Chapter 6: Immunosuppression and Co-infection with HIV

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Individuals with immunosuppression caused by HIV infection or organ transplantation are at increased risk of human papillomavirus (HPV)-associated anogenital cancers compared with age-matched healthy individuals. The exact role of immunosuppression in conferring increased risk is not known. Although it is unknown which stages of progression from dysplasia to cancer are most affected by immunosuppression, current data suggest that immunosuppression is most strongly associated with the early stages of dysplasia, and that progression to cancer per se is not associated with immunosuppression. Studies to determine this relationship in detail are hampered by the paucity of precise biomarkers of cell-mediated immune response to HPV. This chapter will address these and other issues to provide a better understanding of the biology of HPV infection among immunocompromised individuals. Questions remain about the biology of HPV infection among immunocompromised HIV-negative individuals (e.g., transplant patients) compared with those who are HIV-positive; the impact of highly active antiretroviral therapy on the natural history of anogenital dysplasia and cancer among those who are HIV-positive, and whether the biology of specific HPV types is the same in HIV-positive as in HIV-negative individuals. Understanding HPV infection in those who are immunocompromised offers the potential to better understand its pathobiology in the putatively immunocompetent host. [J Natl Cancer Inst Monogr 2003;31:41–6]

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The relationship between immunosuppression and increased risk of HPV detection or HPV-related lesions is complex for at least four reasons: 1) The mechanisms by which immunosuppression contributes to increased risk of HPV-related disease are not well understood. 2) The role of immunosuppression in detection and persistence of HPV infection and cervical intraepithelial neoplasia (CIN) or anal intraepithelial neoplasia (AIN) may vary according to the underlying etiology of the immunosuppression. Questions remain about the biology of HPV infection among immunocompromised HIV-negative individuals. Understanding HPV infection in those who are immunocompromised offers the potential to better understand its pathobiology in the putatively immunocompetent host. [J Natl Cancer Inst Monogr 2003;31:41–6]

4) Do we need more studies of HAART? 5) How can we measure the immune biomarkers that are most relevant to HPV and translate them to studies in the general population? 6) Is there a differential effect of immunosuppression on HPV types, and what does that mean? 7) Are there many commensal HPV types seen only in immunosuppression?

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increased at a CD4+ level below 200/mm³. This, combined with the Centers for Disease Control definition of AIDS including a CD4+ level below 200/mm³, led some investigators to stratify their CD4+-related data into three categories: greater than or equal to 500/mm³, between 200/mm³ and 500/mm³, and less than 200/mm³. Other investigators have used other, similar classification schemes, including less than or equal to 250/mm³ or more than 250/mm³.

Data from multiple studies of adult HIV-positive men and women show a relationship between immunosuppression as measured by lower CD4+ level (<500/mm³) and increased prevalence of cervical and anal HPV infection with many studies noting even higher risk among those with CD4+ less than 200/mm³ (1-4). However, this relationship is not as apparent among HIV-positive adolescent women. In a study of 133 HIV-positive and 103 HIV-negative girls, cervical HPV infection was associated with HIV status but not CD4+ level (5). The reasons for this discrepancy are uncertain, but in general the adolescents were at an earlier stage of HIV infection than the adults. Detection of cervical HPV is more common among transplant recipients than age-matched controls, but when controlled for number of sexual partners their prevalence was not different from healthy women (6). There is no marker of “relative” immunosuppression among transplant recipients as there is for HIV-positive individuals, e.g., lower CD4+ levels.

Among HIV-positive men and women, there is a relationship between HPV DNA quantity and lower CD4+ level (<500/mm³) with even higher risk among those with CD4+ less than 200/mm³, indicating that immune control may play a role in controlling HPV replication. Along with higher DNA levels there is a relationship between lower CD4+ level and increased number of HPV types in cervical and anal specimens of HIV-positive women and men (2-4). A larger number of HPV types in more immunosuppressed individuals is consistent with more sexual exposures or loss of immune control that permits sufficient viral replication to allow detection using tests such as PCR. The higher HPV DNA levels seen among patients with lower CD4+ levels also may reflect the higher number of HPV types.

Immunosuppression among adult HIV-positive men and women (but not adolescent HIV-positive women) as measured by CD4+ levels is associated with higher prevalence of CIN and AIN in cross-sectional studies, and in many studies with increased incidence of CIN/AIN and faster progression to high-grade CIN/AIN (5, 7-9). The strength of these relationships is stronger for CD4+ level than for HIV viral load, implying that these data from HIV-positive individuals reflects immune dysfunction rather than the direct effect of HIV. CIN is detected more frequently among women with renal transplants, along with precancerous lesions at other anogenital sites such as the vulva, vagina, and anus (6, 10).

Recent data indicate that HIV-positive men and women are at increased risk of anogenital cancer compared with the general population (11). The incidence of cervical cancer is increased in HIV-positive women compared with HIV-negative women to varying degrees in different studies, and one report indicated that HIV-positive men who have sex with men (MSM) had twice the incidence of anal cancer of HIV-negative MSM (12). Likewise in the transplant population, there is a well-documented increase in the incidence of anogenital cancer (10). The reasons for the differences in relative increase in cervical cancer among HIV-positive women compared with HIV-negative women varies depending on the population. In the United States, the largest pockets of increase are in the Northeast, particularly New York City (11). In Europe, the main areas of increase are in the South, particularly among women with a history of injection drug use (12). It is speculated that this reflects diminished access to medical care and Pap smear screening among these at-risk women. Conversely, in many countries in Africa where there is no routine screening, the increase in risk of cervical cancer among HIV-positive women is small (13,14). In these countries, it is speculated that mortality due to HIV precedes the development of cervical cancer. Notably the relative risk for cervical cancer among HIV-positive women compared with HIV-negative women is substantially lower in developing countries than those for other HIV-related malignancies such as Kaposi’s sarcoma and non-Hodgkin’s lymphoma. This reflects the lower incidence of cervical cancer compared with other cancers in HIV-positive women, and the relatively high incidence of cervical cancer among HIV-negative women compared with other cancers. It also is worth noting that the incidence of other anogenital cancers in HIV-positive individuals also may be increased, including cancer of the vulva and the penis. Relatively little is known about the epidemiology of these cancers in HIV-positive patients, nor is it known if their relationship to HPV is similar to that documented in HIV-negative patients.

While there is a relationship between lower CD4+ level and incident low-grade and high-grade CIN and AIN, the relationship between immunosuppression and incidence of anogenital cancer is less clear. Data from AIDS and cancer registry matches show no clear relationship between lower CD4+ levels, e.g., below 500/mm³ or even below 200/mm³, and anal or cervical cancer among men and women diagnosed with AIDS, nor was there a clear increase in incidence with longer time after an AIDS diagnosis (15-18).

The experience using HAART to control HIV replication in individuals dually infected with HIV and HPV has been instructive. Several studies now have been published examining the effect of HAART on the natural history of CIN and AIN. The results have been mixed with some studies showing a beneficial effect and others showing no effect (19-22). However, even in the studies showing a beneficial effect, the majority of women with CIN 2 or 3 failed to regress after institution of HAART even with increases in CD4+ level (23). It is interesting to note that HAART has little effect on HPV levels in the anus (21). There also was little effect on regression of AIN 2 or 3, at least within 6 months of initiation of HAART (21). Together these data suggest that immunosuppression may lead to higher levels of HPV replication with resulting higher HPV DNA levels and increased incidence of low-grade and high-grade CIN and AIN. The higher number of HPV types detected among individuals with lower CD4+ level may reflect an increased number of sexual exposures among these individuals compared with less immunosuppressed individuals, or more likely, greater ease of HPV detection due to the higher level of HPV DNA.

As indicated previously, neither regression of high-grade disease (21) nor progression from high-grade disease to cancer are strongly associated with immune status (15-18). Current data therefore support a model in which immunocompromise leads to an increased risk of developing precancerous high-grade disease, but once high-grade disease develops, other factors such as genetic change play a more direct role in progression from high-grade disease to cancer.
One interpretation of these data is that once a particular level of disease has been reached, “reconstitution” of immune response may be of no or little value. Data suggest that the HPV E6 and E7 proteins induce chromosomal instability and these may lead to accumulation of genetic changes (24, 25). Several studies have shown that the proportion of lesions with genetic changes increases with increasing severity (26, 27), and it is possible that many CIN 3 or AIN 3 lesions have accumulated sufficient genetic damage so that no amount of immune reconstitution will lead to lesion regression. That is, cellular genetic changes and not immunosuppression may be driving persistence of high-grade lesions and in some cases progression to invasive cancer. This has important implications for response to immunotherapeutic approaches such as therapeutic vaccines. Genetic changes may lead to uncontrolled cellular division and the deregulated cells may not be as susceptible to cell-mediated response to HPV antigens. These cells may have down-regulation or alteration in one or more of the many cellular pathways necessary for adequate antigen presentation and response such as TAP-1. It is not yet known if precancerous lesions such as CIN 3 or AIN 3 ever truly reach this “genetic point of no return,” and future data on response of different grades of precancerous lesions to therapeutic vaccines will be informative.

Other mechanisms also may account for the lack of a strong effect of HAART to reduce the incidence of or reverse the course of CIN or AIN: 1) the HAART-associated increase in CD4+ levels does not reflect HPV-specific immune reconstitution because, as described previously, CD4+ levels probably do not reflect HPV-specific immunity; and 2) HAART leads to immune reconstitution related to other pathogens, but has no effect on HPV-specific immunity. Systemic immune response to HPV is difficult to measure even in healthy individuals, and several studies suggest that disease regression is best correlated with infiltration of local lymphocytes (28, 29). In some studies, cytotoxic T cells have been shown to infiltrate CIN 3 (30) and cervical cancer (31). Thus, HAART may have a more limited effect on immune responses that are more compartmentalized, for example those localized to the epithelium.

**CAN WE STUDY WHETHER IMMUNOSUPPRESSION INCREASES THE PROBABILITY OF INVASION?**

Understanding the precise role of immunosuppression in progression from CIN 3/AIN 3 to invasive cancer would be of great intellectual interest. It also would be difficult to study because the standard of care currently requires that women with CIN 3 be treated to prevent progression to malignancy, and most clinicians also treat CIN 2. Similar standards to prevent anal cancer do not currently exist for AIN 2 or 3, and it could be that the best opportunity to study this relationship lies in the anal canal. However, some may argue that it is unethical to leave AIN 2 or 3 untreated when treatment is possible. Even if it were possible to follow the natural history of AIN without treatment, assembling a sufficient number of cases that would progress to cancer would be impractical and prohibitively expensive.

In the absence of following progression from CIN or AIN to invasive cancer, the next best course would be to analyze the immune status of those who develop cancer. As described previously, these studies already have been done and fail to show a clear relationship between advanced immune suppression and cancer, at least using crude measures such as CD4+ level or AIDS diagnosis. Studies of transgenic mice that express HPV proteins and develop the full spectrum of HPV-associated diseases may be the best option to investigate this relationship.

**DO WE NEED MORE EPIDEMIOLOGIC STUDIES OF HPV-ASSOCIATED NEOPLASIA IN THE SETTING OF IMMUNOSUPPRESSION NOT ASSOCIATED WITH HIV, AND DO WE NEED FURTHER STUDIES OF HIV-INFECTED MEN OR WOMEN?**

From an epidemiologic perspective, no more studies of transplant patients are needed with regard to HPV or HPV-related lesions. Transplant patients are a unique group and although the results are somewhat informative they cannot account for the course of disease in the majority of the population. However, from a clinical perspective more data are needed regarding the effect of newer and emerging transplant and immunosuppressive regimens on HPV-related lesions. It would also be of interest to study the contribution of prednisone or other immunosuppressant medication usage outside of the context of organ transplantation to determine whether there is an increased risk of HPV-associated cancers. Analysis of data from large clinical data registries such as those of Scandinavian countries might be useful to address this question.

Studies in transplant patients also offer interesting opportunities to understand the role of immune suppression in disease pathogenesis. The mechanisms of immune suppression are different from those related to HIV infection, and studies comparing immune markers and response in HIV-positive and transplant populations may be of interest. There also is growing interest in transplantation in HIV-positive patients, and national collaborative studies in this population will be of particular interest.

Another area of interest in transplant-related immunosuppression concerns the range of HPV types found in transplant-associated cancers. Skin HPV types are likely to be highly prevalent in this population, and it is possible that the range of HPV types in both genital and cutaneous lesions in transplant populations may differ from those seen in HIV-positive populations.

Studies of less dramatic immunosuppression such as that caused by malaria endemicity or malnutrition would be interesting because these types of immunosuppression are more typical in the developing world and affect a substantial proportion of the population in that setting. Studies that evaluate the effect of these conditions on HPV and cervical or anal cancer would need to be conducted in countries where malaria and malnutrition are common. However, developing countries have numerous additional factors that need to be considered when testing hypotheses that may have been based on results from developed countries. Some of these include unidentified HIV infection, education, other infectious diseases, race (important if there were a genetic component to individual susceptibility), and cultural background.

Additional studies in HIV-infected men and women may be helpful. With few exceptions, the studies conducted to date have been small to moderate in size and larger studies would be needed to have adequate power to test associations between exposure and disease. However, a meta-analysis of the main effects from published studies would be a logical step before an initiation of a series of new studies, and it would be predicated upon the availability of small studies already conducted with published results, similar study designs, and data.
DO WE NEED MORE STUDIES OF HAART?

It will be quite important to continue to study the effect of different HAART combinations on the natural history of CIN, AIN, and anogenital cancer. Further, because the use of HAART is still relatively new and the specific HAART drugs and combinations continue to evolve, it is important to monitor them until a clearer picture of the HAART–disease association evolves. Many drugs and therapies are evaluated in cancer studies for use for 10 years or longer. Drug approval is based on results from short-term studies and little is known about their long-term effects. The cumulative effects are likely to surface during the years after the initial evaluation period. Cancers tend to be slow growing and 10-year latency is reasonable for exposures that are not highly toxic. The effects of HAART also should be compared among different age groups because adolescents may respond differently than adults.

HOW CAN WE MEASURE THE IMMUNE BIOMARKERS THAT ARE MOST RELEVANT TO HPV AND TRANSLATE THEM TO STUDIES IN THE GENERAL POPULATION?

As indicated above, systemic measurement of specific immune response to HPV is difficult. A variety of assays have been used including serology to measure humoral response. Among the assays developed to measure cell-mediated immune response are cytotoxic T-cell (CTL) assays, lymphocyte proliferation assays, ELISPOT assays, tetramer assays, and fluorescence-activated cell sorter (FACS)-based cytokine activation assays. Of all these assays, the serology assays are probably the most robust and as they improved over time began to tell a fairly consistent tale: HPV seroconversion typically follows acquisition of HPV DNA often by a period of months, and often persists for months after the HPV DNA was no longer detected. A relationship between seroconversion and lesion development and regression is not as consistent, reflecting the generally held belief that lesion regression is likely to be mediated by a cell-mediated immune (CMI) response. However, the CMI responses in nearly all studies are very weak when measured in the peripheral circulation, at least when compared with systemic viruses such as Epstein–Barr virus and cytomegalovirus. The relationship between development of these weak responses and the natural history of CIN has been very inconsistent (32–34). These data suggest that either these tests are not sufficiently sensitive, or, more likely, CMI responses measured in the periphery are epiphenomenal and the relevant immune response is local and not measurable using these techniques.

Determination of an individual’s MHC haplotype in some studies is associated with increased risk of CIN or cervical cancer, or in other cases, with decreased risk. Both class I and class II genes have been studied using these assays. They are of interest insofar as they confirm a role for CMI response in determining the natural history of CIN and illuminate some of the involved immune mechanisms. However, because of their relatively weak association with risk of disease, they are primarily of interest at the population level and have relatively little prognostic value at the level of the individual.

Measuring local immune response is challenging. Some investigators have obtained sufficient quantities of tumor infiltrating lymphocytes (TILs) to show HPV-specificity. These techniques are laborious and the large quantities of tissue required do not lend themselves to use in studies in the general population. Local interferon and other cytokines most likely play a role in the immune response to HPV as indicated by therapeutic studies with interferon, imiquimod and other agents. In vitro studies with HPV-transformed keratinocytes have revealed that expression of interferon-response genes are down-regulated in these cells, as is signal transducer and activator of transcription (Stat-1), which plays a role in mediating the interferon response (35).

Studies to examine the role of local cytokines could theoretically be done in relatively accessible specimens such as lesion biopsies using RNA in-situ hybridization or immunohistochemistry. Measurement of cytokine levels in anal swabs, cervical swabs or cervicovaginal lavage is technically feasible using real-time PCR. In one example of the study of the effect on local immune response Crowley-Nowick et al. (36) showed that HIV-positive persons with HPV had high levels of IL10 (Th2 cytokine) compared with HIV-negative persons with HPV. In another study, Scott et al. (37) showed that Th1 cytokines are important in regression of HPV. Microarray analysis of biopsy tissues can be done to examine changes in cytokine expression as a function of lesion severity. Analyses of this kind are needed and could be completed in carefully performed cohort studies. Other methods, such as using “dimers” in-situ in biopsy tissues to determine the presence of HPV-specific lymphocytes (instead of tetramers to measure these cells in the peripheral circulation) are interesting but still in the development stage. Regardless of the success of these assays, each paints a static picture of the relationship between immune biomarkers and disease state. Only by assembling data from a large cohort of individuals and following the natural history of their lesions will a clearer understanding of the meaning of these biomarkers emerge. Studies in transgenic mice also may play an important role.

IS THERE A DIFFERENTIAL EFFECT OF IMMUNOSUPPRESSION ON HPV TYPES, AND WHAT DOES THAT MEAN?

Most of the data investigating the role of immunosuppression on specific HPV types comes from studies of HIV-positive men and women because of their relatively large number and because many are infected with multiple HPV types. Earlier data using PCR in relatively small study populations showed that high-risk HPV types were more likely to persist than low-risk types, and that this effect was more pronounced in HIV-positive women than in HIV-negative women (1). The mechanism of this differential effect is not clear. If HIV-positive women are less able to “clear” their oncogenic HPV types than HIV-negative women, then this may account for the higher risk of CIN in this group.

More recent data from larger studies of HIV-positive women show a fairly uniform increase in the prevalence and incidence of HPV types spanning the spectrum of oncogenicity with progressively lower CD4+ level. One notable exception was HPV 16 in the Women’s Interagency HIV Study and HIV Epidemiology Research Study populations. Like the other HPV types, the prevalence and incidence of HPV 16 increased with lower CD4+ level, but the size of this increase was smaller than that seen with other HPV types (38). Because HPV 16 was one of the most common HPV types among those with CD4+ levels greater than 500/mm3 in this study and because it is the most common oncogenic HPV type in the general population, these findings suggest that HPV 16 escapes immune control more efficiently.
than the other HPV types in HIV-positive individuals who are less immunosuppressed or who are HIV-negative. The investigators who conducted this study speculated that this could account for the observation that HPV 16 is the single most common HPV type in most studies of non-immunosuppressed individuals. The mechanism for the relatively weak control of HPV by the immune system is not clear, but it was notable that other HPV types closely related to HPV 16 in the phylogenetic tree showed similar effects, although not as pronounced. The implication is that these effects may be mediated by amino acid sequences of one or more HPV epitopes held in common between these types that perhaps modulate the strength of the CTL response. In contrast to the WIHS data, lower CD4+ levels were associated with higher persistence of HPV 16-like types in a prospective study of 222 HIV-positive adolescents followed over three years, whereas the persistence of oncogenic HPV types related to HPV 18 or 56 did not vary with CD4+ level (AB Moscicki, personal communication). These data indicate that the relationship between prevalence and persistence of specific HPV types and HIV-related immunosuppression as measured by CD4+ level is complex and may vary in populations with differing risk factors for HIV infection, use of HAART and duration of HIV infection.

If the early observation in HIV-positive women is valid that an increase in the prevalence of HPV 16 infection does not correlate as well with lower CD4+ levels as it does for other HPV types, then HPV 16 should be present in a lower proportion of cervical cancers in HIV-positive women than in the cervical cancers among HIV-negative women. Therefore, testing HIV-positive women to determine the spectrum of HPV types in cervical cancer will be important. Likewise, it will be important to determine the spectrum of HPV types in HIV-positive women with cervical cancer from around the world to compare with known patterns from HIV-negative women in the same region.

ARE THERE MANY COMMENSAL HPV TYPES SEEN ONLY IN IMMUNOSUPPRESSION?

One of the most striking findings in HIV-positive women and men is the high proportion of those with multiple HPV types. In most studies, there was a clear correlation between the number of HPV types and progressively lower CD4+ levels. Although some of these types may have been newly acquired, it seems probable that some, if not most, were acquired earlier, but were at levels too low to permit detection by PCR. If loss of immune control allows for replication of these hitherto unrecognized HPV types, then it would be expected that some previously unknown HPV types might be detected. Results reported at a meeting a year ago (39,40) showed a large number of “new” HPV types in cervical specimens from HIV-positive women. This apparently is not restricted to HIV-positive women, because these types, classified primarily in the “A3” group of papillomaviruses, also were found in a high proportion of HIV-negative women in the Guanacaste study. The A3 clade of HPV types includes a number of HPV types that are not considered to be oncogenic (41,42). Finally, detection of unusual HPV types among patients who are immunosuppressed for reasons other than HIV such as those with renal transplant, indicate that this phenomenon is not HIV-specific.

It is unclear whether these HPV types are commensal or are pathogenic in HIV-positive women, nor whether they play any role in modulating the behavior of co-existing HPV types. Al-

most all of these women had more commonly recognized HPV types in addition to the new types and it was not determined whether any lesions were associated with these “new” types in the absence of infection with one or more of the standard HPV types. Studies will be needed to determine if these newly recognized HPV types can be found in the normal cervix or in cervical lesions of HIV-positive or HIV-negative women in the absence of one or more of the known HPV types. However, the relatively small number of lesions that are detected in the absence of one or more of the typical genital HPV types suggests that if there is a contribution of the new types to lesion pathology it will be limited. It is unknown whether the HPV types that are commensal in HIV-negative women will become pathogenic in HIV-positive women.

How these putatively commensal A3 viruses persist remains unclear. Perhaps after initial infection of the immortalized basal keratinocyte layer they remain transcriptionally silent and hence are not subject to immune targeting. With a normal immune response they may be effectively targeted by the immune system should they become transcriptionally active leading to elimination of lesions before they become clinically evident. In the immunosuppressed patient, replication of these HPV types may not be controlled as effectively and may therefore be more easily detectable. It would be instructive to compare the sequences of these commensal HPV types with those of the types more commonly detected in lesions to determine if there are amino acid sequence patterns that might predict better or worse immune control.

In summary, although commensal HPV types appear to play only a limited role in disease pathogenesis, a more detailed analysis of immune responses to these types, their genomic sequences, and their natural history may well provide important information on the mechanisms of pathogenesis of more onco-

genic HPV types.

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Financial support from grants R01 CA 54053, CA 88739, and M01 RR00079.