesions are less prevalent in men than in women; they are more difficult to investigate, at least partly because no practical sampling technique has yet been established for the ready identification of penile HPV infections. We are evaluating both urethral cell samples and semen, obtained from partners of women referred because of a previous atypical Pap smear, to search and type HPV sequences by PCR with consensus MY09/MY11 primers (as outlined in [30]). To date, 90 males (median age 34 years; range: 18–72 years) have been evaluated, and HPV sequences have been detected in 20 (22%); surprisingly, only 4/20 had HPV in both samples, 7/20 had HPV infection only in the urethra and 9/20 only in semen (Table 3); the vast majority harboured HPV 6, while only five men had a high-risk type. The role of the male in spreading HPV infection to his female partners, thus contributing to the development of cervical cancer, constitutes a major concern. Indeed, the prevalence of HPV DNA (evaluated in urethral cells) was 17.5% among the husbands of women with cervical cancer versus 3.5% among husbands of controls in a large study in Spain [61]; in Colombia, a high-risk area for cervical cancer, the corresponding figures were 25.7% versus 18.9% [62]. In Sweden, a 13% HPV prevalence was observed among

Table 3
Prevalence of HPV sequences in genital samples of male patients, partners of women referred for a previous atypical Pap smear

Samples	No. tested	HPV-positive
		n (%)
Urethral cells	86	11/74[a] (15)
Sperm cells	84	13/84 (15)
	No. patients tested	HPV-positive patients[b]
		n (%)
Urethral and/or sperm cells	90	20/90 (22)

HPV, human papilloma virus; Pap, Papanicolaou.

[a] Twelve samples (14%) excluded from analysis because inadequate.

[b] HPV types: HPV 6: 11/20 (55%); other low-risk types: 4/20 (20%); high-risk types: 5/20 (25%).

147 men attending a Dermatovenereology Department [63], and a significantly higher prevalence was reported for HIV-positive men (>60%) in comparison to HIV-negatives (<15%) [64].

All subclinical (detectable only by colposcopic magnification) HPV lesions in men show a benign clinical course even without treatment [65].

Squamous cell carcinoma of the penis is uncommon, accounting for <1% of adult male cancers in developed countries (although higher in areas of Asia and Africa), and is largely a disease of the elderly. Its low prevalence has made the study of the role of HPV more difficult, but more than half of the cases appear to harbour HPV sequences, mainly type 16 [66]. Two cases of penile squamous cell carcinoma in a 56- and a 78-year-old HIV-infected patient, respectively, were recently reported [67]; both cases were positive for HPV sequences (types 16 and 6/11, respectively), were treated by partial penectomy, and died 8 and 12 months after diagnosis without evidence of tumour dissemination. The occurrence of perianal verrucous carcinoma at the age of 40 years, and of penile squamous cell carcinoma at the age of 43 years, has been described in a man immunodepressed due to chemoradiotherapy for non-Hodgkin lymphoma (NHL); both tumours were HPV 16-associated, and the case is suggestive of an anogenital 'field-effect' in the presence of immunodepression [68].

7. HPV-associated cutaneous and oral manifestations

Productive HPV infection of the skin is clinically manifest in the form of cutaneous warts. Organ transplant recipients (OTR) are at increased risk than immunocompetent individuals, and the risk is linked to the duration of immunosuppression; 25–42% of adults suffer from cutaneous warts 3 years post-transplantation, but this percentage rises to (<90%) more than 5

years post-transplantation [69]. Sun exposure is an important cofactor; patients with protracted immunosuppression manifest large, confluent lesions, which frequently show cytological atypia, particularly in the basal layer, and progression to squamous cell carcinoma (SCC). An increased prevalence of common warts has also been reported in adult and paediatric HIV-infected subjects [70]; 17–18% compared with 1–2% in HIV-negative subjects [71].

Non-melanoma skin cancers (NMSC) develop in 6–7% of OTRs at 10 years and in 30–35% at 20 years post-transplantation, with an inversion of the ratio between basal and squamous cell carcinomas. The risk of NMSC in persons with AIDS was found to be increased 5-fold in a matching and linkage of AIDS and cancer data in USA [42], but the reporting of basal-cell and squamous-cell skin cancers to the registries was considered incomplete. The search for HPV sequences in NMSC has given conflicting results for several years; recent evidence suggests that a wide diversity of HPV types can be detected in cutaneous neoplastic lesions of the skin, particularly in those from immunodepressed individuals.

The incidence of squamous cell carcinoma of the conjunctiva (SCCC), a tumour associated with chronic, intense ultraviolet light exposure and with HPV infection, has been rising in the 1990s in Africa, most probably as a consequence of the HIV spread; in particular, two studies, in Rwanda and Uganda, found HIV antibodies in 75–82% of those with SCCC versus 19–24% in the controls [72,73].

Many diverse lesions affect the oral mucosa of immunodepressed individuals. Among those with HIV infection, the spectrum varies among the different risk groups; KS occurs more frequently in homosexual men than in heterosexual men and women, oral hairy leucoplakia (OHL) mainly affects men who acquired HIV through i.v. drug use. Oral warts, which have a prevalence of 0.2–0.4% in the general population, occur in 1.2% of renal transplant patients and in 4% of HIV-infected patients in one prospective study [74]. The appearance of multiple recalcitrant oral warts has been observed in homosexual men on combination antiretroviral therapy, in replacement of intractable oral ulceration, most commonly observed before the advent of HAART [70]. Oral warts occurring in immunodeficient patients often have an uncharacteristic morphology, and contain unusual HPV types, belonging to both cutaneous and mucosal groups. No increase in the prevalence of oral SCC has been observed to date.

8. Conclusions

HIV-induced immune depression is associated with higher prevalence rates of HPV infections and associated lesions in both women and men; the anogenital area is the most frequently involved site, but the oral cavity and the skin are also showing increased rates of HPV manifestations. Since a direct effect of antiretroviral therapy on HPV infections and associated lesions seems unlikely, regular screening for the detection and treatment of HPV-associated lesions in conjunction with immune reconstitution is mandatory, and appears an adequate preventive measure for (ano)genital neoplastic lesions.

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