

## Research Team

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## Introduction

Anal cancer is a serious and pervasive health problem among and gay and bisexual men. Before the onset of the AIDS epidemic, the incidence of anal cancer among men with a history of receptive anal intercourse has been estimated at about 35 per 100,000. This is about the same incidence as that for cervical cancer prior to the implementation of broad screening programs promoting early detection and treatment among at-risk women.

As with many cancers, the exact causes of anal cancer are not clearly understood. However, there is general scientific consensus that human papillomavirus (HPV) is at least partly to blame. HPV is a sexually transmitted infection, found in many different types in different parts of the body.

Infection with HPV is common, with one large study at UCSF detecting HPV in 61% of HIV-negative and 93% of HIV-positive of gay and bisexual men. Typically, infection is with not one but several different types of HPV. In this same study, 23% of HIV-negative and 61% of HIV-positive men were infected with multiple HPV types. Several studies have suggested that having multiple types of HPV increases risk of progression to cancer.

The evidence for an association between HPV and anal cancer is strong. Similar to cervical cancer, the DNA for HPV is often detected in anal cancer tissues. The types of HPV detected are also those known to cause cancer. Conversely, anal cancer is rarely found without also finding some type of HPV also present.

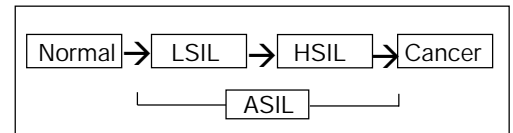
## Anal Squamous Intraepithelial Lesions

Infection with HPV does not automatically result in the development of cancer; it may in fact result in no disease at all. Some people develop tissue abnormalities in the anus and not cancer. Several of these tissue abnormalities are not known to be harmful, but several are believed to be precursors to cancer.

## Common Terms

These abnormalities are lesions or growths that occur in the surface layer of the skin (the epithelial layer) in the anus chamber (the squamous) and are described in two stages: low-grade squamous intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL). They are differentiated by size, shape, color, texture, and risk of further progression to cancer. Together they are referred to as anal squamous intraepithelial lesions (ASIL). Other terms sometimes used include “dysplasia” or “intraepithelial neoplasms.” (See Figure 1)

Figure 1  
Anal Cancer: From Normal Cells to Cancer



## Risk of Progression

Several UCSF studies have looked at the incidence and natural history of HPV-related anal lesions. They have been able to identify factors that appear to increase risk for HPV-related ASIL. These include HPV infection, a history of receptive anal intercourse, and a lower CD4 cell count (typically the result of HIV-related immune system damage).

Scientists have also been able to observe the rates at which individuals develop LSIL or HSIL and progress (and regress) from one stage to another. Because HIV infection appears to dramatically affect the risks for progression, research results are usually distinguished for those who are living with HIV from those that are not.

One study, concluded in 1997, looked at incidence and progression of ASIL over a two-year period among a group of gay and bisexual men. The study found that the prevalence of ASIL at baseline (at the start of the two-year period) was 36% among men living with HIV and 7% among those who were HIV-negative. Of those that were normal at baseline, half of those living with HIV developed ASIL during the two-year period as compared with only 17% of HIV-negative men. Of those who had some

abnormalities at baseline (these are sometimes referred to as atypical squamous cells of undetermined significance or ASCUS), 30% of those who were HIV-negative progressed to LSIL compared to 70% progression rate for those living with HIV. (See Table 1)

The same research team was also able to assess the relative risk of a number of factors for their

positive or negative impact on the progression of disease. The researchers' data indicate that the same factors most strongly associated with detection of an anal lesion are also associated with disease progression

(HPV infection, HIV infection, history of receptive anal intercourse).

A larger UCSF follow-up study completed in 1998 found equally alarming rates of anal HSIL among a group of gay and bisexual men, with a disproportionate impact on those living with HIV. Of the HIV-positive study participants, 38% developed HSIL during the study as compared with 17% for HIV-negative men. For those with LSIL, 52% of the HIV-positive men progressed to HSIL as did 41% of the HIV-negative men.

The researchers for both studies caution that their data are drawn from dense urban areas with highly sexually active populations of gay men and therefore cannot fully reflect other areas. Yet the high prevalence of anal HPV infection demonstrated in HIV-negative and HIV-positive gay men appears to be true as

well of individuals who have more recently initiated sexual activity. At a recent cancer conference, researchers reported a high prevalence of anal HPV infection in a cohort of HIV-negative and HIV-positive adolescent men and women. (See Table 2)

## Infection with Multiple Types of HPV

There are dozens of different types of HPV, many of which have been found in anal lesions. The 1998 UCSF study on incidence and progression, referenced above, used sophisticated genetic testing to identify the different types of HPV found in those who were infected. The researchers also tried to determine whether specific types of HPV were more closely associated with disease progression.

The role of individual HPV types could not be determined because most subjects were infected with multiple types. The researchers were able to determine that infection with multiple HPV types was associated with an increased incidence and progression of disease. Using statistical analysis, they identified the following risk factors for developing HSIL:

- Lower CD4 cell levels (for those who were living with HIV)
- Persistent HPV infection
- Anal infection with multiple HPV types
- Infection with HPV types known to be carcinogenic.

The researchers noted that for a small number of individuals who developed ASIL during the course of the study, no HPV was detected. They suggest a possible explanation is the presence of types of HPV not detectable using current testing methodology. Researchers also noted that the increased risk for developing HSIL with multiple HPV types suggests the possibility of cooperation between specific HPV types in disease pathogenesis.

## Methods of Detecting ASIL

Infection with HPV is certainly an important factor in risk for possible disease. Yet the high prevalence of infection in groups known to be at risk for anal cancer makes screening for infection alone an unproductive exercise. Instead, scientists have been working to identify reliable methods of identifying those with ASIL.

Several UCSF studies have established that cytological screening is reliable and effective. In much the same way a Pap smear is used for identifying those at increased risk for cervical cancer, clinicians can use a swab to gather cells from the area of the anus where cancer typically develops. This is the transitional area where the

**Table 1**  
Baseline Prevalence and Incidence of Progression/Regression Over 2 Years to HPV-Related Anal Lesions Among A Group of Gay and Bisexual Men

	HIV-negative	HIV-positive
ASIL at baseline	7%	36%
Normal baseline, developed ASIL over 2 years	17%	52%
Normal baseline, developed HSIL over 2 years	8%	20%
Progression from ASCUS at baseline to LSIL	31%	70%
Progression from LSIL at baseline to HSIL	36%	62%
Regression from ASCUS at baseline to normal	62%	30%
Regression from LSIL at baseline to normal	50%	5%

**Table 2**  
Prevalence of Abnormal Anal Pap Smears In A Group of Male and Female, HIV-Positive and HIV-Negative Adolescents\*

	Male	Female
HIV-positive	53%	21%
HIV-negative	17%	6%

\* Data from the Reaching for Excellence in Adolescent Care and Health (REACH) study, conducted in 15 sites in 13 US cities (Moscicki, 2000).

epithelial lining of the anus meets the epithelial lining of the rectum. The swab contents are then “smear” on a slide, observed under microscope, and analyzed for the presence of abnormal cells.

If abnormalities are detected, direct observation can be done using colposcopy, in which a small camera and light source, enclosed within a tube, are inserted. A trained colposcopist, again using many of the same observational methodologies developed for cervical cancer, can usually identify HPV-related lesions and cancer. Biopsies of visible lesions are also used to confirm their source and classify them as LSIL, HSIL, or cancerous.

## Cost Effectiveness of Screening

Much of the success in reducing the incidence of cervical cancer has come from expanded screening programs. Similarly, the prevention of anal cancer depends on the early identification and treatment of HSIL. For those living with HIV, anal cancer may be one of the few malignancies that can actually be prevented.

To assess the implications of screening those at the highest risk—gay and bisexual men living with HIV—a Harvard-UCSF research team set up a complex mathematical model to forecast the cost of screening and subsequent related treatments with the savings in suffering and lost productivity. They were able to use the work of the UCSF and other researchers who had studied the incidence of ASIL and anal cancer, as well as cost figures from the screening for and treatment of cervical cancer.

The researchers concluded that screening every 2 years for those early in HIV disease (CD4 counts greater than 500/mm<sup>3</sup>) was cost effective over a wide range of assumptions. For those with more advanced HIV disease (CD4 counts less than 500/mm<sup>3</sup>), screening every year was most cost effective. Screening every 6 months provided little additional benefit over that of annual screening in nearly all sensitivity analyses.

Regardless of when screening was initiated, the cost-effectiveness of either a yearly or bi-annual screening schedule was comparable with other accepted preventative measures in clinical medicine, including cervical cancer screening using Pap smears.

## Treatment

Standard treatment of anal cancer is a protocol of combined chemotherapy and radiotherapy. Typically, a diagnosis of LSIL results only in more frequent monitoring in case it progresses to HSIL. When HSIL is diagnosed, treatment may be called for to reduce the likelihood of progression to cancer. This may include surgical removal of the lesions.

Data on the efficacy of treatment are scarce. However, treatment of cervical lesions has been shown to be effective in substantially reducing the risk of progression to cancer.

## Conclusion

Infection with HPV is highly prevalent among gay and bisexual men. This population also has a high incidence of HPV-associated anal lesions and cancer. Gay and bisexual men living with HIV have an even higher incidence and progression of disease.

This was the same story for cervical cancer. However, with strong advocacy and a concerted effort by researchers, clinicians, and public health leaders, dramatic reductions in the incidence of cervical cancer have been achieved.

A similar effort may well be in order targeting the gay and bisexual men who are most at risk, particularly those who are living with HIV. Further research is needed to determine the prevalence and incidence of ASIL in the general population of gay and bisexual men outside of major urban centers.

Training programs are needed to train colposcopists in the skills of identifying and biopsying ASIL; training of colorectal surgeons is needed to optimize identification and treatment of ASIL. Further research is also needed on newer, medical therapies for ASIL so that costly and painful surgery can be avoided.

Finally, research is needed to identify other groups that may benefit from anal screening, including women, and to document the efficacy of anal screening programs in lowering the incidence of anal cancer among

those at risk. Widespread screenings of high risk groups may be a cost effective opportunity to prevent anal cancer and may well result in lower rates of this disease. Public health leaders should give serious consideration to encouraging bi-annual screening for all gay and bisexual men, and annual screening for those gay and bisexual men who are living with HIV.

## References

- Darragh T, Jay N, Tupkelewicz B, Hogeboom C, Holly E, Palefsky J. Comparison of Conventional Cytologic Smears and ThinPrep Preparations from the Anal Canal. *Acta Cytol.* 1997; 41,4:1167-1170.
- Goldie S, Kuntz K, Weinstein M, Freedberg K, Welton M, Palefsky J. The Clinical Effectiveness and Cost-Effectiveness of Screening for Anal Squamous Intraepithelial Lesions in Homosexual and Bisexual HIV-Positive Men. *JAMA.* 1999;281:1822-1829.
- Jay N, Berry JM, Hogeboom C, Holly E, Darragh T, Palefsky J. Colposcopic Appearance of Anal Squamous Intraepithelial Lesions; Relationship to Histopathology. *Dis Colon Rectum.* 1997;40:919-928.
- Moscicki A-B. HPV in HIV positive adolescents. Abstracts of the 4<sup>th</sup> International AIDS Malignancy Conference; May 16-18, 2000; Bethesda, MD. *J Acquir Immune Defic Syndr Hum Retrovirol.* 2000;23:A14. Abstract S26.
- Palefsky J, Holly E, Hogeboom C, Berry JM, Jay N, Darragh T. Anal Cytology as a Screening Tool for Anal Squamous Intraepithelial Lesions. *JAIDS.* 1997;14:415-422.
- Palefsky J, Holly E, Hogeboom C, Ralston M, DaCosta M, Botts R, Berry JM, Jay N, Darragh T. Virologic, Immunologic, and Clinical Parameters in the Incidence and Progression of Anal Squamous Intraepithelial Lesions in HIV-Positive and HIV-Negative Homosexual Men. *JAIDS.* 1998;17:314-319.
- Palefsky J, Holly E, Ralston M, Jay N, Berry JM, Darragh T. High incidence of anal high-grade intra-epithelial lesions among HIV-positive and HIV-negative homosexual and bisexual men. *AIDS.* 1998;12:495-503.
- Palefsky J, Holly E, Ralston M, Jay N. Prevalence and Risk Factors for Human Papillomavirus Infection of the Anal Canal in Human Immunodeficiency Virus (HIV)-

Positive and HIV-Negative Homosexual Men. *J Inf Dis.* 1998;177:361-367.

Palefsky J. Anal Squamous Intraepithelial Lesions: Relation to HIV and Human Papillomavirus Infection. *JAIDS.* 1999; 21:542-548.

## Acknowledgements

We would like to acknowledge our incredible study subjects, study volunteers, lab technicians, the National Cancer Institute and the National Center for Research Resources (NIH grants CA54053, CA63933, and 5 M01-RR-00079), and the UCSF/Moffitt General Clinical Research Center.

Editorial assistance from Progressive Health Partners  
www.phpartners.com

## Materials Available

CancerNet, a service of the National Cancer Institute (one of the US National Institutes of Health), can be accessed through the internet at: <http://cancer.net.nci.nih.gov>

The American Cancer Society has some helpful information at: <http://www.cancer.org>

The Body, an internet-based HIV and AIDS information source, has a section on AIDS-related cancers, including anal cancer, at: <http://www.thebody.com/treat/cancers.html>