

Perspective

Human Papillomavirus–Related Malignancies in HIV Infection: Anal and Oropharyngeal Cancers

Human papillomavirus (HPV)-related cancers, including anal cancer and oropharyngeal cancer, occur more frequently in individuals living with HIV infection than in the general population. Strategies for prevention among individuals with HIV infection include HPV vaccination, anal cancer screening programs, and early initiation of antiretroviral therapy (ART). HPV vaccination is not yet optimally used; a stronger and more persistent effort is needed to increase vaccination rates. Although anal cancer screening is not recommended by all authorities, there is at least some evidence that screening and treatment of anal high-grade squamous intraepithelial lesions may prevent progression to cancer. However, more definitive evidence is needed. Early initiation of ART reduces the risk of infection-related cancers, with some evidence of benefit in preventing HPV-associated cancer in individuals with HIV infection. This article summarizes a presentation by Timothy J. Wilkin, MD, MPH, at the IAS–USA continuing education program held in Los Angeles, California in April 2018.

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Rates of anal cancer in women and men who have sex with men (MSM) with HIV infection are far higher than in the general population, and higher than current rates of cervical cancer, a human papillomavirus (HPV)-associated disease, in the general population of women in the United States (Figure 1) and globally.¹ Rates of cervical cancer in the general population have been dramatically reduced through prevention services including active screening, and more recently by HPV vaccination. HPV vaccination and screening efforts offer the best chance to reduce risk of HPV-related cancers in the population with HIV infection.

Anal Cancer

Most initial anal HPV infections are cleared by host immune responses. A subset of infection persist, sometimes leading to low-grade squamous intraepithelial lesions (LSILs). In a subset of these cases, infection continues with integration of HPV into cellular DNA and progression to high-grade squamous

intraepithelial lesions (HSILs). A subset of HSILs progress to invasive anal cancer. In individuals living with HIV infection, immunosuppression including reduced cell-mediated immunity reduces clearance of HPV and increases risk of progression to HSILs and invasive cancer.

The approaches to prevent invasive anal cancer are HPV vaccination and preventive screening. The goal of screening is to identify precancerous areas (eg, HSILs) of the anus that can be removed to prevent invasive cancer. Screening is performed via cytology (or by HPV testing, although such testing is not approved by the US Food and Drug Administration [FDA] for screening). Diagnosis of HSILs is performed with high resolution anoscopy (HRA). The procedure uses staining with acetic acid and Lugol's iodine to identify areas in which HSILs are suspected; the suspicious areas are biopsied for histologic examination. If HSILs are diagnosed, the areas are treated with ablation or

topical therapy. In some cases, early and limited invasive disease may be identified, which can be treated promptly and effectively via excision. However, the majority of anal cancers are already extensive enough at diagnosis to require treatment with chemotherapy and radiation. Such treatment is effective in most cases, but is associated with substantial morbidity. Practitioners performing HRA require formalized training, and substantial experience is needed to reliably identify HSILs for diagnosis and treatment.

MSM living with HIV infection have elevated rates of HSILs (reaching 50% in some studies) and anal cancer, and are thus candidates for screening. Other men and women with HIV infection also have elevated rates of anal cancer, indicating that they, too, are potential candidates for anal cancer screening. A study recently reported by Stier and colleagues² found an anal HSIL prevalence of 28% among women

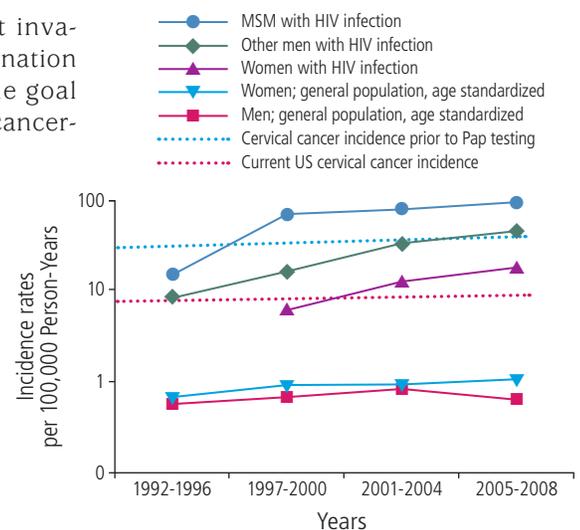


Figure 1. Incidence of anal cancer in individuals with HIV infection and the general population in the United States. Dashed horizontal lines indicate incidence of cervical cancer in the general population prior to and after introduction of Papanicolaou (Pap) testing. MSM indicates men who have sex with men. Adapted from Schim van der Loff et al.¹

Dr Wilkin is an Associate Professor of Medicine at Weill Cornell Medicine in New York, New York.

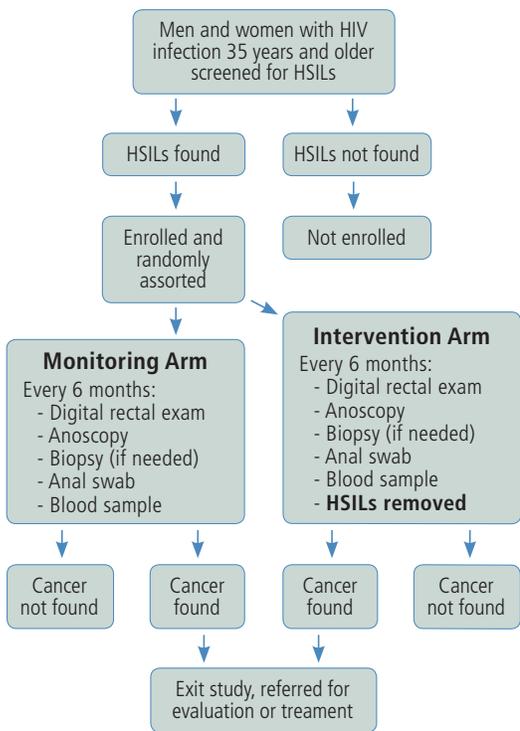


Figure 2. Design of the National Cancer Institute–sponsored ANCHOR (Anal Cancer HSIL Outcomes Research) study. HSIL indicates high-grade squamous intraepithelial lesions.²⁰

with HIV infection (77 of 253). Most of the HSILs were found in women with an abnormal anal cytology, although 22% of HSILs occurred in women with normal anal cytologic results. Such findings suggest that, similar to cervical cytology, anal cytology must be repeated in serial screenings, with repeated testing being more likely to yield an abnormal result if HSILs are present.

Another issue in cancer prevention is the success in treating HSILs, for which relatively few data are available. The recently reported AIDS Malignancy Consortium 076 trial has shown benefit of ablation of HSILs in clearing disease using infrared coagulation.³ In the trial, 120 individuals with HIV infection who had relatively limited anal HSILs were randomly assigned to infrared coagulation ablation ($n = 60$) or careful monitoring for 1 year (control group; $n = 60$). Complete response was observed in 63% of the ablation group versus 27% of the control group ($P < .001$), with complete or partial response being observed in 75% versus

43% ($P < .001$). Numerous issues in anal cancer screening remain to be confronted. One is that the large majority of people with anal HSILs will never develop anal cancer, meaning large numbers of individuals with anal HSILs must be treated to prevent a relatively few cancers, making the cost-effectiveness unclear. Further, treatments for anal HSILs are not well studied and are clearly less effective than those for cervical HSILs. Recurrent anal HSILs are the norm, with numerous treatments usually needed to clear disease. Accessing HRA and treatment for anal HSILs remains difficult, with a relative dearth of skilled HRA practitioners for patient referral. Currently, screening is not yet recommended by all organizations setting standards for health care maintenance.

Anal cancer screening is recommended in HIV Medicine Association⁴ and New York State guidelines,⁵ but is not recommended in Centers for Disease Control and Prevention (CDC) opportunistic infection guidelines.⁶ The age at which to begin screening remains unclear. Although there is a high prevalence of anal HSILs in younger individuals, a screening program should probably target patients age 35 years or older based on cost-effectiveness modeling. Many HSILs resolve without intervention, and younger patients often have more difficulty adhering to HIV medications, without adding additional complicated procedures at an age when the rate of anal cancer is so low. In addition, definitive data that treating anal HSILs reduces the risk of anal cancer are needed.

Oropharyngeal Cancer

Unlike HPV-related anal, cervical, vulvar, penile, and other cancers, HPV-related oropharyngeal cancer (OPC) does not have an identifiable premalignant lesion and there is no analogous cytologic test to aid in early identification currently recommended. It is

possible to do HPV testing, but this is not part of standard clinical practice. Currently, there are no accepted screening programs for prevention of HPV-related OPC.

Approximately 70% of OPC is caused by HPV. Of HPV-related OPC, HPV-16 is the cause in approximately 85% of cases, with the serotypes in the 9-valent HPV vaccine being accountable for 94% of HPV-related OPC.⁷ Studies using SEER (Surveillance, Epidemiology, and End Results) data from 2005 to 2008 showed that the incidence of OPC is 2- to 3-times higher in individuals living with HIV infection than in the general population, and 4-fold higher in men with HIV infection than in women with HIV infection.⁸ As of 2010, the estimated rates of OPC in men exceed rates of cervical cancer in women in the general population, with the trend projected to continue as cervical cancer rates continue to decline and OPC rates in men increase.⁹

Reducing HPV-Related Cancer in HIV

The ongoing large-scale National Cancer Institute-sponsored ANCHOR (Anal Cancer HSIL Outcomes Research) study will address whether removal of anal HSILs effectively prevents anal cancer (Figure 2). In the trial, more than 17,000 men and women living with HIV infection, age 35 years or older, are being screened for anal HSILs. Approximately 5000 individuals with anal HSILs are being randomly assigned to a monitoring arm or an intervention arm in which HSILs are treated with the best modalities available including ablative and topical treatments. Participants will be followed up for 5 to 8 years, with those in the intervention arm being treated again upon recurrence of HSILs. Enrollment in the study is open at sites across the United States including Puerto Rico, and information can be found at www.anchorstudy.org/.

With regard to prevention by vaccination, a study reported in 2011 by Palefsky and colleagues¹⁰ showed that the quadrivalent HPV vaccine was approximately 95% effective in preventing persistent anal infection in a

subgroup of approximately 600 young MSM, considered to be a relatively HPV-naïve group, with a significant reduction in anal squamous intraepithelial lesions also being observed. The outcome of the trial resulted in FDA approval of the quadrivalent vaccine for preventing anal cancer in both men and women.

Clinical studies have found that HPV vaccination is safe and highly immunogenic in adults and children living with HIV infection. The question then became whether HPV vaccine could be effective in individuals with HIV infection who are already highly exposed to HPV and have high rates of ongoing HPV infection. In the AIDS Clinical Trials Group 5298 study, individuals with HIV infection 27 years of age or older with no history of HPV-related cancers and any CD4+ cell count or plasma HIV-1 RNA level were randomly assigned to receive quadrivalent vaccine or placebo at 0, 8, and 24 weeks.¹¹ Participants were screened with HRA, anal cytology, and anal and oral HPV testing, followed by anal and oral HPV testing and cytology every 6 months. Men were required to have a history of recent receptive anal intercourse. Treatment of anal HSILs during the study was performed using local standards of care.

The results showed non-statistically significant reductions in the composite of persistent anal HPV of quadrivalent HPV vaccine types or single detection at last visit (n = 26 in the vaccine group and n = 33 in the placebo group; hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.45-1.26) and in persistent anal HPV alone (13 patients vs 17 patients; HR, 0.73; 95% CI, 0.36-1.52), but no impact on anal HSILs (46 vs 45 patients; HR, 1.0; 95% CI, 0.69-1.44). A significant reduction was observed in persistent oral HPV in the vaccination group (1 patient vs 8 patients; HR, 0.12; 95% CI, 0.02-0.98), although the number of cases was low.

Other data support a protective effect of HPV vaccine against oral HPV infection. For example, in a study in Costa Rica, a large number of women received bivalent vaccine (covering HPV 16 and 18) and were followed

up for 4 years for cervical infection and disease. The vaccine efficacy in preventing cervical infection was approximately 75%. A one-time assessment at the end of the 4 years showed efficacy of approximately 95% in preventing oral infection and 60% in preventing anal infection.^{12,13} The mechanism of protection against oral disease appears to be achieving high levels of anti-HPV IgG in oral fluids. One study showed a high correlation of serum and oral gargle antibodies in vaccine recipients (Spearman's rho, 0.8432; $P < .0001$) after 7 months.¹⁴

Data from NHANES (National Health and Nutrition Examination Survey) from 2011 to 2014 indicate a vaccine effect in preventing oral HPV infection. Oral HPV infection was found in 22 (1.7%) of 1311 men not receiving vaccine and 1 (0.8%) of 116 who received vaccination ($P = .019$), and in 8 (0.8%) of 1021 women not receiving vaccine versus 1 (0.2%) of 447 who received vaccination ($P = .05$).¹⁵

Reducing Risk of HPV-Associated Cancer—Need for Increased Vaccination

A concerning aspect to be noted from the NHANES data mentioned above is that only a minority of individuals eligible for HPV vaccine had received vaccination. There is considerable evidence proving efficacy of HPV vaccination for prevention of HPV infection and associated disease, yet vaccination rates remain less than optimal, representing missed chances at preventing disease.

Thus far, 3 HPV vaccines have been FDA-approved: the bivalent vaccine (covering HPV 16 and 18); the quadrivalent vaccine (covering HPV 6, 11, 16, and 18); and the 9-valent vaccine (adding HPV 31, 33, 45, 52, and 59 to the quadrivalent coverage). As noted, the 9-valent vaccine provides coverage against HPV types that are responsible

Table. Advisory Committee on Immunization Practices Human Papillomavirus Vaccine Recommendations. Adapted from Meites et al.¹⁶

Girls and Women
<ul style="list-style-type: none"> • Routine vaccination of girls ages 11 to 12 years • Catch-up vaccination up to age 26 years
Boys and Men
<ul style="list-style-type: none"> • Routine vaccination of boys ages 11 to 12 years • Catch up vaccination up to age 21 years • Routine vaccination of boys with HIV infection, other immunosuppressed individuals, and men who have sex with men through age 26 years
Dosing Schedule
<ul style="list-style-type: none"> • 2 doses (0 and 6 months) when starting prior to age 15 years • 3 doses (0, 1-2, 6 months) after age 15 years and if having any immune suppression

for more than 90% of HPV-related cancers and is the only vaccine that is currently available. The current Advisory Committee on Immunization Practices (ACIP) HPV vaccine recommendations are shown in the Table.¹⁶ For girls, routine vaccination at age 11 to 12 years is recommended, with catch-up vaccination up to age 26 years for those who have not received vaccination. For boys, routine vaccination is recommended at age 11 to 12 years, with catch-up vaccination to age 21 years in the general population. The guidelines state that catch-up vaccination should be extended to age 26 years for men with HIV infection, other immunosuppressed men, and MSM. For the 9-valent vaccine, there is a 2-dose schedule if vaccination is started before the age of 15 years. The standard 3-dose schedule should be used if vaccination is started at an older age or in individuals with immunosuppression.

Another mechanism for reducing risk of HPV-related cancers in HIV infection is to ensure early initiation of antiretroviral therapy (ART). Benefits of early initiation of ART in reducing risk of cancers was demonstrated by the START (Strategic Timing of Antiretroviral Treatment) trial examining early versus delayed ART.¹⁷ The study showed that early initiation of ART reduced risk of HIV-related cancers by 76% ($P = .002$). Additional modeling suggested that early initiation of ART

with yearly cytology or yearly anoscopy could reduce risk of anal cancers by 25%.¹⁸ Statin use was associated with a 72% reduction (95% CI, 0.18-0.90) in anal cancer among people living with HIV in an analysis of the Veteran Affairs population.¹⁹ Broad use of statins may be a potential approach to reducing cancer risk among people with HIV infection.

Summary

Anal cancer is a common cancer in HIV-infected populations. Screening for anal cancer should be considered for HIV-infected populations, although data to support screening are limited and further study is needed. HPV vaccination is the best hope for prevention of HPV-related cancers. Ideally HPV vaccination should be administered prior to sexual activity for maximal benefit. All HIV practitioners should be advocates for HPV vaccination. Emerging data support the efficacy of vaccination against HPV-related oropharyngeal cancer. It remains a question whether a clinical trial is needed to definitively prove efficacy. A world-wide push for early initiation of ART should lead to reduced incidence of HPV-related cancer. 

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References

- Schim van der Loeff MF, Mooij SH, Richel O, de Vries HJ, Prins JM. HPV and anal cancer in HIV-infected individuals: a review. *Curr HIV/AIDS Rep.* 2014;11(3):250-262.
- Stier E, Lee J, Lensing S, et al. Anal high-grade squamous intraepithelial lesions (Hsil) in HIV positive (HIV+) women, prevalence and risk factors: Aids Malignancy Consortium (AMC) 084. *HPV 2017.* 2017; Cape Town, South Africa.
- Goldstone SE, Lensing SY, Stier EA, et al. A randomized clinical trial of infrared coagulation ablation versus active monitoring of intra-anal high-grade dysplasia in HIV-infected adults: An AIDS Malignancy Consortium trial. *Clin Infect Dis.* 2018;[Epub ahead of print].
- Aberg JA, Gallant JE, Ghanem KG, Emmanuel P, Zingman BS, Horberg MA. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV medicine association of the Infectious Diseases Society of America. *Clin Infect Dis.* 2014;58(1):e1-34.
- New York State Department of Health. Clinical Guidelines, Standards & Quality of Care. <https://www.health.ny.gov/diseases/aids/providers/standards/>. Accessed on July 16, 2018.
- Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. <https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/0>. Accessed on July 16, 2018.
- Saraiya M, Unger ER, Thompson TD, et al. US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. *J Natl Cancer Inst.* 2015;107(6):djv086.
- Jemal A, Simard EP, Dorell C, et al. Annual Report to the Nation on the Status of Cancer, 1975-2009, featuring the burden and trends in human papillomavirus(HPV)-associated cancers and HPV vaccination coverage levels. *J Natl Cancer Inst.* 2013;105(3):175-201.
- Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol.* 2011;29(32):4294-4301.
- Palefsky JM, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. *N Engl J Med.* 2011;365(17):1576-1585.
- Wilkin TJ, Chen H, Cespedes M, et al. ACTG A5298: A phase 3 trial of the quadrivalent HPV vaccine in older HIV+ adults [CROI Abstract 161]. In Special Issue: Abstracts From the 2016 Conference on Retroviruses and Opportunistic Infections. *Top Antivir Med.* 2016;24(e-1):391.
- Herrero R, Quint W, Hildesheim A, et al. Reduced prevalence of oral human papillomavirus (HPV) 4 years after bivalent HPV vaccination in a randomized clinical trial in Costa Rica. *PLoS One.* 2013;8(7):e68329.
- Kreimer AR, Gonzalez P, Katki HA, et al. Efficacy of a bivalent HPV 16/18 vaccine against anal HPV 16/18 infection among young women: a nested analysis within the Costa Rica Vaccine Trial. *Lancet Oncol.* 2011;12(9):862-870.
- Pinto LA, Kemp TJ, Torres BN, et al. Quadrivalent human papillomavirus (HPV) vaccine induces HPV-specific antibodies in the oral cavity: Results From the Mid-Adult Male Vaccine Trial. *J Infect Dis.* 2016;214(8):1276-1285.
- Sonawane K, Suk R, Chiao EY, et al. Oral human papillomavirus infection: differences in prevalence between sexes and concordance with genital human papillomavirus infection, NHANES 2011 to 2014. *Ann Intern Med.* 2017;167(10):714-724.
- Meites E, Kempe A, Markowitz LE. Use of a 2-dose schedule for human papillomavirus vaccination - updated recommendations of the advisory committee on immunization practices. *MMWR Morb Mortal Wkly Rep.* 2016;65(49):1405-1408.
- Borges AH, Neuhaus J, Babiker AG, et al. Immediate antiretroviral therapy reduces risk of infection-related cancer during early HIV infection. *Clin Infect Dis.* 2016;63(12):1668-1676.
- Blaser N, Bertisch B, Koller M, et al. Impact of ART coverage and screening on anal cancer in HIV+ men who have sex with men [CROI Abstract 596]. In Special Issue: Abstracts From the 2017 Conference on Retroviruses and Opportunistic Infections. *Top Antivir Med.* 2017;25(e-1):985.
- Bedimo R, Shebl F, Sigel KM, et al. Statin Exposure is associated with decreased risk of cancer [CROI Abstract 132]. In Special Issue: Abstracts From the 2018 Conference on Retroviruses and Opportunistic Infections. *Top Antivir Med.* 2018;26(suppl 1):483.
- ClinicalTrials.gov. Topical or Ablative Treatment in Preventing Anal Cancer in Patients With HIV and Anal High-Grade Squamous Intraepithelial Lesions (ANCHOR). <https://clinicaltrials.gov/ct2/show/NCT02135419>. Accessed on September 17, 2018.

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