HHS Public Access

Author manuscript

Contemp Clin Trials. Author manuscript; available in PMC 2023 February 01.

Published in final edited form as:

Contemp Clin Trials. 2022 February ; 113: 106679. doi:10.1016/j.cct.2022.106679.

Design of the Anal Cancer/HSIL Outcomes Research Study (ANCHOR Study): a Randomized Study to Prevent Anal Cancer among Persons Living with HIV

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests

Supplementary data

Supplementary material

Abstract

It is well established that persons living with HIV (PLWH) have highly elevated rates of anal HSIL and anal cancer compared with those who are not living with HIV. The 5-year risk of anal cancer following anal HSIL has been reported to be as high as 14.1% among PLWH compared with 3.2% among those who are not living with HIV.

To address these concerns, the AIDS Malignancy Consortium has completed a large-scale, randomized trial to compare strategies for the prevention of anal cancer among PLWH with anal HSIL. The objective of the study was to determine whether treating anal HSIL is effective in reducing the incidence of anal cancer in PLWH compared with active monitoring. This paper describes the design of the Anal Cancer/HSIL Outcomes Research Study (ANCHOR) with respect to estimating the anal cancer event rate in this high risk population.

Keywords

anal cancer prevention; persons living with HIV; clinical trial design

Introduction

The incidence of anal cancer in the United States (per 100,000) from 2011–2015 was 1.56 and was slightly higher for women (1.93) than for men (1.15)[1]. PLWH have highly elevated rates of anal HSIL and anal cancer compared with those who are HIV-negative[2–12] where HSIL is defined as anal intraepithelial neoplasia grade 2 with positive p16 immunostaining or AIN grade 3[13]. The 5-year risk of progression to anal cancer following HSIL has been reported to be as high as 14.1% among PLWH compared with 3.2% among those who are not living with HIV[14].

Anal cancer shares many biological similarities with cervical cancer, including a causal association with human papillomavirus (HPV)[15]. Cervical cancer is preceded by a precancerous lesion, known as high-grade squamous intraepithelial lesion (HSIL). Likewise, anal cancer has been shown to be preceded by anal HSIL[16].

Treatment of cervical HSIL has proven to be a highly successful approach to reducing the incidence of and mortality from cervical cancer[17–19]. Women at risk of having cervical HSIL are identified through screening with cervical cytology and/or HPV testing, with referral for colposcopy depending on the guidelines being followed. At colposcopy, women undergo biopsy of visible lesions with treatment of biopsy-proven HSIL to reduce the risk of progression to cervical cancer. Given the similarity between cervical and anal cancer and their HSIL precursor, treatment of anal HSIL may likewise reduce the incidence of anal cancer. A primary prevention paradigm for anal cancer could include a screening test to identify individuals at high risk of anal cancer such as anal cytology, followed by the equivalent of colposcopy, a technique known as high resolution anoscopy (HRA), and HRA-guided biopsy to identify HSIL and rule out prevalent anal cancer. Areas shown to contain HSIL would be treated using a variety of targeted tissue destruction options, and the patient would be followed over time to determine if there is recurrence of the lesion, development of new lesions (metachronous disease) or progression to cancer.

To date, there are no prospective, randomized controlled trials that demonstrate the efficacy of treating anal HSIL to reduce progression to anal cancer, nor have risk factors for progression been identified. The absence of these data has been one of the main barriers to the formulation and implementation of standard of care anal screening and treatment guidelines for those at highest risk of anal cancer. While some professional entities have recommended anal screening in high risk individuals despite this lack of evidence, such as the New York State Department of Health[20] and the International Anal Neoplasia Society[21], there are no official guidelines recommending anal cancer prevention programs as standard of care. The lack of standard of care guidelines has had a negative impact on the availability of these programs, and most individuals with anal HSIL do not have access to these procedures.

To address these concerns, the AIDS Malignancy Consortium (AMC) conducted a large-scale, multi-center, randomized controlled trial to compare two strategies for the prevention of anal cancer among PLWH with anal HSIL. The objective of the study was to determine whether treating HSIL is efficacious in reducing the incidence of anal cancer in PLWH compared with active monitoring. This paper describes the design of this protocol, the Anal Cancer/HSIL Outcomes Research Study (ANCHOR Study; clinicaltrials.gov registration number NCT02135419).

Material and Methods

Inclusion/Exclusion Criteria:

To be eligible for the study, participants were required to be PLWH 35 years of age or older, have anal HSIL (defined as morphologic interpretation of AIN2 with positive p16 immunohistochemistry [IHC], or AIN3)[13] at baseline based on local pathologic interpretation of a biopsy guided by high resolution anoscopy (HRA), excellent performance status (ECOG performance status ≤ 1 or Karnofsky performance status ≥ 70% which means that the participant was able to perform normal activities or, if symptomatic, was ambulatory and able to carry out work of a light or sedentary nature), life expectancy of greater than 5 years, must have met the following hematologic laboratory criteria within 90 days prior to enrollment: absolute neutrophil count ≥ 750/mm^3, platelet count ≥ 75,000/mm^3, and hemoglobin level ≥ 9.0 g/dL and provide informed consent.

Individuals were ineligible for the trial if they had recently received any chronic systemic immunomodulatory agents; had received investigational agents within the 4 weeks before randomization, other than investigational antiretroviral agents for HIV or investigational or approved agents for Hepatitis C; had a history of anal, penile, vulvar, vaginal, or cervical cancer, or signs of any of these malignancies at baseline; were treated for anal HSIL less than 6 months prior to randomization, had symptoms related to HSIL that would benefit from immediate treatment; or were receiving treatment for other conditions with systemic chemotherapy or radiation therapy that could potentially cause bone marrow suppression.

The rationale for the age criteria was that younger individuals have a lower risk of anal cancer and including them would require a much larger sample size. The cut-off levels for hematologic function were based on minimizing the risk of bacterial abscess or

infection or bleeding. The performance status criteria was included due to concerns that those with a lower performance status level would have a higher all-cause mortality rate and be less likely to be able to be followed for 5 years. The Lower Anogenital Tract (LAST) terminology of the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology was used to classify HSIL[13]. A detailed list of exclusion criteria and guidance for women of childbearing potential and men who wished to father children is provided in the supplementary methods.

Interventions:

There were two intervention strategies: active monitoring and treatment. As there are no data that support treating HSIL to prevent progression to anal cancer, active monitoring was selected as the comparator for this study. Participants randomized to the active monitoring arm did not receive treatment for their anal HSIL lesions. They were observed with anal cytology and HRA-guided biopsies in accordance with the follow-up schedule described below. Participants randomized to the treatment arm received treatment for their anal HSIL using one of the study-designated treatments: participant-applied topical imiquimod cream, participant-applied 5-fluorouracil cream, ablation with hyfrecation, infrared coagulation or laser, or surgical excision. Treatments were to continue through the course of study to remove anal HSIL as detected during follow-up. Selected treatments were those for which there were the most data on efficacy in clearing HSIL and safety[22–25]. We sought to provide clinicians with at least one provider-applied therapy and one patient-applied topical therapy. The medical devices permitted for treatment procedures were to be used within their labeled indications for use in the destruction of tissue and/or the treatment of lesions caused by HPV (genital condyloma), and were granted an exemption from the requirement for an Investigational Device Exemption (IDE) by the U.S. Food and Drug Administration; an IND exemption was granted for use of the topical treatments. The choice of treatment was at the discretion of the clinician, usually in consultation with the participant, and once the choice was made, the clinician was required to follow the protocol-defined regimen for that treatment (details are provided in the supplemental methods)

Follow-up schedule:

Participants in both arms were examined by HRA every 6 months. Biopsies of areas of suspected HSIL were obtained every year among those in the active monitoring arm to confirm the absence of anal cancer, and every 6 months in the treatment arm to confirm the presence of anal HSIL that might require additional treatment. Clinicians had the discretion to follow participants as often as every 3 months and were required to biopsy any lesion in any participant if there was suspicion of cancer.

Outcome Determination:

A diagnosis of anal cancer by the local site pathologist led to immediate referral for treatment. A diagnosis of “suspicious for invasion” or “cannot rule out invasion” required a repeat biopsy. The determination of whether a case met the definition of anal cancer was made by the ANCHOR Central Pathology group and the protocol Quality Assurance Committee based on clinico-pathological characteristics and the protocol definition of a qualifying cancer case (see supplementary methods).

Randomization, Stratification and Masking:

Participant randomization was stratified by study site, nadir CD4 count (less than or equal to 200 cells/mm^3, greater than 200 cells/mm^3), and lesion size at baseline (greater than 50%, less than or equal to 50% of anal canal/perianal region). Participants were randomized 1:1 to active monitoring or treatment using a permuted random block design. Masking participants and study staff with respect to assignment to active monitoring or treatment was not feasible due to the nature of the study procedures.

Sample Size and Statistical Analysis:

For this study, we assumed an incidence rate of anal cancer of 100/100,000 among all PLWH, which by definition includes those with and without prevalent anal HSIL. We assumed that the obligate anal cancer precursor was HSIL, and that all cases of cancer developed from HSIL. If half of the population developed HSIL, then the incidence of cancer among those with HSIL was expected to be 200/100,000. Of note, in their meta-analysis, Machalek et al. estimated that 1/377 HIV-infected MSM progress from anal HSIL to anal cancer each year[26]. This is equivalent to 265/100,000 per year. All participants must have had biopsy-proven HSIL to be enrolled in the ANCHOR study and, thus, we estimated that an incidence of 200/100,000 among study participants in the active monitoring arm was conservative to perform an intent-to-treat analysis of our primary objective. The ITT analysis included all randomized study participants, including those who failed treatment of anal HSIL in the treatment arm, and those who developed new (metachronous) lesions, which may or may not have been fully treated by the end of study follow-up.

Sample size estimates were based on using a log-rank test to compare the treatment and active monitoring arms under the following assumptions: three-year accrual period, five years of follow-up, 5% annual drop-out rate for both arms, and 7% annual drop-in rate for the active monitoring arm[27,28]. Drop-ins were participants in the active monitoring arm who receive treatment for HSIL any time after randomization. Drop-outs were study participants in either arm who withdrew informed consent or who died during the study. For both drop-ins and drop-outs, observation time was censored at the time of drop-in or drop-out. The annual incidence rates of anal cancer were assumed to be constant over time. Detection of a difference between an annual incidence of anal cancer of 0.2% (200/100,000) in the active monitoring arm and 0.05% in the treatment arm (75% reduction in the treatment arm) at the two-sided 0.05 significance level with power of 0.90 required 2,529 study participants per arm for a total of 5,058 study participants. Under these assumptions, the expected number of events was 7.0 and 23.7 in the treatment and active monitoring arms, respectively.

If the study enrolled 2,529 in each arm (5,058 total), power was estimated for three levels of drop-in from the active monitoring arm, and 3 levels of drop-in rates from the active monitoring arm to the treatment arm. Power estimates ranged from a low of 58.3% with drop-in and drop-out rates of 20% and 15%, respectively, to a high of 90% with drop-in and drop-out rates of 7% and 5%, respectively.

In planning the study, we expected that 87.5% of the study population would be men and 12.5% would be women, based on the projected prevalence of anal HSIL[29–33]. Assuming

that 40% and 10% of screened men and women, respectively, enrolled in the study, the study needed to screen 11,065 men and 6,320 women for a total of 17,385 screenees.

Interim analyses:

Two interim analyses of the primary efficacy outcome were planned to assess the futility of achieving a significant result if the study continued and to potentially demonstrate efficacy before all participants are enrolled. The Lan and DeMets spending function was used to specify the O'Brien-Fleming boundaries based on a one-sided log-rank test 0.025[34]. At the final test, an overall two-sided alpha level of 0.05 (which corresponds to a one-sided 0.025 alpha level) and 90% power was maintained. Interim analyses for superiority and futility were planned after 50% and 75% of the projected cancer cases were observed, and presented to the Data Safety and Monitoring Board (DSMB). Consideration was given to halting the study if the futility or efficacy boundary was crossed during the interim analysis. The total number of anal cancer cases expected over the course of the study was 30.7. Interim analyses were conducted after 16 and 24 cases were cumulatively detected.

An independent DSMB was appointed by the National Cancer Institute to monitor the study. The DSMB met annually to review study progress including enrollment rates, safety, drop-in rates, and retention (drop-out rates), and to review the interim efficacy and futility analyses.

Statistical Analysis Plans:

The primary analysis population for this study is the intent-to-treat population, which includes all randomized study participants. Since the study compares two strategies for cancer prevention, rather than defined interventions, a per-protocol population could not be defined so a per-protocol analysis was not planned. For each study participant, time to anal cancer was defined as the time from randomization to diagnosis of anal cancer, and censored at the date of last follow-up. The log-rank test was used to compare the treatment and control arms with respect to time to detection of anal cancer. For each arm, the hazard rate and its 95% confidence interval were estimated.

Adverse events were summarized at the event level and at the participant level by type of adverse event and severity grade for each of the treatments (infrared coagulation, laser, electrocautery, imiquimod, and 5- fluorouracil treatments), for the treatment arm as a whole and for the active monitoring arm over the course of study participation. For adverse events that occurred in more than 5% of any of the treatments, the plan is for Poisson rates to be used to estimate the number of adverse events per unit time. The binomial proportion and its 95% confidence interval are planned to estimate the proportion of participants who reported the event.

Site Selection Criteria:

Sites were selected for participation in the ANCHOR Study based on a number of criteria. The primary criterion was that each site had access to a population of PLWH large enough to allow the site to meet its screening and recruitment goals. Sites were required to have a minimum of 2 clinicians certified by the ANCHOR Quality Assurance Committee to be competent in performing HRA and at least one clinician certified in treating HRA

lesions using at least one ablation method; sites were required to have a plan to complete certification for 3 clinicians in both procedures following protocol activation. Sites were also required to have all of the necessary infrastructure to meet all of the clinical, administrative and regulatory requirements. Clinics in the same locality were permitted to collaborate to meet the site selection criteria for target enrollment and number of clinicians trained in HRA and treatment procedures. Access to populations with specific demographic characteristics were considered to maximize the diversity of the study population. Twenty-five sites participated in the study.

Recruitment Strategies: This study employed numerous approaches to the recruitment of study participants: referrals from health care providers; referrals from family and friends; promotion of the study through collaborations with HIV service organizations and case workers; promotion at community centers and at events frequented by PLWH; advertising in multiple media types; use of a study-specific website, and advertising on websites that are frequently accessed by men who have sex with men. The goal was to enroll participants in proportions reflecting the demographics of PLWH in the U.S. Sites had the option to tailor recruitment strategies for their site. The study also formed a National Community Advisory Board (CAB), comprised of volunteer representations from each participating site, to provide input on the protocol and participant-facing materials and to offer feedback on national and local recruitment and retention approaches. To enhance recruitment of women, the study reached out to national studies of women living with HIV such as the Women's Interagency HIV Study (WIHS). The sites reached out to groups and centers known to focus on women living with HIV and encouraged women participants to tell family and friends about the study. Word-of-mouth was a successful approach to recruiting study participants[35].

Discussion

The ANCHOR study was designed to determine whether treating HSIL is effective in reducing the incidence of anal cancer in PLWH compared with active monitoring. The ethics of following anal HSIL without treatment were strongly considered in the design of the study, including the frequency of cytology and biopsy procedures to monitor closely for signs of potential progression, and the protocol was reviewed and approved by the institutional review boards at 25 clinical centers. Following anal HSIL without treatment in the active monitoring arm was deemed acceptable because of the absence of data on the efficacy of treating anal HSIL to prevent progression to anal cancer, because the main goal of the study was to generate these data; and because the clinical observation standard employed for the active monitoring arm was greater than the standard most commonly available through routine clinical care.

The ANCHOR study was closed in September 2021 following release of the results of the targeted number of cancer cases to the DSMB, and treatment was shown to have a beneficial effect in reducing the progression from anal HSIL to anal cancer. This is an important step toward implementation of treatment of anal HSIL as standard of care for PLWH with anal HSIL.

In designing the ANCHOR study, finding estimates of the anal cancer incidence rate was challenging. While most of the studies cited showed the anal cancer incidence rate for PLWH or HIV-negative individuals, there are few published data on the anal cancer incidence rate among persons with HSIL, a group known to be at enhanced risk. The ANCHOR study took a conservative approach in estimation of the sample size to ensure that the study was adequately powered to detect a difference between the treatment and active monitoring arms. Studies to determine the efficacy of treating HSIL at any location, including the cervix, to prevent progression to cancer are very challenging to perform. Cervical cytology screening with treatment of cervical HSIL was adopted as standard of care in the absence of rigorous evidence of efficacy, and efficacy was only demonstrated through observation of declining cervical cancer incidence in regions that had adopted screening[17–19]. Randomized controlled trials to rigorously demonstrate efficacy would not be currently possible because treatment of cervical HSIL once identified is the global standard of care. High rates of progression of untreated cervical HSIL to cervical cancer have been reported, but research approaches that would involve following the those with HSIL without treatment, particularly in the absence of acceptable informed consent, have been widely criticized as being unethical[36,37].

Similar to other cancer prevention trials that evaluated dietary supplements, surgical or medical interventions, the ANCHOR study used a time-to-cancer diagnosis endpoint[38–41]. Studies that evaluated interventions to reduce cancer incidence in individuals at high risk for cancer used this endpoint[42,43]. In the Minnesota Colon Cancer Control Study, the beneficial effects of polypectomy among those with colon polyps were evaluated by assessing the time to colorectal cancer incidence[42]. Similarly, in a study of male smokers, beta carotene and vitamin E, alone or in combination, were not found to reduce the time to lung cancer diagnosis against a control group[43]. The prostate cancer prevention trial (PCPT) that compared finasteride, a 5-alpha reductase inhibitor, to placebo, used a constant hazard rate similar to the one used in ANCHOR[38]. The SELECT trial which used a 2 × 2 design to evaluate selenium and vitamin D, alone and in combination, against placebo, split the follow-up duration into two segments with differing hazard rates for each segment[39,40]. The SELECT trial had the benefit of the results from the PCPT trial, which used the PCPT event rate for the first time segment (through year 3) and the prostate cancer rate from the Surveillance Epidemiology and End Results (SEER) Program of the National Cancer Institute. The expectation was that the initial prostate cancer incidence rate would be lower in the initial period due to PSA lead-time bias. The Vitamin D and Omega-3 Trial (VITAL) used a 2 × 2 factorial design similar to that used in SELECT to evaluate these dietary supplements alone or in combination to prevent cancer and cardiovascular disease[41,44,45]. For the cancer endpoint, the study targeted a rate ratio of 0.85 using a constant cancer event rate based on prior studies[41]. All of these cancer prevention studies were designed to evaluate the role of specific agents, in contrast to ANCHOR, which is intended to evaluate the strategy of treating HSIL lesions over time compared to active monitoring. Although the study of tamoxifen to prevent breast cancer compared incidence rates of cancer as opposed to using a time-to-event outcome measure, it also assumed a constant incidence rate of cancer[46,47].

Although the PCPT trial was double-blinded, the study design factored in the potential for 5% of study participants assigned to the placebo arm to drop-in to the finasteride arm by receiving finasteride outside of the study[48]. The study team measured the level of 5α-dihydrotestosterone annually in a subset of participants to determine the drop-in rate[49 49]. The SELECT trial projected that 10% of placebo participants would drop-in to another dietary supplement[39]. ANCHOR's projected drop-in rate of 7% is between those for SELECT and PCPT. Loss to follow-up rates or drop-out rates for PCPT and SELECT were estimated at 15%[48] and 0.5% per year[50], respectively. The ANCHOR drop-out rate of 5% annually is between those rates.

One of the features of the PCPT study was that all participants underwent a prostate biopsy at the conclusion of the study to confirm disease status. It has been suggested that the final biopsy, which was not driven by clinical symptomology, may have overestimated the prostate cancer incidence rate[48,51]. Similarly, it is unclear whether, in the ANCHOR study, the practice of conducting a HRA every six months might increase the anal cancer incidence in both arms since the examination frequency may exceed that commonly used in the community.

There are some limitations to the ANCHOR study. We selected sites based on their ability to recruit a sufficient number of study participants and to represent the diverse PLWH with anal HSIL. Thus, the final study population may not wholly reflect the PLWH with anal HSIL in the U.S. Another limitation is that the study required that participating clinicians were required to demonstrate a high skill level in performing high resolution anoscopy, biopsy and anal HSIL treatment. The use of high resolution anoscopy was required in this study. Thus, the outcomes achieved in the study might not be achieved with clinicians with less training and clinical support, and without the availability of high resolution anoscopy.

Conclusions

In summary, the ANCHOR study is the first prospective randomized controlled trial to be performed to determine the efficacy of treating anal HSIL to reduce the incidence of anal cancer. If the study shows efficacy in reducing the incidence of anal cancer, and other factors such as cost-benefit analyses are favorable, it is expected that anal screening will become standard of care not only for PLWH but for all populations at increased risk of anal cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

ANCHOR National Coordinating Center: Joel Palefsky (principal investigator), Abigail Arons (national coordinator); **ANCHOR Operations and Data Management Center (ODMC)**: Donald Vena (principal investigator), Julia Pugliese (ODMC coordinator); **ANCHOR Statistical Center**: Jeannette Y. Lee (principal investigator), Shelly Lensing (statistician). **ANCHOR Clinical Sites** (in alphabetical order): *Anal Dysplasia Clinic Midwest*: Gary Bucher (principal investigator), Karen Rottler (sub-investigator); *Boston Medical Center*: Elizabeth Stier (principal investigator), Irene Owusu Pokuaa (study coordinator); *Capital Digestive Care*: Jessica Korman (principal investigator); Shamekia Murray (study coordinator); *DAP Health*: Anthony Velasco (sub-investigator); *Denver Public Health*: Edward Gardner (principal investigator), Jeffrey Logan (sub-investigator); *Dupont Circle*

Physicians Group: Ben Stearn (principal investigator), Joel Bromwell (study coordinator); *Emory University*: Lisa Flowers (principal investigator), Rachel Farah-Abraham (study coordinator); *Harborview Medical Center*: Jeffrey Schouten (sub-investigator); *Laser Surgery Care Center*: Stephen E. Goldstone (principal investigator), Jonathan Baker (sub-investigator); *Louisiana State University*: Michael Hagensee (principal investigator), Amber Trauth (study coordinator); *Montefiore Medical Center*: Rebecca Levine (principal investigator), Renee Huang (sub-investigator); *Rutgers University New Jersey Medical School*: Mark Einstein (principal investigator), Bernadette Cracchiolo (sub-investigator); *University of California Los Angeles*: Ronald Mitsuyasu (principal investigator), Nikkole Valdez (study coordinator); *University of California San Francisco*: Christina Brickman (principal investigator), Arezou Sadighi Akha (study coordinator); *University of Colorado Denver*: Hillary Dunlevy (principal investigator) Christine Conageski (sub-investigator); University of Miami: Isabella Rosa-Cunha (principal investigator), JoNell Potter (sub-investigator); *University of Puerto Rico*: Maribel Tirado (principal investigator), Christina C Munoz Masso (study coordinator); *Virginia Mason Medical Center*: David Aboulafia (principal investigator), Jeffrey Schouten (sub-investigator); *Wake Forest Baptist Health*: Luis F. Barroso (principal investigator), Elizabeth Zieser-Misenheimer (study coordinator); *Weill Cornell Medical*: Timothy Wilkin (principal investigator), Christina Megill (study coordinator).

Funding

This work was supported by the National Cancer Institute of the National Institutes of Health (grant number UM1CA121947).

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