Anal Cancer and HIV

March 5, 2011 By Joseph Sonnabend, MD

Kaposi's sarcoma (KS), and non- Hodgkin lymphoma (NHL) were common AIDS associated malignancies before potent antiviral therapy became available. The incidence of these two malignancies used to be 50-200 times higher among HIV positive individuals than in those who were HIV uninfected. These two malignancies are caused by herpes viruses, HHV8 in the case of KS and EBV in the case of NHL.

Cervical cancer and anal cancer also occur more frequently in association with HIV infection. These two cancers, like KS and NHL are also caused by viruses. These viruses are members of the human papillomavirus family (HPV), types 16 and 18 being the most frequent. Over 90% of anal cancers are associated with HPV type 16. HPV viruses are more usually the cause of common warts.

Potent anti-HIV therapy has reduced the incidence of KS and NHL by 80-85%. Unfortunately treatment has not had the same effect on HPV associated cancers. Some studies show an increasing trend in the incidence of cervical and anal cancers, an effect most likely due to increased survival.

I was prompted to write this entry after reading an important report about HIV and anal cancer which has just appeared in an advance access edition of the Journal, Clinical Infectious Diseases. The lead author is Alexandra de Pokomandy.

Its title is: **HAART and progression to high grade anal intraepithelial neoplasia in men who have sex with men and are infected with HIV.**

Many of the article's conclusions have been reported before, but this one is important because it has the power of a prospective study. A prospective study is one in which participants are examined at regular intervals after entering the study and checked for the development of any changes over time. Most previous studies on the association of anal cancer and HIV infection were not prospective studies.

6 months for 3 years. They were tested by examining anal smears for high grade anal intraepithelial neoplasia (AIN). AIN is a local condition in the anus that can progress to invasive cancer, higher grades of AIN being more likely to do so.

The number studied is not huge, but we cannot ignore the findings.

Firstly, in line with previous studies (most were not prospective), treatment with HAART did not reduce the incidence of AIN. There was a hint that treatment lasting over four years might have an effect. .

The study attempted to define what the risk factors were for developing AIN among men who entered the study,

Firstly this is the cumulative rate at which AIN increased during the study.

The illustration shows the increasing proportion of men with more advanced forms of AIN (AIN2 and AIN3) over time. The increase is shown for three groups of men. Those very very few who were HPV negative at baseline (lower line), those with high risk HPV type 16 at baseline (top line), and in the middle line those with HPV types other than type 16 at baseline.

Just looking at the top line, under 50 % of those who had HPV type 16 at baseline already had AIN 2/3 at the start of the study. By 36 months the proportion with AIN 2/3 had risen to about 75%.

The authors attempted to define what the risks for developing AIN 2/3 were. As noted, antiviral treatment made no difference.

What was significant in increasing the risk of progression to AIN2/3 was the CD4 nadir, and the number of different HPV types isolated.

A word about anal intraepithelial neoplasia - AIN:

The development of aggressive anal cancer occurs in stages that can be identified by examining cells obtained by PAP smears. Progression from one stage to the next is not inevitable.

For example, in the above study 39% of HIV positive men developed AIN 2/3 over 3 years. But extrapolating from other data only 0.12 % of men would be expected to develop aggressive anal cancer over the same period, according to an editorial accompanying the report.

The editorial concludes as follows:

"These results show that HAART has not reduced the prevalence of HPV infection, has not changed the natural history of anal HPV infection in HIV-positive MSM, and has not mitigated the progression to high-grade AIN (which is likely to be a precursor to anal cancer, in much the same way that cervical dysplasia is the precursor to cervical cancer").

This is not good news but it does give us a very clear basis on which to act.

We know what has to be fixed, and the study has provided us with a few suggestions.

These are some that jumped at me:

The risk for developing aggressive anal cancer is related to the CD4 nadir. This is yet an additional and powerful reason to be tested forHIV and make sure the CD4 count does not fall further.

1. Screening of women for cervical dysplasia with regular PAP smears has had an effect in preventing

cervical cancer. There are several treatment options. It's important that MSM be screened with regular anal PAP smears. It's important that health care providers know how to do this and that the PAP smears are competently examined. It goes without saying that every effort needs to be made to insure that problems with reimbursement for the procedures are not an obstacle.

2. Very unfortunately treatment of AIN is not as simple as dealing with cervical lesions. This means that efforts to improve the management of AIN must be studied and that funds be made available for this.
3. Another risk for the development of AIN 2/3 that was identified was the number of different HPV types present. Although there is no clear evidence on the role of condoms in preventing anal HPV infection it seems absolutely reasonable to accept that there are circumstances when receptive partners in anal intercourse would be safer to insist that their partner use a condom. The more HPV types there are the greater the risk for more advanced forms of AIN and therefore aggressive anal cancer.
4. HPV vaccines. These obviously work best if given before the onset of sexual activity so the vaccination of boys and young men is a good idea. For older individuals it's possible that some have not yet acquired HPV 16 or 18. Apart from cost, there appears to be no harm. Studies on therapeutic HPV vaccines should be supported.
5. Although this study was done in men we should consider the implications for women. In the general population anal cancer is rare, but more cases have been reported in women than in men, and HIV infection increases the risk in both. New York State health department guidelines recommend annual anal PAP smears for HIV positive women with abnormal cervical smears. These are 2007 guidelines; there may be updates that I have not seen. Even if it remains unclear if anal intercourse adds to the risk of anal cancer in women, this seems likely and so we should work out ways to offer regular screening to women who might be at greater risk.

So many aspects of HIV infection can be ameliorated by antiviral treatment, but sadly not everything. Cancers of the cervix and anus are among these. But there are measures that we can take to lessen risk, some mentioned above.

Readers of my blog will know that I think that the promotion of daily Truvada to prevent HIV infection is unwise. I find it incomprehensible that the CDC has issued an interim guidance on its use. It does not even halve the chance of acquiring a life threatening infection, one for which treatments cannot prevent the increased risk for cervical and anal cancer. Condoms are much more effective, they are cheaper, safer and readily available, and we should not be distracted from promoting and facilitating their use, and continuing to provide support for their use with an alternative that just does not work well enough.
