Published in final edited form as:

Sex Transm Dis. 2016 July ; 43(7): 436–437. doi:10.1097/OLQ.0000000000000467.

Uncertainty Abounds in the World of Anal Dysplasia Screening

Wesley G. Willeford, MD and

Wake Forest Baptist Medical Center, Medical Center Blvd, Winston-Salem, NC 27157, Telephone: 931-397-1821, Fax: 336-716-7359

Laura H. Bachmann, MD, MPH

Wake Forest Baptist Medical Center, Medical Center Blvd, Winston-Salem, NC 27157

Wesley G. Willeford: Wgwillefor21@gmail.com

In this month's issue of *Sexually Transmitted Diseases*, McNeil *et al* discuss an innovative approach to anal dysplasia screening methodology utilizing the anal Pap smear (APS). The APS represents the first critical step in screening for squamous cell carcinoma of the anus (SCCA), a still uncommon disease process that nevertheless has steadily increased in recent decades in the United States and around the world.^{1–4} With the advent of highly active antiretroviral therapy, patients with human immunodeficiency virus (HIV) infection live longer and have higher quality lives. Concurrent with the extended lifespan of HIV-infected individuals, there have been large shifts in the incidence of SCCA in HIV-positive cohorts, likely reflecting the impact of co-infection with HIV and human papillomavirus (HPV) on the natural history of anal intraepithelial neoplasia and the subsequent development of SCCA. Amongst men who have sex with men (MSM), the incidence of anal carcinoma is approximately 35 cases per 100,000 population, which is similar to the incidence of cervical cancer before the introduction of Pap smears, and rates of anal cancer in HIV-positive MSM approach 128 cases per 100,000 population in some studies.^{5–11} These data have proven challenging to the infectious diseases community given the biological, logistical, and new provider training challenges, as outlined by Palefsky *et al*, in translating the cervical cancer screening paradigm to a newer dimension of sexual health in HIV-positive populations.¹²

At present, there are no nationally-accepted guidelines to address the question of how to best approach screening for anal cancer precursors in the HIV-positive population, and more fundamentally, it remains unclear whether or not current screening and treatment methodology impacts the future development of SCCA. Several important studies currently underway will hopefully shed light on the natural history of anal SCCA and whether or not current screening methods impact the incidence of this malignancy (ANCHOR (Anal Cancer HSIL Outcomes Research), SPANC (Study of the Prevention of Anal Cancer), *et al*).

Central to the screening process is the APS. This procedure, similar to the cervical Pap smear, often yields abnormal results, as high as 46% for HIV-infected individuals, and its

Correspondence to: Wesley G. Willeford, Wgwillefor21@gmail.com.

Conflict of Interest: Dr. Bachmann receives funding through the AIDS Malignancy Clinical Trials Consortium and from the ANCHOR Study.

Sources of Support: No sources of support to disclose.

overall performance is suboptimal.^{13,14} The work presented by McNeil *et al* in this issue demonstrates that patients find performing a self-administered APS to be both acceptable and feasible when compared to a physician-administered APS. While not fully addressed in the existing literature, we feel that many aspects of the screening and treatment of anal dysplasia are viewed as uncomfortable at best and painful at worst. By advocating for self-care and health-care ownership, where appropriate, the self-collection process could potentially seem less burdensome to the patient, and McNeil *et al*'s work is clearly a step in the right direction. However, more work is needed to thoroughly sort through the myriad issues related to anal dysplasia screening and treatment. For instance, with this propensity for high rates of abnormal APS results, many HIV-positive individuals will go on to have high resolution anoscopy (HRA) performed in order to detect mucosal abnormalities that may prove histologically to be high-grade intraepithelial lesions (HSIL). Once HSIL is identified, a variety of treatment modalities may be pursued including ablative (i.e. infrared coagulation therapy (IRC), hyfrecation/electrocautery or laser) and topical modalities (i.e. imiquimod cream or 5-fluorouracil). While each treatment has varying degrees of efficacy with regard to regression from HSIL to low SIL by histopathological analysis, each treatment modality is associated with high rates of recurrence of HSIL after treatment (ranging from 39 to 77% at various follow up intervals)—resulting in the need for frequent re-screening and treatment cycles.^{15–20} Ablative therapy is often preferred as it assures adequate delivery of treatment to the diseased area, and it is difficult to guarantee complete and adequate administration of the patient-administered intra-anal medications—a vexing issue for research into the efficacy of these drugs.

With each cycle of screening and retreatment, there exists the possibility that a patient may become overwhelmed with the often repetitive procedures, and may opt to exit the screening and treatment process altogether. It is important to keep in mind that patients who start down the path of anal dysplasia screening are being asked to endure more than a small amount of inconvenience and discomfort in the hopes of a future payoff. As a community of clinicians, scientists, and patient advocates, the inherent hope is that the interventions being delivered to our patients will spare them from having to endure SCCA and the myriad complications and toxicities associated with its treatment, but definitive data regarding the long-term efficacy of such an invasive process are sorely needed.

While we have outlined above some potential concerns and barriers associated with anal dysplasia screening, it is imperative to clearly understand the natural history of anal dysplasia so that we can construct the best methods for screening and treating our patients. There is no question that anal cancer has a substantial impact not only on mortality (relative 5-year survival ranges from 80.7% for localized disease to 30.4% for distant disease) but also on morbidity and quality of life.²¹ Attendees at the 2014 International Anal Neoplasia Society (IANS) meeting were afforded the rare opportunity of hearing stories from anal cancer survivors with particular emphasis on the numerous ill effects that they endured and continued to live with due to the treatment of SCCA. These side effects, which can vary somewhat based upon the regimen offered, may include bowel incontinence, erectile dysfunction in men (up to 100%), and radiodermatitis (~73% having moderate to severe symptoms), all of which negatively impact the lifestyle of the individual in a variety of ways.^{22–25} Simply reviewing these side effects in medical texts diminishes the suffering

endured by these patients, and while on stage, the survivors helped the attendees understand that these effects are far from trivial. The panel session provided a moment of clarity and resolution amongst the audience to approach the problem of anal dysplasia and neoplasia with renewed vigor. So while it is projected that 8080 new cases of anal cancer (0.5% of all new cancers) will be diagnosed in 2016, resulting in approximately 1080 deaths, it is clear that the impact of anal cancer not only is disproportionately distributed within the human population (with HIV-positive individuals experiencing the greatest impact), but also, that this disease continues to increase and the morbidity associated with treatment of the condition (if the anal cancer is discovered early and the patient survives) is substantial.²¹

At present, uncertainties about the long term outcomes of the current anal dysplasia screening and treatment methodology exist. The fundamental question of whether the existing process has the potential to prevent the development of SCCA remains a specter over the majority of our interventions. The ANCHOR trial, a large, multi-center study, will attempt to answer just that. Additionally, there are aspects of the very nature of HSIL of the anal canal that come into question—whether or not HSIL will uniformly progress onward to SCCA or whether it can regress without intervention. Recently, Grulich *et al* presented data at the 2014 AIDS conference suggesting clearance of HSIL is possible, but the most worrisome lesions seem to be those which remain persistent over time.²⁶ The hope is that data from ongoing and future studies will help us to understand which individuals should be aggressively screened, which HSIL should be treated, and whether or not there are individuals who do not warrant aggressive treatment. We have learned much about anal dysplasia in recent years, but many key questions remain.

References

1. Johnson LG, Madeleine MM, Newcomer LM, Schwartz SM, Daling JR. Anal cancer incidence and survival: The Surveillance, Epidemiology, and End Results experience, 1973–2000. *Cancer*. 2004; 101:281–288. [PubMed: 15241824]
2. Chiao EY, Krown SE, Stier EA, Schrag D. A population-based analysis of temporal trends in the incidence of squamous anal canal cancer in relation to the HIV epidemic. *J Acquir Immune Defic Syndr* 1999. 2005; 40:451–455.
3. Brewster DH, Bhatti LA. Increasing incidence of squamous cell carcinoma of the anus in Scotland, 1975–2002. *Br J Cancer*. 2006; 95:87–90. [PubMed: 16721368]
4. Brøndegaard Winther S, Baatrup G, Pfeiffer P, Qvortrup C. Academy of Geriatric Cancer Research (AgeCare). Trends in colorectal cancer in the elderly in Denmark, 1980–2012. *Acta Oncol Stockh Swed*. 2016; 55(Suppl 1):29–39.
5. Kreuter A, et al. Anal carcinoma in human immunodeficiency virus-positive men: results of a prospective study from Germany: Anal carcinoma in HIV-positive men. *Br J Dermatol*. 2010; 162:1269–1277. [PubMed: 20184584]
6. Crum-Cianflone NF, et al. Anal cancers among HIV-infected persons: HAART is not slowing rising incidence. *AIDS Lond Engl*. 2010; 24:535–543.
7. Amirian ES, Fickey PA, Scheurer ME, Chiao EY. Anal Cancer Incidence and Survival: Comparing the Greater San-Francisco Bay Area to Other SEER Cancer Registries. *PLoS ONE*. 2013; 8:e58919. [PubMed: 23484057]
8. Silverberg MJ, et al. Risk of Anal Cancer in HIV-Infected and HIV-Uninfected Individuals in North America. *Clin Infect Dis*. 2012; 54:1026–1034. [PubMed: 22291097]
9. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *The Lancet*. 2007; 370:59–67.

10. Shiels MS, Cole SR, Kirk GD, Poole C. A Meta-Analysis of the Incidence of Non-AIDS Cancers in HIV-Infected Individuals. *JAIDS J Acquir Immune Defic Syndr*. 2009; 52:611–622. [PubMed: 19770804]
11. Bedimo RJ, McGinnis KA, Dunlap M, Rodriguez-Barradas MC, Justice AC. Incidence of Non-AIDS-Defining Malignancies in HIV-Infected Versus Noninfected Patients in the HAART Era: Impact of Immunosuppression. *JAIDS J Acquir Immune Defic Syndr*. 2009; 52:203–208. [PubMed: 19617846]
12. Berry-Lawhorn JM, Chrobak D, Jay N, Palefsky JM. Who Is Ready to Screen for Anal Squamous Intraepithelial Lesions and Why Should They Perform High-Resolution Anoscopy? *Sex Transm Dis*. 2014; 41:254–256. [PubMed: 24622637]
13. Cranston RD, et al. The prevalence, and predictive value, of abnormal anal cytology to diagnose anal dysplasia in a population of HIV-positive men who have sex with men. *Int J STD AIDS*. 2007; 18:77–80. [PubMed: 17331275]
14. Maia LB, et al. A comparative study between conventional and liquid-based cytology in screening for anal intraepithelial lesions in HIV-positive patients. *Diagn Cytopathol*. 2014; 42:840–845. [PubMed: 24591207]
15. Darragh TM, et al. The Lower Anogenital Squamous Terminology Standardization Project for HPV-associated Lesions: Background and Consensus Recommendations From the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *Int J Gynecol Pathol*. 2013; 32:76–115. [PubMed: 23202792]
16. Fox PA, et al. A double-blind, randomized controlled trial of the use of imiquimod cream for the treatment of anal canal high-grade anal intraepithelial neoplasia in HIV-positive MSM on HAART, with long-term follow-up data including the use of open-label imiquimod. *AIDS*. 2010; 1doi: 10.1097/QAD.0b013e32833d466c
17. Goldstone SE, Johnstone AA, Moshier EL. Long-term Outcome of Ablation of Anal High-grade Squamous Intraepithelial Lesions: Recurrence and Incidence of Cancer. *Dis Colon Rectum*. 2014; 57:316–323. [PubMed: 24509453]
18. Nathan M, Hickey N, Mayuranathan L, Vowler SL, Singh N. Treatment of anal human papillomavirus-associated disease: a long term outcome study. *Int J STD AIDS*. 2008; 19:445–449. [PubMed: 18574114]
19. Pineda C, Welton M. Management of Anal Squamous Intraepithelial Lesions. *Clin Colon Rectal Surg*. 2009; 22:094–101.
20. Snyder SM, Siekas L, Aboulafia DM. Initial Experience with Topical Fluorouracil for Treatment of HIV-Associated Anal Intraepithelial Neoplasia. *J Int Assoc Physicians AIDS Care Chic Ill*. 2011; 10:83–88.
21. [Accessed: 17th April 2016] SEER Stat Fact Sheets: Anal Cancer. SEER Stat Fact Sheets: Anal Cancer. 2016. Available at: <http://seer.cancer.gov/statfacts/html/anus.html>
22. Ghosn M. Anal cancer treatment: Current status and future perspectives. *World J Gastroenterol*. 2015; 21:2294. [PubMed: 25741135]
23. Ozgen Z, et al. Long-term effects of neoadjuvant chemoradiotherapy followed by sphincter-preserving resection on anal sphincter function in relation to quality of life among locally advanced rectal cancer patients: a cross-sectional analysis. *Radiat Oncol*. 2015; 10
24. Provencher S, et al. Quality of life and tumor control after short split-course chemoradiation for anal canal carcinoma. *Radiat Oncol*. 2010; 5:1. [PubMed: 20070901]
25. Oblak I, Petric P, Anderluh F, Velenik V, Fras P. Long term outcome after combined modality treatment for anal cancer. *Radiol Oncol*. 2012; 46
26. AIDS. [Accessed: 12th April 2016] 2014 - Abstract Incidence and clearance of anal high-grade squamous intraepithelial lesions (HSIL) in HIV positive and HIV negative homosexual men. Available at: <http://pag.aids2014.org/Abstracts.aspx?SID=1141&AID=6194>