

Screening and Treatment of Anal Intraepithelial Neoplasia to Prevent Anal Cancer: Where Do We Stand?

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THE PRECEDING ARTICLE BY DR. STEPHEN GOLDSTONE NICELY OUTLINES the issues around anal human papillomavirus (HPV) infection, anal intraepithelial neoplasia (AIN), and anal cancer. The article highlights several areas in which we are sure of the facts: 1) anal HPV infection is very common among men who have sex with men (MSM); 2) the prevalence and incidence of the putative anal cancer precursor, high-grade squamous intraepithelial lesions (HSIL) are very high among MSM; 3) the annual incidence of anal cancer among MSM is unacceptably high; 4) each of the above is more common among HIV-positive MSM than HIV-negative MSM; and 5) combination antiretroviral therapy has little, if any, impact on HSIL, portending the possibility—with some data supporting this suggestion—that the incidence of anal cancer among HIV-positive men on antiretroviral therapy will continue to rise in the future. Taken together, these observations would suggest that we should be mounting all-out campaigns to educate people around these issues and immediately implement screening and treatment programs to prevent anal cancer, modeled after the highly successful programs to prevent cervical cancer.

To help understand why this has not yet happened, it is reasonable to ask ourselves what is not yet known, specifically the areas in which the evidence does not yet support implementation of an official anal screening and treatment program. In so doing, it is critical that we remember the adage, “absence of evidence is not evidence of absence.” In other words, if the data are not yet available to support implementation of a program, it simply means that the data have not yet been collected. Collecting the necessary data should be one of our highest priorities. In some cases, however, it may be impractical to do so, at least in the short term. In these situations, we need to decide whether or not to proceed, despite our not having all of the supporting evidence that we might like.

Answers to some very specific questions are needed to inform the implementation of a screening program for AIN. First, can HSIL be effectively treated (i.e., does not recur after a complete course of therapy)? Second, does effective treatment of HSIL prevent anal cancer? Third, if treatment of HSIL prevents anal cancer, what is the most cost-effective way to identify MSM with HSIL?

The question as to whether treatment of HSIL prevents anal cancer really has a more existential subtext: does HSIL progress to cancer and, conversely, are most if not all anal cancers preceded by HSIL? I believe that the data are clear that HSIL, particularly AIN 3 (severe dysplasia), can progress to anal cancer (Cleary, 1999; Scholefield, 2005). In our experience at the University of California, San Francisco (UCSF) Anal Neoplasia Clinic, we have also clearly documented progression to invasive anal cancer. In addition, the biological similarities between cervical cancer, cervical intraepithelial neoplasia (CIN), anal cancer, and AIN are very compelling. Do we need further data documenting malignant

progression of HSIL? More is always better, of course, but performing a natural history study to document the progression rate to invasive cancer would be tricky, if not unethical.

Can HSIL be effectively treated? This is a tractable question, and the data that are emerging increasingly appear to indicate that HSIL can in fact be treated. While the field is still in its infancy, some techniques are showing promise, such as infrared coagulation. Data from Dr. Goldstone suggest that the majority of discrete HSIL lesions can be treated with this technique given a sufficient number of treatments (Goldstone, 2005). However, long-term follow-up data are not yet available and it will be important to know the duration of response. One might speculate, however, that even if the response is not permanent, there is still benefit from the point of view of cancer prevention.

It has become increasingly clear that host genetic changes play a critical role in progression from HSIL to invasive anal cancer (Gagne, 2005). Even if HSIL does recur after successful treatment, it is possible that it does not possess the full spectrum of changes that the original lesion(s) may have accumulated. In a sense, the “molecular clock” may have been turned back. The cardinal question, of course, is whether treatment of HSIL will prevent anal cancer. This too is a tractable question, but one that will require many study participants, and much time and treasure to answer. Efforts are in progress to develop such a study.

There are many questions about screening and treatment for HSIL and relatively few answers as of now. Yet our patients are still developing HSIL and an unacceptably high number are developing a likely preventable, potentially fatal cancer. How do we best approach this problem until the answers are in? At a minimum, all MSM need to be screened for anal cancer. This is a very simple procedure—digital rectal exams (DRES)—in which the examiner feels for superficial and submucosal masses. This procedure is simple, cheap, and fast. DRES need to be done, even if a patient is having anal cytology screening and or high resolution anoscopy (HRA), since cancers are not always visible or detectable on the surface.

Should we be doing anal cytology, HRA, and providing treatment of AIN given the current state of our knowledge? I believe so. Cost-effectiveness analyses using conservative assumptions indicate that screening and treatment of AIN to prevent anal cancer fall well within the range of economic acceptability (Goldie, 2001; Goldie, 1999). Anal cytology is a relatively inexpensive and technically simple test. However, any single cytology sample suffers from low sensitivity to detect HSIL; it is the cumulative sensitivity of repeated testing over a number of years that renders the test sufficiently sensitive to detect a high proportion of HSIL, similar to the approach taken to compensate for the low sensitivity of a single cervical cytology test to detect CIN. An approach that may hold some promise for the future is self-sampling. We and others have

shown that individuals can collect samples for testing with the same degree of precision as clinician-performed sampling. Efforts to improve the sensitivity of anal cytology to detect HSIL are clearly needed.

Yet the prevalence of HSIL is so high among MSM that an argument could be made to dispense with cytology altogether and proceed directly to the next step in the evaluation, namely to visualize tissues using HRA and to biopsy suspect lesions. Here the problem is a different one, primarily the shortage of clinicians skilled in HRA. Like cervical colposcopy, HRA has a long learning curve and being trained to identify HSIL in the anal canal can be challenging. This is a problem that is gradually being addressed through the efforts of our group—as well as Dr. Goldstone and societies such as the American Society for Colposcopy and Cervical Pathology, and the American College of Surgeons—to train clinicians in HRA. Given the extraordinary prevalence of HSIL in high-risk populations such as HIV-positive MSM, the shortage of trained clinicians will likely remain a problem for the foreseeable future. Further, relative to anal cytology, HRA is expensive and incurs the additional cost of histopathology if a biopsy is done.

One potential approach to screening in settings where access to HRA is limited would be to continue using anal cytology as the primary screening tool and to prioritize HRA referrals for individuals whose cytology shows HSIL. This approach makes sense because we and others have shown that HSIL on cytology has a high predictive value to detect HSIL on HRA and biopsy. In this manner, the HRA clinician will be spending his or her time seeing patients with the highest likelihood of having HSIL. The disadvantage is that many individuals with HSIL will not be referred for HRA since a high proportion of these individuals have LSIL or less on cytology. In this scenario, it is hoped that HSIL will eventually be detected if the patient continues to be screened annually if they are HIV-positive, and hopefully HSIL will be detected before progression to cancer occurs. Unfortunately, further risk stratification based on criteria such as CD4+ cell counts is not feasible. Although individuals with lower CD4+ cell counts may be at higher risk of HSIL (Palefsky, 1998), the risk of anal cancer is not clearly linked to CD4+ cell counts (Frisch, 2001).

What does the future portend for screening and treatment of AIN to prevent anal cancer? As described above, I believe that we should be performing this service for our patients whenever and wherever possible. In the meantime, though, it is essential that we initiate organized efforts to collect the data that we will need to formally determine the cost-effectiveness of a screening and treatment program. Work must also continue on better understanding the biology of AIN and progression to anal cancer. The molecular mechanisms underlying progression to cancer are not yet understood. Many MSM will develop HSIL, yet only a small minority will progress to cancer. Understanding who progresses and when is critical, particularly if it can lead to the identification of biological markers of progression that can help us target individuals at highest risk of malignant progression.

Finally, there is potentially great news on the horizon for the long-term prevention of HSIL and anal cancer. Merck and GlaxoSmithKline have developed and are testing vaccines to prevent primary HPV-16 and HPV-18 infection of the cervix in women. Reports from Phase II studies show complete or nearly complete prevention of acquisition of HPV-16 and HPV-18 infection, as well as CIN due to these types (Harper, 2004; Villa, 2005). The results of the pivotal Phase III studies are not yet published but oral presentations at recent scientific meetings indicate similar results in these larger studies.

If the vaccine works to prevent cervical HPV-16 and HPV-18 infection

in women, it may well work to prevent anal HPV-16 and HPV-18 infection and AIN associated with these types. The Merck vaccine is also active against HPV-6 and HPV-11, which has the additional advantage of potentially preventing anal warts, an important problem among MSM. Research is needed on the efficacy of the HPV vaccine in men and specifically on the prevention of AIN in men and women. Its potential utility should also be explored in HIV-positive men and women.

It is also important to remember that HPV infection is typically acquired soon after initiation of sexual activity. To be maximally effective, HPV vaccination would ideally be done prior to this point. This means that the best time to vaccinate both men and women would be in early adolescence or possibly sooner, depending on the duration of vaccine protection.

Despite the great long-term promise to substantially reduce the incidence of AIN and anal cancer, a word of caution about the HPV vaccines is in order. HPV-16 and HPV-18 account for approximately 70% of cervical cancers, and a similar or higher proportion of anal cancers. The vaccines appear to be type-specific and they likely will not prevent infection with other oncogenic HPV types. It may be that we will still need to screen and treat for AIN, even if the vaccine is used by all at-risk men and women, and even if the vaccines perform perfectly in real-life conditions. It is similarly envisioned that screening for CIN will still be required in vaccinated women, albeit at possibly longer intervals. Second generation vaccines that contain additional oncogenic HPV types are on the drawing board and may mitigate this problem. But in the meantime, we need to assume that there will be a continued need to screen and treat for AIN, even if the HPV vaccines lead to reduced intensity of such a program. Lastly, we must remember that these vaccines have not been shown to have therapeutic potential, and even if the vaccines work perfectly, we will still need to care for the millions of men and women that have already been exposed to HPV-16 and HPV-18, and who are at risk of anal cancer in the future. 

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