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*Brief Research Report*

# Compliance with Highly Active Antiretroviral Therapy (HAART) does not Prevent Human Papilloma Virus (HPV)-Related Cancers in Women Infected with Human Immunodeficiency Virus (HIV)

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## ABSTRACT

**Introduction**
Cancer is one of the leading causes of death in people with human immunodeficiency virus and acquired immune deficiency syndrome (HIV/AIDS), due to behavioral choices and overlapping risk factors.

**Aim**
The purpose of this report is to determine the long-term incidence of human papilloma virus (HPV)-associated cancer in women with pre-invasive cervical neoplasia, and compliance with medication and cancer screening recommendations.

**Methods**
HIV-infected women diagnosed with pre-invasive cervical neoplasia and an HPV-associated malignancy between 1995-2008 were identified. Data collected includes: demographics, HIV treatment/response, malignancy treatment/response, other healthcare utilization, use of health navigators, and compliance.

**Results**
Seventy one subjects were identified with HIV infection, cervical dysplasia, and at least ten years' follow-up. 17/71 (24%) were identified with an HPV-related malignancy. The mean age of those diagnosed with HPV-related malignancy was 39-years. Malignancies included: Cervix-9, Vulva-7, Anal-4, Vagina-3, Uretha/Bladder-2, Oropharyngeal-3. Eight also had *in-situ* neoplasms: Cervix-4, Vulva-3, Oropharyngeal-1. Four subjects had 3 separate malignancies, and two others had 2 malignancies. Compliance with HAART correlated strongly with immunocompetence, response to therapy, use of patient navigators, and survival. Sixty out of saventy one (84.5%) subjects underwent screening mammography, 57/71 (80.3%) underwent colonoscopy, and 67/71 (94.3%) underwent pap smear testing. Compliance with screening compared favorably with the general population, and overall survival was similar.

**Discussion and Conclusion**
The long-term incidence and mortality from cancer in women with HIV and cervical dysplasia appears to be comparable to that seen in the general population, with the possible exception of oropharyngeal cancers. Compliance with cancer screening recommendations appears to be higher than in the general population. This suggests that structured primary care programs for HIV-infected women are effective in prevention/early diagnosis of cancer. Standardized screening programs for oropharyngeal cancers should be considered in this population.

**Keywords**
Human immunodeficiency virus (HIV); Cancer; Human papilloma virus(HPV); Women; AIDS;
Highly active anti-retroviral therapy (HAART).

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## INTRODUCTION

Cancer is one of the leading causes of death in people with human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS).[1,2] With the introduction of highly active anti-retroviral therapy (HAART) in the mid-1990s, the overall incidence and mortality of cancer has decreased in this population, largely due to striking declines in AIDS-defining cancers such as Kaposi sarcoma and non-Hodgkin lymphoma.[3] However, the incidence of invasive cervical carcinoma, (also an AIDS-defining cancer) has been relatively stable; while a number of non-AIDS defining cancers have increased in incidence (presumably due to the increasing numbers and age of HIV-infected individuals) and now constitute the majority of cancers in this population.[4,5] Factors suspected to contribute to increased cancer incidence in HIV-infected persons include HIV viremia, immune deficiency, oncogenic virus co-infection, and lifestyle exposures (e.g. tobacco, alcohol).[6,7,8] In particular, among individuals with AIDS, a statistically significant elevated risk of human papilloma virus (HPV)-associated cancers has been reported, with the level of risk strongly correlated with increased levels of immune suppression.[9]

Although HIV-associated malignancies have been extensively analyzed and reported, the data on cancers in women, with the exception of invasive cervical cancer, has been relatively limited due to an overall paucity of women in study populations.[10] Further, many of these studies involved populations with multiple additional risk factors for cancer in addition to HIV infection, such as intravenous drug users or men who have sex with men.[11] In contrast to earlier reports, which typically included relatively few HIV-infected women, as well as a relatively short follow-up, the goal of this study is to determine the incidence and outcomes of HPV-related genital and non-genital tract malignancies in HIV-infected women with a diagnosis of pre-invasive cervical neoplasia (dysplasia) and at least a 10-year follow-up. Further, as screening programs have been shown to be very effective in reducing the incidence of invasive cervical cancer in HIV-infected women,[12] the secondary goal of this study is to evaluate the degree of compliance with cancer screening recommendations in this cohort.

## METHODS

As part of a facility-based quality improvement (QI) program, all HIV-infected women diagnosed with an HPV-associated malignancy between 1995-2008 were identified. Data sources included standard medical records, tumor registries, and clinical research trial records. Data collected includes: demographics, HIV treatment/response, malignancy treatment/response, other healthcare utilization, use of health navigators, and compliance. The data was analyzed using standard statistical tests, and the study was determined to be exempt from Institutional Review Board (IRB) review.

## RESULTS

Seventy one subjects were identified with HIV infection, cervical dysplasia, and at least ten years' follow-up data from a large, inner-city academic institution in New Orleans, Louisiana, USA. Seventeen out of seventy one (24%) were identified with an human papilloma virus (HPV)-related malignancy. The mean age of those diagnosed with HPV-related malignancy was 39-years and all were African-American. Invasive malignancies included: Cervix-9, Vulva-7, Anal-4, Vagina-3, Uretha/Bladder-2, Oropharyngeal-3. Eight

**Table 1.** *Characteristics of HIV-Infected Women with Cervical Dyplasia and at Least one HPV-Associated Malignancy*

| Subjects | Age | Cervix | Vulva | Anal | Vagina | Urethra/ bladder | Oropharyngeal | Cervix IS | Vulva IS | Oro IS | HAART Compliance | CD4>200 | Patient navigator | Survival |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 45 | x | x | | | | x | | | | | | | 27 |
| 2 | 52 | | x | | | | | x | | | x | x | x | N/A |
| 3 | 50 | x | | x | | | x | | x | | | | | 19 |
| 4 | 34 | x | x | | | | | | | x | x | x | x | N/A |
| 5 | 30 | | | x | | | | x | | | x | x | x | N/A |
| 6 | 35 | x | | | | x | | | | | | | | 21 |
| 7 | 37 | | | | x | | | x | | | x | x | x | N/A |
| 8 | 51 | x | x | | x | | | | | | | | | 9 |
| 9 | 29 | | | | x | | | | | | x | x | x | N/A |
| 10 | 45 | | x | | | | | | | | x | x | x | N/A |
| 11 | 38 | x | | | | | x | | x | | x | | | 13 |
| 12 | 33 | x | | | | | | | | | x | x | x | N/A |
| 13 | 60 | | | x | | | | x | | | x | x | x | N/A |
| 14 | 32 | x | x | | | x | | | | | x | x | x | N/A |
| 15 | 30 | | | | | | | | | | x | x | x | N/A |
| 16 | 36 | x | | x | | | | | x | | x | x | x | 28 |
| 17 | 28 | | x | | | | | | | | | | | 18 |

*IS=In-Situ; Survival in months; N/A=living at time of this analysis*

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additional subjects had *in-situ* neoplasms which included: Cervix-4, Vulva-3, Oropharyngeal-1. Four subjects had 3 separate malignancies, and two others had 2 malignancies correlated strongly with survival. Compliance with HAART correlated strongly with immunocompetence, (as measured by CD4>200/μL) response to anti-malignancy therapy, and survival. Further, compliance correlated strongly with the use of patient advocate/navigators (Table 1).

Thirty five out of saventy one (49%) participated in federally-sponsored clinical trials, including AIDS Clinical Trial Group (ACTG) 200, ACTG 293, Southwest Oncology Group (SWOG) 8797, Gynecologic Oncology Group (GOG) 154, and GOG 155. Sixty out of saventy one (84.5%) subjects underwent screening mammography, 57/71 (80.3%) underwent colonoscopy, and 67/71 (94.3%) underwent pap smear testing, all in accordance with American Cancer Society (ACS) guidelines. The level of compliance with guideline-based screening compared very favorably with that seen in the general population of New Orleans and Louisiana, USA, and overall survival at 5-years was similar.[13]

## DISCUSSION

In this cohort, the long-term incidence and mortality from HPV-associated cancers in HIV-infected women with a history of cervical dysplasia was comparable to that seen in women with cervical dysplasia in the general population of this area. This appears to be in contrast with previous reports, which found an increased risk of both AIDS-defining and non-AIDS defining cancers in similar populations.[14] It seems clear from these findings that while the use of HAART can reduce the risk of HPV-associated cancers in this group to at least that of the general population, it does not prevent those cancers, and therefore active screening remains important, even in those HIV-infected individuals who remain compliant with their medications. A possible explanation for these findings include strong compliance with HAART as seen here, which is known to be protective for both AIDS-defining and non-AIDS defining cancers. Another explanation could be the increased level of compliance with cancer screening recommendations in this group. While HIV-infected patients with cervical dysplasia are at risk for HPV-associated cancers, that risk does not seem to exceed that seen in the general population of this area, which has long been among the highest in the US.[15] This apparent success in cancer screening is likely due to the work of a well-organized and (relatively) well-funded clinic system for HIV-infected individuals in the New Orleans Metropolitan area. This system has been in existence for over 25-years, makes extensive use of patient advocate/navigators, and has been credited with dramatic improvements in multiple health outcomes.[16] This suggests that communities where HIV infection is common will benefit from organized primary care delivery systems, with emphasis on adherence to HAART.

Another possible explanation for the findings reported here is that the baseline characteristics of this group differ from those in prior studies. This study population, while limited in size, was exclusively female and appeared to have both similar levels of personal risk factors and similar demographics to the general population of the area. Prior studies of cancer risks in HIV-infected persons typically comprised a cohort that was predominantly male and included many additional known risk factors for cancer, including high rates of intravenous drug use, alcohol use, smoking, and infection with known cancer- causing viruses such as Hepatitis B and C viruses, (HBV and HCV) in addition to HPV.[17]

It is well-known that HIV-infected women from the pre-HAART era demonstrated an elevated risk for and mortality from cervical abnormalities and dysplasia.[18] A study by Ellerbrock et al, reported that 1 in 5 HIV-infected women without previous evidence of cervical dysplasia developed biopsy-confirmed cervical squamous intraepithelial lesions.[19] In addition, HIV-infected women with a greater level of immune suppression have an increased risk of persistent HPV infection and progression to cervical dysplasia.[20] Interestingly, a separate study showed that the incidence of cervical dysplasia in HPV-negative, cytology-negative HIV-infected women with CD4 counts greater than 500/μL was comparable to that in HIV-negative women.[21] Massad et al found that while the risk for an abnormal Pap test was greater in HIV-infected women than seronegative women, once an HIV-infected woman develops an abnormality, her risk for high grade cervical dysplasia was only marginally greater than that of seronegative women.[22] Of importance for patient care, another study of HIV seropositive women from 1994-2001 from the same investigators found the risk of invasive cervical cancer to be indistinguishable from that of the general population when the HIV seropositive women were enrolled in a program of cervical cancer screening and prevention.[23,24]

An intriguing finding from the current study is that the long-term incidence of oropharyngeal cancers may be higher than expected. This may be partially explained as a reflection of the overall increase in oral HPV infection and oropharyngeal cancers in recent years.[25] However, understanding of the pathophysiology of HPV is incomplete, and may differ in the female genital tract compared to the oropharyngeal tract. Consistent with this, a study by Beachler, et al, found an elevated prevalence of oral HPV in HIV-infected persons after controlling for differences in cigarette smoking and sexual behavior.[26] This unexpected number of oropharyngeal cancers in HIV-infected persons suggests that standardized screening programs for oropharyngeal cancers should be considered.

Compliance with cancer screening recommendations in this study group appeared to be higher than in the general population. Although there is limited data on certain cancers in HIV-infected women, prior studies have indicated benefits of screening these patients for cervical cancer, anal cancer, breast cancer, and hepatocellular carcinoma.[27] Currently there is insufficient evidence to recommend lung cancer screening for HIV-infected women without other risk factors such as smoking. Although the incidence of lung cancer is elevated in HIV patients, it has also been reported that they have a greater cumulative pack-year smoking history.[28]

## CONCLUSION

The long-term incidence and mortality from cancer in women with HIV and cervical dysplasia appears to be comparable to that seen in the general population, with the possible exception of oropha-

ryngeal cancers. Compliance with cancer screening recommendations appears to be higher than in the general population. This suggests that structured primary care programs for HIV-infected women are effective in prevention/early diagnosis of cancer. Standardized screening programs for oropharyngeal cancers should be considered in this population.

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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