Treating Anal Cancer
Precursor Lesions

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Faculty Disclosure

- Vir Biotechnology, Virion Therapeutics, Antiva Biosciences - consultant
- Merck - advisory board member - speaker
Objectives

Upon completion of this educational activity, you will be able to:

1. Describe the epidemiology of anal cancer in people living with HIV
2. Describe the results the findings of the ANCHOR study
3. Describe the implications of the ANCHOR study for clinical practice
Figure 4. Estimated cancer burden (incident cancer diagnoses) among adults living with HIV in the United States, by cancer type, in 2010, 2020, and 2030.


Age-Adjusted Incidence of Invasive Anal Cancer by Gender and Year of Diagnosis: United States

Anal cancer incidence compared to other HPV-associated cancers (US women)

Deshmukh et al. JNCI. 2021
The cervical model

- Anal and anal cancer are very similar diseases
- Cervical cancer and anal cancer are preceded by high grade squamous intraepithelial lesions (HSIL)
The cervical model of cancer prevention

- Treatment of cervical HSIL is proven to reduce the incidence of cervical cancer
- Why do we not routinely screen for and treat anal HSIL?
- Lack of evidence that it will work
Why anal screening and treatment of HSIL might not work

- In many at-risk people lesions are large and multifocal
- Clinicians may miss lesions
- Clinicians may inadequately treat lesions
- New lesions often arise - anal whack-a-mole!
Why try to prevent anal cancer?

- About 50% in the general population present with localized disease, with relatively high survival rate

<table>
<thead>
<tr>
<th>SEER stage</th>
<th>5-year relative survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>82%</td>
</tr>
<tr>
<td>Regional</td>
<td>66%</td>
</tr>
<tr>
<td>Distant</td>
<td>34%</td>
</tr>
<tr>
<td>All SEER stages combined</td>
<td>69%</td>
</tr>
</tbody>
</table>

Why try to prevent anal cancer?

- Survival rate is lower for more advanced disease
- Among those who do survive, there is substantial morbidity associated with standard treatment, primarily due to radiation therapy
The ANCHOR Investigators Group
Protocol A01 of the AIDS Malignancy Consortium
UM1CA121947
Aim 1: To determine whether treating anal high-grade squamous intraepithelial lesions (HSIL) is effective in reducing the incidence of anal cancer in PLWH

Aim 2: To determine the safety of treatment for anal HSIL
- **Aim 3:** To develop and implement an instrument to measure the impact of ANCHOR procedures on QoL (ANCHOR Health-Related Symptom Index (A-HRSI))

- **Aim 4:** Collect clinical specimens and data to create a bank of well-annotated specimens that will enable correlative science:
  - Identify host and viral factors in HSIL progression to cancer
  - Identify host and viral biomarkers of progression from HSIL to cancer
Study schema

PLWH ≥35 years old
Screened for anal HSIL

- HSIL not found
- HSIL found
- Cancer found

Not enrolled
Enrolled and randomized

Active monitoring arm
Treatment arm

- No cancer found
- Cancer found
- Cancer found
- No cancer found

Exit study
Refer for evaluation and treatment

Enroll 5,058
Methods

• Powered to detect difference between 50/100,000 PY in the treatment arm and 200/100,000 PY in the AM arm at the two-sided 0.05 significance level with power of 0.90
• Event-driven analysis, primary outcome= time-to-cancer
• N=2,529 per arm (total 5,058) to detect 31 anal cancers
Treatment arm

• Treated immediately- hyfrecation, IRC, 5-FU, imiquimod

Figure 4-B: IRC, hyfrecation, or electrocautery performed at visit 1 (randomization visit)

- No lesion seen → Visit 2 (6 months) → Lesion(s) seen and biopsied → No HSIL on biopsy → Re-treat within 8 weeks
- No lesion seen → Next 6-month visit → Lesion(s) seen and biopsied → No HSIL on biopsy → Initiate alternative therapy if there is poor participant tolerability or clinician decides to initiate alternate therapy
- If no lesions are seen, participant will return for HRA at the next 6 month visit. If HSIL is found, alternative treatment is initiated per guidelines.
Treatment arm

- Followed according to treatment algorithm
- Biopsied if suspicion for HSIL
- Anal cytology, swabs, HRA, blood every 6 months after HSIL cleared
- Every 3 months if concern for cancer
- Biopsied at any visit if concern for cancer
Active monitoring arm

- Anal cytology, swabs, HRA, blood every 6 months
- Biopsied annually to confirm persistent HSIL
- Every 3 months if concern for cancer
- Biopsied at any visit if concern for cancer
Screening

- 10,723 PLWH from 9/24/2014 to 8/5/2021
  - 53.3% of men
  - 47.2% of women
  - 67.1% of transgender individuals
- 17 individuals (0.16%, 160/100,000) were diagnosed with anal cancer
Demographics of randomized population (1)

<table>
<thead>
<tr>
<th></th>
<th>Randomized population N=4,446</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment arm</td>
<td>Active monitoring arm</td>
</tr>
<tr>
<td>N</td>
<td>2,227</td>
<td>2,219</td>
</tr>
<tr>
<td><strong>Median age at randomization (years, IQR)</strong></td>
<td>51.0 (44.0-57.0)</td>
<td>51.0 (44.0-57.0)</td>
</tr>
<tr>
<td><strong>Median years at randomization since HIV diagnosis (years, IQR)</strong></td>
<td>17.0 (10.0-24.0)</td>
<td>17.0 (10.0-25.0)</td>
</tr>
<tr>
<td><strong>Months of follow-up (median, IQR)</strong></td>
<td>25.3 (11.7 – 42.0)</td>
<td>27.2 (12.0 – 42.1)</td>
</tr>
<tr>
<td><strong>Gender identity N (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1793 (80.5)</td>
<td>1782 (80.3)</td>
</tr>
<tr>
<td>Female</td>
<td>346 (15.5)</td>
<td>365 (16.5)</td>
</tr>
<tr>
<td>Transgender</td>
<td>85 (3.8)</td>
<td>68 (3.1)</td>
</tr>
<tr>
<td>Neither male nor female</td>
<td>2 (0.1)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Decline to answer</td>
<td>1 (0.0)</td>
<td>2 (0.1)</td>
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## Demographics of randomized population (2)

<table>
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</tr>
<tr>
<td></td>
<td>N=2,227</td>
<td>N= 2,219</td>
</tr>
<tr>
<td><strong>Race/ethnicity N (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>695 (31.2)</td>
<td>737 (33.2)</td>
</tr>
<tr>
<td>African-American</td>
<td>935 (42.0)</td>
<td>939 (42.3)</td>
</tr>
<tr>
<td>Hispanic, non-African-American</td>
<td>381 (17.1)</td>
<td>339 (15.3)</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>27 (1.2)</td>
<td>29 (1.3)</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>189 (8.5)</td>
<td>175 (7.9)</td>
</tr>
<tr>
<td><strong>CDC HIV risk group N (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homosexual</td>
<td>1738 (78.0)</td>
<td>1742 (78.5)</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>532 (23.9)</td>
<td>510 (23.0)</td>
</tr>
<tr>
<td>Injection drug use</td>
<td>152 (6.8)</td>
<td>177 (8.0)</td>
</tr>
<tr>
<td>Transfusion</td>
<td>53 (2.4)</td>
<td>47 (2.1)</td>
</tr>
<tr>
<td>Hemophilia</td>
<td>2 (0.1)</td>
<td>4 (0.2)</td>
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<tr>
<td>Other high-risk group</td>
<td>34 (1.5)</td>
<td>27 (1.2)</td>
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Demographics of randomized population (3)

<table>
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<tr>
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<th>Randomized population N=4,446</th>
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<tr>
<td></td>
<td>Treatment arm</td>
<td>Active monitoring arm</td>
</tr>
<tr>
<td>N=2,227</td>
<td>N= 2,219</td>
<td></td>
</tr>
<tr>
<td>Current smoker N (%)</td>
<td>710 (31.9)</td>
<td>743 (33.5)</td>
</tr>
<tr>
<td>Plasma HIV-1 RNA copies/mL at randomization N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>1852 (83.7)</td>
<td>1800 (81.8)</td>
</tr>
<tr>
<td>51-199</td>
<td>155 (7.0)</td>
<td>160 (7.3)</td>
</tr>
<tr>
<td>200-1000</td>
<td>83 (3.8)</td>
<td>93 (4.2)</td>
</tr>
<tr>
<td>&gt;1000</td>
<td>122 (5.5)</td>
<td>148 (6.7)</td>
</tr>
<tr>
<td>CD4 cells/uL at randomization (median, IQR)</td>
<td>602 (393-827)</td>
<td>607 (410-837)</td>
</tr>
</tbody>
</table>
### Demographics of randomized population (4)

<table>
<thead>
<tr>
<th>Stratification factors at randomization N (%)</th>
<th>Randomized population N=4,446</th>
<th>P value¹</th>
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</thead>
<tbody>
<tr>
<td>Treatment arm</td>
<td>N=2,227</td>
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<td>Treatment arm</td>
<td>Active monitoring arm</td>
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<tr>
<td>N=2,219</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Nadir CD4 cells/µL

- \( \leq 200 \text{ cells/µL} \)
  - 1130 (50.7)
  - 1121 (50.5)
- >200 cells/µL
  - 1097 (49.3)
  - 1098 (49.5)

#### HSIL size at screening

- >50% of anal canal/perianal region
  - 285 (12.8)
  - 282 (12.7)
- \( \leq 50\% \) of anal canal/perianal region
  - 1942 (87.2)
  - 1937 (87.3)

² Chi-square test
Results

- For the participants in the treatment arm, initial treatment:
  - Office-based electrocautery ablation (92.9%)
  - Infrared coagulation (5.6%)
  - TUA (4.6%)
  - Topical 5-fluorouracil cream (7%)
  - Topical imiquimod (1.2%)

- Over the course of the study:
  - 1921 (86.0%) with therapeutic modality
  - 233 (10.4%) with two modalities
  - 33 (1.5%) with three modalities
  - 1 (<0.1%) with four modalities
Results

- DSMB notified when 32 cancers diagnosed
  - final analysis based on 30 cases
- 9 participants were diagnosed with invasive anal cancer in the treatment arm and 21 in the AM arm
- Median follow-up of 25.8 months, 57% reduction in anal cancer (95% CI 6% to 80%, chi-squared = 4.74, P=.029)
- Cancer incidence in the treatment arm was 173/100,000 PY of follow-up, compared with 402/100,000 PY in the AM arm
Kaplan-Meier curve of time-to-confirmed cancer cases

Log-rank test p=0.029

Cumulative % Risk of Anal Cancer

Months

<table>
<thead>
<tr>
<th>Arm</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM</td>
<td>2219</td>
<td>1856</td>
<td>1671</td>
<td>1459</td>
<td>1230</td>
<td>992</td>
<td>758</td>
<td>572</td>
<td>407</td>
</tr>
<tr>
<td>Treatment</td>
<td>2227</td>
<td>1871</td>
<td>1655</td>
<td>1473</td>
<td>1224</td>
<td>989</td>
<td>753</td>
<td>557</td>
<td>409</td>
</tr>
</tbody>
</table>

AETC Southeast
AIDS Education & Training Center Program
Results

- DSMB recommended stopping the study for efficacy
- Recommendation made to treat all individuals in the monitoring arm
- We will continue to follow all individuals who wish to be treated and/or followed
Case history

• 73 year old male living with HIV
• CD4 nadir <200, current CD4 504, VL ND, no OIs
Case history

• 37 yo male
• Nadir CD4 54, current CD4 429; VL ND
• H/O intra anal condyloma in 2014 treated with laser
Screening 11/17   Visit 4 06/19
<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Treatment arm</th>
<th>Active monitoring arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events (N)</td>
<td>683</td>
<td>635</td>
</tr>
<tr>
<td>Deaths</td>
<td>54</td>
<td>48</td>
</tr>
<tr>
<td>Serious adverse events (N)</td>
<td>586</td>
<td>568</td>
</tr>
<tr>
<td>Study-related adverse events (N)</td>
<td>43</td>
<td>4</td>
</tr>
<tr>
<td>Study-related serious adverse events (N)</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Skin ulceration due to 5-fluorouracil</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Anal abscess due to electrocautery</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pain due to electrocautery</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pain due to treatment under anesthesia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pain due to infrared coagulation</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Infection or abscess due to anal biopsy</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
Implications of the study findings

- Treatment of anal HSIL is effective in reducing the incidence of anal cancer
- These data should be included in an overall assessment for inclusion of screening for and treating anal HSIL as standard of care
Implications of the study findings

- There is room for improvement in treatment of anal HSIL
- There is a need for biomarkers for HSIL progression or regression
Implications of the study findings

• There is a need for optimization of screening algorithms for HSIL
• There is a need for a large scale-up of HRA training programs
• Extrapolation of our results to other groups at high risk of anal cancer
What to do in the short term

- DARE on all PLWH annually
- Screen PLWH over 35 years IF you do HRA and treatment or you can refer to someone trained in HRA and treatment
How to screen (for now)

- Refer PLWH directly for HRA starting with:
  - symptomatic patients
  - the oldest patients
- Screen younger PLWH (under 50 years old) with cytology
  - Refer HSIL>ASC-H>LSIL>ASC-US
How to treat

- Office-based hyfrecation for amenable lesions
- Referral to surgery for disease too bulky to treat in office
- Treat with 5-fluoro-uracil cream to de-bulk
With deep gratitude to:

- ANCHOR Investigators Group and the study staffs at all of the ANCHOR sites
- Study participants
- ANCHOR Community Advisory Board
- AIDS Malignancy Consortium
- Emmes Corporation
- NCI/Office of HIV and AIDS Malignancies
Thank you!