

Anogenital Human Papillomavirus Coinfection and Associated Neoplasia in HIV-positive Men and Women

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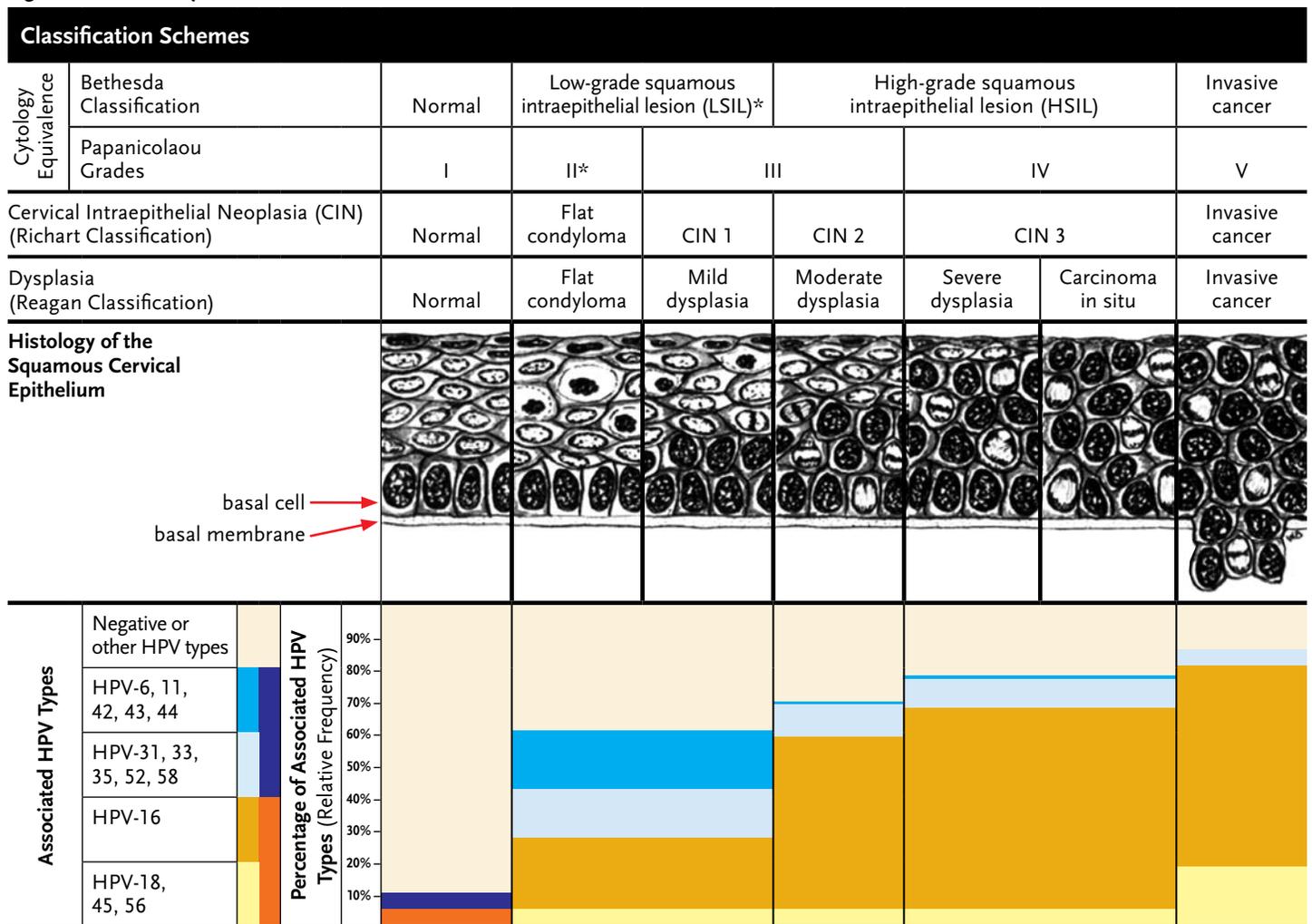
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Human Papillomavirus Background

With more than 100 known types, the human papillomavirus (HPV) is the most common sexually transmitted infection with approximately 75% of sexually active adults acquiring one or more genital HPV types at some point in their lifetimes.¹ HPV is spread from skin to skin because HPV lives only in keratinocytes. When used 100% of the time, condoms have been shown to reduce HPV transmission by up to 70%.² Although HPV infects a high proportion of sexually active men and women, most do not show clinical manifestations of the infection.

HPV types 6, 11, 42, 43, and 44 are the causative agents of anogenital condylomas and cervical flat condylomas, which are not considered to be cancer precursors. HPV types 16 and 18 are found in a high proportion of advanced cervical intraepithelial neoplasia (CIN) and are considered to be precursors to invasive cancer in about 50% and 20% of all cervical cancer cases in the United States, respectively. The percentages of cervical cancers associated with HPV types 31, 33, and 35 are lower and vary from country to country.³ This review will discuss

Figure 1. From Condyloma to Cancer



* LSIL also includes atypical squamous cells of unknown significance (ASCUS).

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the pathogenesis of HPV in HIV-positive patients, provide an update regarding anal intraepithelial neoplasia (AIN), and outline screening guidelines for patients at risk for HPV-related disease.

Natural History of Cervical HPV Infection

The progression of HPV-related cervical disease is well characterized and proceeds through distinct phases. The Bethesda System Classification, which categorizes cervical cytology, organizes HPV-associated lesions into low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions (HSIL) and invasive cancer (Figure 1).⁴

LSIL corresponds to the histologic diagnoses of flat condylomas and CIN 1, whereas HSIL corresponds to the histologic diagnoses of CIN 2 and 3. As the degree of severity increases, the more oncogenic HPV types become increasingly predominant. In most cases, the time from development of initial HPV infection to CIN 2-3 is believed to be less than five years, whereas the progression of CIN 2-3 to invasive cancer may take several decades.⁶

Cervical HPV Coinfection and CIN in HIV-positive Women

Studies in the United States have shown that the peak prevalence of HPV infection occurs in younger women, usually before 24 years of age (Figure 2).⁷ This may be attributed to the high rate of HPV infection after exposure to infected sexual partners and the absence of naturally occurring antibodies that would protect against infection.⁷ Most women with HPV never develop detectable CIN, and with immune control, HPV DNA reverts to undetectable levels using standard HPV detection tests.⁷

However, a small proportion of women have persistent detectable HPV infection.⁷ Women who continue to have detectable levels of HPV at the age of 30 years and older are considered to have persistent HPV infection, which is one of the strongest predictors of eventual development of cervical cancer. Given the limited sensitivity of a single cervical Papanicolaou (Pap) cytology to detect CIN 2-3, some have advocated supplementing cervical cytology with HPV-detection testing in women over the age of 30.⁸ Many believe that any woman above the age of 30 with an oncogenic HPV type should undergo colposcopy, independent of the cervical cytology results.⁸

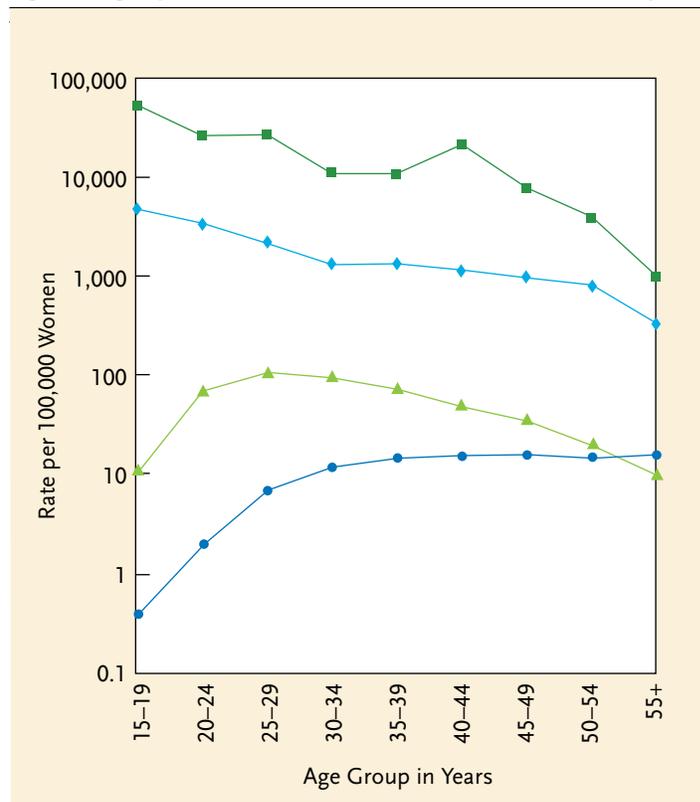
In the United States, 8 to 10 per 100,000 women develop cervical cancer, with 14,000 new cases per year.⁹ Cervical cancer occurs disproportionately in lower socio-economic subgroups due to lack of adequate access to healthcare and routine cervical cytology screening. Cervical cancer is one of the most common causes of cancer-related mortality worldwide, particularly in countries with a high prevalence of HIV infection.¹⁰ Other risk factors for cervical cancer include smoking, oral contraceptive use, chronic Chlamydia infection, nutritional deficiency, and immune deficiency associated with HIV infection or iatrogenic immunosuppression in the setting of solid organ transplantation.⁶

The Women's Inter-Agency HIV Study investigated the link between HIV infection and cervical abnormalities; after matching for all other factors, researchers found that women with HIV were more likely to have persistent HPV infection, as well as abnormal cervical cytology, compared with HIV-negative women.¹¹ The risk of detection of both HPV DNA in the cervix and abnormal cervical cytology was inversely proportional to CD4⁺ T-Cell counts.¹¹⁻¹⁴

Consistent with the high risk of cervical HPV infection and CIN in HIV-positive women, several studies have shown that the incidence of

cervical cancer has increased compared with the general population.^{15,16} The magnitude of the increase varies worldwide, but in developed countries the increase appears to be highest in clinical settings where women have limited access to medical care and routine cervical cytology screening.¹⁶ Recent studies have also shown an increased incidence of cervical cancer in developing countries.^{17,18} To date there has been no decline in the incidence of cervical cancer since the introduction of effective antiretroviral therapy for HIV; it is likely that antiretroviral therapy has only a modest benefit on the natural history of cervical

Figure 2. Age-Specific Patterns of HPV Infection and Cervical Neoplasia



- Point prevalence of HPV DNA in cytologically normal women decreases with age, based on data from 463 women screened in 1989–1990 at Kaiser-Permanente in Portland, Oregon.
- ◆ Point prevalence of the early cytopathologic effect of HPV infection, called condylomatous atypia, also declines with age, based on data from 19,571 women who obtained Pap smears in 1989–1990 at the same Kaiser-Permanente gynecology and obstetrics clinics.
- ▲ In contrast, the incidence of cervical intraepithelial neoplasia 3 among white women in the United States increases with age to a peak at ages 25–29 years, then declines, perhaps due in part to a decrease in Pap smear screening.
- The incidence of invasive cervical cancer rises to a plateau around ages 35–39 years in white women in the United States, but continues to rise at later ages in black women (data not shown). The incidence data for cervical intraepithelial neoplasia 3 and invasive cancer are derived from the National Cancer Institute Surveillance, Epidemiology, and End Results Program cancer registries for the years 1984–1988 and are restricted to white women for comparability with the Portland data.⁷

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HPV-associated disease.¹⁹ In developing countries, competing mortality from HIV-related causes may have masked the risk of cervical cancer because progression from CIN to cancer may take decades. However, in the absence of routine Pap smear screening and medical care, improved longevity as a result of effective antiretroviral therapy may lead to a further increase in cervical cancer.¹⁹

Natural History of Anal HPV Infection

There is biological similarity between the cervix and the anus with respect to the preferred location of HPV infection; this is an additional area of interest in the pathogenesis of HPV. The transformation zone of the cervix is the target area for HPV due to the transition of two types of epithelium: keratinized squamous epithelium on the exocervix and columnar epithelium on the endocervical canal (Figure 3).

Similarly, the anorectal junction has a transformation zone at the dentate line, where the squamous epithelium of the anus meets the columnar epithelium of the rectum. This area, as well as the distal squamous epithelium, is susceptible to HPV infection and is the area of interest when performing anal cancer screening (Figure 4).

The histopathologic classification of AIN 1, 2, and 3 corresponds to CIN 1, 2, and 3. Although there are few data showing direct progression of an AIN 2-3 lesion to anal cancer, patients with AIN 2-3 are at high risk of progression; the assumption is that these lesions progress to cancer similarly to lesions in the cervix.²¹

Anal HPV Coinfection and AIN in HIV-negative and -positive Men who have Sex with Men

In contrast to the data regarding women and cervical HPV, anal HPV in the HIV-negative men who have sex with men (MSM) population seems to follow a different course. For MSM, HPV prevalence typically remains high (50% to 60%) and is constant throughout life, rather than prevalence peaking in the 20s age-range and declining by the age of 30, as it does in women (Figure 5).^{7,22}

This may be attributed to differences between the biology of the anal canal and the cervix, but more likely it is a result of the acquisition of other HPV types from new sexual partners over time.

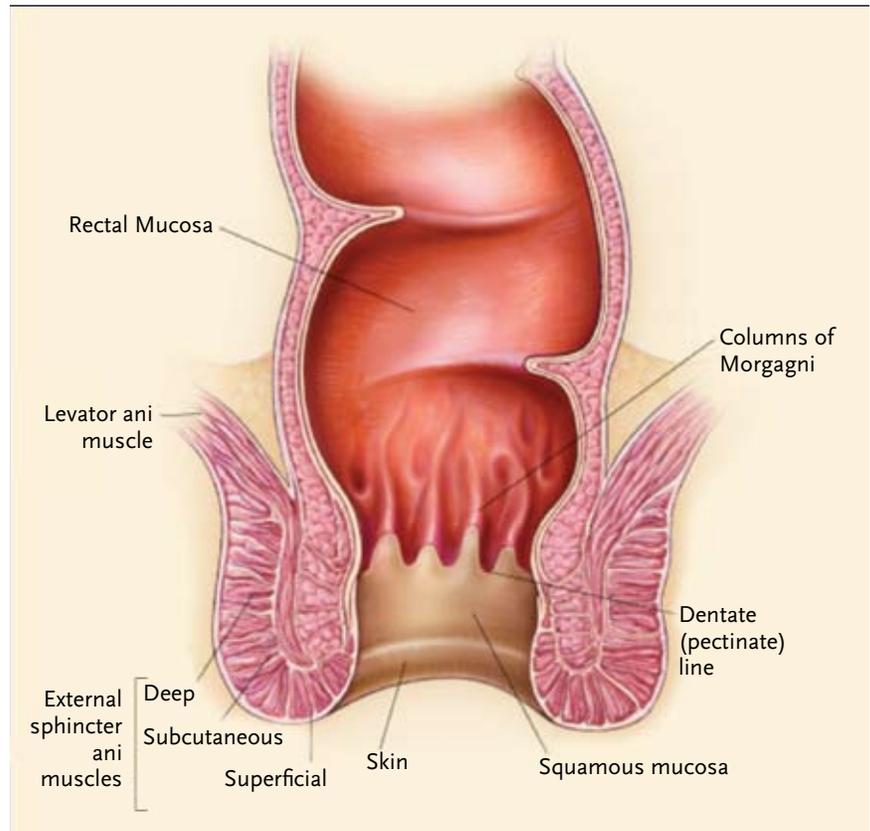
The pattern of HPV prevalence is also consistent in anal cytology, with 25% to 30% of MSM having either AIN 1 or AIN 2-3 after the age of 20. Between 5% to 10% of MSM have high-grade disease, which increases slightly above the age of 50 (Figure 6).²³

Figure 3. Cervical Squamocolumnar Junction (SCJ) and Transformation Zone



Figure Courtesy of Merck & Co., Inc.²⁰

Figure 4. Anatomy of the Anus



From Ryan D, Compton C, and Mayer R. Medical progress: carcinoma of the anal canal. *N Engl J Med.* 2000;342(11):792-800. Reprinted with permission from the publisher. Copyright © 2000 Massachusetts Medical Society. All rights reserved.

Although the estimated prevalence of abnormal anal cytology is between 18% to 23% in HIV-negative men, these numbers underestimate the true prevalence of AIN; anal cytology, like cervical cytology, is relatively insensitive.²⁴ The prevalence of AIN, as measured by anal cytology, is even higher among HIV-positive MSM, and nearly all have anal HPV infection (Figure 7).^{25,26} Additionally, the incidence of AIN 2-3 is higher among HIV-positive MSM compared with HIV-negative MSM.^{27,28}

HIV patients also tend to be coinfecting with multiple oncogenic types of HPV.¹⁶ Furthermore, the level of HPV DNA in the anal Pap specimens is higher in HIV-positive MSM compared with HIV-negative MSM, most likely reflecting larger anal lesions.²⁶

Anal HPV Coinfection and AIN in HIV-negative and -positive Women

In women, the prevalence of anal HPV is actually higher than the prevalence of cervical HPV, independent of HIV status and level of immunosuppression (Figure 8) and the incidence of anal cancer is 7-fold higher in HIV-positive women compared with HIV-negative women at high risk for HIV.^{16,29,31} The relationship between anal HPV infection and cervical HPV infection is poorly understood, as is the effect of anal HPV infection on the biology of cervical disease.

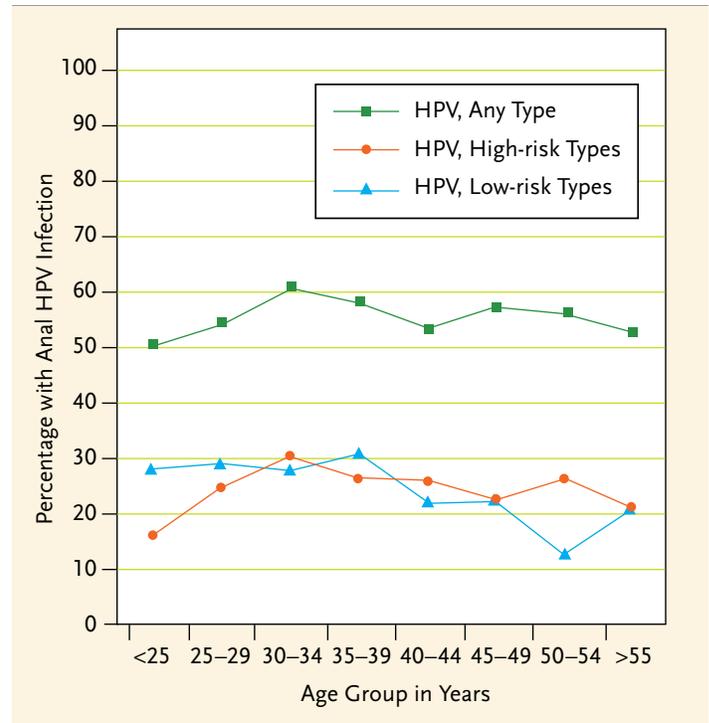
Effects of Highly Active Antiretroviral Therapy on the Natural History of HPV

Patients acquire multiple HPV types early, most acquire HIV subsequent to their initial HPV infection, and as long as they remain immunocompetent, they will have a relatively low risk of developing high-grade AIN or CIN compared to those with more advanced immunosuppression (Figure 9).³²

As patients become more immunosuppressed due to HIV, their risk of developing low-grade and high-grade anogenital neoplasia increases as reflected by the inverse relationship between CD4⁺ T-cell levels and measures of anogenital neoplasia.^{27,33} However, while the risk of developing high-grade HPV disease increases as immune status declines, that relationship does not appear to hold for progression from high-grade AIN to invasive anal cancer, or from high-grade CIN to invasive cervical cancer.¹⁶ The reason for this is unclear, but may reflect an increasingly important role for genetic changes, rather than immune deficiency, at this late stage of disease. HPV proteins such as E6 are known to induce chromosomal instability; it has been shown that the proportion of precancerous lesions with genetic changes increases with increasing grade of intraepithelial neoplasia.³⁴ These changes may play a critical role in progression to and maintenance of invasive cancers (Figure 9).

If this model of pathogenesis is correct, then highly active antiretroviral therapy (HAART) would be expected to be maximally beneficial to reduce the incidence of high-grade anogenital neoplasia if an individual has no disease or low-grade disease when beginning HAART, as restoration of the immune response might still be of value to control the development of high-grade disease. This assumes that HAART is capable of restoring HPV-specific immunity, but this has not yet been shown. At the other end of the pre-cancerous spectrum, following initiation of HAART, restoration of immune competence in general and of HPV-specific immunity in particular should have limited or no benefit for regression of high-grade AIN or CIN. It should also have limited impact on reduction in anal or cervical cancer, given the limited role of the immune response at these stages of disease (Figure 9).

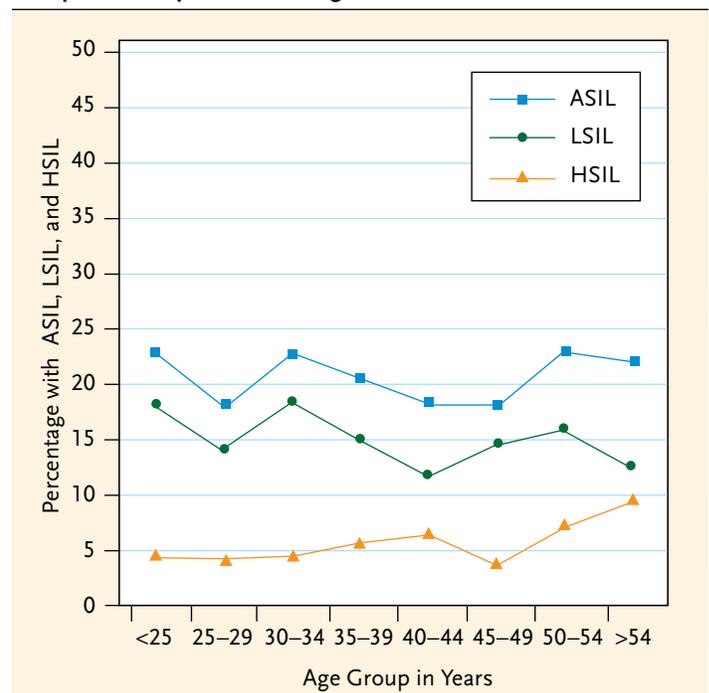
Figure 5. Anal HPV Infection by Age Group in Sexually Active HIV-negative MSM



Prevalence of human papillomavirus (HPV) DNA in the anal canals of HIV-negative men who have sex with men (MSM), by age group and by cancer-associated risk type. High-risk (HR) types include 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 73; low-risk types include 6, 11, 53-56, 66, Pap 155, and Pap 291.

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Figure 6. Any Anal Squamous Intraepithelial Lesions (ASIL) by Age Group in Sexually Active HIV-negative MSM



ASIL includes both low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL).

Adapted with permission from Oxford University Press.²³

Data have now been accumulating regarding the effect of HAART on the natural history of HPV disease, and the evidence to date suggests that there is limited or no benefit for reduction of high-grade disease and cancer. In studies examining CIN, HAART seems to have little or no effect on regression of CIN 2-3. None of the studies show that HPV is eradicated from the cervix; there is neither a regression nor a lower incidence of high-grade AIN.^{19,35} Additionally, the incidence of anal cancer has continued to increase since the introduction of HAART. The rate of anal cancer incidence during the pre-HIV era was 0.6 per 100,000; this climbed to 0.8 per 100,000 in the midst of the pre-HAART HIV epidemic. However, with the introduction of HAART, the incidence increased to 1.0 per 100,000 in the general population.³⁶

During this time, the female-to-male ratio has declined from 1.6:1 to 1.2:1, indicating a gender narrowing of what historically was a female predominant disease.³⁶ The San Francisco AIDS Surveillance Registry reported the risk of anal cancer increased nearly 3-fold in the post-HAART era after 1995 when compared with pre-1995 data.³⁷

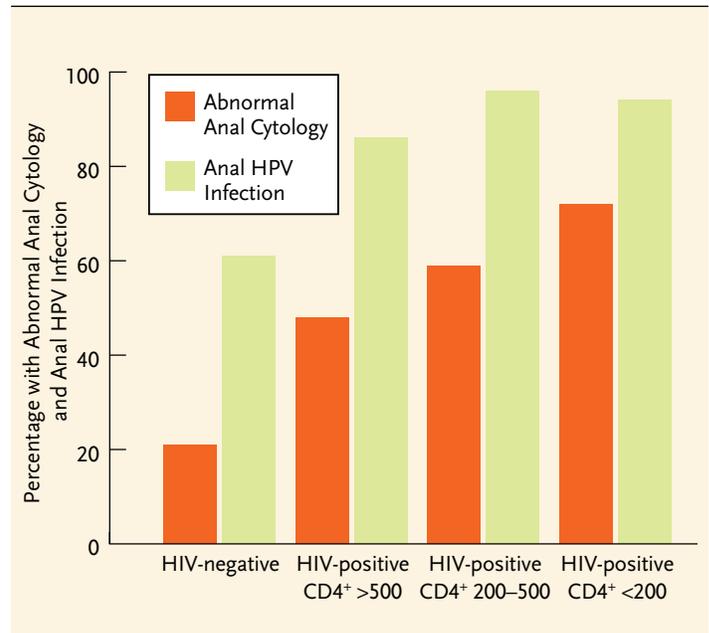
The 2008 Multicenter AIDS Cohort Study (MACS) recently reported an overall incidence rate of anal cancer in MSM of 37 per 100,000 person years.³⁸ The MACS study found that the rate of HIV-positive MSM with anal cancer was 5-fold compared with HIV-negative MSM (69 versus 14 per 100,000 person years, respectively) and the incidence did not decrease since the introduction of HAART.³⁸ In another recent analysis, anal cancer was the only cancer found to be increasing in incidence among HIV-positive individuals as well as relative to the general population.⁴⁰ Additionally, a research group in Paris recently reported an increase in the incidence of anal cancer since HAART was introduced.³⁹ Overall, the evidence points to a growing risk of anal cancer among HIV-positive individuals in the HAART-era, rather than a reduced incidence as is the case for other cancers such as Kaposi's sarcoma or non-Hodgkin's lymphoma. Additional risk factors for anal cancer in MSM include having an increased number of unprotected anal receptive sexual partners, being 50 years of age or older, having an HIV-positive status, using tobacco consistently, and having a low nadir CD4⁺ T-cell count.^{38,40} Other HPV-related carcinomas, such as vulvovaginal, penile and oral cancers, are also higher in HIV-positive patients. However, there are few current data concerning how the incidence of these cancers has changed since the introduction of HAART.¹⁶

Cervical Cytology Screening Recommendations for HIV-positive Women

The 2006 Consensus Guidelines recommend HIV-positive women be evaluated for CIN. The recommendations include:

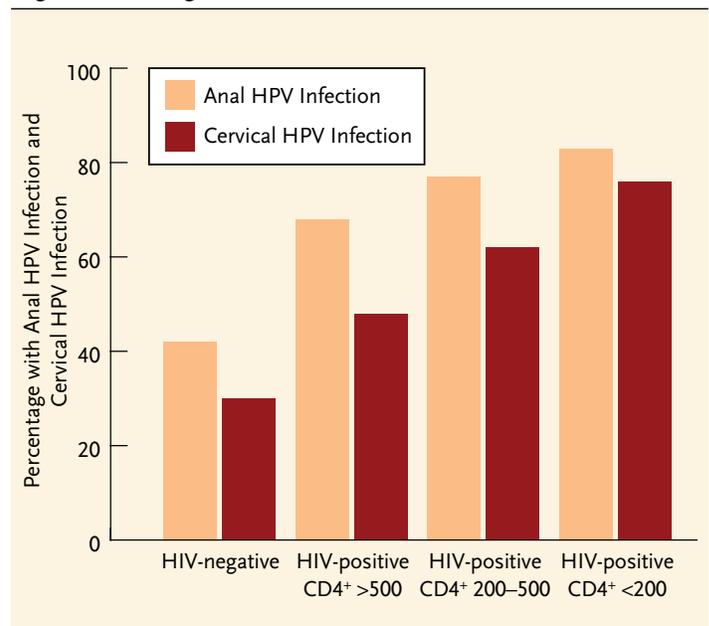
1. Perform Pap smear at initial evaluation;
2. Repeat Pap smear at 6 months;
3. If both Pap smears are negative, continue with annual Pap smear; and
4. If any abnormality is detected, including atypical squamous cells of undetermined significance (ASCUS), perform colposcopy.⁴¹

Figure 7. Percentage of HIV-positive and HIV-negative MSM with Anal HPV Infection and Abnormal Anal Cytology



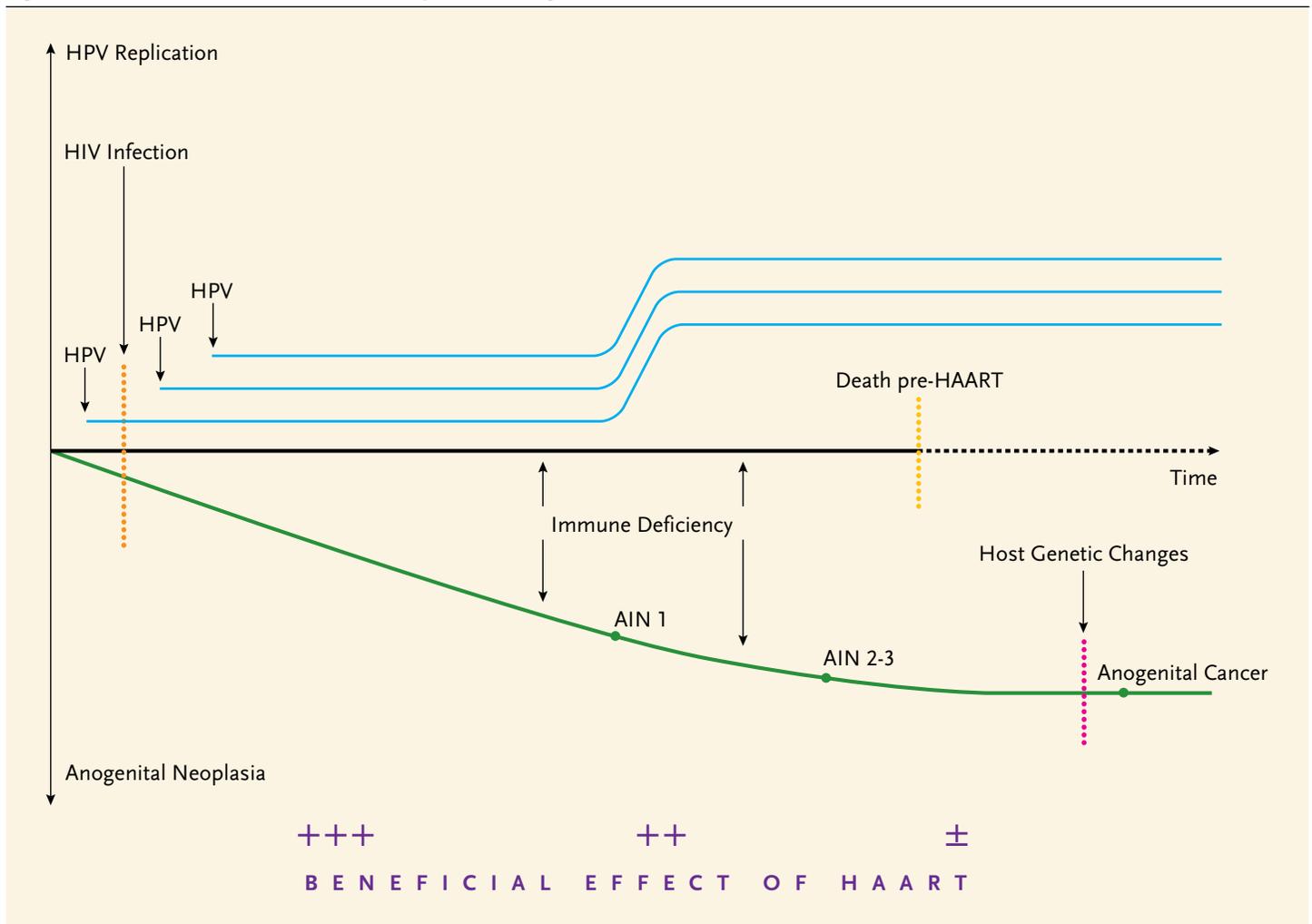
Data derived from Palefsky J, Holly E, Ralston M, et al. ^{25, 26}

Figure 8. Anal and Cervical HPV Infection in HIV-positive and High Risk HIV-negative Women



Data derived from Palefsky J, Holly E, Ralston M et al, and Palefsky J, Minkoff H, and Kalish L, et al. ^{29, 30}

Figure 9. HPV and HIV Infection in the Development of Anogenital Cancer



Pathogenesis of HPV-associated neoplasia and effect of highly active antiretroviral therapy (HAART). Most individuals are assumed to acquire HPV infection early after the initiation of sexual activity, and may acquire HIV infection sometime thereafter. Infection with multiple HPV types may occur, but as long as HIV-associated immunosuppression remains minimal, there is good control of HPV replication and little anogenital disease. As HIV-associated immunosuppression progresses, there is increased HPV replication and the development of AIN 1 or AIN 2-3. Progression from AIN 2-3 to invasive cancer may take many years or decades, in which the key progression events are driven by host genetic change. Less-advanced immunosuppression and early stages of AIN may therefore respond to the initiation of HAART, due to the restoration of HPV-specific immune responses. The beneficial effect of HAART may be less pronounced by the time an individual is diagnosed with AIN 2-3, either because HIV-associated immune response has been damaged so severely that immune restoration due to HAART fails to restore HPV-specific immunity, or because a proportion of AIN 2-3 has accumulated sufficient genetic changes by the time of HAART initiation that HAART-associated restoration of HPV-specific immunity is insufficient by itself to lead to lesion regression. In this model, HIV-associated immune suppression plays a key role in the pathogenesis of cancer by allowing AIN 2-3 lesions to persist long enough to allow sufficient time to accumulate the genetic changes necessary for progression to cancer.³²

Adapted with permission from *Advances in Dental Research*.³²

Anal Cytology Screening Recommendations for HIV-positive Men and Women

The New York State Public Health AIDS Institute created recommendations for the care of all HIV-infected individuals that include screening for AIN.⁴² The recommendations for anogenital examination include:

1. Inquire about anal symptoms at baseline and annually; symptoms include itching, bleeding, diarrhea, and pain;
2. Perform visual inspection of the anal region at baseline and annually;
3. Perform a digital rectal examination (DRE) at baseline and annually;

4. Perform anal cytology at baseline and annually in:
 - a. Men who have sex with men (MSM)
 - b. Patients with history of anogenital condylomas
 - c. Women with abnormal cervical/vulvar histology; and
5. Patients with abnormal anal Pap smear findings should be referred for high resolution anoscopy (HRA) and/or examination with biopsy.⁴²

The benefits of anal screening may be realized at all stages of anal disease.⁴³ With proactive screening in at-risk populations, smaller lesions are more likely to be detected. Smaller lesions tend to be easier to treat than larger lesions, and can be treated in the office with

simple techniques such as cryotherapy with liquid nitrogen or topical application of trichloroacetic acid.³⁶ In most cases, larger or multifocal lesions may also be treated in the office using newer modalities such as infrared coagulation.^{44, 45} Larger lesions can be treated surgically.⁴⁶ While chemoradiation therapy is the standard of care for anal cancer it should not be used to treat AIN.⁴⁷ At later stages of disease, when the lesions are too large or widespread to be removed, there is still benefit to screening because it allows for careful monitoring for progression to invasive cancer.

As with cervical cancer, survival from anal cancer is improved by early diagnosis.⁴⁸ Anal cancer screening techniques, such as the DRE to feel for masses, combined with visualization through HRA and biopsy, are important in the care of patients with AIN. Performing the DRE to feel for subcutaneous masses is particularly important to fully assess for presence of anal cancer, because these tumors may be entirely below the epithelial surface and can occasionally be missed on visual inspection of the surface using HRA. DRE should be performed at least annually on all patients at risk for anal cancer, and is an especially important tool in clinical settings where anal cytology or HRA are not available. At present there are no data on the effect of AIN screening on the incidence of anal cancer. Future studies are needed to examine this relationship.

Future Approaches and Vaccination

While the efficacy of therapeutic vaccines to treat AIN is still under investigation, much attention has been given to the recently approved preventive HPV vaccines. The vaccines work by expressing a major capsid protein encoded by the L1 gene of HPV in eukaryotic cells.⁴⁹ The L1 proteins, or virus-like particles (VLP) auto-assemble into a three-dimensional structure that closely resembles that of the native HPV viral capsid. When injected into humans, these VLPs stimulate immunity against the real HPV virus.

There are two different vaccines, one of which is currently FDA-approved in the United States. Merck has created Gardasil, which is an FDA-approved quadrivalent vaccine comprised of four HPV types, including 16 and 18 (oncogenic types) and 6 and 11 (wart-producing types).⁴⁹ GlaxoSmithKline has created Cervarix, which is a bivalent vaccine composed of HPV types 16 and 18; this vaccine is pending FDA approval.⁵⁰

Among women who had no evidence of prior exposure to HPV types in the vaccine, vaccination is nearly 100% effective to prevent disease associated with those HPV types in the vaccine.^{49,50} However, the vaccines generally do not have any effect on development of CIN if a woman has already been infected with the HPV types in the vaccine.⁴⁹ The vaccines would therefore not be expected to be as efficacious in women with extensive sexual exposure. There is some confusion about the reported efficacy of the vaccines since the efficacy will depend on the proportion of women in the study population (or general population) that has not previously been exposed to the HPV types in the vaccine. Another source of reduced vaccine efficacy is disease due to HPV types other than 16, 18, 6 or 11. In published studies of Gardasil, the efficacy was only 39% since it included patients with prior exposure to HPV vaccine types, as well as development of CIN in some patients from HPV types not included in the vaccine.^{49,51} Since the vaccine is recommended for girls 9 to 12 years of age, it is expected that the efficacy will more closely resemble that of patients without prior exposure, ie, nearly 100% protection against disease associated with vaccine types, and relatively little protection against disease due to non-vaccine types.

These vaccines have the potential to prevent both penile and anal HPV infection and their associated diseases in men. Studies of both heterosexual men and MSM are in progress, and if the vaccines are shown to be effective in this setting, discussions will be initiated to determine the merits of vaccinating both men and women. Since AIN can be challenging to treat, and since a high proportion of anal cancers are associated with HPV 16, vaccines may be an excellent prevention strategy for anal cancer in the long-term, provided that at-risk individuals receive the vaccine before they have been exposed to HPV. In the case of MSM and the psychosocial dynamics of coming out and seeking health care, this may be especially challenging if boys in the general population are not routinely vaccinated prior to sexual debut.

HPV vaccination presents another challenge in the HIV-positive population. HIV-positive men and women are clearly at high risk of disease due to HPV types in the vaccines, and may benefit from vaccination.⁵² However, it is not known how effective vaccination will be in the HIV-positive population since immunosuppression may attenuate development of protective titers of HPV antibodies. The safety of the vaccine has not yet been studied in HIV-positive adults and this population may already have been exposed to some or all of the types in the vaccine. Overall, HIV positive patients most likely will have a reduced efficacy of vaccination, and as with MSM in general, the optimal strategy to prevent HPV infection in this population would be to vaccinate all boys and girls before sexual debut. Given the current debate about vaccinating girls prior to sexual debut, such a recommendation would undoubtedly stimulate even more vigorous debate.

Conclusions

The incidence of AIN and anal cancer is much higher in HIV-positive women and MSM than in the general population, and HAART has had little or no impact on this trend. There is a growing need for definitive guidelines to assess for AIN, and with better treatment options available, it is even more crucial to identify these patients at an earlier stage. New York is the first state to institute guidelines for anal cytology screening in HIV-positive patients. If anal cytology and HRA are not available, all high-risk patients should be screened with a DRE as there are many benefits to early detection of anal cancer. HPV vaccines have the potential to reduce the incidence of anal cancer, but more studies are needed to evaluate the efficacy in patients infected with HIV.

Peer Review Contributions

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