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# The Impact of HAART on HPV-Related Cervical Disease

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## Abstract

**Purpose of Review—**Highly active antiretroviral therapy (HAART) has had an unequivocally positive impact on morbidity and mortality in HIV-infected individuals. These benefits have clearly extended to some HIV-related malignancies, including Kaposi's sarcoma and non-Hodgkin's lymphoma. The impact of HAART on cervical cancer, however, remains uncertain. The objective of this review is to summarize the last ten years of registry-based and clinical research into the impact of HAART on human papillomavirus (HPV) related cervical disease.

**Relevant Findings—**Compared to their HIV-uninfected counterparts, HIV-infected women have an increased prevalence of HPV infection, increased risk of progression of HPV-related cervical disease, and an increased risk of invasive cervical cancer. While the partial immune reconstitution afforded by HAART might be expected to decrease susceptibility to HPV infection and cervical disease, the local effects of improved immunosurveillance on the cervix are uncertain and the increased longevity of patients on HAART may increase risk of exposure to HPV and provide the time required for progression of cervical disease. Registry-based evidence has been consistent in identifying the lack of decrease in cervical cancer incidence in the HAART era. Clinical research on the subject, however, has produced conflicting evidence with regards to both the effect of HAART on HPV infection and its impact on cervical disease progression/regression.

**Summary—**The incidence of cervical cancer has not decreased in the HAART-era. Furthermore, clinical research has not shown a clear benefit of HAART in decreasing HPV-related cervical disease in HIV-infected women. A better understanding of this subject will have an impact on cervical disease surveillance practices.

### Keywords

HPV; Human papillomavirus; HAART; Cervical dysplasia; Cervical cancer; HIV

## INTRODUCTION

Human papillomaviruses (HPV) cause cervical cancer [1]. Annually, approximately 500,000 women develop cervical cancer, and over 270,000 women die from the disease [2]. Globally, the burden of cervical cancer occurs disproportionately among the poorest and most vulnerable women who often have inadequate access to screening programs and treatment of the precursor lesions of cervical cancer. Cervical cancer is the number one cancer cause of years of life lost (YLL) in the developing world [3, 4].

Women infected with the human immunodeficiency virus (HIV) are at increased risk of HPV-related cervical disease [5–7]. Prior to the introduction of effective antiretroviral therapy, AIDS-related malignancies were major causes of death in HIV-infected women



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living in industrialized nations. With the widespread use of highly-active antiretroviral therapy (HAART) tremendous improvement has been achieved in AIDS-related morbidity and mortality over the last decade and a half. The specific impact of HAART on HPV-related cervical disease, however, remains uncertain. This review summarizes the last ten years of registry-based and clinical research into the impact of HAART on human papillomavirus (HPV) related cervical disease. Articles were identified for review through a PubMed search conducted in January 2010. Additional articles were identified through cross-referencing.

## BACKGROUND

The CDC designated invasive cervical cancer as an AIDS defining illness in 1993 [5]. HIV infection has a significant impact on HPV infection and the course of HPV-related cervical disease. Compared to their HIV-uninfected counterparts, HIV-infected women have increased overall HPV prevalence and an increased rate of multiple infections. In a 2006 meta-analysis of HPV genotypes among HIV-infected women that included over 5,500 subjects from around the globe, HIV-infected women were found not only to have a high prevalence of HPV infection (36.3% among those without any cervical cytological abnormalities), but also to be more likely infected with multiple HPV genotypes concurrently [8]. An increased likelihood of multiple coexistent HPV genotype infections among HIV-infected women has been observed in a number of other studies as well [9–12].

Not only are HIV-infected women more likely to be infected with HPV overall, they are also more likely to be infected with one of the 15–18 HPV genotypes that are “high-risk” or “probable high-risk” for progressing to cervical cancer (HR-HPV). In a study of over 2000 women, HIV-infected women were found to have an odds ratio of 5.07 for infection with HR-HPV when compared to HIV-uninfected women [10]. Importantly, the greater overall prevalence of HR-HPV among HIV-infected women occurs in a genotype distribution that is distinct from that in HIV-uninfected women. A recent meta-analysis reported that several non-vaccine oncogenic genotypes were found to be more prevalent than HPV 16 (one of the two high-risk vaccine types) among HIV-infected women with high-grade squamous intraepithelial lesions (SIL), including genotypes 51, 52, and 58 [8]. Similarly, when compared to their HIV-uninfected counterparts, HIV-infected women with HSIL were significantly less likely to be infected with HPV 16 [8]. These data have obvious implications for the potential efficacy of the currently available HPV vaccines among HIV-infected women.

HIV infection has a significant impact on the natural history of HPV infection. Regardless of the level of HIV associated immunosuppression, regression of cervical dysplasia is reduced among HIV-infected women [6]. While most HPV infections are transient, among HIV-infected women rates of persistent infection are increase multifold [13]. In contrast to other HIV associated malignancies such as Kaposi’s sarcoma and non-Hodgkin’s lymphoma, extreme immunosuppression is not required to observe an increase in the incidence of invasive cervical cancer among HIV-infected women – in fact the majority of cervical cancer cases in HIV-infected women occur in those with CD4 counts greater than 200 [14]. Still, more advanced HIV disease (lower CD4 and higher viral load) is strongly associated with increased cumulative HPV prevalence, more advanced cervical dysplasia, and increased rate of progression of cervical disease [6, 10, 12, 13, 15].

Interestingly, the relationship between immunosuppression and HPV disease is least pronounced for HPV16. The prevalence ratio values for HPV16 between women with low versus high CD4 counts are small compared to most other HPV types [16]. HPV genotypes that are phylogenetically related to HPV16 do not demonstrate this weak correlation with

CD4. This may suggest that HPV16 is better able than most genotypes to avoid immunosurveillance and is less dependant on a weakened immune system to cause cervical disease.

In summary, compared to their HIV-uninfected counterparts, HIV-infected women have:

- Increased overall prevalence of HPV
- Increased prevalence of HR-HPV
- More multiple infections
- Higher relative prevalence of non-vaccine oncogenic HPV genotypes
- Increased persistence of HPV infections
- Increased risk of progression of cervical disease caused by HPV
- Increased risk of invasive cervical cancer

## THE EFFECT OF HAART ON CERVICAL DISEASE INCIDENCE AT THE POPULATION LEVEL

The use of HAART has had a tremendous impact on morbidity and mortality related to HIV infection. The partial immune reconstitution afforded by HAART has resulted in significantly decreased rates of some AIDS associated cancers, namely Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL) [17]. Data on the impact of HAART on invasive cervical cancer, however, has thus far been equivocal. The systemic benefits of HAART have been clearly established, but the impact of HAART on cervical disease has not been. While use of HAART might be expected to lead to a reduction in cervical cancer incidence and progression of cervical dysplasia as a result of improved immunologic function, the prolonged survival afforded by HAART, along with only partial restoration of immune function, could result in a rising incidence of cervical cancer as increased longevity allows time for disease progression.

Registry data from the United States and elsewhere suggests that unlike KS and NHL, the risk of invasive cervical cancer among HIV-infected women has not decreased in the HAART era. In 2009, Chaturvedi and associates linked data on nearly 500,000 people with AIDS to U.S. cancer registry data spanning the pre-HAART and HAART eras and found the standardized incidence ratio (SIR) for cervical cancer among women with AIDS to be 8.9 (95% CI = 8.0–9.9) compared to the general population and to have remained stable despite the introduction of HAART. Among this group, low CD4 count was found to be non-statistically significantly associated with increased risk of cervical cancer (RR=1.32, 95% CI = 0.96–1.80, p=0.077) [18]. A related registry-linkage study found that while the incidence of KS and NHL decreased in the HAART era, the incidence of cervical cancer did not [19]. A similar Italian study comparing SIRs of HIV-associated malignancies in the pre-HAART and HAART eras among over 21,000 AIDS cases found the SIRs for cervical cancer among HIV-infected women to be increased to a similar extent before and after the introduction of HAART [20]. If the SIR of cervical cancer decreased by a smaller proportion than that of KS or NHL, that could be due to the lower baseline SIR of cervical cancer among AIDS patients. However, the fact that the incidence of cervical cancer has not been observed to decrease at all in the HAART era is in contrast to the very significantly decreased SIRs measured for KS and NHL.

Clifford and colleagues linked data from the Swiss HIV Cohort Study to Swiss cancer registries and found that among HAART users there was no clear impact on the SIR of cervical cancer compared to non-users. Moreover, there was not a statistically significant

association between SIR for cervical cancer and CD4 count at enrollment. This was in contrast to the decreased SIRs identified for KS and NHL among HAART users and the inverse relationship identified between CD4 count and KS/NHL incidence [21].

A meta-analysis of 23 prospective studies that included 47,926 HIV-infected individuals from North America, Europe and Australia compared adjusted incidence rates of cancer before and after the introduction of HAART. While the incidence of KS dropped to a third of what it was, and the incidence of NHL to nearly half of the pre-HAART level, no significant change in cervical cancer incidence was identified [17].

In summary, there is uniformity in the literature regarding the lack of decrease in cervical cancer incidence in the HAART era. Population-based registry research is essential to monitoring trends in disease incidence but may be subject to bias due to irregular reporting or surveillance. Clinical research is required to assess the impact of HAART directly on the individuals who receive it.

## CLINICAL RESEARCH INTO THE EFFECT OF HAART ON HPV AND CERVICAL DISEASE

Several clinical studies have been conducted to investigate the impact of HAART on HPV infection and HPV-related cervical disease. In contrast to the studies described above, the clinical research on this subject has been conflicting and inconclusive. Much of this research will be summarized below in chronological order, beginning over 10 years ago.

In 1998 Heard and colleagues published a report describing a cohort of 49 women who were followed before and after initiation of HAART [22]. They found that the prevalence of SIL decreased from 69% to 53% during a median five months of treatment. No change was found in the prevalence of HPV infection over this period. A greater increase in absolute CD4 cell count was found among women whose cervical disease regressed. Overall, 35% of patients receiving HAART had spontaneous regression of cervical lesions compared to only 12.5% who did not take HAART. This early study supported the notion that HAART has a positive impact on HPV related cervical disease despite no change in HPV prevalence being detected.

Although not a study of the impact of HAART per se, Delmas and colleagues studied a cohort of 485 HIV-infected women and found that women with CD4 counts less than 200 had approximately twice the prevalence and incidence of SIL compared to women whose CD4 counts exceeded 500 [23]. While an inverse relationship between CD4 count and prevalence and incidence of SIL appears to support the benefit of HAART on cervical disease, the specific effect of HAART was not assessed in this study. In contrast, Lillo and colleagues conducted a cohort study of 163 HIV-infected women with the specific objective of determining the effect of HAART on HR-HPV associated cervical disease [24]. This study is notable in that it addresses the impact of HAART on HPV infection as well as HPV-related cervical disease. Over a mean 15.4 months of follow-up, persistence of HR-HPV infection and rates of progression of SIL were comparable among the HAART group, an untreated group, and a group receiving reverse transcriptase inhibitors. Although this study did not demonstrate a positive impact of HAART on HPV-related cervical disease, it did find an inverse relationship between CD4 count and risk of HPV infection and disease. Additional studies mentioned below also fail to identify concordance between the relationship of CD4 count and HAART use as they relate to HPV-related cervical disease. This suggests that increased CD4 count is an imperfect surrogate for HAART use and that additional immunologic factors are at play in HPV suppression in the cervix.

In 2001, Minkoff and colleagues published a large cohort study (N=741) that aimed to assess the impact of HAART on cervical disease regression and progression over a six month period [25]. After adjustment for CD4 count, women on HAART were found to be 40% more likely to have regression of their cervical lesions. Women are HAART were also found to have a decreased risk of disease progression (OR 0.68; 95% CI = 0.52–0.88). This study, therefore, provided early evidence from clinical research that HAART does have a positive impact on HPV-related cervical disease. Heard and colleagues published a second study of this subject in 2002 [26]. A cohort of 168 HIV-infected women with HPV-related cervical disease were followed with biannual Pap smears. Ninety-six of the women were on HAART. The probability of disease progression was measured using survival analysis over a median follow-up period of 13.4 months. Adjusting for CD4 count, they found that disease regression was 1.93 times more likely among HAART recipients - supporting the positive impact of HAART. That same year Moore and colleagues published the results of a cohort study in which 71 women beginning HAART were followed for a median of 10 months [27]. The prevalence of HPV-related cervical disease was 55% at the beginning of the study and was 62% at the end (p=0.20). The authors concluded that HAART did not significantly impact the prevalence of cervical disease in their study population. This study was limited, however, by the lack of a control group. A subsequent cohort study of 154 HIV-infected women found that regardless of whether or not they were receiving HAART, only women with clinically stable AIDS has decreased progression of cervical disease when compared to the patients with worsening HIV disease [28]. This finding underscores the uncertainty regarding the local cervical effect of HAART and suggests that broader indices of health play a role in the course of HPV-related cervical disease.

In 2003, Schuman and co-workers published the results of a longitudinal study in which 774 HIV-infected women were evaluated semiannually for up to 5.5 years [29]. Incident SIL and correlates of progression of cervical lesions were reported. Although both incidence of SIL and risk of progression of disease were found to be increased among women with CD4 counts less than 500, HAART was not found to decrease the risk of progression or increase the likelihood of regression. Incidence of SIL was also not found to decrease with HAART. This was among the largest studies to conclude that HAART had no beneficial effect on SIL. In contrast, the following year it was reported that in a cohort study of 312 HIV-infected women with normal cervical cytology at baseline, incident SIL significantly decreased after the introduction of HAART [30]. That same year, Del Mistro and colleagues reported that among 201 HIV-infected women who underwent gynecologic examinations every 6–12 months, regression of low-grade SIL was more common among those receiving HAART [31].

In 2006, Heard and colleagues reported the results of their third cohort study investigating the impact of HAART on HPV-related cervical disease [32]. A total of 298 HIV-infected women with normal Pap smears at enrollment were followed for a median of 28 months. The incidence of SIL was not statistically different between the HAART group and non-HAART group. These findings are at odds with the authors' previous report [26]. Notably, unlike most other studies of this issue, the risk of SIL was not found to be correlated with low CD4 count. Soncini and coworkers followed 101 HIV-infected women without a history of HPV-related cervical disease with yearly Pap smears and reported in 2007 that those on HAART were significantly less likely to develop HPV-related cervical disease (hazard ratio 0.3; p=0.004) during the follow-up period than those not on HAART [33]. Sirera and colleagues also studied a cohort of HIV-infected women without cervical dysplasia and conducted a survival-analysis of time until incident SIL [34]. Although they found that the probability of developing SIL at three years was slightly higher among the no-HAART group than the HAART group this finding was not statistically significant (p=0.387).

In 2009, Paramsothy and colleagues reported a study of 537 women with HIV. Similar to the 2001 Lillo study [24], participants were followed with serial Pap smears as well as HPV DNA analyses [35]. They found that among women without SIL HAART was not associated with increased HPV clearance. In contrast, among women with preexisting SIL HAART was associated with increased HPV clearance. HAART was not found to be associated with increased likelihood of regression of cervical lesions. Most recently, Fife and colleagues reported a study of 146 HIV-infected women initiating HAART and tested them for cervical HPV DNA four times over nearly two years [36]. No cytologic or histologic data was collected. The prevalence of HPV DNA dropped from 66% at baseline to 49% at the end of the study period. The prevalence of HR-HPV DNA dropped from 62% to 39%. There was not, however, a significant correlation between response to HAART and clearance of HPV DNA.

## SUMMARY AND IMPLICATIONS

In summary, over the last decade a number of clinical studies have been published assessing the impact of HAART on HPV infection, incidence and prevalence of HPV-related cervical disease, and risk of regression/progression of cervical dysplasia. To date the weight of the data on this subject has not clearly shifted in support for or against a positive impact of HAART on HPV-related cervical disease. Two reviews of this subject were published in 2003 and 2004, respectively, and reported similarly that no clear benefit of HAART on HPV-related cervical disease had been substantiated by available evidence [37, 38]. In a much more recent review of the broader relationship between HIV and HPV, a brief section specifically addressing the impact of HAART was included which asserted that HAART does not have a clearly beneficial effect on HPV-related cervical disease in HIV-infected women [39].

The variation in findings generated by the clinical research into this issue may in part be due to methodological differences. The primary end-points in some of the above studies are time to incident SIL among women who have normal Pap smears at enrollment. In other studies women with pre-existing cervical disease are followed to assess rates of progression and regression. The assessment of progression/regression can also be conducted differently. One method is to compare the first and last Pap smears of a participant during the study period and define progression/regression and the change between these two data points. An alternative approach, employed by Minkoff and colleagues, is to treat each pair of consecutive Pap smears as a dyad in which progression or regression may occur [25]. In this way, a single study participant could contribute episodes of both regression and progression during the same study period. Finally, virological end-points have been used alone or in combination with cytological end-points in some studies and not in others.

The impact of HAART on HPV-related disease has implications for screening practices. Currently, cervical screening recommendations differ for HIV-infected and uninfected women. The American Cancer Society’s guidelines for early detection of cervical neoplasia and cancer among HIV-uninfected women recommend initial screening approximately three years after initiation of intercourse (but no later than age 21), yearly until age 30, and then every two to three years if preceding screenings have been normal [40]. The US Public Health Service’s guidelines for prevention of cervical cancer in HIV-infected women, however, require two Pap smears in the first year after diagnosis of HIV infection and annually thereafter, regardless of age [41]. If clear evidence existed that HAART reduced the risk of incidence and progression of HPV-related cervical disease in HIV-infected women to that of the general population, screening practices might be relaxed to reflect this, with the consequent savings in resources. Unfortunately, given the conflicting evidence

summarized above, no decrease in the vigilance of cervical disease screening among HIV-infected women on HAART can be recommended.

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