Literature Reviews

National HIV Curriculum Podcast

The ANCHOR Study: Does Treatment of Anal HSIL Prevent Anal Cancer?

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Season 1, Episode 15

This episode reviews a landmark study published in 2022 that aimed to answer the question of whether treating anal high-grade squamous intraepithelial lesions (HSIL) prevents anal cancer for persons with HIV, a question that was previously unanswered and that was key to informing the new anal cancer screening guidelines.

Topics:

- HSIL
- anal cancer
- cancer screening
- HPV
- HIV

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Disclosures

Disclosures for Brian R. Wood, MD
None

References

Paper #1

Transcript

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introduction**[00:00] Introduction**

Hello everyone. I'm Dr. Brian Wood from the University of Washington in Seattle. Welcome to the *National HIV Curriculum* podcast. This podcast is intended for health care professionals who are interested in learning more about the diagnosis, management, and prevention of HIV.

Today, I'm going to focus on one part of cancer prevention, which I see as a critical aspect of HIV primary care. For this episode, I will review a landmark study that was published in the *New England Journal of Medicine* in June 2022. I've chosen to review this study because it served as a catalyst for new anal cancer screening recommendations, which were recently added to the Opportunistic Infection guidelines. In addition, this study will serve as background for a future episode in which I will be joined by an expert to discuss considerations for *implementing* those new anal cancer screening guidelines into clinical practice.

trial-rationale**[01:01] Trial Rationale**

Palefsky JM, Lee JY, Jay N, Goldstone SE, Darragh TM, Dunlevy HA, et al. Treatment of anal high-grade squamous intraepithelial lesions to prevent anal cancer. N Engl J Med. 2022;386(24):2273-2282. **[PubMed Abstract]**

So, let's talk about the ANCHOR trial. This trial was led by Dr. Joel Palefsky from University of California San Francisco. Dr. Palefsky and the coauthors offer several points as background for why this study was necessary to conduct.

First, the incidence and mortality of anal cancer are rising in the United States. I would note that this is starkly different than the situation for cervical cancer, for which we have long-standing national screening and prevention guidelines, and for which treatment of cancerous precursor lesions has been recommended for many years. For cervical cancer, the incidence and mortality are actually decreasing overall.

Second, the risk of anal cancer is disproportionately high for certain individuals, including individuals with HIV. The incidence is highest for men who have sex with men (MSM) with HIV, but other individuals with HIV also have a higher incidence of anal cancer, as compared to people who do not have HIV. Furthermore, the incidence of anal cancer in men and women with HIV is rising, and this is occurring despite earlier and more widespread use of effective ART [antiretroviral therapy].

Now, as with cervical cancer, anal cancer is caused by oncogenic strains of HPV [human papillomavirus], particularly HPV-16 and, less often, HPV-18. In addition, anal cancer is preceded by high-grade squamous intraepithelial lesions. I will use the abbreviation HSIL. We've known for a long time that individuals with HIV have disproportionately high rates of HPV infection and of anal HSIL, and individuals with HIV have a high rate of progression of HSIL to anal cancer. However, what we *didn't* know was whether treatment of anal HSIL would be effective at preventing the development of anal cancer. This was a key question and key piece of missing research. For anal cancer, as with cervical cancer, the two critical points of prevention are primary prevention with HPV vaccination and secondary prevention, which means treatment of cancerous precursor lesions. But again, what we didn't know and what needed to be studied was whether treatment of cancerous precursor lesions would be effective at preventing anal cancer, and I'll go in to a bit more why that was a controversial question.

purpose--study-design**[03:37] Purpose & Study Design**

So, the purpose of the ANCHOR trial, which was named ANCHOR for **A**nal **C**ancer-**H**SIL **O**utcomes **R**esearch, was to ask this question: Does treatment of anal HSIL for individuals with HIV provide safe and effective prevention of anal cancer? Now, theoretically, identification and treatment of HSIL may not be effective because lesions can be large, they can be multifocal, treatment may not eradicate all sites of anal HSIL, HSIL might recur quickly following treatment, and also treatment might have unfavorable side effects. So, this question really needed to be answered.

In order to do that, investigators of the ANCHOR trial designed a phase 3, randomized, controlled study. It was

conducted at 25 sites in the United States. In terms of who participated in the trial, individuals were included if they had HIV, were older than 35 years of age, and had biopsy-proven, asymptomatic HSIL at baseline. At screening, each volunteer had a sample collected by anal swab for cytology, which is sometimes referred to as anal PAP smear, also for HPV co-testing. They also underwent physical exam and high-resolution anoscopy (or HRA). At the time of HRA, any suspicious lesions were biopsied. The purpose of the screening was to identify volunteers with HSIL. Individuals were only eligible for the trial if HSIL was identified on at least one biopsy sample. So, to summarize, participants had HIV, were older than 35, and all had biopsy-proven, asymptomatic HSIL at the time of enrollment.

The main exclusion criteria was a history of certain cancers, including anal cancer, or detection of any those specific cancers during the screening evaluation.

Participants in the trial were randomized 1:1, meaning they were randomized in equal numbers to one of two groups. The two groups were a treatment arm and an active monitoring arm. Participants randomized to the treatment arm underwent an intervention to treat and try to eradicate all anal HSIL lesions. Specialists at the study sites could choose between a variety of treatment options to try to eradicate the HSIL. The study really wasn't designed to power or compare different treatment modalities. There were options that a trained specialist could choose from to treat the identified HSIL.

In both arms, participants followed up every 6 months. At each follow-up, they had repeat digital anal rectal exam (or DARE), HRA, biopsy if indicated, anal swab for cytology, as well as blood tests to identify biomarkers and other factors predictive of anal cancer. So again, the difference between the arms was in the treatment of any identified HSIL. All participants had identified HSIL but one group had it treated and eradicated and the other did not.

The primary outcome for the statistical analysis was progression of HSIL to anal cancer, comparing those two groups. The investigators did a time-to-event analysis, sometimes called a survival analysis, which compares how long it takes for a specific event to occur between two groups. In this case, that event was development of anal cancer. This type of analysis is useful because it takes into account both whether an event occurred and the time to occurrence of that event. The investigators also assessed the safety of treating anal HSIL as a secondary outcome.

study-participants**[07:36] Study Participants**

So, let's turn to the study results. Between 2014 and 2021, 10,723 individuals underwent screening; of these, 4,459 underwent randomization, so this led to just over 2,200 participants in each of the two study groups. An important note here is that about half of the individuals screened were found to have anal HSIL and thus met eligibility for enrollment. To me, this emphasizes the high prevalence of anal HSIL among people with HIV. Again, of those screened, about 50% had anal HSIL, and this, again, is in the absence of symptoms. Seventeen individuals were excluded from participation because anal cancer was detected at that baseline evaluation.

In terms of who participated in that trial, the median age was 51 in both arms. Overall, in each arm, about 80% of participants were male and 16% female. Groups were overall well balanced when considering demographic factors and clinical characteristics. I would say the trial participants were more racially and ethnically diverse than in many trials that include people with HIV. The most commonly reported HIV risk factor was male to male sex. Most participants have long-standing and currently well-controlled HIV. I'd note that over 80% had a viral load that was below 50, and the median CD4 count was above 600. About half of participants did have a history of CD4 count below 200 at the time of enrollment; for most, the HIV was well controlled. About one-third of enrollees in the trial reported smoking tobacco and about 12% had relatively large HSIL lesions at baseline—large being defined as greater than 50% of the anal canal or perianal region, and I'll come back to why that was important.

The initial HSIL treatment was electrocautery ablation (or hyfrecation) in more than 80% of cases. Use of

topical treatments was pretty rare; that occurred in under 5%. Again, the trial was not designed to compare efficacy of different treatment modalities. So, I would just note that most treatment here was hyfrecation, again, by specialists who had special training in HRA and in HSIL treatment.

findings**[10:17] Findings**

Now, the most important finding from this study was that there were nine incident cases of anal cancer confirmed in the treatment group, as compared to 21 cases in the active monitoring group. This means the rate of progression to anal cancer was 57% lower in the HSIL treatment group, as compared to the active monitoring group. This difference was statistically significant and actually so significant that the Data Safety and Monitoring Board (DSMB) recommended stopping enrollment once they found this difference, and they recommended offering everyone in the active monitoring arm treatment for the anal HSIL.

One thing I'd like to highlight is that the incidence rates of anal cancer were *much* higher than predicted—actually, in both arms. The incidence was quite high in both arms, higher than predicted and it really emphasizes the relatively high risk of anal cancer for people with HIV. Now, treatment of anal HSIL obviously was effective at reducing the risk of development of anal cancer. Efficacy was not 100%. It did not eliminate the risk, but it clearly had significant benefit. It also was overall very well tolerated, which I think is another important finding.

Now, in the analysis, the time to progression of anal cancer was associated with lesion size. Those relatively large lesions that I described earlier were associated with a higher risk of progression to anal cancer. This analysis did not show a correlation between incident anal cancer and low nadir CD4 count but other analyses in the literature have found that low nadir CD4, as well as longer duration of HIV infection, likely increase the risk of developing anal cancers.

take-home-messages**[12:13] Take-Home Messages**

So, overall, what is the take-home message here? I think the results demonstrate that for people with HIV who have no symptoms and who are over 35 years old, treatment of anal HSIL does indeed reduce the likelihood of progression to anal cancer. In addition, the incidence of anal cancer in people with HIV is disproportionately high, so we should be screening for anal cancer regularly. And again, this study was highly influential in the new anal cancer screening guidelines, which are now available, which I encourage you to review.

In the publication, the authors also emphasize that most cancers were detected early, including in the active monitoring arm. Most cancers were detected at stage I or stage II. I think this is important because, clearly, mortality and morbidity are better if anal cancer is detected at earlier, less advanced stages.

Now, strengths of the trial: I would say it was large, multicenter, included a relatively diverse patient population. In addition, the study procedures were performed by trained and experienced HRA providers. I would say that the major limitation of the study is that there are many areas in the country that do not have providers with that specialized HRA training, so many clinicians in many clinics will not have access to HRA-trained specialists. But I would emphasize that the new anal cancer screening guidelines do give algorithms and recommendations based on whether a clinic has access to an HRA-trained referral specialist or not. So, again, I'd encourage you to look at those guidelines, and we'll have more discussion about implementing those guidelines in the future.

summary**[14:04] Summary**

To summarize the most important take-home points from the ANCHOR trial:

- The incidence of anal cancer is high for people with HIV; treatment of anal HSIL is safe, well-tolerated, at least when performed by providers trained in HRA, providers who are experienced and practiced in

the anal HSIL eradication treatment modalities.
- Second, as with cervical cancer and treatment of cervical HSIL, there is now evidence that treating anal HSIL significantly reduces the likelihood of progression to anal cancer.
- Finally, we need protocols for preventing anal cancer that incorporate both primary prevention, meaning HPV vaccination, and secondary prevention, that's treatment of anal HSIL. As HIV primary care clinicians, we also need to address modifiable risk factors, things that may increase the risk of anal cancer, such as tobacco cessation.

So, please take time to review a recently posted mini-lecture on the *National HIV Curriculum*, which reviews the new anal cancer screening recommendations. Please also look out for a future episode of this podcast, which will focus on considerations for implementing those new anal cancer screening guidelines into clinical practice.

Thank you very much for listening to today's episode. Please subscribe and please stay tuned for more on this and other topics important to HIV primary care.

credits**[15:26] Credits**

Transcripts and references for this podcast can be found on our website, the National HIV Curriculum at www.hiv.uw.edu. The production of this National HIV Curriculum Podcast was supported by Grant U10HA32104 from the Health Resources and Services Administration of the U.S. Department of Health and Human Services. Its contents are solely the responsibility of the University of Washington IDEA program and do not necessarily represent the official views of HRSA or HHS.

prevent-anal-cancer