Effect of increasing the frequency of cervical cancer screening among HIV-infected women

Jessica Rae Skinn

Medical University of Ohio

Follow this and additional works at: http://utdr.utoledo.edu/graduate-projects

This Scholarly Project is brought to you for free and open access by The University of Toledo Digital Repository. It has been accepted for inclusion in Master's and Doctoral Projects by an authorized administrator of The University of Toledo Digital Repository. For more information, please see the repository's About page.
Effect of Increasing the Frequency of Cervical Cancer Screening Among HIV-infected Women

Submitted by

Jessica Skinn

In partial fulfillment of the requirements for the degree of
Master of Science in Biomedical Sciences

Date of Presentation:

December 15, 2005

Academic Advisory Committee

Major Advisor
Joan Duggan, M.D.

Department Chairperson
Patricia Hogue, M.S., PA-C

Dean, College of Health Sciences
Christopher E. Bork, Ph.D., P.T.

Dean, College of Graduate Studies
Keith K. Schlender, Ph.D.
Effect of Increasing the Frequency of
Cervical Cancer Screening among HIV-Infected Women

Jessica Rae Skinn

Medical University of Ohio

2005
Dedication Page

Special thanks to my wonderful family and friends for their continuous support and unconditional love throughout the completion of this project.
Acknowledgements Page

I would like to take this opportunity to recognize the many people that were a part of this project. Dr. Joan Duggan was an exceptional advisor and guiding light whose expertise and enthusiasm were an inspiration. Special thanks to Dr. Duggan for spending her valuable time and energy on this project and also for recommending this great topic to research. Others who deserve special recognition are Dr. Sadik Khuder, Ann Locher, Amy Clark, Michelle McKenzie, and Kristi Hayes. I can not thank you all enough.
# Table of Contents

Introduction........................................................................................................... 1  
Review of Literature.............................................................................................. 3  
  Cervical Cancer Screening in HIV-negative Women ........................................ 4  
  HIV and Cervical Dysplasia ........................................................................... 6  
  Invasive Cervical Cancer and HIV .............................................................. 7  
  Cervical Cancer Screening ........................................................................... 8  
Demographic and Behavioral Predictors ........................................................... 11  
Human Papillomavirus and HIV ..................................................................... 12  
Management of Cervical Abnormalities ........................................................... 14  
  Future Directions and HAART ................................................................. 15  
Methods ............................................................................................................. 17  
Results .............................................................................................................. 20  
Discussion ......................................................................................................... 23  
Conclusion ......................................................................................................... 27  
References ......................................................................................................... 28  
Tables ................................................................................................................. 35
Effect of Increasing the Frequency of Cervical Cancer Screening among HIV-Infected Women

In the United States, women compromise the fastest growing population of persons with Acquired Immune Deficiency Syndrome (AIDS). At the end of 2002, it was estimated that 82,764 of the 384,906 persons living with AIDS in the United States were women (Centers for Disease Control and Prevention [CDC], 2002). Compared to their human immunodeficiency virus (HIV)-negative counterparts, HIV-infected women have a greater incidence of both cervical intraepithelial neoplasia (CIN) and invasive cervical cancer, which tends to be more progressive and aggressive (Wallace & Carlin, 2001).

In previous decades, women frequently succumbed to HIV/AIDS prior to the development of invasive cervical cancer. Recently, however, the clinical course of HIV has been substantially changed by more effective treatments, making these women a significant group of patients with an increased risk of developing CIN and cervical cancer (Branca et al., 2001). In 1993, the Centers for Disease Control designated invasive cervical cancer as an AIDS defining illness, meaning that cervical cancer is sufficient to diagnose AIDS in an HIV-infected woman, exclusive of other conditions (CDC, 1992).

Due to the increased incidence of cervical cancer in HIV-infected women, it is important to perform frequent cervical cancer screening. Current United States Public Health Service (USPHS) and Infectious Diseases Society of America (IDSA) standards recommend a Papanicolaou (Pap) test every six
months during the first year after HIV diagnosis. If both cytology specimens are normal, it is recommended that the patient be screened by annual Pap test thereafter (CDC, 1993). According to some research, though, relatively more frequent cervical cancer screening may lead to earlier detection and treatment of cervical abnormalities and improve prognosis of women with HIV (Maiman et al., 1998; Massad et al., 1999; Spinillo, Capuzzo, Tenti, De Santolo, Piauzzi, & Lasci, 1998). The optimal frequency of screening remains in doubt.
Invasive cervical cancer is the third most common cancer among people diagnosed with AIDS, preceded only by Kaposi’s sarcoma and non-Hodgkin’s lymphoma (Gallagher, Wang, Schymura, Kahn, & Fordyce, 2001). However, among HIV infected women, it may be the most common AIDS-related malignancy (Cohn & Clark, 2003). Maiman et al. (1997) found a high rate of cervical cancer, accounting for 55% of the AIDS related malignancies in a Brooklyn hospital between 1987 and 1995. In response to the growing body of research in the early 1990’s that demonstrated that HIV-infected women had an increased prevalence of cervical dysplasia, invasive cervical cancer became an AIDS defining diagnosis in 1993 (Cejtlin, 2003). Fortunately, Cohn and Clark reported that the incidence of invasive cervical cancer remained low among HIV-infected women even though the prevalence of squamous intraepithelial lesions (SILs) and cervical intraepithelial neoplasia (CIN) was high.

Maiman et al. (1997) conducted a retrospective study examining data of cervical cancer and AIDS in New York City. They concluded that although it was too early to determine whether the AIDS epidemic would influence the prevalence and mortality rates for cervical cancer nationwide, the incidence of cervical cancer in New York City had increased from fewer than 5 cases per 100,000 women in 1987 to more than seven cases per 100,000 in 1994. While the relationship between HIV and cervical cancer is still being established, it is
important at this time to take preventative measures and identify risk factors and institute appropriate cervical cancer screening and management guidelines.

*Cervical Cancer Screening in HIV-negative Women*

Cervical cancer is a potentially preventable disease when preinvasive cervical lesions are detected through screening (Massad et al., 1999). Cervical cancer screening guidelines in the United States have recently been updated and are supported by a wealth of scientific evidence. Approximately 50 million women undergo Papanicolaou (Pap) testing in the United States each year. Of these, approximately 3.5 million (7%) are diagnosed with a cytological abnormality requiring additional follow-up for evaluation (Wright, Cox, Massad, Twiggs, & Wilkinson, 2002). It is generally concluded that the benefits of screening substantially outweigh potential harms.

It is recommended that women who have been sexually active and have a cervix be screened for cervical cancer (United States Preventive Services Task Force [USPSTF], 2003). Screening with cervical cytology decreases the incidence of and mortality from cervical cancer. USPSTF suggests that screening should begin within three years of onset of sexual activity or age 21, whichever comes first. Thereafter, three consecutive normal annual Pap smear results are required before consideration is given to decrease Pap smear frequency to once every two to three years.

Wright et al. (2002) recognized the challenge of determining which women with cervical cytological abnormalities are at risk for significant cervical disease and sought to provide evidence-based consensus guidelines for the diagnosis
and management of cytological abnormalities and cervical cancer precursors. A panel of experts convened in Bethesda, Maryland and developed guidelines based on formal literature reviews and professional input (Wright et al., 2002). It was concluded that atypical squamous cells of unknown significance (ASC-US) should be managed by one of three methods: two repeat cytology tests, immediate colposcopy, or DNA testing for high-risk types of human papillomavirus (HPV). The panel also suggested that other cervical cytological abnormalities such as low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions (HSIL), atypical squamous cells, cannot exclude HSIL (ASC-H), and atypical glandular cells should be referred for immediate colposcopic evaluation. It is important to note that in many instances the guidelines were based on a limited amount and quality of data and that they should never be a substitute for clinical judgment.

In 2002 in the United States, there were approximately 13,000 new cases of cervical cancer and 4,100 cervical cancer related deaths. Between the years of 1973 and 1994, the rates of new cases of cervical cancer decreased by almost 50 percent, from 14.2 new cases per 100,000 women to 7.8 cases per 100,000 women (USPSTF, 2003). Despite the falling incidence, cervical cancer continues to be the tenth leading cause of cancer death in the United States (American Cancer Society, 2002). The rate of deaths from cervical cancer has remained near 3.0 deaths per 100,000 women since 1998 (United States Department of Health and Human Services, 2000).
**HIV and Cervical Dysplasia**

Abnormal cervical cytology is more common among HIV-positive than HIV-negative women. In comparison to HIV negative women, HIV infected women exhibit cytologic abnormalities in 30-60% of Pap smears and 15-40% have evidence of dysplasia. These rates are 10-11 times greater than those observed among HIV-negative women (Maiman et al., 1998). In addition, two large US multicenter cohort studies, Women’s Interagency HIV Study (WIHS) and HIV Epidemiology Research (HER) Study, examined similar matters on a larger scale. They demonstrated a prevalence of cervical abnormalities on cytology in the 17-18% range for HIV-infected women and the 3-5% range for a seronegative control population with similar risk factors (Massad et al., 1999; Duerr et al., 2001).

In New York City, Ellerbrock et al. (2000) conducted a cohort study between 1991 and 1996 with the addition of a significant follow-up period. The study demonstrated that the increased risk of cervical abnormalities in HIV infected patients persists over time. After three years, the incidence of new histologically confirmed lesions was 20% in HIV-seropositive patients and 5% in HIV-seronegative women. The risk of incident cervical abnormalities depended on HIV serostatus, HPV serostatus, CD4 cell count, and HIV RNA level. A significant limitation of this study is that it was conducted prior to the widespread use of highly active antiretroviral therapy, which has had a profound effect on the incidence of cervical lesions.
Multiple studies have also established that the prevalence of abnormal cytology is associated independently with the degree of immunosuppression (Wright, Ellerbrock, Chiasson, van Devanter, & Sun, 1994; Maiman et al., 1993; Maiman et al., 1998; Six et al., 1998). In the HER Study, HIV-infected women with a CD4 count of 500 or more cells/microliter had a prevalence of squamous intraepithelial lesions (SILs) equivalent to that in seronegative controls, and women whose CD4 counts were 100 or fewer cells/microliter demonstrated a prevalence of SILs as high as 11 to 27% (Duerr et al., 2001). Delmas et al. (2000) demonstrated that both frequency and severity of abnormal Pap smears and cervical dysplasia increased with declining CD4 counts. While the incidence of cervical dysplasia has been associated with increased HIV-related immunodeficiency, presently there is contradiction as to whether a relationship exists between immune compromise and increased rate of progression to invasive cervical cancer.

**Invasive Cervical Cancer and HIV**

There is increasing evidence supporting the idea that HIV infection has a significant impact on cervical cancer rates. Few studies have been published to date that calculated an increased relative risk for HIV-positive women developing cancer versus the general population. As Vonau and Boag (2000) stated in a review article, Serraino et al. (1999), Goedert et al. (1998), and Chin, Sidhu, Janssen, & Weber (1998) quoted a relative risk for cervical cancer in HIV as being 5.5, 5.0, and 1.7, respectively. In a recent analysis of women in the HER study, HIV-positive women had an invasive cervical cancer rate of 144 per 1,000
person-years as compared with 0 per 1,000 person-years in HIV-negative women (Duerr et al., 2001).

Women with HIV and cervical cancer tend to be younger, present at more advanced states of invasive cervical cancer, have poorer responses to standard therapy, and have higher recurrences and death rates compared with HIV negative women of similar stage (Klevens, Fleming, Mays, & Frey, 1996). One study reported a higher prevalence of invasive cervical cancer among 20 to 34 year old African American and Hispanic HIV infected women (Chin et al., 1998). One study in Kenya showed that HIV-seropositive patients with invasive cervical cancer were ten years younger at presentation than their HIV-seronegative counterparts, even after controlling for education, number of sex partners, and previous history of STD (Gichangi et al., 2003). The researcher believes this could suggest that HIV infection may shorten the progression from premalignant cervical lesions to invasive cervical carcinoma, resulting in earlier presentation. Due to significant limitations, caution should be used when interpreting Gichangi’s study of Kenyan women as other factors such as nutritional status may play a role. Regardless of whether there is a small or large impact of HIV on the outcome of invasive cervical cancer, early detection remains the key to effective treatment.

Cervical Cancer Screening

Guidelines for cervical cancer screening in HIV-seropositive women have not been revised since 1995. This is important to note, since the era of highly active retroviral therapy did not begin until 1996. The guidelines state that HIV-
seropositive women should obtain two Pap smears six months apart after the initial HIV diagnosis and, if results are both normal, should undergo annual cervical cytological screening thereafter (CDC, 1993). It is proposed that HIV infected women should have more frequent Pap smears obtained if: (1) there is a history of untreated abnormal Pap smear; (2) they are infected with HPV; (3) they have had treatment of cervical dysplasia and preinvasive lesions; and/or (4) they have symptomatic HIV infection. Currently, there is a lack of consensus about how to screen HIV-infected women and multiple studies have been designed to evaluate this topic.

For HIV-positive and negative women alike, Pap smear results are reported according to the Bethesda system (National Cancer Institute Workshop, 1998) (Table 1). The mildest form of cervical abnormality in the Bethesda system is atypical squamous cells of undetermined significance (ASCUS). Studies that compare cervical cytology and histology encounter a major limitation in that the significance of ASCUS and other minimally abnormal smears is unknown. Interpretations tend to differ tremendously due to substantial interreader variability (Maiman et al., 1998). Young et al. (1994) reported that when five expert panelists classified slides using the Bethesda system, there was unanimous agreement in only 35% of cases, and in 30% there was a range of more than one classification category. The importance of recognizing the variability of ASCUS classification is that studies have found that HIV-positive women with ASCUS were twice as likely to have underlying dysplasia compared with HIV-negative women (Wright et al., 1996; Holcomb et al., 1999). Because of
this discrepancy, some researchers suggest more frequent cytological screening for HIV-infected women and recommend colposcopic evaluation with the initial report of atypical cells (Spinillo et al., 1998).

While there is discrepancy among researchers concerning the types of screening that should be conducted, there are also questions regarding the frequency of screening. Researchers (Goldie, Weinstein, Kuntz, & Freedberg, 1999; Goldie, Freedberg, Weinstein, Wright, & Kuntz, 2001) have attempted to provide cost-effectiveness analyses using a Markov model to evaluate cervical cancer screening. In 1999, Goldie et al. reported that following the USPHS recommended regimen resulted in an increase of 2.1 months of life expectancy at $12,800 per quality-adjusted life years (QALY) saved, whereas semiannual cytology yielded only 0.04 additional months of life expectancy at additional cost of $14,800 per QALY saved (Goldie et al., 1999). As in all model studies, this was limited by the available data and necessity for simplification. Multiple studies not using a Markov model contradict Goldie and suggest relatively more frequent cervical cancer screening may lead to earlier detection and treatment of cervical abnormalities and improve prognosis of women with HIV (Maiman et al., 1998; Massad et al., 1999; Spinillo et al., 1998). A similar analysis of QALY (Goldie et al., 2001) subsequently demonstrated that if HPV testing were added to the initial cytologic screening with a modification of subsequent screens based on the results of the HPV assay, more cost-effective strategies would ensue. It is possible in the future that cervical cancer screening could be modified according to the presence or absence of HPV and other risk factors.
Demographic and Behavioral Predictors

Multiple studies have evaluated the risk factors associated with cervical disease. Due to the massive amount of conflicting data, it is difficult to draw clear conclusions concerning factors associated with abnormal cervical cytology. Numerous studies are limited by their relatively small size, which limits detailed analysis, and by lack of geographical diversity, which limits generalizability.

Massad et al. (1999) attempted to overcome this barrier by reporting from a large national multicenter prospective cohort study, the Women’s Interagency HIV Study (WIHS). Baseline cervical cytology was obtained from 1713 women seropositive for HIV and 482 at-risk control women. The study concluded that the only significant sociodemographic and behavioral predictors of abnormal cervical cytology were lack of employment and number of male sexual partners within six months prior to enrollment in the study. After adjusting for HIV status, the presence of genital warts and the number of years since first intercourse were also significantly associated with abnormal cytology. Factors not achieving significance in this study were employment, marital status, education, income, pregnancy at time of evaluation, history of sexually transmitted diseases other than genital warts, and history of prostitution.

Multiple studies contradict the conclusions drawn by the WIHS. Wright et al. (1996) suggested that a reported history of intravenous drug use or prostitution was associated with cervical cytologic atypia in HIV infected women. Six et al. (1998) reported that risk factors found to be associated with the detection of SIL were geographic origin, lifetime number of partners, smoking,
and a younger age. Intravenous drug use, age at leaving school, parity, age at first sexual intercourse, and contraceptive pill use were factors found to be not associated with SIL detection. Ellerbrock et al. (2000) reported potential statistically significant risk factors to be age less than 37.5 and race. Their research suggested young HIV-positive black and Hispanic women in the United States had a four to seven fold increased risk of invasive cervical carcinoma when compared to HIV-positive white women. In another study, cervical intraepithelial neoplasia in HIV infected women was found not to be associated with age (Fruchter et al., 1996). As is already apparent from this long list of conflicting data, prospective studies are needed to better define the relative importance of risk factors in the development of cervical abnormalities.

**Human Papillomavirus and HIV**

One risk factor that is no longer in dispute regarding its significant relationship with both HIV and cervical dysplasia is human papillomavirus (HPV). High-risk oncogenic HPV infection is now postulated to be the most important factor in the etiology of cervical carcinoma while HIV is recognized to be an important risk factor for HPV infection. It is thought that the susceptibility to HPV infection is increased due to HIV-induced immunosuppression, and the body is then unable to limit the neoplastic consequences of HPV on the cervix because of the progressive immune dysfunction (Maiman et al., 1997).

Currently, HPV test results are not considered in the guidelines for cervical cancer screening in HIV-positive women even though economic models have suggested that HPV testing in HIV-seropositive women might be cost effective
More important than economic factors of HPV testing is research showing the presence of HPV, independent of HIV, increases the risk for the development of cervical dysplasia ten to twenty fold (Stier, 2003). HPV is the most common sexually transmitted disease in the United States and there have been over seventy subtypes identified, with types 16 and 18 accounting for 64% of the HPV found in cervical cancer specimens (Cohn & Clark, 2003). While HPV is common and can be identified in over 60% of sexually active women, less than three percent of all women develop cervical dysplasia (Nobbenhuis et al., 1999; Ho, Bierman, Beardsley, Chang, & Burk, 1998). Persistent HPV infection and infection with multiple types of HPV are significant risk factors for cervical cancer. Walboomers et al. (1999) identified HPV DNA in over 99% of a large representative sample of cervical cancer specimens.

Common sexual behavioral risk factors predispose to the acquisition of both HIV and HPV. While a causative relationship has been established between HPV and cervical dysplasia, the HIV Epidemiology Research (HER) Study group collected data to assess whether HIV infection is an independent risk factor for developing cervical dysplasia (Jamieson et al., 2002; Ahdieh et al., 2001; Duerr et al., 2001). Data was collected on cytology and HPV infection from 709 HIV-infected patients and 341 uninfected women. They found that the greatest risk factors for HPV infection were a low CD4 count and an elevated HIV viral load (Jamieson et al., 2002). Dysplasia was most common in women infected with HPV with the next most important risk factor being low CD4 count (Ahdieh et al., 2001). These results contrast the New York Cervical Disease Study which found
the greatest risk for developing dysplasia was being HIV seropositive, followed by persistent HPV infection (Ellerbrock et al., 2000). Given the conflicting reports, it is appropriate to be cautious when interpreting the findings of these studies. Due to the fact that so much has been learned over recent years concerning HIV, HPV, and cervical cancer, it is also appropriate to expect much more research on this topic in the near future.

Management of Cervical Abnormalities

Because management guidelines have not been outlined specifically for cervical abnormalities in HIV infected women, it is recommended that these women follow the same guidelines as those for the general public. Recommended management for abnormal Pap smears as suggested at the 2001 American Society of Colposcopy and Cervical Pathology (ASCCP)-sponsored Consensus Conference (Wright et al., 2002) is outlined in Table 2. Although treatment modalities are the same between HIV-positive and negative women, they are individualized by cancer location, extent of disease, and patient health status.

Documentation of a high-grade cervical lesion or invasive cervical cancer in an HIV-positive woman requires the same manner of treatment as in an immunocompetent patient. According to Wright et al. (2002), high-grade lesions should be managed by colposcopy with biopsy and treated with loop excision or conization. Invasive cervical cancer should be treated surgically or with radiation with or without adjunctive chemotherapy.
Due to a high persistence and recurrent rate, close surveillance after treatment is recommended for all immunocompromised patients who are treated for high-grade cervical lesions or cervical cancer. Fruchter et al. (1996) followed 127 HIV-positive women after treatment for cervical lesions and found that 62% developed recurrent lesions after 36 months versus 18% of negative controls. If the CD4 count was less than 200 this increased to 87%. Overall only 30% of HIV-positive women remained disease free. Other research has also recognized the relationship between increased incidence of recurrence after treatment and the degree of immunosuppression (Fruchter et al., 1996; Holcomb et al., 1999). It will be interesting to see if and how the persistence and recurrence rates of cervical abnormalities and cervical carcinoma change due to the effect of better management of HIV in the future.

**Future Directions and HAART**

The role of HIV treatments in the future are expected to influence the relationship between HIV and cervical cancer. A small study conducted by Robinson and Freeman (2002) showed an improvement in cancer prognosis for patients optimally managed on highly active antiretroviral therapy (HAART). In another recent study, women with HIV infection receiving HAART had an invasive cervical cancer incidence of only 1.2 per 100,000 woman-years, a low risk indistinguishable from that in HIV seronegative women (Massad et al., 2004). In contrast to these findings, other studies have suggested that invasive cervical cancer rates have remained high among HIV seropositive women even in the era of HAART (Frisch, Biggar, & Goedert, 2000; Gallagher et al., 2001; Serraino et
al., 1999). Duerr et al. (2001) found no difference in regression of abnormalities on Pap smear, HPV acquisition, or persistence after up to 24 months on HAART compared with untreated women or women receiving non-HAART treatment.

It is clear that larger and longer-term studies are needed to assess the impact of HAART on cervical carcinoma. At the current time, it is recommended that HIV-positive women should continue to be followed closely for evidence of cervical neoplasia, regardless of antiretroviral therapy, HPV status, and degree of immunosuppression (Stier, 2003; Vonau & Boag, 2000). Because the prevalence of cervical dysplasia is increased in HIV-infected women, the importance of continued close surveillance is very important. Also, as women with HIV infection and AIDS are living longer and healthier lives they are at an even greater risk for developing a cervical cancer precursor sometime during the course of their HIV infection (Ellerbrock et al., 2000). Therefore, it is imperative that aggressive detection and meticulous surveillance of cervical neoplasia in HIV-infected women remain the focus of successful patient care.
Methods

A retrospective chart analysis was performed on data reported from May 1, 1999 through May 1, 2003. The data source was the Ryan White Title IV clinic at the Medical University of Ohio. Data included females infected with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS). Ethical approval for the study was received from the Medical University of Ohio institutional review board.

In May of 2005, sixty-nine individual medical records were extracted from the total number of patient charts maintained by the clinic. Information in four general categories was attained from the chart of each patient and entered electronically into a database. Categories of information extracted included: (1) general demographic information such as age and race; (2) laboratory values, including CD4+ cell counts and measurements of plasma HIV RNA; (3) genitourinary information such as pregnancy history and risk factors for cervical cancer; and (4) all Papanicolaou (Pap) smear/pelvic exam results and frequency of exams within the study time period. After all information was collected, all identifying information was removed, and a study number was assigned to each record.

The study population consisted of women of known HIV serostatus with residence in or near Lucas County, Ohio. Age was calculated by date of study endpoint minus date of birth. Regarding racial/ethnic background, the women
were divided into African American, Caucasian, or other/unknown origin based on the classification in each chart.

The laboratory values that were extracted from each chart included CD4 cell counts and HIV RNA levels. During the time period studied, the lowest and highest CD4 cell counts documented in each chart were recorded. In addition, the most recent CD4 cell count to the study endpoint was recorded. The same process was performed for HIV viral load.

For analysis of progression of cervical abnormalities, women in the study file were eligible if they were diagnosed with atypical squamous cells of undetermined significance (ASCUS), atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesions (ASC-H), low-grade squamous intraepithelial lesions (LSIL), or high-grade squamous intraepithelial lesions (HSIL) between the years of 1999 and 2003, inclusive, with no prior diagnosis that was more severe. Since the outcome had to occur after the start date, records were excluded if they had only one Pap smear result, if the outcome of interest occurred at the first dysplastic smear, if obstetrical/gynecological information was absent from the chart, or if the patient was deceased. This reduced the number of eligible records from sixty-nine to fifty-seven.

One record represented one woman, and all smears for the same woman were kept together in the one record. Each woman had been scheduled for gynecologic examinations at six month intervals during the time studied. Only 42.1% of women (twenty-four of fifty-seven) adhered to at least one Pap exam at a six month interval. Cervical abnormalities were recorded in accordance with the
United States national recommendations, which were classified according to the Bethesda System (Solomon et al., 2002).

Logistic regression, Pearson’s Chi-squared tests, and Fisher’s exact test were used to assess statistical significance as appropriate. P<0.05 was set for significance. Analyses were conducted with SPSS version 13.0 (SPSS for Windows, Chicago, IL).
Results

Of fifty-seven charts reviewed, twenty-nine (50.9%) were African American women, twenty-three (40.3%) were Caucasian women, and five (8.8%) were of other or unknown ethnic origin. Among the twenty-nine African American patients, four were diagnosed by Pap smear with progression of cervical abnormalities while a total of nine of the twenty-three Caucasian patients were diagnosed with cervical abnormality progression (13.8% vs 39.1%, P=0.10) (Table 3).

The median age of the study population was 36.4 years (ranging from twenty-one to seventy-seven years). Thirty of the fifty-seven (52.6%) women included in the chart review were less than thirty-seven years of age and twenty-seven of fifty-seven (47.4%) were greater than thirty-seven years of age. Of the thirty patients less than age thirty-seven, eight were diagnosed by Pap smear with progression of cervical abnormalities while six of the twenty-seven patients greater than age thirty-seven were diagnosed with progression of cervical abnormalities (26.7% vs 22.2%, P=0.43) (Table 3).

Table 4 shows the data collected regarding CD4 cell count and HIV RNA level. The mean of the lowest CD4 cell counts documented during the study time period was 315.63 cells/microliter while the mean of the highest documented CD4 cell counts was 674.82 cells/microliter. The mean at study endpoint was 525.60 cells/microliter. Table 5 further breaks down the CD4 cell counts and shows the significance of the relationship between CD4 cell count and cervical
abnormality progression. The lowest CD4 cell count documented during the study time period was categorized as less than 200, 200 to 500, or greater than 500 cells/microliter. The same was done for the highest CD4 cell count documented during the study. A significant relationship (P=0.02) was determined between a CD4 cell count at the lowest point during the study less than 200 cells/microliter and progression of cervical abnormalities. A significant relationship (P=0.02) was also found for a CD4 cell count at the highest point during the study less than 200 cells/microliter and progression of cervical abnormalities.

The relationship between HIV viral load and Pap smear determined progression of cervical abnormalities was examined using the same process. For example, the lowest and highest HIV RNA levels documented during the study time period were categorized as less than 500, 500 to 4000, or greater than 4000 x 10^6 copies/L. The mean of the lowest HIV viral load documented during the study time period was 1443.42 x 10^6 copies/L while the mean of the highest documented HIV viral load was 38672.98 x 10^6 copies/L (Table 4). Table 5 shows that no specific category or value of HIV RNA level was determined to be significantly related to progression of cervical abnormalities.

A final test was performed to evaluate the relationship between Pap smear determined progression of cervical abnormalities and the length of time between Pap smear examinations. As stated earlier, twenty-four of the fifty-seven women had at least one Pap test at a less than six month interval. Of those twenty-four, seven patients were reported to have a cervical abnormality progression.
Regarding the remaining thirty-three patients that had their Pap smear examination at a greater than six month interval, seven were reported to have cervical abnormality progression. According to Pearson’s Chi-squared test, Pap smear examinations at six month intervals or less compared to greater than six months intervals (29.2% vs 21.2%, P=0.59) was not statistically significant.
Discussion

In 1993, the Centers for Disease Control and Prevention designated invasive cervical cancer as an AIDS-defining illness. Because there is reasonable evidence to suggest that HIV-positive women are at an increased risk of developing cervical abnormalities, there is a responsibility to further investigate the need for improved screening guidelines. Although this study found that Pap smear examinations at six month intervals or less compared to greater than six month intervals was not statistically significant, there are multiple other related issues to examine such as screening methods, presence of HPV and other potential risk factors, degree of immunosuppression, and the use of HAART.

Multiple studies have suggested relatively more frequent cervical cancer screening may lead to earlier detection and treatment of cervical abnormalities and improve prognosis of women with HIV (Maiman et al., 1998; Massad et al., 1999; Spinillo et al., 1998). Although our study did not show a statistically significant difference between six month and twelve month interval examinations in determining Pap smear progression of cervical abnormalities, it is still important to note that seven of the fourteen cervical abnormalities reported were found at the six month visit. It is also unknown as to whether the seven abnormal cytology cases reported at the twelve month interval could have been recognized earlier if the patient would have had a Pap test at six months as opposed to twelve. Goldie et al. (1999) attempted to evaluate this issue of shorter examination intervals by providing a cost-effectiveness analysis using a Markov
model. They found that while semiannual cytology as opposed to annual cytology yielded only 0.04 additional months of life expectancy, there was an increased cost of $12,800 per quality-adjusted life year saved. Although these results must be interpreted carefully due to limited available data and oversimplification, per Goldie et al., the minimal gain in detection of cervical abnormalities that occurs from performing Pap tests in HIV-infected women every six months is not cost-effective. Although it may seem straightforward, many other determinants such as risk factors for cervical disease must be assessed when examining the frequency of cervical cancer screening.

As stated previously, there is a massive amount of conflicting data regarding demographic and behavioral predictors of abnormal cervical cytology. Although multiple potential risk factors have been evaluated in numerous studies, this study is limited to data regarding race and age. While race and age were both found to lack statistical significance in relation to progression of cervical abnormalities, this both supports and refutes the current research on this topic. Six et al. (1998) reported that risk factors associated with the detection of abnormal cervical cytology were geographic origin, lifetime number of partners, smoking, and a younger age. In agreement, Ellerbrock et al. (2000) found that young HIV-positive black and Hispanic women in the United States had a 4-7 fold increased risk of invasive cervical carcinoma in comparison to HIV-positive white women. Many other studies disagree with this conclusion. For example, Fruchter et al. (1996) and Maiman et al. (1998) both found cervical intraepithelial neoplasia not to be associated with age. Because much of the research that can
be found regarding predictors of abnormal cervical cytology, including this study, is limited by relatively small size and lack of geographic diversity, detailed analysis and generalizability are both difficult to determine. As apparent from the conflicting data, prospective studies are needed to better define the relationship and relative importance of risk factors in the development of cervical abnormalities.

In contrast, most of the current research is in agreement that there is a correlation between the degree of immunosuppression caused by HIV and the prevalence of abnormal cervical cytology (Wright et al., 1994; Maiman et al., 1993; Maiman et al., 1998; Six et al., 1998). The most common measurement in most of these studies is CD4 cell count. Our study confirmed this relationship by finding a statistically significant association between CD4 cell count less than 200 cells/microliter and progression of cervical abnormalities. These results agree with Duerr (2001) that women whose CD4 cell counts were 100 or fewer cells/microliter demonstrated an increased prevalence of cervical dysplasia. While those women had an 11 to 27 percent prevalence of cervical abnormalities, HIV infected women with a CD4 cell count of 500 or more cells/microliter had a prevalence of cervical dysplasia equal to that of HIV-negative controls. The mechanism postulated to be responsible for the higher risk is a loss of specific T-cell dependent immune responses to HPV (Spinillo, Tenti, Zappatore, Seta, Silini, & Gauschino, 1993), which has been linked to cervical dysplasia in HIV-positive and negative women (Maiman et al., 1997; Stier, 2003; Walbloomers et al., 1999; Ellerbrock et al., 2000).
Several factors limit the conclusions that can be drawn from our study regarding immunosuppression and cervical abnormalities. The relatively small sample size limits the generalizability and makes it challenging to control for individual risk factors. It is then difficult to prove independent associations, such as separating the effects of CD4 cell count, HIV viral load, and HPV infection. Another limitation is the lack of data collected about other potential risk factors that may impact the prevalence of cervical cytologic abnormalities. Some of these include sexually transmitted disease history, early age at first sexual intercourse, number of sexual partners, history of smoking or contraceptive use, and pregnancy history. One other important factor to mention is that the use of HAART was not taken into account and not controlled for during the data analysis process.
Conclusion

As medical therapy continues to improve the management of HIV-infected patients, life will be extended and more women may develop a cervical abnormality during the course of their lifetime. Additional research is needed on the topic of cervical cancer screening frequency. Although our study found that there is not a significant difference between six and twelve month screening intervals, it is a fact that seven cervical abnormalities were diagnosed at six months as opposed to twelve allowing earlier initiation of therapy. Also, based on the results of this and previous research, it would be interesting to propose individualized cervical cancer screening programs for HIV-infected women taking into account factors such as infection with HPV and degree of immunosuppression. Most importantly, aggressive detection and meticulous surveillance of cervical neoplasia in HIV-infected women will remain the cornerstone of successful patient care.
References


Fruchter, R., Maiman, M., Sedlis, A., Bartley, L., Camilien, L., & Arrastia, C.
Multiple recurrences of cervical intraepithelial neoplasia in women with the human immunodeficiency virus. *Obstetrics & Gynecology*, 87(3), 338-344.


Acquired Immune Deficiency Syndromes, 21(1), 33-41.


Robinson, W., & Freeman, D. (2002). Improved outcome of cervical neoplasia in HIV-infected women in the era of highly active retroviral therapy. AIDS Patient Care and STDs, 16(2), 61-65.


Table 1

**Pap Smear Report Format According to the Bethesda System**

<table>
<thead>
<tr>
<th>Statement on specimen adequacy</th>
<th>Satisfactory for interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Less than optimal</td>
</tr>
<tr>
<td></td>
<td>Unsatisfactory</td>
</tr>
</tbody>
</table>

| General categorization         | Within normal limits            |
|                               | Other/ descriptive diagnosis     |

| Descriptive diagnoses          | Benign cellular changes          |
|                               | Reactive and reparative cellular changes |

| Epithelial cell abnormalities  | Atypical squamous cells of undetermined significance |
|                               | Low-grade squamous intraepithelial lesions, including HPV changes and mild dysplasia/ CIN 1 |
|                               | High-grade squamous intraepithelial lesions, including moderate and severe dysplasia, CIN 2, CIN 3, carcinoma in situ |
|                               | Squamous cell carcinoma          |
|                               | Glandular cell abnormalities     |

Table 2

*Recommended Management for Abnormal Pap Smears as Suggested at the 2001 American Society of Colposcopy and Cervical Pathology (ASCCP)-Sponsored Consensus Conference*

<table>
<thead>
<tr>
<th>Pap Smear Result</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe inflammation</td>
<td>Evaluate for infection</td>
</tr>
<tr>
<td></td>
<td>Repeat Pap if inadequate</td>
</tr>
<tr>
<td>Atypia, atypical squamous cells of undetermined significance</td>
<td>Colposcopy, biopsy if indicated</td>
</tr>
<tr>
<td></td>
<td>Repeat Pap every 6 months</td>
</tr>
<tr>
<td>Low-grade squamous intraepithelial lesion (CIN 1)</td>
<td>Colposcopy, biopsy if indicated</td>
</tr>
<tr>
<td></td>
<td>Repeat Pap every 6 months</td>
</tr>
<tr>
<td></td>
<td>Consider annual colposcopy</td>
</tr>
<tr>
<td>High-grade squamous intraepithelial lesion (CIN 2 or 3, carcinoma in situ)</td>
<td>Colposcopy, biopsy</td>
</tr>
<tr>
<td></td>
<td>Treat with loop excision or conization</td>
</tr>
<tr>
<td>Invasive carcinoma</td>
<td>Colposcopy with biopsy or conization</td>
</tr>
<tr>
<td></td>
<td>Treat with surgery or radiation</td>
</tr>
<tr>
<td></td>
<td>Refer to gynecologic oncologist as needed</td>
</tr>
</tbody>
</table>

Table 3

*Potential Predictors of Cervical Abnormality Progression in HIV-Infected Women, N = 57*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Progression</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n )</td>
<td>( %^{a} )</td>
<td>( n )</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td>( p )</td>
</tr>
<tr>
<td>( \leq 37 )</td>
<td>30</td>
<td>53</td>
<td>8</td>
</tr>
<tr>
<td>( &gt; 37 )</td>
<td>27</td>
<td>47</td>
<td>6</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>( p )</td>
</tr>
<tr>
<td>African American</td>
<td>29</td>
<td>51</td>
<td>4</td>
</tr>
<tr>
<td>Caucasian</td>
<td>23</td>
<td>40</td>
<td>9</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>5</td>
<td>9</td>
<td>1</td>
</tr>
</tbody>
</table>

*Note.* Number of HIV infected women included in the analysis = 57.

\(^a\)Percentages represent proportions of the total number of HIV infected women in the study.

\(^b\)Percentages represent proportions of the total number of cervical abnormality progressions for the corresponding group.

\(^c\)Comparison done using logistic regression with progression to cervical abnormality as outcome.
Table 4

*CD4 Cell Counts and HIV RNA Levels in the Study Population, N = 57*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (Range)</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 cell count, cells/μL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest point during study</td>
<td>315.63 (2 - 2111)</td>
<td>308.79</td>
</tr>
<tr>
<td>Highest point during study</td>
<td>674.82 (114 - 2050)</td>
<td>377.47</td>
</tr>
<tr>
<td>At study endpoint</td>
<td>525.60 (13 - 1647)</td>
<td>328.14</td>
</tr>
<tr>
<td>HIV RNA level, x 10^6 copies/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest point during study</td>
<td>1443.42 (49 - 41330)</td>
<td>5742.26</td>
</tr>
<tr>
<td>Highest point during study</td>
<td>85998.60 (75 - &gt;750000)</td>
<td>109493.36</td>
</tr>
<tr>
<td>At study endpoint</td>
<td>38672.98 (75 - &gt;750000)</td>
<td>149436.04</td>
</tr>
</tbody>
</table>
Table 5

*Potential Risk Factors of Progression of Cervical Abnormalities in HIV-Infected Women, N = 57*

<table>
<thead>
<tr>
<th>Potential Risk Factor</th>
<th>Total n&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Progression n (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>p value&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CD4 cell count (cells/μL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At lowest point during study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 200</td>
<td>18</td>
<td>8 (44)</td>
<td>.02*</td>
</tr>
<tr>
<td>200-500</td>
<td>32</td>
<td>5 (16)</td>
<td>.08</td>
</tr>
<tr>
<td>&gt; 500</td>
<td>7</td>
<td>1 (14)</td>
<td>.48</td>
</tr>
<tr>
<td>At highest point during study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 200</td>
<td>4</td>
<td>3 (75)</td>
<td>.02*</td>
</tr>
<tr>
<td>200-500</td>
<td>15</td>
<td>3 (20)</td>
<td>.63</td>
</tr>
<tr>
<td>&gt; 500</td>
<td>38</td>
<td>8 (21)</td>
<td>.38</td>
</tr>
<tr>
<td><strong>HIV RNA level (x 10^6 copies/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At lowest point during study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 500</td>
<td>48</td>
<td>11 (23)</td>
<td>.51</td>
</tr>
<tr>
<td>500-4000</td>
<td>6</td>
<td>1 (17)</td>
<td>.64</td>
</tr>
<tr>
<td>&gt; 4000</td>
<td>3</td>
<td>2 (67)</td>
<td>.08</td>
</tr>
<tr>
<td>At highest point during study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 500</td>
<td>10</td>
<td>1 (10)</td>
<td>.24</td>
</tr>
<tr>
<td>500-4000</td>
<td>5</td>
<td>1 (20)</td>
<td>.80</td>
</tr>
<tr>
<td>&gt; 4000</td>
<td>42</td>
<td>12 (29)</td>
<td>.23</td>
</tr>
</tbody>
</table>

*Note.* Number of HIV infected women included in the analysis = 57.

<sup>a</sup>Numbers represent proportions of total number of HIV infected women included in the analysis.

<sup>b</sup>Percentages represent proportions of the total number of cervical abnormality progressions for the corresponding group.

<sup>c</sup>Comparison done using Chi-squared or logistic regression with progression of cervical abnormalities as outcome.

*<sup>p</sup> < 0.05.
Abstract

**Objective**: To evaluate the importance of cervical cancer screening frequency on the detection of cervical abnormalities in HIV infected women. Secondly, to assess the impact of immunodeficiency and potential risk factors on the occurrence of cervical abnormalities.

**Method**: A retrospective chart analysis was performed on 57 medical records from 1999 through 2003 at the Medical University of Ohio.

**Results**: Seven of 24 women who had Pap testing at less than 6 months and 7 of 33 at greater than six months were reported to have progression of cervical abnormalities (29.2% vs 21.2%, P=0.59). HIV viral load, age, and race were also not significantly related to cervical abnormalities, while there was a relationship with CD4 cell count <200 cells/μL (P=0.02).

**Conclusion**: Although a significant difference between six and twelve month screening intervals was not found, aggressive and individualized screening programs are important for cervical cancer prevention in HIV infected women.