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Screening for anal high-grade squamous intraepithelial lesions and anal cancer- has its time come?

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The incidence of anal cancer is rising and has been clearly doing so among both women and men in the general population since the 1970s.[1,2] The incidence of anal cancer is particularly high among those with HIV and other forms of immune suppression, and among women there is a clear relationship between history of cervical or vulvar cancer and anal cancer.[3,4] In some populations of women, the incidence of anal cancer exceeds that of cervical cancer. The natural history of anal HPV infection to the anal cancer precursor, anal high-grade squamous intraepithelial lesion (HSIL) to cancer is similar to that for cervical HPV infection to cervical HSIL and cancer. Screening for and treating cervical HSIL is well known to reduce the risk of cervical cancer, so why is it not yet standard of care to do so for anal HSIL?

There is one major reason for this- in this era of evidence-based medicine, there is a need for high quality evidence that treating anal HSIL reduces the risk of anal cancer. The ANal Cancer/ HSIL Outcomes Research (ANCHOR) study (U01CA121947), funded by the U.S. National Cancer Institute, is a large randomized controlled trial to determine if treatment of anal HSIL reduces the incidence of anal cancer compared with active monitoring without treatment. This study is focused on the group at highest risk of anal cancer, men and women living with HIV over 35 years of age with biopsy-proven anal HSIL. If a meaningful level of anal cancer reduction can be demonstrated in the treatment arm of this very high risk, challenging population, it is expected that anal HSIL treatment will become standard of care for this group, as well as for the other groups at increased risk of anal cancer.

However the challenges don't stop there. If treating anal HSIL becomes standard of care, then optimal screening algorithms to detect it will need to be defined. Anal cytology has many of the same limitations as cervical cytology, primarily low sensitivity and tendency to under-call the severity of disease. As in the cervix, HPV testing offers better sensitivity than cytology but lower specificity, particularly in men and women living with HIV who have an especially high prevalence

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and incidence of anal HPV infection. The optimal combination of cytology and HPV genotyping, and second tier tests such as methylation markers, HPV oncoprotein detection and other methods still needs to be defined, and the best algorithms will likely vary depending on the risk group.

Another issue that will need to be addressed is optimal treatment for anal HSIL. The ANCHOR study will be by far the largest study examining the efficacy of anal HSIL treatment, but it is a "treatment strategy" study and is not designed to compare one treatment to another. There are very few published randomized controlled trials of anal HSIL to date, and all of the data published to date point to serious challenges with each of the modalities studied thus far. These include low efficacy and recurrence at treatment sites.[5,6] HPV is likely to be a "field infection" particularly in immunocompromised individuals, and consistent with this, there is also a high rate of incident lesions at untreated sites, known as metachronous disease.

If treatment of anal HSIL becomes standard of care in high-risk groups, 1) optimal screening algorithms to detect HSIL will need to be defined and 2) a very large proportion of men and women in those groups may need HSIL treatment at some point.

Then there is an issue of numbers. If treatment of anal HSIL becomes standard of care in high-risk groups, a very large proportion of men and women in those groups may need HSIL treatment at some point. It is currently estimated that half or more of men living with HIV and about a third of women living with HIV will have anal HSIL in cross-sectional analyses.[7-9] Even though there may be spontaneous regression of some HSIL, there will also be incident HSIL over time in many. Given the limited numbers of individuals trained in high resolution anoscopy (HRA) and HRA-guided treatment of HSIL, it is easy to imagine that the existing pool of HRA providers will be quickly overwhelmed. There will be a need for a rapid expansion of the pool of well-trained HRA providers, necessitating expansion of high-quality training programs guided by rigorous metrics and practice standards. There is also urgent need for more scientific investigation of progression from anal HSIL to cancer and identification of biomarkers of progression to cancer. Not all HSIL is the same, and it may well be that some, but not all HSIL need to be treated. The ANCHOR Study includes a specimen biorepository that will be of great value for understanding anal cancer pathogenesis and identification of biomarkers of progression. Given the similarity between cervical cancer and anal cancer, identification of biomarkers of progression from anal HSIL to anal cancer could also be relevant to identification of similar biomarkers in the cervix. Perhaps in the future, with this information, we can limit our treatment of HPV-associated HSIL at any anatomic location only to those understood to be at highest risk of progression to cancer.

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There is of course the good news that HPV vaccination works very well to prevent anal HPV infection and likely anal cancer among those not yet exposed to the relevant HPV types. This will be the key to anal cancer prevention in the future, and should be aggressively implemented in a gender-neutral manner wherever possible.

But for those who remain at high risk of having anal HSIL, has the time come to screen for and treat it? Based on the considerations listed above, the answer may be "not yet". One approach would be to wait for the answers that ANCHOR will provide: don't screen for it or treat it unless ANCHOR tells us that doing so is effective in reducing the incidence of anal cancer. In the absence of treatment for anal HSIL, we recommend that all individuals at high risk of anal cancer undergo digital anorectal examination (DARE) at regular

intervals to palpate masses that could indicate the presence of anal cancer.

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However, like many experts around the world, at the University of California, San Francisco Anal Neoplasia Clinic, Research and Education Center we take a different approach. In addition to performing DARE, until we get the answers from ANCHOR, we choose to actively treat anal HSIL given its known precancerous potential and the high incidence of cancer in our high-risk populations. We will consider other approaches only if the ANCHOR Study tells us that treating anal HSIL with our currently available methods is futile. One way or the other, we need to be ready to implement HSIL treatment as standard of care, and/or to continue to develop the infrastructure needed to explore other approaches to prevent anal cancer in high-risk populations.

Each of these issues will be explored further in this issue of HPV World. ■

DISCLOSURE
The author declares nothing to disclose.

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