The Role Of Human Papillomavirus (HPV) And The Increasing Incidence Of Oral Pathology In The Era Of Highly Active Antiretroviral Therapy (HAART)

K Shetty, J Leigh

Citation

Abstract
Oral HPV infection and disease results from increases in oral-based immune suppression in the HIV co-infected individual that cannot be restored and is possibly compromised further by HAART. This review provides greater insight into the rate of oral HPV infection in the HIV+ individual, the effect of HAART on oral HPV infection, it's role in oral pathology, and the host's immune response against HPV under immune compromised (HIV without effective HAART) and potentially immune restored (effective HAART) conditions.

INTRODUCTION
The human immunodeficiency virus (HIV) epidemic continues to grow at a significant rate worldwide with over 34 million people infected. This disease leads to progressive immune suppression with selective depletion of CD4+ T lymphocytes. There are numerous opportunistic infections that occur secondary to this decrease in systemic immunity, particularly in the oral cavity with over 50% of HIV-infected individuals developing oral pathology. One pathogen which is commonly found in both the oral and genital tracts of HIV-positive patients is the mucosatropic human papillomavirus (HPV), however infection can occur with or without mucosal pathology. HPV-associated oral lesions include condyloma, focal epithelial and some squamous cell carcinomas. Both oral and genital lesions caused by HPV are more commonly seen in those co-infected with HIV. Systemic immune reconstitution for the HIV-positive patient has been accomplished with highly active anti-retroviral therapy (HAART) leading to decreases in systemic and oral infections, including regression in HPV-induced cervical lesions. Paradoxically, recent reports have noted increases in oral pathology consistent with HPV infection in the presence of HAART. If this observation can be confirmed, it suggests that the host defense against oral HPV is independent of that restored by HAART and may be adversely affected. Unfortunately, little is known about the prevalence, natural history and immune response against oral HPV infection, especially in the HIV co-infected individual.

HUMAN PAPILLOMAVIRUS IN ORAL DISEASE
Seventy types of human papillomavirus (HPV) have been described with types divided by site of infection and their risk oncogenic potential (see table 1). HPV is associated with several oral lesions compatible with oral warts (veruca vulgaris, squamous cell papillomas, condyloma acuminata, focal epithelial hyperplasia (FEH) and also oral leukoplaia with dysplastic changes. Such lesions have been reported in 0.4% of the general population however, the HPV DNA detection rate in individuals without any obvious oral pathology has varied widely depending on the study population, type of sample collected, method of DNA detection (hybridization vs. PCR), and the primers and specific probes utilized. HPV DNA detection in oral squamous cell carcinomas (SCC) is reported to range from 20-30% of cases with HPV DNA, particularly type 16 and 18, detected in 20-30% of oral squamous cell carcinomas (SCC). What is lacking in these studies is a detailed analysis of the exact site of HPV oral infection as well as detailed delineation of the role of HPV in abnormal or cancerous oral tissue.

HPV IN HIV DISEASE.
As with the HIV population there are large differences between the infection rates with HPV and the occurrence of oral lesions however, these HPV associated lesions occur more commonly under conditions of immune suppression. In addition, oral lesions similar to those seen in HIV individuals contain additional or novel HPV
types in a significant subpopulation. (2.5-4% of HIV+ patients)\textsuperscript{30}. Greenspan et al have described cauliflower and spiky warts containing HPV type 7 and flat warts, similar in appearance to FEH, containing HPV 13,18 and 32\textsuperscript{31,32}. A study of benign oral lesions, not restricted to warts, Volter et al found HPV DNA sequences in 67% of the specimens\textsuperscript{33}. The most common types found were HPV 32 (28%) and HPV 7 (19%), which would have been missed if testing only for genital HPV types. A study on oral squamous cell carcinomas in HIV+ individuals have demonstrated an early age of onset, an aggressive course, and a high rate of HPV DNA detection\textsuperscript{34}.

Comparative studies have shown that HPV infection is increased in the HIV+ individual as demonstrated by Coutlee et al where HPV DNA was detected in 2.6% of the oral cavities of HIV+ adults compared to 14.4% of the HIV+ individuals\textsuperscript{35}. Again, only genital types of HPV were studied and no specific methods to detect non-genital types of HPV were attempted, which could lead to an underestimation of the HPV prevalence rates. Genital HPV infection is also increased in HIV+ women compared to HIV- women with more women infected with multiple types of HPV, particularly high-risk HPV infections leading to anogenital malignancies\textsuperscript{36,37}. Women represent a growing percentage of the HIV+ population and indeed the risk factors for oral HPV infection in HIV+ women may differ from HIV+ men, as may the rates of HPV-related oral disease. In addition, the genital tract could serve as a reservoir for current or future oral infection. Clearly, studies are needed to more fully examine the site of oral HPV infection as well as the genotype(s) involved.

**HOST DEFENSES AGAINST HPV**

**HUMORAL**

Most immune responses studied in both the oral and genital cavities have been limited to humoral mechanisms. Similar to that reported at other mucosal sites, levels of both serum and mucosal anti-HPV antibodies in HIV+ individuals were found to be normal or elevated but appear to offer no protection from established infection\textsuperscript{38,39}. In the study by Hagensee et al\textsuperscript{40}, cervical HPV-16 DNA detection 12 months prior to cervical antibody sampling correlated with the detection of cervical HPV-16-specific IgG (Odds ratio, OR 3.3, confidence intervals, CI 1.4-7.8)\textsuperscript{41}. Although recent studies have detected HPV antibodies in oral fluids\textsuperscript{36}, these studies were cross-sectional in design and did not closely examine the HPV infectious status of the oral cavity.

**CELL MEDIATED IMMUNITY**

Although the incidence of HPV infection and disease is higher in patients with cellular immunodeficiencies such as renal transplant recipients and HIV+ individuals\textsuperscript{42}, the cellular immune mechanisms that control HPV infection have not been clearly elucidated. Recently, the role of systemic cytokines in the immune response to various pathogens has been investigated\textsuperscript{43}. These studies have shown that the immune response can be characterized as a Th1 type (IL-2, IL-12, IFN-\gamma, IgG1 production) that is involved in control of intracellular (i.e., viral) infections, by the induction of cytolytic activity\textsuperscript{44,45}. Conversely, a Th2-type response (IL-4, IL-5, IL-10, IgG4, IgA production) is functionally important against extracellular pathogens (i.e., bacteria and parasitic infections) through antibody-mediated mechanisms\textsuperscript{46}. In HIV disease a shift in the Th1/Th2 response has been suggested during progression to AIDS, though this has proved controversial\textsuperscript{47}. Preliminary data have shown that women with abnormal Papanicolou smears or cervical neoplasia have lower systemic IL-2 levels and higher IL-4 and IL-10 than do controls which suggests that HPV disease occurs with a relative decrease in Th1 cytokines and with a relative increase of Th2 cytokines\textsuperscript{48,49}. However, no study of systemic cytokines or local mucosal cytokines in oral HPV infection has been done.

**IMMUNE RESTORATION DUE TO HAART**

The introduction of protease inhibitors and the development of combination highly active anti-retroviral therapy (HAART) in the late 1990’s has had a profound impact on HIV disease with the associated decreases in systemic HIV viral loads and increases in CD4+ cells\textsuperscript{50}. This has also been associated with a marked decrease in the risk of many oral opportunistic infections including oral candidiasis, Kaposi’s sarcoma, major aphthous ulcers and necrotizing stomatitis\textsuperscript{13,14}. Paradoxically, recent reports have noted increases in oral pathology consistent with HPV infection in the presence of HAART, which suggests that defense against oral HPV infection is independent of that restored by HAART and may be adversely affected\textsuperscript{51}. Although, many have studied the impact of HAART on systemic immune function, relatively little is known about the reconstitution of mucosal immunity.

**SUMMARY**

Human papillomavirus is a ubiquitous pathogen that infects mucosal surfaces especially the genital tract and oral cavity.
The current clinical observation of an increase in oral pathology due to HPV in the HIV+ individual in the setting of active anti-retroviral therapy implies the lack of mucosal immune reconstitution.

Figure 1

Table 1: Site and Type of HPV

<table>
<thead>
<tr>
<th>Low risk HPV</th>
<th>High risk HPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>4, 6, 7, 10, 11, 13, 32, 66</td>
</tr>
<tr>
<td>Genital</td>
<td>16, 18, 31, 33, 35, 16, 18, 26, 31, 39</td>
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