INTERVIEW WITH:

Joel Palefsky, MD

Tackling tough questions on anal cancer incidence, screening, and HPV vaccination

Articles by Mark Mascolini

Soaring anal cancer incidence in the combination ART era

Risk factors for anal lesions and anal cancer in people with HIV

Anal cancer screening approach awaits more data and clinical expertise

HPV vaccination for people with HIV— who, when, why?
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Abstract: People with HIV infection have strikingly higher anal cancer incidence and prevalence than people the same age in the general population. From the dawn of the HIV epidemic through the early combination antiretroviral therapy (cART) era, researchers calculate that HIV-positive women had more than a 14 times higher incidence of invasive anal cancer than similarly aged women without HIV, HIV-positive men had a 35 times higher invasive anal cancer incidence, and HIV-positive men who have sex with men (MSM) had a 52 times higher incidence. Most anal cancer research in HIV populations involves MSM, but numerous studies show that 20% to almost 50% of HIV-positive women have receptive anal sex, and HIV-positive women have a higher risk of anal intraepithelial neoplasia—an anal cancer precursor—than women without HIV. Anal cancer incidence in HIV-positive people did not drop after the arrival of cART, and in some cohorts incidence rose substantially. But recent multicohort studies and other research suggest that anal cancer rates in the cART epoch may have peaked or even begun falling. One study found an association between longer cART-induced HIV control and lower odds of incident anal cancer.

When combination antiretroviral therapy (cART) arrived in the mid-1990s, things changed. ART halted runaway HIV epidemics in many countries with high HIV prevalence, like Botswana, which had 71% fewer AIDS deaths in 2011 than in 2005. In many countries, people who respond well to ART and don’t inject drugs live as long as anyone else. In the United States, 5-year cumulative incidence of the three AIDS cancers plunged from 18% in 1980-1989 to 4.2% in 1996-2006.

But cART didn’t change everything. For example, as fewer and fewer people got diagnosed with AIDS cancers after cART prescribing began, more and more got diagnosed with certain non-AIDS cancers, notably anal cancer. The same population-based US analysis of 472,378 people with AIDS that charted a dwindling of AIDS cancers found that 5-year cumulative incidence of anal cancer jumped from 0.02% in 1980-1989 to 0.07% in 1990-1995 and up to 0.09% in 1996-2006, the first cART decade.

AIDS cancers remain substantially more common than non-AIDS cancers in people with HIV. But besides the just-noted reversal in incidence, AIDS continued...
and non-AIDS cancers emerge at strikingly different rates after ART begins. Among 11,485 HIV-positive people starting cART between 1996 and 2011 in eight US cohorts, incidence of the AIDS cancers Kaposi sarcoma and non-Hodgkin lymphoma peaked in the first 6 months of therapy at 1342 cases per 100,000 person-years than plummeted to 164 cases per 100,000 from 6 months through 10 years of therapy. Although anal cancer incidence remained much lower than AIDS cancer incidence in the overall study period, the anal cancer rate changed hardly at all from 72 per 100,000 in the first 6 months of cART to 69 per 100,000 in the following 9.5 years of therapy.

A 2012 meta-analysis of anal cancer incidence (the new-diagnosis rate) in men who have sex with men (MSM), figured an incidence of 21.8 cases per 100,000 person-years in the pre-cART period, a rate almost 15 times higher than anal cancer incidence in the general population of US men. But studies of anal cancer incidence in MSM in the cART era reckoned an incidence of 77.8 per 100,000 person-years, more than triple the already high rate among MSM in the pre-cART era.

Why has anal cancer become such an intransigent menace to people with HIV, even those responding well to cART? Which HIV-positive people run a particularly high risk of anal cancer? How should people with HIV be screened for anal cancer? How much can HPV vaccination help? This issue of RITA! addresses those questions and many more in four review articles and an interview with Joel Palefsky (University of California, San Francisco), long a leader in HPV-related cancer research and care in people with HIV. The box “Anal cancer basics” offers a quick refresher on key points.

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**Anal cancer basics: from condyloma to invasive cancer**

**Squamous cell (epidermoid) carcinomas**, which include **cloacogenic** (basaloid transitional cell) tumors, account for most anal cancers, with **adenocarcinoma** accounting for the rest.

**Condylomas (warts)** develop just outside the anus and in the lower anal canal. Anal cancer is more likely in people with anal condyloma.

**Human papillomavirus (HPV)**, a DNA virus, causes both condyloma and anal cancer. HPV is the most common sexually transmitted infection in the United States and many other countries.

**Dysplasia** is a cluster of abnormal anal cells in the membrane lining the anal canal.

**Anal intraepithelial neoplasia (AIN)** and **anal squamous intraepithelial lesions (SILs)** are names for the lesions caused by dysplasia.

Depending on how the anal membrane cells look, AIN and anal SIL can be divided into **low-grade lesions** and **high-grade lesions**. High-grade AIN is less likely to go away without treatment and more likely to develop into anal cancer.
**Carcinoma in situ** is the term used to describe cells on the anal lining that look like cancer cells but have not grown into deeper layers of the anus.

**Invasive anal cancer** is the term used to describe growth of cancer cells beyond the surface of the anus into deeper layers.

For terms related to anal cancer screening, see the box “Screening for anal cell abnormalities and cancer” in the article “Anal cancer screening approach awaits more data and clinical expertise.”


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**Anal cancer and HIV: first hints and harbingers**

HIV can affect every inch of the body, from the cerebral cortex to the toes. The inch-and-a-half-long anal canal is no exception. A 2009 study of 473 randomly selected HIV-positive outpatients in a Paris clinic found that 208 of them (44%) had visible anal lesions, including HPV-related lesions in 23%, hemorrhoidal disease in 14%, and anal fissures in 11% (Figure 1). And MSM did not account for all these lesions. The study group included 200 MSM, 123 heterosexual men, and 150 women. Respective proportions with at least one anal lesion were 53.5%, 41.5%, and 33.3%.

**Figure 1.** A random sample of 473 HIV-positive patients in Paris found that almost half had one or more macroscopic anal lesions, including one quarter who had HPV-related lesions and 11% who had anal fissures. (Source: Abramowitz L, et al. 2009.)

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continued...
Findings like these are nothing new among MSM. The first PubMed citation linking anal carcinoma and homosexuality, originating in Brooklyn, appeared more than 15 years before anyone noticed AIDS in an article on “proctologic lesions” in MSM.10 A dozen years later—and still a half-decade before the first AIDS cases emerged—a group of New York City proctologists described what they called “gay bowel syndrome” in 260 MSM who made up 10% of their practice.11 Although these clinicians later endured censure for using this term to describe a mélange of maladies not specifically gay, limited to the bowels, or syndromic, they offered the first early warning that men who have anal sex with other men often suffer from anal warts, anal fissures, viral hepatitis, and a swarm of other insults that abet passage of sexually transmitted infections (STIs) and—it turned out—heightened the risk of anal cancer.

In 1979 researchers at Philadelphia’s Fox Chase Cancer Center reported four cases of cloacogenic anal cancer (see “Anal cancer basics” on page 6) in four men who “engaged in longstanding receptive anal intercourse.”12 Because the anorectal transitional zone where cloacogenic tumors arise shares an embryologic origin with the uterine cervix, a site of cancers related to sexual intercourse, the Fox Chase team posed “the serious question of the etiologic potential of receptive anal intercourse in the development of cloacogenic carcinoma.”

In 1984, researchers at New York’s Beth Israel Medical Center published four cases of anal carcinoma in situ in 7 MSM with anal warts.14 Lesions in all these men had morphology consistent with papillomavirus infection. Because 4 of the 7 men had histories “suspicious for or diagnostic of the acquired immunodeficiency syndrome,” the Beth Israel team urged colleagues to consider AIDS in MSM with persistent or recurrent perianal lesions.

Two years after that, researchers in Melbourne offered the first study linking HPV, HIV, and anal cancer in MSM.15 Examining anorectal mucosal cells from 61 MSM, they found cytological evidence of dysplasia and HPV in 24 men and evidence of HPV without dysplasia in 26 men. Four factors made dysplasia more likely: history of anal warts, frequent receptive anal intercourse, antibody to HIV, and immune dysfunction signaled by a low CD4/CD8 ratio. The link between HIV antibodies and long-lasting dysplasia was independent of the association with immune dysfunction.

A boom in anal cancer burden

In the general US population, anal cancer remains rare. SEER Stat Fact Sheets from the National Cancer Institute list an annual incidence of 1.5 cases per 100,000 men and 1.9 per 100,000 women.8 In contrast, annual colorectal cancer incidence is 52.2 per
100,000 men and 39.3 per 100,000 women. Respective lung cancer rates are 74.3 and 51.9 per 100,000. But anal cancer incidence was much lower decades ago. In Connecticut, for example, invasive anal cancer incidence doubled from 0.14 per 100,000 in 1940-1959 to 0.27 per 100,000 in 1980-1988. Across the United States from 1973 through 1989, the SEER cancer registry showed a 24% to 34% jump in anal cancer incidence among men and a 10% to 13% jump among women. Among white men in the San Francisco area, anal cancer incidence vaulted more than 100% from 0.5 per 100,000 in 1973-1975 to 1.2 per 100,000 in 1988-1989.

A study of cancer incidence in 15,565 MSM in New York City and San Francisco from 1978 through 1990 charted an overall standardized incidence ratio (SIR) of 1.6, meaning the observed overall cancer rate was 60% higher than the expected cancer rate in the general population after statistical adjustment for age. In contrast, the SIR comparing MSM with the general population was 2.5 for Hodgkin lymphoma and 24.4 for anal cancer. In other words, MSM tracked from the cusp of the US HIV epidemic through 1990 got diagnosed with anal cancer at a rate 24 times higher than expected for men their age. Three quarters of the San Francisco men tested positive for HIV, but anal cancer incidence did not correlate with HIV status, a finding indicating that all MSM in this urban center ran a skyscraping risk of anal cancer.

A more recent anal cancer incidence study involved 499,230 US patients diagnosed with AIDS from 1980 through 2004. Focusing on HPV-related cancers, a National Cancer Institute team calculated that these people with AIDS had a 60% higher than expected rate of invasive oropharyngeal cancer compared with the general population (SIR 1.6), women with AIDS had more than a 5 times higher rate of cervical cancer (SIR 5.6), women with AIDS had more than a 14 times higher rate of anal cancer (SIR 14.5), men with AIDS had almost a 35 times higher rate of anal cancer (SIR 34.6), and MSM with AIDS had a 52 times higher rate of anal cancer (SIR 51.8). Among men, every 100-cell lower CD4 count at AIDS onset raised the risk of invasive anal cancer almost 60% (relative risk per 100-cell lower CD4 count 1.59, 95% confidence interval [CI] 1.09 to 2.34, P = 0.016).

Meta-analyses of studies published through November 1, 2011 found a pooled anal cancer incidence of 5.1 per 100,000 HIV-negative MSM, more than triple the 1.5 per 100,000 men in the general US population (Figure 2). Still, the authors believe the 5.1 incidence may be an underestimate because it rests on only two studies with only three incident cases of anal cancer.

Among HIV-positive MSM, this meta-analysis reckoned an anal cancer incidence of 45.9 per 100,000 men, more than 30 times the US general population rate. When the researchers divided the HIV population into the pre-cART era (four studies before 1996) and the cART era (four studies from 1996 onward), they charted an anal cancer incidence of 21.8 per 100,000 MSM pre-cART and 77.8 per 100,000 with cART. Although the reasons for this jump remain unclear, the authors speculate that “the immune restoration related to [cART] may not be sufficient to clear persistent long standing HPV infection and the improved survival associated with [cART] may allow for sufficient time for chronically HPV infected men to develop invasive anal cancer.” (see “Complex impact of cART on anal cancer incidence” below).
Comparing incidence of non-AIDS malignancies in 33,420 US veterans with HIV and 66,840 without HIV, researchers found a 60% higher incidence of all non-AIDS cancers in the HIV group (incidence rate ratio 1.6) after adjustment for age, race, and gender. For individual cancers assessed, the incidence difference between HIV-positive and negative veterans was greatest for anal cancer, at an incidence rate ratio of 14.9 (111.2 versus 7.4 cases per 100,000 person-years). The next greatest incidence difference among non-AIDS malignancies involved Hodgkin lymphoma, at an incidence rate ratio 4.9.

The observation period for this study lay entirely in the HAART era (1997 through 2004), and an estimated 80% of veterans in this cohort took antiretroviral therapy.

Sifting numbers in 15 linked HIV and cancer registries in the United States, National Cancer Institute investigators estimate that from 1991-1995 to 2001-2005, the number of AIDS cancers in people with AIDS swooned more than 3-fold from 34,587 to 10,325 ($P < 0.001$) (Figure 3). Over the same two periods, the number of non-AIDS cancers in people with AIDS rose 3-fold from 3192 to 10,059 and the number of anal cancers in AIDS patients rocketed more than 7.5-fold from 206 to 1564. In comparison, the number of lung cancers in people with AIDS rose just over 2-fold and the number of liver cancers jumped 5-fold.

**Figure 2.** Meta-analyses of anal cancer incidence in MSM with or without HIV calculated a rate of 5.1 per 100,000 person-years in HIV-negative men, more than triple the rate of 1.5 per 100,000 in the US general population of men. Anal cancer incidence was higher still in HIV-positive MSM, especially since the advent of combination antiretroviral therapy (cART). (Source: Machalek DA, et al.)
While US AIDS cancer prevalence plummeted from the pre-cART era to the mid-cART era, numbers of non-AIDS cancers—including anal cancer—rose. (Source: Shiels MS, et al.20)

The gravity of anal cancer in people with HIV lies not merely in its vertiginously higher incidence and prevalence compared with the general population but in the age at which it strikes. This message resolved into crystalline focus in a canny study by National Cancer Institute researchers.21 Previous research suggested that many cancers in people with HIV developed up to two decades before they did in HIV-negative populations. But this capacious gap turned out to reflect a consistent flaw in calculations. Studies were reckoning age at diagnosis in HIV populations that had much larger proportions of middle-aged people than the comparison general populations—for the very good reason that many fewer HIV-positive people survived into their 60s and 70s than did people without HIV. When the National Cancer Institute team corrected their statistical machinations for this cohort make-up difference, the age-at-diagnosis difference between HIV and non-HIV groups vanished for most cancers—except anal cancer and a few others.

The study involved 212,055 people with AIDS enrolled in the US/AIDS Cancer Match Study from 1996 to 2007, entirely within the cART era.21 People 65 and older in the general population contributed 12.5% of follow-up time to the analysis. In contrast, age 65 and older people with AIDS contributed only 1.5% of follow-up time to the analysis. Before statistical correction for this imbalance, median ages at cancer diagnosis in the AIDS population and the general population were, for example, 52 and 73 for colon cancer, 46 and 60 for melanoma, 58.5 and 68 for prostate cancer, 50 and 70 for lung cancer, and 42 and 62 for anal cancer (Figure 4). With these adjustments for these five cancers, only the AIDS/
general population age differences for lung cancer (50/54 years, \( P < 0.001 \)) and anal cancer (42/45 years, \( P < 0.001 \)) remained statistically significant.

For HIV providers and people in their care, the bottom line is that anal cancer in this AIDS population developed at a remarkably young median age—and at an age 3 years younger than in the general population.

**Anal HPV and dysplasia in women with HIV**

Most research on anal dysplasia and cancer in people with HIV has focused on MSM, but HIV-positive women also face a heightened risk of anal dysplasia. In the US general population, anal cancer incidence is higher in women than in men (1.9 versus 1.5 per 100,000 person-years), although that distribution flips among African Americans (1.6 in women versus 1.9 in men).\(^6\)

HIV-positive women are no strangers to anal intercourse, an anal cancer risk factor, according to two analyses of the SUN Study cohort (**Figure 5**).\(^{22,23}\) One study involved 142 HIV-positive women seen at seven clinics in four cities—Denver, Minneapolis, Providence, and St. Louis.\(^{22}\) Just over half (57%) were African American, 30% were non-Hispanic white, and 10% Hispanic. Fifty-seven of these 142 women (40%) reported receptive anal intercourse. A separate analysis of 120 women in the same cohort found that 43 (36%) ever had receptive anal

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**Figure 4.** After statistical correction for the imbalanced age composition of US groups with AIDS and the general population, median age at cancer diagnosis in AIDS patients did not differ from the expected age in the general population for colon cancer, melanoma, or prostate cancer. But after adjustment median age at diagnosis was significantly lower in the AIDS group for anal cancer \((P < 0.001)\)* and lung cancer \((P < 0.001)\).* (Source: Shiels MS, et al.\(^{21}\))
intercourse and 12 (10%) had receptive anal sex in the past 6 months. From 20% to 47% of HIV-positive women in two other HIV cohorts, reviewed below, also reported having receptive anal sex.

One of the SUN Study analyses and two other studies found an independent association between receptive anal intercourse and abnormal anal cytology or AIN in women. Three of these studies found higher rates of AIN or abnormal anal cells in HIV-positive women than in women without HIV.

The first SUN Study assessment of AIN involved 170 women seen in 2004-2006. Median age at first evaluation was 39, and 40% of women reported receptive anal intercourse. While 15% of women had atypical squamous cells, 17% had low-grade AIN and 3% high high-grade AIN. Having receptive anal intercourse in the past 6 months more than tripled the odds of abnormal anal cytology (aOR 3.46, 95% CI 1.10 to 12.1, P = 0.038), while infection with more high-risk HPV types upped the odds 22% (aOR 1.22, 95% CI 1.03 to 1.46, P = 0.022).

A study reported in 2001 involved 251 HIV-positive and 68 HIV-negative women in a San Francisco contingent of the Women’s Interagency HIV Study (WIHS), an ongoing study of HIV-positive women and HIV-negative women with similar sociodemographics. About 60% of women with and without HIV were African American, and median age at the baseline visit was 40 years (range 20 to 61).

Among women with anal cytologic results, 26% with HIV versus 8% without HIV had some abnormality (atypical squamous cells of undetermined significance or low- or high-grade AIN). High-grade AIN could be detected in 6% of HIV-positive women and 2% of HIV-negative women. Compared with HIV-negative women, those with HIV had a tripled risk of abnormal anal cells (relative risk [RR] 3.2, 95% CI 1.3 to 7.5). In women with HIV, lower CD4 count (P < 0.001) and higher viral load (P = 0.02) made anal cell abnormalities more likely. Four factors raised the risk of abnormal anal cytology in women with HIV: abnormal cervical cytology (RR 1.5, 95% CI 0.97 to 2.2), genital warts (RR 1.4, 95% CI 0.98 to 2.1), anal intercourse (RR 2.0, 95% CI 1.3 to 3.1), and diarrhea for more than 1 month (RR 1.8, 95% CI 1.2 to 2.7).

Figure 5. Four studies of US women with HIV found that 20% to 47% reported ever having receptive anal intercourse, including 221 of 470 (47%) in WIHS, 57 of 142 (40%) in the SUN Study, 43 of 120 (36%) in a separate SUN Study analysis, and 47 of 238 (20%) in REACH.
In a study involving 470 HIV-positive and 185 HIV-negative women in the San Francisco, Chicago, and Brooklyn units of the Women’s Interagency HIV Study, about two thirds of women were African American and 47% ever had anal sex. Rates of low-grade AIN in women with and without HIV were 12% and 5%, while rates of high-grade AIN were 9% and 1%. Overall AIN prevalence was 16% in women with HIV. Any receptive anal intercourse tripled the odds of low-grade AIN (adjusted OR 3.2, 95% CI 1.5 to 6.8%), while anal HPV infection raised chances of high-grade AIN more than 7 times (aOR 7.6, 95% CI 1.5 to 38).

A multisite analysis of the Reaching for Excellence in Adolescent Care and Health (REACH) Project involved 238 behaviorally HIV-infected adolescent girls between 12 and 18 years old and 139 girls without HIV. Almost three quarters of the HIV group (73%) were black, as were 63% of the HIV-negative group. A slightly lower proportion of HIV-positive than HIV-negative girls reported receptive anal intercourse (20% versus 28%, \( P = 0.08 \)). Only 58% of girls with HIV had ever taken antiretroviral therapy. Compared with HIV-negative girls, HIV-positive girls had a higher incidence of any anal HPV infection (30 versus 14 per 100 person-years, \( P = 0.002 \)), high-risk anal HPV (12 versus 5.3 per 100 person-years, \( P = 0.04 \)), anogenital warts (6.7 versus 1.6 per 100 person-years, \( P = 0.002 \)), and anal dysplasia (12 versus 5.7 per 100 person-years, \( P = 0.05 \)). Late versus early CDC disease stage boosted the risk of anal dysplasia 7 times (adjusted hazard ratio [aHR] 7.02, 95% CI 2.18 to 22.59), while ever having high-risk anal HPV infection almost quadrupled the risk (aHR 3.72, 95% CI 1.52 to 1.92). Smoking in this teenage group independently tripled chances of infection with high-risk HPV (aHR 3.46, 95% CI 1.21 to 9.89).

Complex impact of cART on anal cancer incidence

Because a weakened immune system cannot muster enough robust cancer-fighting cells, you would expect HIV-positive people with depleted CD4 cells to succumb more readily to cancer, perhaps especially virus-related cancers like anal cancer. The converse expectation might be that people who replenish their CD4 squad when responding to cART would stand a better chance of warding off anal cancer. But that hasn’t happened.

Analysis of 263 people with histologically confirmed anal cancer in the French Hospital Database on HIV determined that incidence has remained intractably high since the introduction of cART. The French team figured SIRs to compare incidence in HIV-positive people with incidence in the general population across four periods: 1992-1996 (pre-cART period), 1997-2000 (early cART period), and 2001-2004 and 2005-2008 (recent cART periods). Risk of anal cancer in the three ART periods more than doubled risk in the pre-cART period (hazard ratio 2.5, 95% CI 1.28 to 4.98), with no difference from one cART period to the next.

In the most recent cART period, 2005-2008, HIV-positive MSM had more than a 100 times higher anal cancer incidence than the general population (SIR 109.8, 95% CI 84.6 to 140.3), other HIV-positive men had almost a 50 times higher incidence...
(SIR 49.2, 95% CI 33.2 to 70.3), and HIV-positive women had a 15 times higher incidence (SIR 13.1, 95% CI 6.8 to 22.2). Even people who reached a CD4 above 500 cell/mm$^3$ had extraordinarily higher anal cancer incidence than the general population—with an SIR of 67.5 when the CD4 nadir lay below 200 cells/mm$^3$ and an SIR of 24.5 when the nadir lay above 200 cells/mm$^3$. Combination ART, the French team concluded, “appears to have no preventive effect on anal cancer, particularly in MSM.”

Parallel evidence comes from London, where researchers at Chelsea and Westminster Hospital analyzed pre-cART and cART era anal cancer incidence in their cohort of 8640 HIV-positive people. They counted 26 people with invasive anal cancer for an incidence of 60 per 100,000 person-years, a rate 120 times higher than in the age- and gender-matched general population. Incidence of invasive anal cancer stood at 35 per 100,000 in the pre-cART era and 92 per 100,000 in the cART era, rates 67 and 176 times higher than in the general population. Five-year disease-free survival stood at 66% and did not differ between the two treatment periods.

Studies from San Diego County, San Francisco, the US Multicenter AIDS Cohort Study (MACS), and a US military cohort also yielded evidence that anal cancer incidence rose after cART arrived.

Two statistical wrinkles could contribute to higher anal cancer incidence after people with HIV started taking cART—competing risks and ascertainment bias. Competing risks is a fancy term that explains why surviving longer with HIV could make one more vulnerable to cancers that develop as we age. For example, an HIV group being assessed for incident anal cancer may die first from an AIDS disease like non-Hodgkin lymphoma (the competing risk). But if that HIV group starts cART and cART cuts chances of non-Hodgkin lymphoma (as it does), they could survive long enough to succumb to a slowly developing anal cancer. As a result, it looks like anal cancer incidence is lower in pre-cART days when people

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HPV infection is the most common STI in the United States, and people with HIV—another STI—tend to pick up HPV and high-risk (cancer-causing) HPV genotypes more often than HIV-negative people with relatively sedate sex lives. HPV infection often regresses without treatment, and that helps explain why the billions of HPV-infected people in the world don’t end up with anal or cervical cancer. But people with HIV—even those who respond to cART—have a maimed immune system that lets HPV’s toehold turn into a foothold then into dysplasia. Anal cancer expert Joel Palefsky suggests that the CD4s added with cART “may reflect only partial restoration of the immune response to HPV antigens, or a limited role of this immune response in clearing [high-grade] AIN lesions once they have passed a certain point in their development.”

Why did anal cancer incidence seem to swell with cART’s advent instead of dropping, as incidence of AIDS cancers did? There’s no easy answer but lots of suggestions that, together, probably explain this vexing epidemiology. cART helps HIV-positive people live longer, and prolonged survival allows HPV-induced cellular abnormalities to bud into cancers—especially since screening for high-grade AIN (an anal cancer precursor) is far from routine.

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were dying of competing risks before they could get anal cancer. Ascertainment bias means that clinicians started screening HIV-positive people for anal abnormalities as reports of anal dysplasia and cancer proliferated in the cART era, and this heightened ascertainment makes it look like more HIV-positive people have anal cancer in more recent years.

**Has the anal cancer bounce leveled off?**

Studies showing climbing anal cancer incidence since cART came of age 27-33 paint only part of the picture. Two recent megacohort inquests in North America and other studies suggest that anal cancer rates in the cART epoch may have topped out or even begun falling. 4,36-38 A 13-cohort North American analysis involving 34,189 people with HIV (55% MSM, 19% other men, and 26% women) carved cART time into three slices: 1996-1999, 2000-2003, and 2004-2007. 36 Taking the middle period as the reference era, these investigators determined that people diagnosed with anal cancer in 1996-1999 had a 50% lower rate of anal cancer (adjusted rate ratio 0.5, 95% CI 0.3 to 0.9) while people diagnosed in 2004-2007 had nearly the same anal cancer rate as those diagnosed in 2000-2003 (adjusted rate ratio 0.9, 95% CI 0.6 to 1.2). Anal cancer rates rose after the early cART era, these investigators conclude, then plateaued.

A study of eight US HIV cohorts examined AIDS and non-AIDS cancer incidence in 11,485 cART-treated people over a longer period, 1996 through 2011. 4 Gauging anal cancer incidence from the time cohort members started cART, these researchers found that incidence stayed flat for a decade—measuring 72 per 100,000 person-years in the first 6 months of treatment and 69 per 100,000 in the following 9.5 years. Overall, these researchers found, the year when cART began did not affect cancer incidence.

A case-control comparison of 20,277 HIV-positive and 202,313 HIV-negative people in the Kaiser Permanente Northern California system charted a non-significant drop in anal cancer incidence through three cART periods. 37 Poisson regression models adjusted for HIV status, age, gender, calendar period, and HIV status/calendar period interaction tracked a gradual dwindling of the anal cancer rate ratio comparing HIV-positive with negative people as the cART era evolved: 159.9 in 1996-1999, 122.9 in 2000-2003 and 94.0 in 2004-2007 (P = 0.83).

Rather than scrutinizing anal cancer risk year-by-year or cART era-by-era, a Houston team analyzed anal cancer incidence according to time spent on cART with an undetectable viral load (Figure 6). 38 This study involved male veterans with follow-up over some period from 1985 through 2009. Age-adjusted anal cancer incidence was similar in men who ever received cART and never received cART (146.8 and 134.3 per 100,000 person-years).

Focusing on cART-treated veterans, an analysis adjusted for demographics, nadir CD4 count, and most recent CD4 count determined that men with an undetectable viral load during 81% to 100% of follow-up time had 45% lower odds of incident anal cancer (adjusted odds ratio 0.55, P = 0.0004) when compared with men who had an undetectable load less than 20% of the time. And veterans with an un-
detectable load 60% to 80% of the time had almost the same decrease in anal cancer odds when compared with the under-20% group (adjusted odds ratio 0.56, \( P = 0.04 \)). These investigators propose that “optimizing cART adherence and HIV viral load control may decrease the risk of subsequent squamous cell cancer of the anus.”

In an editorial on these issues, Joel Palefsky observes that today’s cART combinations are much stronger and easier to take than those of the past, and that should lead to “more pronounced and sustained HIV viral load suppression” in people starting a contemporary cART regimen. It’s too early to tell whether better HIV control will decrease anal cancer incidence, Palefsky writes. “What is clear,” he adds, “is that the problem of anal cancer, a potentially preventable disease, will not be going away soon.”

**Figure 6.** US veterans who had an undetectable HIV load during 81% to 100% of follow-up time had 45% lower odds of incident anal cancer than veterans with an undetectable HIV load during less than 20% of follow-up time. Veterans with an HIV load undetectable during 60% to 80% of follow-up time had 44% lower odds of incident anal cancer. (Source: Chiao EY, et al.38)

**References**


**continued...**


Tackling tough questions on anal cancer incidence, screening, and HPV vaccination

An interview with Joel Palefsky, MD

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Dr. Palefsky is Professor at the University of California, San Francisco, where he directs the Anal Neoplasia Clinic and is Director of the Clinical and Translational Research Fellowship Program for predoctoral students. He is founder and President of the International Anal Neoplasia Society, President of the International Papillomavirus Society, and Board Member of the American Society for Colposcopy and Cervical Pathology. Long recognized as a leader in HPV-related cancers, he has coauthored more than 200 peer-reviewed articles, many of them concerning anal cancer and its precursors.

Understanding anal cancer rates and risks

Mascolini: Why is anal cancer incidence so much higher in HIV-positive than HIV-negative people?

Palefsky: That’s something we don’t fully understand, but clearly HIV-associated immune suppression plays a role. People with lower nadir CD4 counts appear to be at higher risk of anal cancer.

But the role of immune suppression is a little confusing because anal cancer rates have not gone down since combination antiretroviral therapy became available. In fact, those rates increased in many places. These findings indicate that restoration of the immune response does not necessarily reduce anal cancer incidence. That implies that it’s not just loss of the immune response that was responsible in the first place. Instead, some form of irreversible damage may have occurred before antiretroviral therapy fully controlled HIV infection. While immune restoration may help prevent many other forms of infection, some permanent damage to the human papillomavirus (HPV)-specific immune response may put HIV-positive people at higher risk for persistent HPV infection and development of the high-grade anal lesions that progress to cancer.

Mascolini: Aside from a compromised immune system, what are the other key risk factors for anal pre-cancer and cancer in people with HIV?

Palefsky: HPV is by far the most important risk factor, and specifically the oncogenic HPV types. And among the oncogenic HPV types, HPV-16 appears to be in a class by itself in conferring an increased risk of anal cancer. So behaviors that increase the risk of
getting HPV infection are important risk factors—number of sexual partners, age of sexual debut, and so on. But ultimately acquiring HPV-16 and some of the other oncogenic HPV types is the most important risk factor for anal cancer. Other factors, such as smoking, are probably additive, but HPV outdoes them all in raising anal cancer risk.

Impact of age and CD4 count on HPV vaccine response

Mascolini: Which HIV-positive people are candidates for HPV vaccination?

Palefsky: I would say everybody who’s 26 or younger. The benefits of vaccinating people over the age of 26 are still not clear, regardless of their HIV status. This is an area of active investigation, and the answer to that question may change in the coming years as more data come in.

The real question isn’t one of safety but rather—given the prior HPV exposure that many people over the age of 26 have had and the fact that the HPV vaccine is a preventive vaccine—we don’t know whether people older than 26 have had too much exposure to HPV types for vaccination to have much benefit.

Mascolini: Some research shows that sizeable proportions of people in their 30s and 40s with or without HIV don’t test positive for HPV-16 or 18, the two oncogenic types covered by available HPV vaccines. Would’t those people benefit from vaccination?

Palefsky: Possibly, but there are two things to think about. One is their level of prior exposure to HPV, and the other is their level of future exposure. If people are not going to get exposed to new viruses, vaccination has no benefit. Clearly, though, many middle-aged and older HIV-positive people probably would benefit from vaccination because of continuing sexual activity.

The issue of prior exposure is more complicated. Traditional HPV testing suggests that a substantial proportion of people have not been exposed to HPV-16. However, without a lot of direct evidence, many of us believe that some of these HPV-16-negative people have indeed been exposed to HPV-16. We know, for instance, that a person’s immune response to a given HPV type, even when they’re healthy, wanes over time. Our working hypothesis is that many if not most individuals who appear to be naive to a given HPV type have in fact been exposed to that HPV type and that sufficient time has passed so that all traces of the virus are gone. It’s unclear whether the potential benefit from the vaccine is the same in these people as in those who’ve never truly met the virus. That’s one of the things we’re trying to find out.

Mascolini: So far we don’t have much data on vaccine immunogenicity or safety in people with a CD4 count below 200, and guidelines say the vaccine may not be as potent in those people. Should HIV clinicians wait until antiretroviral therapy pushes CD4 counts above 200 before starting HPV vaccination?

Palefsky: That’s a good question. I would say the data thus far suggest that clinicians do not need to wait. It is true that in some cases and for some of the HPV types, individuals with lower CD4 counts may have lower antibody titers in response to vaccination than people with higher CD4 counts. But even in those people with lower CD4 counts, the titers are still way above what we think we need for protection. The proportion of people with lower CD4 counts who seroconvert with highly protective titers is high enough that I don’t think I would necessarily wait until their CD4 count rises above 200.

continued...
New trial may resolve screening quandary

Mascolini: Which HIV patients should be screened with digital rectal exam and anal cytology? What screening protocol do you recommend?

Palefsky: First, I believe everybody at risk for anal cancer, whether they’re HIV-positive or negative, should get an annual digital rectal exam. That’s always part of our protocol. At the moment cytology is the test most clinicians use to screen. There are other tests available that have different sets of characteristics and that may or may not add to cytology. Cytology is not an ideal screening test; it has problems, primarily with sensitivity.

But these problems are not different from the problems we see with cervical cytology. With cervical cytology we try to minimize the sensitivity problem by having women come back for repeat tests in the hope that if the result was falsely negative the first time, it won’t be the second time. In the same way, our anal screening guidelines call for bringing HIV-infected men and women back annually, if their cytology is negative. If cytology indicates anal cell abnormalities, then we refer them for high-resolution anoscopy and biopsy of suspicious lesions. For HIV-negative men and women, we recommend repeating cytology every 2 to 3 years.

HPV testing has a possible role in the screening algorithm, but that’s still under investigation.

Mascolini: Why is this cytology-anoscopy approach taken in people with HIV when there’s no proof that it reduces incidence of anal cancer?

Palefsky: Lack of proof is the reason this screening approach is not yet established as the standard of care in HIV clinics. But we follow that protocol based on everything we know about the biology of HPV and high-grade disease elsewhere in the body. We just published a study showing that high-grade disease can progress to anal cancer; there’s no question about that. But that doesn’t necessarily mean all our efforts to treat high-grade lesions actually lead to a reduction in anal cancer. We know that treatment of high-grade cervical disease does reduce the incidence of cervical cancer. But we know that only after following millions of women for decades.

To try to get an answer faster than that with anal cancer, we recently got funding approval for a large randomized controlled trial to determine whether treating high-grade anal lesions lowers the incidence of anal cancer. We will be opening this study at 15 sites in the United States and enrolling more than 5000 HIV-positive men and women with high-grade disease and randomizing them to treatment versus close observation.* Then we will compare anal cancer incidence in the two arms. That will give us the level of evidence we need to adopt screening and treatment as standard of care—or not to adopt that approach if it doesn’t lower incidence.

Mascolini: How long will it take this trial to yield results?

Palefsky: The plan is to enroll patients over a 3-year period and follow each patient for up to 5 years. So it could take as long as 8 years to get an answer. We’ll have a data and safety monitoring board looking at results regularly, and if the need arises the study will be stopped earlier.

* Close observation will consist of digital anorectal exam, anal cytology, high-resolution anoscopy with biopsy of visible lesions every 6 months, or more often than that if the clinician believes it is necessary.
There will be a major community effort to encourage participation by people with HIV. We’re hoping for enthusiastic community involvement. The study is not just for men who have sex with men (MSM); it’s for anyone who’s HIV-positive. Participants have to be over the age of 35, because anal cancer rarely occurs under that age.

**Filling the gap in trained clinicians**

**Mascolini:** You and others have pointed out the lack of trained clinicians and technicians to perform the various screening and treatment steps needed to prevent anal cancer in people with HIV. What can be done about that?

**Palefsky:** Within the AIDS Malignancy Consortium (http://pub.emmes.com/study/amc/public/index.htm), the HPV Working Group that I chair has been training people for the last 10 years, primarily to do AMC studies. Another group that I’m involved with, the American Society for Colposcopy and Cervical Pathology (ASCCP, http://www.asccp.org/), has courses twice a year designed to begin the training process for high-resolution anoscopy. We train between 70 and 80 people from around the world in each course. There’s a fairly lengthy subsequent learning process required to get people to the skill level they need. High-resolution anoscopy and treatment of high-grade lesions are challenging.

That’s one of the reasons there’s a shortage of trained people—it’s not see-one, do-one, teach-one.

But slowly the critical mass of skilled specialists is growing. The new randomized trial will also accelerate the availability of trained clinicians, because we do have to expand our activities around the country to fully enroll the trial.

To promote education and collaboration in this field, we have also founded a new professional society, the International Anal Neoplasia Society (IANS). We are actively engaging amongst ourselves, with other professional societies, and with the community to raise awareness of this disease. IANS just held the world’s first meeting on anal cancer and its precursors on November 22-24, 2013, in San Francisco. Our Website (www.iansoc.org) includes lots of good information for clinicians.

**Mascolini:** Is there anything else you would like to add that you think primary HIV clinicians should know about anal cancer?

**Palefsky:** I would stress that anal cancer incidence is increasing in people with HIV. It is now the third most common cancer in HIV-infected MSM, and it’s potentially preventable. So it’s critical that HIV clinicians have anal cancer on their radar screen. If a patient has anal signs or symptoms that aren’t readily explained by common conditions, clinicians should consider anal cancer as a possibility and, if there is concern, refer that patient to someone trained in high-resolution anoscopy.

**References**


Abstract: Many HIV-positive people have an array of anal cancer risk factors, beginning with a challenged immune system and frequent sex. Among the several anal cancer risks listed by the American Cancer Society for the general population, most have particular pertinence for people with HIV. Among 21 studies that analyzed risk factors in people with HIV, 10 found an association with low CD4 counts, eight confirmed the impact of anal intercourse, five saw links with frequent sex, five implicated infection with multiple HPV types, and four linked smoking to anal precancer or cancer. All of the just-itemized factors can be avoided, reversed, or modified.

People with HIV infection run a high risk of anal cancer.

Why do people with HIV run a high risk of anal cancer?

Because HIV cripples their immune system.

With a reference back to ample documentation in the first article in this issue, this risk-factor article could end right here. Of course HIV infection and a flaccid immune system are hardly the only risk factors for precancerous anal lesions and anal cancer. But they provide the linchpins from which much else depends when explaining why people hosting the intransigent retrovirus have almost a 30 times higher anal cancer incidence than the general population.¹ Andrew Grulich (University of New South Wales, Sydney) and Australian colleagues made that estimate in a clever analysis involving two groups with enfeebled immunity—people with HIV and immunosuppressed transplant recipients.

The Australian team ran a meta-analysis of seven cancer incidence studies involving 444,172 people with HIV and five incidence studies embracing 31,977 immunosuppressed people getting solid organ transplants.³ Calculating standardized incidence ratios or SIRs (comparing cancer incidence in each of the immunosuppressed groups with incidence in general-population groups), they figured that people with HIV had almost a 30 times higher anal cancer incidence than the general population (SIR 28.75, 95% confidence interval [CI] 1.6 to 38.3). Transplant patients had almost a 5 times higher anal cancer incidence than comparison populations (SIR 4.85, 95% CI 1.36 to 17.3).

People with HIV and transplant recipients also had significantly higher incidence of four other human papillomavirus (HPV)-related cancers (cervical, vulvar and vaginal, penile, oral cavity and pharynx) and five possibly HPV-related cancers (nonmelanoma skin, lip, esophagus, larynx, eye). In the HIV group, the 28.75 SIR for anal cancer exceeded SIRs for each of the nine other HPV cancers by 4.5-fold or more.

continued...
Most but not all cancers with higher SIRs in the two immune-beleaguered groups are infectious cancers caused by HPV, Epstein-Barr virus, HBV, HCV, HHV-8, or *Helicobacter pylori*. Grulich and coworkers “believe that the striking similarity in patterns of increased cancer risk that we have shown [in people with HIV and transplant patients] indicates that immune deficiency is the probable explanation for the increased cancer risk.”1 They argue that their study “suggests a broader than previously appreciated role for the immune system in the prevention of cancers related to infection.”

Besides ravaging cancer-fighting immune cells, how else does HIV pose a threat of anal cancer? One way to answer that question is to review the American Cancer Society’s list of risk factors for anal cancer and see how many fit an HIV-positive population:2

- **Infection with high-risk (cancer-causing) HPV:** A dozen or more studies summarized in this article and in the HPV vaccination analysis confirm lofty rates of cancer-causing HPV types in people with HIV.
- **Low condom use:** Infrequent or inconsistent condom use has been amply demonstrated in HIV populations from one side of the globe to the other. Indeed, condom-free sex largely explains high HIV rates in most people who get infected.
- **Frequent sexual activity:** Vigorous sex lives spread HIV across six continents and sustain the epidemic to this day.
- **Anal intercourse:** Anal intercourse is highly prevalent among HIV-positive men who have sex with men (MSM) and is often practiced by HIV-positive women.

- **Other HPV-related cancers:** Women with cervical cancer (an AIDS cancer), vaginal cancer, or vulvar cancer face a higher risk of anal cancer, and three studies outlined below make the link between abnormal cervical cytology and anal cancer risk in women with HIV.
- **Smoking:** In study after study, smoking rates in people with HIV routinely double those in the general population.
- **Circumcision:** Uncircumcised men run a higher risk of HPV and HIV infection.
- **Lowered immunity:** See above.1 And below.

To dissect anal cancer and precancer risk factors more precisely in people with HIV, RITA! reviewed 21 studies that probed for risk factors through standard statistical analyses. Seventeen studies sized up risk of HPV infection, anal warts, and/or anal intraepithelial neoplasia (AIN), a potential harbinger of anal cancer (Table 1); four studies homed in on risk of anal cancer itself (Table 2).1,5-22

Ten of these 21 studies—including all four anal cancer studies—forged one or more links between low CD4 count and anal risk. Three studies reached the related finding that a high viral load inflates risk of high-risk HPV infection, abnormal anal cells, or anal cancer, while two studies found antiretroviral therapy protective. Five studies figured that having lots of sex puts one in harm’s way—not a surprise since HPV is a sexually transmitted virus—while eight studies determined that anal intercourse heightens anal-related risk. Five studies found that infection with more HPV types spells trouble, while six saw ties between a history of anal HPV lesions or anal HPV infection and anal cancer forerunners.
CD4 counts, more sex, anal sex

Evidence yoking low CD4s, high viral loads, or previous AIDS to anal cancer precursors and cancer risk—and so buttressing Andrew Grulich’s conclusion—is just short of tsunamiic. Among the choice examples, a case-control study in Switzerland found that a CD4 count below 200 cells/mm³ versus above 499 cells/mm³ 6 to 7 years before cancer diagnosis upped the odds of anal cancer 14 times. A study of 52,278 HIV-positive people in France figured that every year with a CD4 count below 200 inflated anal cancer risk 30%, while every year with a viral load above 100,000 copies made anal cancer 20% more likely. A EuroSIDA analysis of 14,453 people with HIV determined that every twice higher current CD4 count cut the anal cancer risk 14%.

Reason—and a pile of data points—affirm that more sex, more anal sex, and more sex partners will crank up chances of getting anal HPV infection, anal warts, precancerous anal lesions, or anal cancer. HPV ranks as the most frequently sexually transmitted infection in the United States, and the CDC figures it causes 4300 cases of anal cancer every year—2800 of them (65%) in women. More frequent sex or more sex partners raised chances of HPV infection, anal warts, or AIN in five studies outlined in Table 1.

Receptive anal sex poses a steep risk of anal HPV infection and anal cell abnormalities in MSM. A cross-sectional study of 92 HIV-positive New York City MSM, including 37 (40%) who never had receptive anal sex, figured that a history of receptive anal sex upped odds of anal HPV infection 7 times (odds ratio [OR] 7.1, 95% CI 2.6 to 20, P < 0.001) and raised chances of anal cell abnormalities 10 times (OR 10, 95% CI 3 to 36, P < 0.001). Men who reported receptive anal sex had more than a tripled chance of AIN, an anal cancer precursor (OR 3.6, 95% CI 1.2 to 11, P = 0.02).

But gay men can hardly claim exclusive rights to anal intercourse. A cross-sectional study of anal warts and AIN in 473 HIV-positive people at a Paris clinic included 200 MSM, 123 heterosexual men, and 150 women. Every MSM told the researchers they had receptive anal intercourse. So did almost 1 in 5 women, including 2 of 5 (40%) with anal warts and 5 of 8 (62%) with anal dysplasia, compared with 20 of 122 (16%) with no anal lesions. For the whole study group, every additional sex act per month raised odds of genital warts 4% (OR 1.04, 95% CI 1.01 to 1.06, P = 0.003), while receptive anal sex more than doubled chances (OR 2.3, 95% CI 1.11 to 4.77, P = 0.0026). Receptive anal intercourse more than quadrupled odds of AIN, though that association stopped short of statistical significance (OR 4.29, 95% CI 0.99 to 1.04, P = 0.144).

A study of 471 MSM and 150 women in four US cities—all of them with HIV infection—separately analyzed receptive anal intercourse in women. In the overall study population, receptive anal sex at any time boosted odds of abnormal anal cytology 2.5 times (OR 2.51, 95% CI 1.63 to 3.91, P < 0.001). In women, anal intercourse in the past 6 months made abnormal anal cells almost 3.5 times more likely (OR 3.46, 1.10 to 12.1, P = 0.038). A later analysis of 120 women in the same HIV cohort did not confirm a link between anal sex and abnormal anal cytology or anal HPV infection. But two studies of HIV-positive women in the Women’s Interagency HIV Study did find links between receptive anal sex and abnormal anal cytology or AIN.
A 4% higher wart risk for every sex partner per month, the Paris finding, may seem like a fair tradeoff to some sexually athletic people—until you realize that a few more sex mates per month add up fast in some groups. A study of 48 HIV-positive San Francisco MSM, for example, reckoned that men who had 201 to 1000 lifetime sex partners versus under 201 (so far), had a 60% higher risk of anal infection with HPV-16, the HPV type that causes most anal cancers (relative risk [RR] 1.6, 95% CI 1.1 to 2.4, \( P = 0.01 \)). A man who became sexually active at 18 and had 1000 partners by age 28 would average about 8 sex mates per month.

The San Francisco study found that MSM who also inject drugs had a 50% higher risk of anal HPV-16 (RR 1.5, 95% CI 1.2 to 1.9, \( P = 0.003 \))\(^{13}\). Inhaled or swallowed drugs may also hoist chances of AIN, at least low-grade AIN, according to a study of 1262 HIV-negative MSM in four US cities. Men who snorted poppers (alkyl nitrates) in the past 6 months had 60% higher odds of low-grade AIN (OR 1.6, 95% CI 1.1 to 2.5, \( P = 0.03 \)). In comparison, men who injected drugs more than once in the past 6 months had 19 times higher odds of low-grade AIN (OR 19, 95% CI 1.3 to 277, \( P = 0.03 \)).

### Impact of condoms and circumcision

The American Cancer Society and the CDC agree that condoms offer some protection against HPV but do not completely block infection.\(^2,^{22}\) The CDC says condoms may also cut chances of HPV-related diseases.\(^{23}\) But anal cancer expert Andrew Grulich cautions that “the high prevalence of HPV and the fact that it can be transmitted on hands and fingers during sexual contact mean that condom use and reduction in partner numbers can provide only very partial protection”\(^{24}\) against anal cancer.

None of the 21 risk analyses framed in Tables 1 and 2 singled out erratic condom use as an independent risk factor for anal cancer or its precursors. But a study of 245 HIV-positive and 1427 HIV-negative MSM in Sydney calculated that condom-free anal sex with an HIV-positive partner, or one with an unknown HIV status, made new HPV-16 infection more likely \( (P = 0.049) \).\(^{18}\) A cross-sectional study of 212 HIV-positive MSM and 459 HIV-negative MSM in Beijing found that HIV-positive men who reported always using condoms during insertive anal sex in the past 6 months had 50% lower odds of HPV infection (odds ratio 0.49, 95% CI 0.31 to 0.77).\(^{25}\) Multivariate analysis determined that oral sex without a condom in the past 6 months doubled the odds of HPV infection in men with HIV (OR 2.12, 95% CI 1.00 to 4.48). Of course HPV infection, the endpoint in these two studies, does not always lead to anal dysplasia, AIN, or cancer.

One might assume that the eight studies seeing a link between receptive anal intercourse and anal dysplasia or cancer involved lots of people not keen on condoms,\(^3,7,8,10,11,17,18,22\) but those studies did not identify iffy condom use as a separate risk factor for anal dysplasia or anal lesions. None of the four studies with anal cancer as an endpoint focused on condom use.\(^1,6,12,19\)

The American Cancer Society says uncircumcised men run a higher risk of picking up HPV infection and passing it to sex partners,\(^2\) and a recent 23-study meta-analysis figured that circumcised men were
about 40% less likely to have prevalent genital HPV infection than uncircumcised men.26

A cross-sectional study of 706 MSM and heterosexual men with HIV in Spain found no association between circumcision and prevalent penile HPV in the overall group.27 Among HIV-positive MSM, penile prevalence of high-risk HPV types tended to be lower in circumcised than uncircumcised men (14% versus 21%), but that difference lacked statistical significance (OR 0.6, 95% CI 0.3 to 1.1, P = 0.088). In the study of 245 HIV-positive and 1427 HIV-negative MSM in Sydney, circumcision cut the risk of new HPV-16 infection 57% in men practicing mainly insertive anal sex (HR 0.43, 95% CI 0.21 to 0.88, P = 0.021).18

Strong evidence of potential HPV benefits from circumcision came from a randomized trial of 210 HIV-positive heterosexual men in the Rakai, Uganda cohort.28 The Rakai team randomized men to immediate circumcision or delayed circumcision and assessed high-risk HPV rates at enrollment and after 24 months. At month 24 the immediate-circumcision group ran a 23% lower risk of high-risk HPV prevalence (rate ratio [RR] 0.77, 95% CI 0.62 to 0.97), a 47% lower risk of multiple high-risk HPV types (RR 0.53, 95% CI 0.33 to 0.83), a (nonsignificant) 26% lower risk of new high-risk HPV types over 24 months (RR 0.74, 95% CI 0.54 to 1.01, P = 0.06), and a 60% lower risk of multiple new high-risk HPV types over 24 months (RR 0.40, 95% CI 0.19 to 0.84). But the same researchers found that circumcision of HIV-positive men did not affect transmission of high-risk HPV to their female partners.29

Smoking and anal cancer

Besides making tobacco barons more baronial, smoking does no one any good. Smoking prevalence among HIV-positive people in the United States exactly doubles the rate in the general population (42% versus 21%), according to a 2013 nationally representative survey of people in care for HIV.30 On top of causing or contributing to non-AIDS diseases that take a heavy toll in HIV populations (cardiovascular disease, stroke, low bone density), smoking amplifies the risk of anal cancer. A study of 336,381 male Swedish construction workers with detailed tobacco use data and up to 37 years of follow-up determined that smoking more than doubled the risk of anal cancer (HR 2.41, 95% CI 1.06 to 5.48), while only modestly inflating rectal cancer risk (HR 1.16, 95% CI 1.04 to 1.30) and marginally raising colon cancer risk (HR 1.08, 95% CI 0.99 to 1.19).31

Three risk studies summarized in Tables 1 and 2, largely involving MSM, link smoking to a higher risk of anal cancer or high-grade (grade 2 or 3) AIN in people with HIV. The Swiss case-control study involving 59 HIV-positive people with anal cancer and 295 HIV-positive people without anal cancer found that most anal cancers (73%) occurred in MSM.6 Current smokers had more than doubled odds of anal cancer (OR 2.59, 95% CI 1.25 to 5.34). Odds of high-grade AIN were even higher among current smokers in a prospective Montreal study of 247 HIV-positive MSM (OR 4.8, 95% CI 1.3 to 18.6) after statistical adjustment for age and CD4 count.4
The most detailed analysis of how smoking affects AIN comes from a cross-sectional study of 305 HIV-positive MSM cared for by the Kaiser Permanente group in northern California. In an analysis adjusted for age at enrollment, ethnicity, CD4 count, number of male partners, and history of chlamydia in 241 men positive for high-risk (cancer-causing) HPV, ever smoking, former smoking, and smoking more cigarettes yearly all raised the odds of high-grade AIN:

- Ever smoking: OR 2.71 (95% CI 1.43 to 5.14)
- Smoking but not in last 12 months vs never: OR 2.30 (95% CI 1.11 to 4.80)
- Smoking in last 12 months vs never: OR 3.20 (95% CI 1.46 to 7.09)
- Smoking <10 years vs never: OR 3.39 (95% CI 1.29 to 8.93)
- Smoking >10 years vs never: OR 3.09 (95% CI 1.33 to 7.18)
- Smoking <0.5 pack daily vs never: OR 2.90 (95% CI 1.27 to 6.60)
- Smoking >1 pack daily vs never: OR 5.50 (95% CI 1.19 to 10.28)

Current smoking yielded somewhat higher odds of anal precancer than past smoking, and smoking more versus fewer packs daily heightened the odds. But former smokers and men who smoked less still had independently higher odds of high-grade AIN than men who never smoked.

A study of 238 HIV-positive US adolescent girls linked smoking to more than a tripled risk of high-risk anal HPV infection (HR 3.46, 95% CI 1.21 to 9.89). It is notable that this association emerged in multivariate analysis of girls 12 to 18 years old.

None of the 21 cited risk studies for HPV infection, AIN, or anal cancer risk discovered independent predictors involving gender or race. In the general population, anal cancer affects a higher proportion of African Americans than whites and more women than men, but anal cancer develops in more African-American men than women.

The good news for people with HIV infection is that many of the principal anal cancer risk factors can be avoided, modified, or reversed: smoking, multiple sex partners, receptive anal intercourse (especially without a condom), other sexually transmitted infections, low CD4 count, and high viral load. The table “Avoiding anal cancer risk factors” explains these variables for people with HIV.
### Table 1. Risk factors for HPV infection, anal warts, or AIN in people with HIV

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| Abramowitz 2007\(^3\)        | 2003-2004   | Paris          | 200 MSM, 123 HTX men, 150 women | **Risk factors for genital warts:**  
Every additional sex act per month: OR 1.04  
CD4 count <200: OR 3.22  
History of anal HPV lesions: OR 4.57  
Receptive anal intercourse: OR 2.3  
**Risk factors for AIN:**  
History of anal HPV lesions: OR 2.82  
Receptive anal intercourse: OR 4.29 |
| Alvarez 2010\(^4\)           | 2003-2005   | Montreal       | 247 MSM         | **Risk factors for high-grade AIN:**  
More HPV types: OR 1.4  
Current smoking: OR 4.8 |
| Baranoski 2012\(^5\)         | 2006-2007   | Boston         | 100 women       | **Risk factors for abnormal anal cytology:**  
Current CD4 count <200: OR 12.8  
Anal HPV infection: OR 6.2  
History of STI: OR 3.6  
**Risk factors for high-grade AIN:**  
History of cervical cytologic abnormality: OR 10.0, \(P = 0.06\)  
History of STI: OR 7.9, \(P = 0.06\) |
| Chin-Hong 2005\(^7\)         | 1999-2001   | Four US cities | 1262 HIV-negative MSM | **Risk factors for low-grade AIN:**  
>5 male receptive anal partners: \(P = 0.03\)  
Older age at first anal receptive sex: \(P = 0.004\)  
Poppers in past 6 months: OR 1.6  
IDU \(\geq 2\) times in past 6 months: OR 19  
Infection with increasing number of HPV types: \(P < 0.001\)  
**Risk factors for high-grade AIN:**  
Any anal HPV infection: OR 3.2  
Infection with increasing number of HPV types: \(P < 0.001\) |

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*Abbreviations: MSM = men who have sex with men; HTX = heterosexual; IDU = injecting drug use; STI = sexually transmitted infection; OR = odds ratio.*  
*P-values in bold indicate statistical significance.*
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<td>Baseline CD4 count &lt;500: OR 1.71</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ever having receptive anal intercourse: OR 2.51</td>
</tr>
<tr>
<td>Gonzalez 2013</td>
<td>2007-2011</td>
<td>Madrid</td>
<td>551 MSM</td>
<td>Risk factors for AIN:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥ 5 high-risk anal HPV types vs 1: OR 7.4</td>
</tr>
<tr>
<td>Hessol 2009</td>
<td>2001-2003</td>
<td>Brooklyn, Chicago,</td>
<td>470 HIV+ women, 185 HIV- women</td>
<td>Risk factor for low-grade AIN in HIV+ women:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>San Francisco</td>
<td></td>
<td>Younger age: OR 0.59</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Receptive anal intercourse: OR 3.2</td>
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<td></td>
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<td></td>
<td>Anal HPV: OR 11</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Low- and high-risk HPV types: OR 11</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Cervical HPV: OR 3.5</td>
</tr>
<tr>
<td>Holly 2001</td>
<td>Baseline</td>
<td>San Francisco</td>
<td>251 HIV+ women, 68 HIV- women</td>
<td>Risk factor for high-grade AIN in HIV+ women:</td>
</tr>
<tr>
<td></td>
<td>1993-1994 with 6-month follow-up</td>
<td></td>
<td></td>
<td>Anal HPV infection: OR 7.6</td>
</tr>
<tr>
<td>Hernandez 2013</td>
<td>NA</td>
<td>San Francisco</td>
<td>348 MSM</td>
<td>Risk factors for abnormal anal cytology in HIV+ women:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Genital warts: RR 1.4 (NS)</td>
</tr>
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<td></td>
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<td></td>
<td>Anal intercourse: RR 2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Abnormal cervical cytology: RR 1.5 (NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diarrhea &gt; 1 month: RR 1.8</td>
</tr>
</tbody>
</table>

* All study participants HIV-positive unless otherwise noted.
† Not associated with abnormal anal cytology in women in same cohort in Kojic (Table 1).

AIN, anal intraepithelial neoplasia; HTX, heterosexual; IDU, injection drug use; MSM, men who have sex with men; NA, not available; NS, not statistically significant; OR, odds ratio; RR, relative risk; STI, sexually transmitted infection.
<table>
<thead>
<tr>
<th>First author</th>
<th>Study years</th>
<th>Location</th>
<th>n</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Konopnicki 201315</td>
<td>2002-2011</td>
<td>Brussels</td>
<td>652 women†</td>
<td>Risk factors for high-risk HPV infection: Younger than 30: OR 3.13 CD4 count &gt;500 &gt;18 months: OR 0.88** Viral load &lt;50 for &gt;40 months: OR 0.81**</td>
</tr>
<tr>
<td>Piketty 200317</td>
<td>NA</td>
<td>Paris</td>
<td>50 IDU men with no anal sex, 67 MSM</td>
<td>Univariate risk factors for abnormal anal cytology or histology in IDUs: CD4 count &lt;250: OR 5.7 Viral load &gt;50 copies: OR 8.9 Previous AIDS: OR 4.3 Anal HPV detection: OR 5.7 Univariate risk factors for abnormal anal cytology or histology in MSM: &gt;10 lifetime anal receptive episodes: OR 5.6 Anal HPV detection: OR 8.7</td>
</tr>
<tr>
<td>Poynten 201218</td>
<td>2004-2007</td>
<td>Sydney</td>
<td>245 HIV+ MSM, 1427 HIV- MSM</td>
<td>Risk factors for seroincident HPV-16 in HIV-negative MSM: Younger age: P = 0.049 More male partners in past 6 months: P = 0.089 Unprotected anal intercourse with HIV+ or status-unknown partner: P = 0.046 Risk factors for seroincident HPV-16 in men practicing mainly insertive anal intercourse: Circumcision: 0.43**</td>
</tr>
</tbody>
</table>
**Table 1 continued from page 33**

<table>
<thead>
<tr>
<th>First author</th>
<th>Study years</th>
<th>Location</th>
<th>n</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Risk factors for high-grade AIN if high-risk HPV-positive: Smoking: OR 2.71 Smoking but not in last 12 months vs never: OR 2.30 Smoking in last 12 months vs never: OR 3.20 Smoking ≤ 10 years vs never: OR 3.39 Smoking &gt;10 years vs never: OR 3.09 Smoking &lt;0.5 pack daily vs never: OR 2.90 Smoking &gt;1 pack daily vs never: OR 3.50</td>
</tr>
<tr>
<td>van der Snoek 2012(^{21})</td>
<td>2007-2009</td>
<td>Rotterdam</td>
<td>250 MSM</td>
<td>Variables favoring absence of AIN: Use of combination ART: OR 2.28</td>
</tr>
<tr>
<td>Wilkin 2004(^{22})</td>
<td>2001-2002</td>
<td>New York City</td>
<td>92 MSM</td>
<td>Risk factors for anal HPV infection: History of receptive anal intercourse: OR 7.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Risk factors for abnormal anal cytology: History of receptive anal intercourse: OR 10 Current ART: OR 0.09**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Risk factors for AIN: History of receptive anal intercourse: OR 3.6 Current ART: OR 0.18** Age &lt;40: OR 3 Lower nadir CD4 count: (P = 0.01)</td>
</tr>
</tbody>
</table>

* All study participants HIV-positive unless otherwise noted.  
** Lowered risk.  
† Most women (84%) from sub-Saharan Africa. 
AIN, anal intraepithelial neoplasia; ART, antiretroviral therapy; HR, hazard ratio; IDU, injection drug user; MSM, men who have sex with men; NA, not available; OR, odds ratio; RR, relative risk.
## Table 2. Risk factors for anal cancer in people with HIV

<table>
<thead>
<tr>
<th>First author</th>
<th>Study years</th>
<th>Location</th>
<th>n</th>
<th>Key findings</th>
</tr>
</thead>
</table>
| Bertisch 2013<sup>6</sup> | 1988-2011         | Switzerland                       | 59 HIV+ cases with anal cancer, 295 HIV+ controls without anal cancer | Current smoking: OR 2.59  
Antibodies against HPV-16 protein L1: OR 4.52  
Antibodies against HPV-16 oncogene E6: OR  \( \infty \)  
Every 100-cell lower CD4 nadir: OR 1.53  
Every 100-cell lower CD4 at cancer diagnosis: OR 1.24  
CD4 count 6-7 years before cancer diagnosis <200 vs >500: OR 14.0 |
| Grulich 2007<sup>1</sup> | —                 | Meta-analysis of studies in US (2 studies), Australia, Scotland, Italy, Switzerland, England | 444,172 with 303 cases of anal cancer in 7 studies | Standardized incidence ratio for anal cancer in HIV+ vs general population: 28.75* |
| Guiguet 2009<sup>12</sup> | 1998-2006         | France                            | 52,278 HIV+                 | Per year with CD4 count <200: RR 1.3  
Per year with viral load >100,000: RR 1.2 |
| Reckie 2010<sup>19</sup> | 1994 to median follow-up of 9/2008 | Europe                            | 14,453 HIV+ with 69 cases of anal cancer | Per doubling of current CD4 count: IRR 0.86† |

* Highest standardized incidence ratio, by far, for any of five HPV-related cancers or five possibly HPV-related cancers analyzed in people with HIV.
† Lowered risk 14%.

IRR, incidence rate ratio; OR, odds ratio; RR, relative risk.
For people with HIV: avoiding anal cancer risk factors

People with HIV infection run a much higher risk of anal cancer than people without HIV. Some important anal cancer risk factors can be avoided or modified.

<table>
<thead>
<tr>
<th>What to do</th>
<th>Why to do it</th>
</tr>
</thead>
<tbody>
<tr>
<td>Get the HPV vaccine</td>
<td>HPV vaccination—a series of three shots—protects people from the two main cancer-causing types of human papillomavirus (HPV*). US health authorities recommend this vaccine for all boys and girls, for all young adults with HIV infection and for all gay or bisexual men.</td>
</tr>
<tr>
<td>Don't start smoking.</td>
<td>Research links smoking to a higher risk of anal cancer or anal abnormalities that can lead to anal cancer. Nicotine is addictive, and nicotine addiction is hard to break. E-cigarettes deliver nicotine, which can cause addiction. If you don't smoke, don't start.</td>
</tr>
<tr>
<td>Stop smoking.</td>
<td>If you already smoke, try to stop, because smoking can lead to anal cancer. Your provider can help you stop by prescribing nicotine substitution products and recommending other strategies. If you tried to quit smoking and failed, try again. It takes many people several times to quit smoking.</td>
</tr>
<tr>
<td>Have fewer sex partners.</td>
<td>Many studies show that HIV-positive people who have more sex have a higher chance of HPV* infection and anal cell changes that can lead to anal cancer. This is especially true for receptive anal sex (being the “bottom”).</td>
</tr>
<tr>
<td>Wear condoms.</td>
<td>Condoms can help prevent infection with HPV*, HIV, and other sexually transmitted infections. Condoms are especially important if you have receptive anal intercourse.</td>
</tr>
<tr>
<td>Don't inject drugs or use party drugs.</td>
<td>Research shows that injecting drugs or using recreational drugs like poppers raise the risk of conditions that lead to anal cancer.</td>
</tr>
<tr>
<td>Take your anti-HIV drugs regularly.</td>
<td>Studies show that a low CD4 count or a high viral load makes anal cancer more likely. Taking all you anti-HIV drugs (antiretrovirals) on time—exactly as your provider directs—will get your CD4 count higher and keep your viral load low.</td>
</tr>
</tbody>
</table>

* HPV, human papillomavirus, is the virus that causes anal cancer, as well as cancers of the penis, cervix, vagina, and vulva.


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**References**
continued from page 37


Abstract: No US national guidelines spell out a screening protocol for anal cancer in people with HIV. Based on the success of screening for cervical cancer—another malignancy caused by human papillomavirus—some authorities suggest a similar approach for anal cancer: anal cytology with referral for high-resolution anoscopy if any cytologic abnormality appears, followed by treatment of high-grade anal intraepithelial neoplasia (AIN) confirmed by biopsy during anoscopy. Screening for HIV-positive people should also include annual digital rectal exam. No data confirm that this approach prevents anal cancer, though a randomized trial addressing this question will begin shortly. Until that trial yields an answer, clinicians will have to sort through current data, realizing that few centers offer the full range of services necessary for this screening strategy.

Why the difference? Population research shows that the Pap test to screen women for cervical cell abnormalities lowers the risk of death from cervical cancer;1 no evidence ties anal Pap testing to lower anal cancer mortality or even anal cancer incidence. The quadrivalent HPV vaccine is licensed to prevent anal cancer, but all children and young adults should get the vaccine—you don’t need an anal Pap test to pick out candidates.

There have been no randomized trials to establish the value of anal cancer screening in at-risk people because the duration, size, and cost of such a trial are daunting.2,3 But a 5000-person trial has been funded in the United States and will begin recruiting HIV-positive men and women shortly (see the interview with Joel Palefsky in this issue of RITAT! /A). The trial will randomize people with high-grade anal lesions to treatment or to close observation to determine whether detecting and treating such lesions cuts anal cancer incidence. The study may take 8 years to yield an answer, however, and until it does clinicians will have to sort through a welter of relevant data and expert advice in deciding how to screen.

This article summarizes available anal screening advice and explores evidence from anal screening studies. “Screening for anal cell abnormalities” defines the basic steps of screening for anal cell abnormalities and testing for and treating anal intraepithelial neoplasia (AIN).  

continued...
Screening for anal cell abnormalities and cancer

**Anal Pap tests** evaluate anal wall cells for abnormalities (dysplasia) that could represent precancerous anal lesions.

**Cytology** is microscopic examination of cells collected from the anal wall by an anal Pap test to look for abnormalities called dysplasia. Cells are collected by swabbing an area 5 to 6 cm (2 to 2.5 inches) into the anal canal.

**Dysplasia** is abnormal anal cell growth in the lining of the anal canal.

**Anal squamous intraepithelial lesions (SIL)** and **anal intraepithelial neoplasia (AIN)** are names for the lesions caused by dysplasia. SIL and AIN can be at any early stage (low grade) or a later stage (high grade). SIL is detected by cytology (Pap test) and AIN by histology (anoscopy).

**Anoscopy** is examination of the anus and rectum through a short tube to look for lesions. A part of any lesion that looks suspicious can be removed by biopsy.

**Histology** is microscopic examination of tissue removed by biopsy to see if the tissue indicates cancer.

What guidelines say so far

No national US guidelines spell out screening advice for anal cell abnormalities and anal cancer. Opportunistic infection guidelines from the Centers for Disease Control and Prevention (CDC) and other groups suggest that “anal cytology screening of HIV-seropositive MSM [men who have sex with men] and of women might be useful preventive strategies.” But the CDC immediately adds that “definitive recommendations” must await studies that confirm the value of screening. “Until such time”, the CDC outlines what has become the standard model for HIV-positive men and women, as proposed by “certain specialists”:

1. Annual digital rectal exam to detect masses that might be anal cancer.
2. Cytologic screening (with the anal Pap test).
3. High-resolution anoscopy if cytology indicates any abnormality.
4. During anoscopy, biopsy of visible lesions “to determine the level of histologic changes and to rule out invasive cancer.”

New York State does offer HIV-specific screening guidelines that follow the CDC model but provide more detail (Table 1). These guidelines (online at the link in the reference list) discuss further useful details on symptomatology and screening procedures that clinicians should review.

Table 1. New York State guidelines for anal cancer screening and diagnosis in people with HIV

<table>
<thead>
<tr>
<th>Physical examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every year all HIV-positive adults, regardless of age, should be:</td>
</tr>
<tr>
<td>1. Asked about anal symptoms such as rectal itching or bleeding, diarrhea, or pain*</td>
</tr>
<tr>
<td>2. Undergo visual inspection of the perianal region</td>
</tr>
<tr>
<td>3. Undergo digital rectal examination</td>
</tr>
<tr>
<td>4. Any women with cervical high-grade squamous intraepithelial lesions (HSIL) and anyone with abnormal anal findings should be referred for high-resolution anoscopy and/or examination with biopsy of abnormal tissue.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anal cytology (Pap test)</th>
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<tbody>
<tr>
<td>At the initial visit and annually thereafter, the following groups should have anal Pap testing:</td>
</tr>
<tr>
<td>1. Men who have sex with men</td>
</tr>
<tr>
<td>2. Any patient with a history of anogenital condylomas (warts)</td>
</tr>
<tr>
<td>3. Women with abnormal cervical and/or vulvar histology</td>
</tr>
<tr>
<td>4. Any patient with abnormal anal cytology should be referred for high-resolution anoscopy and/or examination with biopsy of abnormal tissue.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Posttreatment follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients treated for high-grade squamous intraepithelial lesions should have annual high-resolution anoscopy.</td>
</tr>
</tbody>
</table>

* Other symptoms listed by the American Cancer Society are change in stool diameter, abnormal anal discharge, and swollen lymph nodes in the anal or groin areas.
Health Services and Resources Administration (HRSA) HIV guidelines follow the New York State advice. HRSA and anal cancer expert Joel Palefsky (University of California, San Francisco) add the important point that anal Pap tests should be offered only if follow-up anoscopy is available. Learning how to perform high-resolution anoscopy competently “takes time, experience and commitment,” Palefsky notes. And the number of HIV-positive people who may need anoscopy is high. As a result, professionals trained to perform anoscopy are in short supply in most areas, even some places with big HIV populations. When a complete work-up is not feasible, people with HIV should at least have a yearly digital rectal exam, and those with suspicious masses should be referred.

Teresa Darragh and Barbara Winkler (University of California, San Francisco) offer a concise summary of differences between anal and cervical cancer epidemiology and screening, including five key screening differences:

1. Palpation detects early anal cancer but not early cervical cancer.
2. Whether cytologic screening is efficacious in preventing anal cancer remains unproven (though probable), while cytology screening has proved valuable in preventing cervical cancer (though not in a randomized trial).
3. Whether testing for high-risk HPV permits triage of anal atypical squamous cells of unknown significance (ASCUS) remains unclear, though it probably does not, while testing for high-risk HPV does permit triage of cervical ASCUS.
4. Testing for high-risk HPV is not useful in primary screening for anal cancer, but it is for cervical cancer in women 30 or older who have a Pap test.
5. Availability of trained, experienced cytopathology and clinical personnel is very limited for anal cancer and widespread for cervical cancer.

Wide-ranging predictive power of anal cytology

Several single-center studies in the combination antiretroviral therapy era have assessed the power of abnormal anal cytology to predict anal intraepithelial neoplasia (AIN) or other outcomes (Table 2). Results vary considerably, depending on the population tested, methods used, and endpoints. Sensitivity (the ability of a test to correctly identify people with a certain condition) ranged from 47% to 98%, while specificity (the ability of a test to classify people who do not have a condition as negative) ranged from 39% to 90%. In studies that compared results in HIV-positive and negative people, sensitivity was always higher in those with HIV. Despite these uneven results, all of these investigators see value in anal cytologic screening for people with HIV.

One 584-person study found that sensitivity of anal cytology varies with the areas (quadrants) of disease present and with CD4 count—results that may partly explain differing sensitivity reported in these studies. A study of 288 men and 41 women with HIV underlined the difficulty of making screening decisions on the basis of risk factors like those suggested
in New York State screening guidelines (Table 1). These investigators divided their population into high-risk people and standard-risk people. Cytology spotted abnormalities that biopsy found to be high-grade dysplasia in 19.5% of the increased-risk group and 28.6% of the standard-risk group.

**Table 2. Predictive power of anal cytology for AIN and other outcomes in people with HIV**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year reported</th>
<th>Location</th>
<th>People screened</th>
<th>Primary results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palefsky⁹</td>
<td>1997</td>
<td>San Francisco</td>
<td>407 HIV+ MSM; 251 HIV- MSM</td>
<td>Sensitivity for detecting biopsy-proved anal SIL 69% at first visit and 81% at later visits in HIV+ men, 47% and 50% in HIV- men</td>
</tr>
<tr>
<td>Panther¹⁰</td>
<td>2004</td>
<td>Boston</td>
<td>100 HIV+ MSM; 55 HIV- MSM</td>
<td>Sensitivity 47% for detecting high-grade AIN and 68% for low-grade AIN; specificity 90% and 48%</td>
</tr>
<tr>
<td>Cranston¹¹</td>
<td>2004</td>
<td>San Francisco</td>
<td>102 HIV+ MSM</td>
<td>Sensitivity to detect AIN 68% with self-collected samples, 70% with clinician-collected samples; sensitivity to detect high-grade AIN 71% and 74%</td>
</tr>
<tr>
<td>Arain¹²</td>
<td>2005</td>
<td>Los Angeles</td>
<td>200 HIV+ or HIV- men</td>
<td>Sensitivity 98% for anal SIL; specificity 50% for predicting severity of abnormality on biopsy</td>
</tr>
<tr>
<td>Cranston¹³</td>
<td>2007</td>
<td>Los Angeles</td>
<td>244 HIV+ MSM</td>
<td>Positive predictive value 96% for any degree of anal SIL, 56% for high-grade anal SIL</td>
</tr>
<tr>
<td>Berry¹⁴</td>
<td>2009</td>
<td>San Francisco</td>
<td>35 HIV+ MSM; 85 HIV- MSM</td>
<td>Sensitivity 87% for high-grade AIN in HIV+ men, 55% in HIV- men</td>
</tr>
<tr>
<td>Nathan¹⁵</td>
<td>2010</td>
<td>London</td>
<td>584 people, 93% men, 54% HIV+</td>
<td>Sensitivity 70% for AIN, specificity 67%; sensitivity 76% for HIV+, 59% for HIV-; sensitivity 81% for high-grade AIN</td>
</tr>
<tr>
<td>Salit¹⁶</td>
<td>2010</td>
<td>Toronto</td>
<td>401 HIV+ MSM</td>
<td>Sensitivity 84%, specificity 39%, positive predictive value 31%, negative predictive value 88% for high-grade AIN</td>
</tr>
<tr>
<td>Mallari¹⁷</td>
<td>2012</td>
<td>Rochester, NY</td>
<td>288 HIV+ men, 41 HIV+ women</td>
<td>Cytology detected high-grade AIN in 25 of 125 patients (20%), regardless of pretest risk stratification</td>
</tr>
<tr>
<td>Botes¹⁸</td>
<td>2013</td>
<td>Sydney</td>
<td>262 HIV+ MSM</td>
<td>High-resolution anoscopy identified high-grade AIN in 54.5% of 101 men undergoing anoscopy, including 52.7% without abnormal cytologic results</td>
</tr>
<tr>
<td>Betancourt¹⁹</td>
<td>2013</td>
<td>Houston</td>
<td>228 HIV+ men and women</td>
<td>Sensitivity 93% for ASCUS, low- or high-grade AIN, or SCC; sensitivity 84% for low-grade AIN; sensitivity 20% for high-grade AIN or SCC</td>
</tr>
</tbody>
</table>

AIN, anal intraepithelial neoplasia; ASCUS, atypical squamous cells of unknown significance; MSM, men who have sex with men; SCC, squamous cell carcinoma; SIL, squamous intraepithelial lesions.
Anal dysplasia does not progress inexorably to AIN and AIN does not progress inexorably to invasive cancer. The critical question for cytologic screening is whether detecting dysplasia—and as a result spotting and treating AIN—prevents cancer often enough to make screening worthwhile. No one knows, because no randomized trial has addressed this question, but some research does.

Most recently, workers at the University of California, San Francisco reviewed data on 138 HIV-positive MSM diagnosed with anal or perianal squamous cell cancer between 1997 and 2011. Before these diagnoses, all these men had been monitored regularly with digital rectal exam, high-resolution anoscopy, and anoscopy-guided biopsy. These clinicians recommended treatment whenever they detected high-grade SIL (HSIL), but not all men got treated and some were lost to follow-up. Among 72 men in whom anal cancer developed while they were under continuing care, 27 (37.5%) had cancer at a previously biopsied HSIL site. The remaining 45 men could not be analyzed because of inadequate documentation of HSIL in relation to subsequent cancer location. These findings confirm that HSIL does become anal cancer if left untreated, but the incomplete results cannot pin down how often HSIL progressed to cancer in these men: it could be anywhere from 37.5% up.

Researchers from the CDC and the San Francisco Department of Public Health tackled this question by charting age-adjusted incidence of AIN 3 (sometimes called carcinoma in situ) and anal cancer among white men in San Francisco County from 1998 through 2005. Local providers began offering anal cancer screening in the late 1990s. The impact of screening from this point can be gauged because California mandates reporting of both invasive anal cancer and AIN 3. AIN 3 can be detected by anoscopy-guided biopsy triggered by abnormal cytologic findings.

From 1988 through 2005, age-adjusted anal cancer incidence stayed essentially flat at 5 to 10 cases per 100,000 person-years. In contrast, age-adjusted AIN 3 rose sharply from between 5 and 10 cases per 100,000 person-years from 1988 through 2000 to 20 or more cases per 100,000 from 2001 through 2005. These trends indicate that, once screening began, detection of AIN 3 jumped in white men, but increased detection of AIN 3 did not result in fewer anal cancer diagnoses. If the primary goal of screening is to lower anal cancer incidence, these results suggest it didn't work.

The investigators are quick to observe that this ecological analysis does not prove that screening failed. Several other interpretations could explain the findings: (1) Invasive anal cancer incidence may have increased without screening. (2) Screening may have reached too few people. (3) Too little time may have passed to see an effect of screening on anal cancer incidence. (4) This type of analysis may lack sensitivity in detecting changes in anal cancer incidence in specific high-risk populations. Still, these researchers propose that, “given the costs and consequences of screening, sufficient evidence does not exist to support routine anal cancer screening for men who have sex with men.”
Is self-swabbing as accurate as clinician swabbing?

Because limited clinician experience and cost are obstacles to routine anal cytology, researchers have tested the feasibility of instructing patients to collect samples and then compared results with patient-collected samples and clinician-collected samples. But as in studies of anal cytology’s ability to predict disease, results of these patient-clinician sampling comparisons defy easy interpretation.

University of California, San Francisco researchers gave 102 HIV-positive or negative MSM self-collection kits with instructions and told them to swab a sample 1 month after their clinic visit. Almost all clinician-collected samples (99%) were adequate for analysis, while a lower proportion of self-collected samples (91%) proved adequate. Sensitivity of abnormal self-collected samples to detect AIN by histology was 68%, nearly the same as the 70% sensitivity with clinician-collected samples. Respective sensitivities to predict high-grade AIN were 71% and 74%. Among men with biopsy-diagnosed high-grade AIN, 33% of self-collected samples and 39% of clinician-collected samples were high-grade.

A few years later, the same research team found a wider sensitivity gap between self-collected and clinician-collected samples for HIV-positive and negative MSM. This time the investigators mailed cytology self-collection kits and instructions to participants and clinicians repeated cytologic sampling in the office. Only 80% of this patient group provided adequate samples, compared with 91% in the earlier study. Sensitivity of cytology to detect AIN in men with HIV was 75% with self-collected samples and 90% with clinician samples; respective specificities were 50% and 64%. Among HIV-negative men, sensitivities were 48% with self-collection and 62% with clinician collection; respective specificities were 86% and 85%. The authors suggest “the probability of AIN in a patient with a negative cytology result may not be low enough (23% for HIV-negative men and 45% for HIV-positive men with a patient-collected specimen) for clinicians to be comfortable recommending no anoscopy for those with a negative cytology result if done as a one-time test.”

Researchers in Vancouver randomized 222 MSM, only 28 (13%) with HIV infection, to self-collection followed by clinician collection or vice versa. Men got swabbing kits plus an illustrated step-by-step guide. As in the San Francisco studies, self-collected samples proved moderately less likely to yield adequate samples (83% versus 92%), but this difference was highly significant \( P < 0.001 \). A pathologist detected cytologic abnormalities in 21% of self-collected samples and 21% of clinician-collected samples. Among 12 men with biopsy-confirmed high-grade AIN, abnormal cytology could be detected in 6 self-swabs (67% sensitivity) and 9 clinician swabs (80% sensitivity). Only 2 of 9 adequate self-swabs and 1 of 11 adequate clinician swabs indicated high-grade SIL.

The Vancouver team suggests adequacy of self-swabs could be improved by giving people longer swabs or having them collect two swabs and placing them in the same container.

Cost-effectiveness remains uncertain

Cost-effectiveness analyses of anal cytology screening in people with HIV yield divergent results. Two North American studies found evidence that HIV-
positive people can be screened in a cost-effective way, but an 82-study review found “little likelihood that screening any of the identified high-risk groups would generate health improvements at a reasonable cost.”

In 1999, with HIV-specific anal cytology screening in its infancy, a Harvard team published its analysis of the cost-effectiveness of screening HIV-positive MSM for anal squamous intraepithelial lesions and anal squamous cell carcinoma. Comparing no screening with several screening strategies deploying Pap testing at different intervals in a hypothetical cohort of US MSM, these researchers found that screening for anal squamous intraepithelial lesions increased quality-adjusted life expectancy at all stages of HIV disease. Annual screening at a CD4 count above or below 500 cells/mm³ yielded incremental cost-effectiveness ratios of $16,000 or $25,000 per quality-adjusted life-year saved. These investigators concluded that screening HIV-positive MSM “offers quality-adjusted life expectancy benefits at a cost comparable with other accepted clinical preventive interventions.”

In 2011 University of Toronto researchers assessed the cost-effectiveness of HPV detection, anal cytology, and high-resolution anoscopy in screening for histologic high-grade AIN in 401 HIV-positive MSM screened for anal cancer at a tertiary-care HIV clinic. They evaluated three strategies: direct high-resolution anoscopy; high-resolution anoscopy only after detection of abnormal anal cytology; and high-resolution anoscopy only after detection of cancer-causing HPV. Direct high-resolution anoscopy proved the most cost-effective approach, detecting high-grade AIN in 98 men at a cost-effectiveness of $809 per high-grade AIN case detected.

In 2006 workers at the Leeds Institute of Health Sciences conducted a comprehensive literature search that yielded 82 studies on anal cancer incidence, screening, outcomes, and costs. For HIV-positive MSM the lowest incremental cost-effectiveness ratio exceeded 44,000 pounds (about $64,000 in 2013) per quality-adjusted life-year gained. The ratio was even worse for HIV-positive women, 88,000 pounds (about $140,000 in 2013) per quality-adjusted life-year gained. These investigators caution that their analysis is limited by lack of “good-quality evidence” on the effectiveness of screening, and they see a need for further study to assess whether the screening model underestimated the impact of anal cancer.

Anal cancer expert Andrew Grulich (University of New South Wales, Sydney) observes that cost-effectiveness analyses vary so widely in their results “largely because the lack of empirical data on the natural history of [anal] HPV infection and the effectiveness of treatment means that such studies have been required to make unproven assumptions about important variables,” and he cites a five-study systematic review illustrating that point.

“Not an option to do nothing”

Taken together, research on anal cytologic screening offers no clear answer on whether to adopt this strategy in people with HIV, or at least certain groups with HIV. In an editorial reviewing these issues, Joel Palefsky proffers a considerable list of arguments against screening:

- Lack of data showing that treating high-grade AIN lowers anal cancer incidence.
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- Limited data on effectiveness of high-grade AIN treatment
- Potential adverse effects of high-grade AIN treatment
- Treating high-grade AIN would mean treating many people
- Lack of enough clinicians trained to screen and treat
- Lack of cost-effectiveness data on screening

Andrew Grulich adds two more reasons to doubt the value of widespread anal cytology in people with HIV:28

- Lofty high-grade AIN prevalence in MSM means most cases never progress to anal cancer and regression clears a “substantial proportion”
- High-grade AIN recurrence tops 70% after a single treatment and 50% after multiple treatments

Gruich believes “we desperately need biomarkers which distinguish which men with high-grade AIN are at risk of developing invasive cancer, and in which men high-grade AIN is likely to regress or remain stable.”28

Palefsky argues that it is unethical to recommend anal cytology without “a viable plan to perform a complete evaluation of an abnormal specimen.”3 But given what’s known about anal cancer prevalence in men and women with HIV, and “regardless of where one stands on the screening debate, it is clear that it is not an option to do nothing.”3 Palefsky believes clinicians should at least perform a yearly digital rectal exam in at-risk people with HIV and refer anyone with a possible tumor. When a clinical practice can offer cytology, pathology, high-resolution anoscopy, office-based treatment, and surgery, he writes, “the likelihood... that screening and treatment of high-grade AIN will be beneficial is high enough that at-risk patients should be screened.”3 A randomized trial to test this approach will start shortly in the United States, but results may not be available for 8 years.

References

HPV vaccination for people with HIV—
who, when, why?

By Mark Mascolini

Abstract: US guidelines recommend HPV vaccination for all girls and boys starting as early as age 9 and for young women or men with a weakened immune system, including those with HIV infection. Although research of HPV vaccination in HIV-positive children and adults remains far from complete, the advice makes sense for several reasons. The vaccines elicit strong immune responses against HPV types that cause cancer or warts and have proved safe in HIV-positive people studied so far. HIV-positive adults are often negative for vaccine-specific HPV types for several years after they start having sex, but they acquire those HPV types as their sexual experience continues. Infection with more high-risk HPV types boosts the risk of cancer. And adults with HIV run a higher risk of anal and cervical cancers—and precursors to those cancers—than do people without HIV.

A robust rationale supports vaccinating HIV-positive people against human papillomavirus (HPV), the cause of anal cancer and warts, and cervical, oropharyngeal, vulvar, vaginal, and penile cancer:

- HIV-positive people usually become infected with the high-risk HPV types that lead to cancer.
- The number of HPV types infecting HIV-positive people rises with age through middle age.
- Infection with more high-risk HPV types boosts the risk of cancer precursors in people with HIV.
- Anal cancer incidence is much higher in HIV-positive than negative people.
- Two HPV types, HPV-16 and HPV-18, cause about 80% of anal cancers.
- The quadrivalent HPV vaccine, Gardasil, elicits immune responses against HPV-6, HPV-11, HPV-16, and HPV-18 in men who have sex with men (MSM), HIV-positive men, and HIV-positive women.
- The quadrivalent HPV vaccine sharply lowers risk of infection with HPV-6, HPV-11, HPV-16, and HPV-18 in MSM and general-population women.
- The quadrivalent HPV vaccine lowers rates of external genital lesions and anal intraepithelial neoplasia (AIN), an anal cancer precursor, in MSM.
- The quadrivalent HPV vaccine prevents recurrent high-grade AIN in MSM.
- The quadrivalent HPV vaccine cut incidence of HPV-associated anogenital disease, cervical dysplasia, and genital warts in general-population women.
- The quadrivalent HPV vaccine is safe and immunogenic in HIV-positive 7- to 12-year-old children.

continued...
But gaps in HPV vaccine research involving HIV-positive people leave questions about how the bivalent or quadrivalent vaccine should be used in this population. (The bivalent vaccine is licensed only for preventing cervical intraepithelial neoplasia and cervical cancer.) Clinical trials have yet to demonstrate that either vaccine prevents infection with cancer-causing HPV types in people with HIV or that either vaccine prevents HPV-related disease in HIV-positive people. Some evidence suggests HPV vaccines elicit weaker immune responses in HIV-positive children than in HIV-negative children (see “Quadrivalent vaccine trials in HIV-positive children” below), and adults with HIV may have slightly impaired immune responses to vaccination.

Current guidelines stress that the quadrivalent HPV vaccine is “not a live vaccine and can be administered to persons who are immunocompromised as a result of infection (including HIV), disease, or medications.” But they caution that “the immune response and vaccine efficacy might be less than that in immunocompetent persons.”

Despite this incomplete HPV vaccine research portfolio, US guidelines on HPV vaccination specifically recommend HPV vaccination for MSM up to 26 years old and for “men and women with compromised immune systems (including HIV/AIDS) though age 26” (Table 1). HPV vaccines cannot cause HPV infection in people with compromised immunity because the vaccines consist of virus-like particles (Figure 1), not live virus. The FDA indication for the quadrivalent vaccine includes prevention of anal cancer and AIN grades 1, 2, and 3 in girls, boys, and young women and men.

Table 1. CDC advice on HPV vaccination for children and adults

- Either the bivalent or quadrivalent HPV vaccine is routinely recommended for 11- or 12-year-old girls.
- Quadrivalent HPV vaccine is routinely recommended for 11- or 12-year-old boys.
- The vaccine series can be started beginning at age 9 years.
- Vaccination is also recommended for 13- through 26-year-old females and 13- through 21-year-old males who have not completed the vaccine series.
- Quadrivalent vaccination is recommended for both men who have sex with men (MSM) and for immunocompromised men and women (including those with HIV) up to 26 years old, if they did not get fully vaccinated when they were younger.
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Figure 1. Virus-like particles, like this one from the L1 protein of HPV-16, make up the bivalent and quadrivalent HPV vaccines. These particles cannot cause HPV infection. (From Centers for Disease Control and Prevention.)

HPV vaccination requires three doses, with the second dose given 1 to 2 months after the first and the third dose 6 months after the first. Clinical trials and a 46-million dose record in the United States through June 2012 show that both vaccines are safe. Mild injection site pain, fever, dizziness, and nausea are the most frequent adverse events.

This article reviews studies establishing the rationale for HPV vaccination of HIV-positive people and trials testing HPV vaccines in women, MSM, and adults and children with HIV.

**HPV rates and change with age in people with HIV**

Ideally, youngsters (with or without HIV) should get an HPV vaccine course before become sexually active and thus exposed to HPV types that can cause cancers or warts. US guidelines recommend HPV vaccination only up to age 26 in women and men because evidence does not support vaccine efficacy in older people. People who pick up HIV during sex are often avidly sexually active, so many of them eventually accumulate most or all of the HPV types covered by the bivalent and quadrivalent vaccines, HPV-6, 11, 16, and 18.

But despite frequent sex, many younger HIV-positive people—prime HPV vaccine candidates—remain free of HPV types that cause cancer into their 20s and beyond, so reason suggests they may continue to benefit from HPV vaccination beyond their 26th birthday. HPV status is anything but stable. HIV clinicians used to thinking of a single-stranded RNA virus that becomes entwined in a person’s genome—almost always for life—can easily forget that HPV is a double-stranded DNA virus that comes and goes as unpredictably as rhinorrhea throughout a person’s sex life. One meta-analysis charted HPV-16 prevalence at 35% in HIV-positive men, incidence at...
13% yearly, and clearance at 15% yearly. And HPV is the most frequently sexually transmitted virus in the United States.

But HPV’s comings and goings in sexually active people are complicated, as Joel Palefsky (University of California, San Francisco) explains in an interview in this issue of RITA! A person may be exposed to an HPV type early in their sexual life. Over time, that person’s immune response to that HPV type wanes, and the response may wane so much that standard testing cannot detect that type. So a person may test negative for HPV-16, for example, despite prior infection with that type. Whether that person can benefit from HPV vaccination in the same way as a person never infected with HPV-16 remains unknown.

A phase 2 clinical trial testing the immune activity and safety of the quadrivalent HPV vaccine in 16- to 23-year-old HIV-positive women at 14 US sites found that 75% tested positive for one or more HPV types, but only 53.5% had one or more high-risk (cancer-causing) types, only 12% had HPV-16, and only 5% had HPV-18. Almost half of these young women (45.5%) were HPV DNA negative and seronegative for both HPV-16 and 18, the two cancer-causing types covered by the HPV vaccines.

These 99 women averaged 21.4 years in age. One third of them (32%) had 6 to 10 lifetime male sex partners, and 38% had more than 10. Two thirds had vaginal sex twice or more in the past 90 days. So most of these young women could be called moderately or highly sexually active, but at this young age most could probably still shield themselves from the two foremost causes of cervical and anal cancer, HPV-16 and 18. It’s easy to imagine that some portion of these women would remain free of HPV-16 and 18 beyond age 26, the current cutoff age for HPV vaccination in the United States.

Researchers screening 235 HIV-positive US men for a quadrivalent HPV vaccine trial found that only 23% tested positive for HPV-16 and only 10% for HPV-18. These men had a median age of 44 (interquartile range [IQR] 37 to 50), almost 2 decades beyond the 26-year-old vaccine guideline cutoff. But as noted three paragraphs above, these men may have been exposed to HPV-16 and 18 and lost a detectable signal of that infection over time. Almost one third of these men (30%) already had high-grade AIN, which proved more prevalent in men with than without HPV-16 (38% versus 17%, \( P = 0.01 \)).

A longitudinal study of 146 HIV-negative and 227 HIV-positive young women at 15 US sites found that 70% tested positive for at least 1 of 30 HPV types analyzed when follow-up began. Of the young women who tested negative at the baseline visit, 70% picked up at least 1 HPV type during follow-up. But incidence and prevalence of the high-risk HPV types targeted by current HPV vaccines (16 and 18) proved less frequent than other HPV types such as 31, 33, 35, 53, 58, 66, 68, and 70, especially in HIV-positive participants.

Among young women with HIV, prevalence rates of HPV-16 and 18 were 17% and 8% before they began antiretroviral therapy (ART) and 10% and 6% after they began. Incidence rates of types 16 and 18 before ART were 6.5% and 6.7% and after ART 6.3% and 7.3%. Cohort members had a median age of 17 (interquartile range [IQR] 16 to 18) and a median of 6 lifetime sex partners (IQR 3 to 11). Despite this
level of sexual activity, a large majority of these young women could still probably protect themselves from HPV-16 and 18 through vaccination.

National Health and Nutrition Examination Surveys of 4150 US women from 14 through 59 years old found that 42.5% had at least one type of HPV, but only 4.7% had cancer-causing HPV-16 and only 1.8% had cancer-causing HPV-18. Prevalence of any HPV type was lowest in 14-to-19-year-olds (32.9%), peaked in 20-to-24-year-olds (53.8%), and fell back to 38.8% in 50-to-59-year-olds. Prevalence of high-risk HPV types rose more than 70% from the 14-to-19 age group to the 20-to-24 group then fell in each older age group (Figure 2).

A National Health and Nutrition Examination Survey in 2003 and 2004 considered only the HPV types covered by the quadrivalent vaccine and included both women and men. This 4303-person analysis of 14-to-59-year-olds found higher overall seroprevalence of HPV-6, 11, 16, and 18 in women (17.0%, 7.1%, 15.6%, and 6.5%) than in men (6.3%, 2.0%, 5.1%, and 1.5%) ($P < 0.001$ for all comparisons). This survey charted increasing seroprevalence of the four vaccine-covered HPV types to age 39. For any of the four types, prevalence rose with age from a low of 9.3% at 14 to 19 years to 23.2% at 20 to 24 years, 34.9% at 25 to 29 years, 42.0% at 30 to 39 years, and 40.9% at 40 to 49 years ($P < 0.001$). Prevalence of these four types declined only at age 50 to 59, to 29.7%. Seroprevalence of HPV-16, the chief cause of anal cancer, rose through age 30 to 39 before falling (Figure 3). These findings suggest that some portion of US men and women could continue to protect themselves from the HPV types countered by the quadrivalent vaccine beyond the age of 26, the current age cutoff in US HPV vaccine guidelines.

Figure 2. In surveys of 4150 US women from 2003 through 2006, high-risk (cancer-causing) HPV prevalence peaked in young adults then fell gradually over the following years. (Source: Hariri S et al.)
A survey of 1427 HIV-negative and 245 HIV-positive Australian MSM found that HPV-16 incidence (the new-infection rate) rose in both groups over time.\textsuperscript{13} For HIV-positive men, HPV-16 seroincidence measured 1.3 per 100 person-years, meaning more than 1 of every 100 men picked up HPV-16 every year. For HIV-negative men, HPV-16 seroincidence stood at 3.1 per 100 person-years, meaning about 3 of every 100 men got infected every year. In the HIV-negative group, HPV-16 incidence remained above 3\% each year until age 45. Sexual risk behaviors raised chances of new HPV-16 infection. Again these findings suggest that some sexually active people can continue to benefit from HPV vaccination into their 30s and perhaps beyond.

In a 2010-2013 study of 98 MSM with HIV and 242 MSM without HIV, this Australian team tracked new infection with an HPV type covered by the quadrivalent vaccine or the experimental nonavalent vaccine (\textbf{Table 2}).\textsuperscript{14} Despite a median age of 49 years and an age range from 35 to 79, 1 in 5 men picked up at least one quadrivalent HPV type every year and more than 1 in 4 picked up at least one nonavalent type. HPV-16 incidence over these 3 years was 5.3 per 100 person-years. Compared with HIV-negative men, those with HIV had 80\% higher odds of acquiring a nonavalent HPV type during follow-up. Because of these findings, the researchers argued that “prophylactic quadrivalent or nonavalent vaccination of older homosexual men would prevent future HPV-associated disease.”

Should clinicians offer HPV vaccination to at-risk HIV-positive people older than 26? Although he cautions that authorities do not recommend vaccination for anyone over 26 and that more research must be completed to address this question, Timothy Wilkin (Weill Cornell Medical College, New York) tells \textit{RITA!} his personal belief is that providers should be vaccinating all HIV-positive people because they run a substantially greater risk of HPV-related conditions and “even a partially effective vaccine would be attractive from a cost-benefit perspective.”

\begin{figure}
\centering
\includegraphics[width=\textwidth]{hpv-16-prevalence.png}
\caption{Prevalence of HPV-16, the leading cause of anal cancer, up to age 39, peaked only at age 30 to 39 in a 4303-person US analysis in 2003 and 2004. (Source: Markowitz LE, et al.\textsuperscript{12})}
\end{figure}
More HPV types boost anal precancer risk

Studies of HIV-positive and negative MSM in the United States, Canada, and Spain yield another line of evidence supporting HPV vaccination even after men start adding HPV types during sex: infection with more HPV types inflates chances of more advanced AIN. So halting further acquisition of HPV types through vaccination may cut the risk of these anal precancers.

A US National Cancer Institute study involved 363 HIV-positive MSM genotyped for HPV and tested for low- to high-grade AIN.\textsuperscript{15} HPV-16, the prime cause of anal cancer, could be detected in 26.4\% of all men and in 55\% of those with high-grade AIN. Prevalence of two or more cancer-causing HPV types rose from 30.9\% in men with AIN below grade 1 to 76.3\% in men with grade 3 AIN ($P < 0.001$). Through modeling, the investigators estimated that up to 61.5\% of high-grade AIN in these HIV-positive men were caused HPV-16 or 18 (targeted by the bivalent and quadrivalent vaccines) and up to 89.4\% were caused by HPV types 16, 18, 31, 33, 45, 52, and 58 (targeted by the nonavalent vaccine) (Table 2).

Table 2. HPV: the virus and the vaccines

<table>
<thead>
<tr>
<th>High-risk HPV types: can cause anal, cervical, vulvar, vaginal, penile, and oropharyngeal cancer</th>
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<tbody>
<tr>
<td>16\textsuperscript{*}</td>
</tr>
<tr>
<td>B</td>
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<tr>
<td>Q</td>
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<td>N</td>
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<table>
<thead>
<tr>
<th>Low-risk HPV types: can cause benign or low-grade cervical cell abnormalities, anal and genital warts, and laryngeal papillomas</th>
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</thead>
<tbody>
<tr>
<td>6\textsuperscript{†}</td>
</tr>
<tr>
<td>Q</td>
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<tr>
<td>N</td>
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\textsuperscript{*} HPV-16 and 18 cause about 80\% of anal cancers and 70\% of cervical cancers.
\textsuperscript{†} HPV-6 and 11 cause about 90\% of anogenital warts.
B, covered by the bivalent vaccine (Cervarix),
N, covered by the nonavalent vaccine (investigational),
Q, covered by the quadrivalent vaccine (Gardasil).

From: Centers for Disease Control and Prevention. Pink Book. HPV.  
A cross-sectional study of 1262 HIV-negative 18- to
89-year-old MSM in four US cities found that 15% had low-grade AIN and 5% had high-grade AIN, and those rates did not change with age. Study participants had a median age of 37, and they had their first receptive anal intercourse at a median age of 20. These men had a median of eight sex partners and three receptive anal sex partners in the past 6 months. And sexual activity did not slow with age: Men younger than 35 and men 35 to 49 had a median of eight partners in the past 6 months, while men 50 or older had a median of 10. “The high prevalence of HPV-related anal disease at all age groups,” the researchers proposed, “reflects a population that continues to have a large number of new sexual exposures over many decades of life.”

Anal HPV infection tripled the odds of high-grade AIN (odds ratio [OR] 3.2, 95% CI 1.1 to 9.4, \( P = 0.039 \)), while infection with an increasing number of HPV types independently boosted chances of both low-grade and high-grade AIN (\( P < 0.001 \) for both linear trends). Compared with men who carried no anal HPV types, those with three or four types had 5 times higher odds of high-grade AIN (OR 5.2, 95% CI 1.7 to 16) and those with five or more types had 55 times higher odds (OR 55, 95% CI 5.4 to 565).

A study of 224 HIV-positive Canadian men with a history of receptive anal intercourse and a median age of 44 (interquartile range [IQR] 38 to 50) identified HPV-16 and 18 as the most common cancer-causing HPV types (38% and 19%), followed by HPV-45 (22%) and HPV-52 (19%). While 43% of these men had a current steady partner, 56% had a median of 5 casual partners. Compared with men who had normal anal histology or grade 1 AIN, those with grade 2 or 3 AIN had a significantly higher number of HPV types per anal swab—5 versus 3.5 (\( P = 0.0005 \)). HPV-16 load was significantly higher in men with grade 2 or 3 AIN than in those with grade 1 AIN or normal histology (5.18 versus 4.73 log10 copies per 10,000 cells, \( P = 0.003 \)). Logistic regression analysis determined that infection with HPV-16 more than doubled the odds of grade 2 or 3 AIN (OR 2.58, 95% CI 1.31 to 5.08, \( P = 0.006 \)), while infection with HPV-31 (covered by the nonavalent vaccine) upped the odds almost 5 times (OR 4.74, 95% CI 2.00 to 11.22, \( P = 0.0004 \)).

A Spanish study of 551 HIV-positive MSM who had anal liquid cytology through April 2011 found a large majority (81.7%) with high-risk (cancer-causing) HPV and more than three quarters (77.7%) with two or more high-risk HPV types. Prevalence of grade 1 to 3 AIN in 450 valid samples was 54.7%. Number of high-risk HPV genotypes was the only variable associated with AIN risk: Compared with men who had only one high-risk HPV type, those with five or more had 7.4 times higher odds of AIN (95% CI 2.8 to 19.6). Age, education, smoking, geographical origin, CD4 count, antiretroviral therapy, and number of sex partners did not predict AIN in this analysis.

A 4-city US study reviewed in the article “Risk factors for anal lesions” documents a higher risk of abnormal anal cytology in HIV-positive women and men infected with more high-risk anal HPV types (Table 1, Conley 2010).
Multiple HPV types more frequent in people with HIV

The correlation between number of HPV types and AIN risk, reviewed in the preceding section, is especially troubling because several studies show that HIV-positive people are more likely than others to harbor multiple HPV types.

In 1990s researchers analyzed anal HPV types in 346 MSM with HIV and 262 HIV-negative MSM in San Francisco.20 HIV-positive men averaged 42 years in age and HIV-negative men 45 years. Men with HIV reported significantly more receptive anal intercourse than men without HIV.

Nearly two thirds of HIV-negative men (61%) and almost all HIV-positive men (93%) had anal HPV DNA detectable by polymerase chain reaction.20 HPV-16, the top cause of anal cancer, proved the most prevalent type in both groups of men. Three quarters of HIV-positive men (73%) versus one quarter of HIV-negative men (23%) had multiple HPV types. In men with HIV, lower CD4 count was associated with more cancer-causing HPV types.

A 2009 meta-analysis of 93 studies from four continents reckoned HPV rates in people with vulvar, vaginal, or anal intraepithelial neoplasia grades 1 to 3 and carcinoma.21 The anal neoplasia studies included 14 from North America, 13 from Europe, and 2 from Asia. Among 671 people with AIN grade 1, 609 with AIN grade 2 or 3, and 955 with anal carcinoma, HPV rates were 91.5%, 93.9%, and 84.3%. Among people with AIN 2/3, HPV prevalence was significantly higher in people with than without HIV (96.7% versus 90.1%, P = 0.0075). And people with HIV had much higher odds of infection with multiple HPV types (OR 12.6, 95% CI 7.05 to 22.51).

A 2008 retrospective study of anal cancer patients at 16 French centers confirmed that almost everyone (96.7%) had detectable HPV, 91% had at least one high-risk HPV genotype, and 78% had HPV-16 and or 18.22 Fifty people had HIV, 48 were HIV-negative, and the rest had an unknown HIV status. Median age at anal cancer diagnosis was almost two decades younger in people with HIV than without HIV (46 versus 65 years, P < 0.001).

Among people with multiple HPV types, HPV-16 plus HPV-18 were more frequent in the HIV group (3.8%) than the HIV-negative group (2.2%) or the status-unknown group (3.0%). HPV-16 plus other high-risk types (excluding HPV-18) were more prevalent with HIV than in the other two groups (15.4% versus 6.5% versus 6.3%). The same held true for HPV-18 plus other high-risk types (excluding HPV-16) (11.5% versus 0% versus 0.7%). Multiple HPV infections occurred in 56% of people with HIV and 19.6% of HIV-negative people (P < 0.001).

Theoretical HPV vaccine impact on AIN or anal cancer with HIV

Both the just-discussed French study22 and the meta-analysis23 found a relative under-representation of HPV-16 in people with than without HIV, and a relative over-representation of other high-risk HPV types in the HIV group. But in the French study low rates of HPV-16 as a single detected HPV type or combined with low-risk genotypes, rather than combined with high-risk genotypes, explains this difference. The meta-analysis did not make this distinction in comparing HPV-16 prevalence in people with and without HIV. Several studies reviewed above5,7,9,10,15,20 found HPV-16 more prevalent than HPV-18 or other high-risk HPV types in HIV-positive people.
No one doubts that HPV-16 dominates development of anal cancer. The American Cancer Society estimates that 80% of anal cancers can be traced to HPV-16 and 18.\textsuperscript{23} In the French study of anal cancer patients with and without HIV, 75% had HPV-16, followed by HPV-11 (7%), HPV-18 (6%), HPV-6 (6%), and HPV-52 (5%).\textsuperscript{22}

A study of 342 Australian MSM with or without HIV found that HPV-16 infection raised chances of newly detected high-grade AIN and lowered chances that high-grade AIN would be cleared.\textsuperscript{24} The study group had a median age of 49 (range 35 to 79), 98 (28.7%) had HIV infection, and 87 of those 98 (88.9%) were taking antiretroviral therapy. At the baseline visit in this 3-year study, 128 men (37.4%) had high-grade AIN, and prevalence was nonsignificantly higher in men with HIV (44.9% versus 34.4%, \( P = 0.072 \)). High-grade AIN developed in 32 of 149 men without that diagnosis at baseline (21.5%) after an average 1 person-year of follow-up. Among 80 men with high-grade AIN at their first visit and at least one follow-up visit, the condition regressed to normal or to low-grade lesions in 35 (43.8%).

HIV infection did not affect risk of new or cleared high-grade AIN in this analysis, but baseline HPV-16 tripled chances (hazard ratio [HR] 3.00, 95% CI 1.46 to 6.16, \( P = 0.003 \)), any baseline high-risk HPV quadrupled chances (HR 4.35, 95% CI 1.67 to 11.35, \( P = 0.003 \)), and baseline HPV-18 quintupled chances (HR 5.00, 95% CI 1.73 to 14.44, \( P = 0.003 \)).\textsuperscript{24} Baseline HPV-16 lowered chances of high-grade AIN clearance 80% (HR 0.20, 95% CI 0.08 to 0.49, \( P < 0.001 \)), while any baseline high-risk HPV cut clearance chances 64% (HR 0.36, 95% CI 0.17 to 0.75, \( P = 0.006 \)). These findings imply that protecting MSM from HPV-16 and 18 with an HPV vaccine could have a substantial impact on AIN development.

As discussed above, US National Cancer Institute researchers estimate that high fractions of high-grade AIN in HIV-positive MSM can be attributed to HPV types covered by the licensed bivalent and quadrivalent vaccine or by the investigational nonavalent vaccine\textsuperscript{15} (Table 2). This analysis involved 363 HIV-positive MSM evaluated for HPV genotype and high-grade AIN. HPV-16 proved the most frequent genotype in the whole study group (26.4%) and in men with high-grade AIN (55%). The NCI team used modeling to figure that 12% to 61.5% of high-grade AIN cases could be attributed to HPV types 16 or 18 (covered by the bivalent or quadrivalent vaccine), while 39% to 89.4% of cases could be attributed to HPV types 16, 18, 31, 33, 45, 52, and 58 (covered by the nonavalent vaccine). The researchers believe their results “suggest that licensed and investigational HPV prophylactic vaccines have the potential to prevent a substantial proportion of high-grade AIN cases in this population.”

**HPV vaccine studies in women**

Placebo-controlled trials establish that the quadrivalent vaccine protects women in the general population from HPV-related disease, including cervical cancer, and researchers have begun to study this vaccine in HIV-positive women.

One notable trial of 552 general-population women 16 to 23 years old found that the quadrivalent vaccine lowered rates of HPV-6/11/16/18-related persistent infection or disease by 96% compared with placebo.
after 5 years of follow-up. Neither precancerous cervical dysplasia nor genital warts developed in any woman who received the vaccine while six cases emerged in the placebo group to yield a 100% efficacy rate (95% CI 12% to 100%) by this measure. Another placebo-controlled trial involving 5455 general-population women with an average 3 years of follow-up found that the quadrivalent vaccine had 100% efficacy as measured by either of two primary composite endpoints in these 16-to-24-year-olds: (1) incidence of genital warts, vulvar or vaginal intraepithelial neoplasia, or cancer, and (2) incidence of cervical intraepithelial neoplasia, adenocarcinoma in situ, or cancer associated with HPV type 6, 11, 16, or 18.

The quadrivalent vaccine has not been evaluated for prevention of anal HPV infection, AIN, or anal cancer in women, but it is licensed for prevention of AIN grades 1, 2 and 3 and anal cancer caused by HPV-16 or 18 in girls and women 9 to 26 years old. Prescribing information notes that “the similarity of HPV-related anal disease in men and women supports bridging the indication of prevention of AIN and anal cancer [in men] to women.” (Cervarix, the bivalent vaccine, is licensed for prevention of cervical cancer, cervical intraepithelial neoplasia, and adenocarcinoma caused by HPV-16 and 18 in girls and women 9 through 25 years old; it is not licensed for men or for prevention of AIN or anal cancer in women.)

Reports on the first quadrivalent vaccine trials in HIV-positive women appeared in 2012 and 2013. These trials did not aim to see whether the vaccine prevents HPV infection or HPV-related disease in women with HIV. But the studies produced strong evidence that the quadrivalent or bivalent vaccine elicits robust immune responses against HPV-6, 11, 16, and 18 in HIV-positive women taking or not taking antiretrovirals.

As discussed above, a phase 2 clinical trial assessing the immune activity and safety of the quadrivalent HPV vaccine in 16-to-23-year-old HIV-positive women at 14 US sites found that only 12% had HPV-16 and only 5% had HPV-18—the cancer-causing HPV types covered by the vaccine—when they entered the study. Four weeks after women got the third vaccine dose, immunogenicity was high when measured as geometric mean titers of antibodies to the four HPV types or seroconversion rates for HPV-6, 11, 16, and 18.

Most women (80%) were non-Hispanic black, 16% were Hispanic, and 4% were non-Hispanic white. Sixty-nine of these women (70%) were not taking antiretrovirals and 30 were. CD4 counts averaged 613 cells/mm³, and only 1 study participant had an initial CD4 count below 200 cells/mm³. To put immune response rates in context, the researchers compared geometric mean titers and seroconversion rates in these women with those in 276 healthy HIV-negative women from Brazil, Europe, and the United States who received the same vaccine.

Geometric mean antibody titers did not differ significantly between the antiretroviral-treated group and the HIV-negative comparison group, while antiretroviral-untreated women had significantly lower titers against HBV-16 and 18 than the comparison group (Table 3). Seroconversion rates were 92% or higher for all HPV types in both treated and untreated HIV-positive women (Table 3). Untreated women had a significantly lower HPV-18 seroconversion rate than the historical comparison group.
Pain proved the most frequent local adverse event, affecting 26.3% of women. Only 1 woman gauged this pain as moderate, while the others called it mild. Fever affected 12.1% of women, with the highest fever rated grade 2 (38.7 to 39.3°C). There was only one severe systemic adverse event, grade 3 fatigue. The investigators recorded no severe or life-threatening lab abnormalities.

The researchers proposed that the slightly better immune responses among women taking antiretrovirals “suggest that treatment with ART could have a positive influence on response to vaccination, and provide support for current recommendations of the Advisory Committee on Immunization Practices to vaccinate HIV-infected individuals.”

### Table 3. Geometric mean titers and seroconversion rates with quadrivalent vaccine in 99 women with HIV

<table>
<thead>
<tr>
<th></th>
<th>Geometric mean titer (mMu/mL)</th>
<th>Seroconversion rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No-ART group</td>
<td>ART group</td>
</tr>
<tr>
<td>HPV-6</td>
<td>658</td>
<td>1294</td>
</tr>
<tr>
<td>HPV-11</td>
<td>727</td>
<td>1522</td>
</tr>
<tr>
<td>HPV-16</td>
<td>2393</td>
<td>5046</td>
</tr>
<tr>
<td>HPV-18</td>
<td>463</td>
<td>979</td>
</tr>
</tbody>
</table>

**ART**, antiretroviral therapy; **NS**, not statistically significant.

* No-ART group versus HIV-negative group.
† No-ART group versus ART group.

Source: Kahn JA et al.

The researchers proposed that the slightly better immune responses among women taking antiretrovirals “suggest that treatment with ART could have a positive influence on response to vaccination, and provide support for current recommendations of the Advisory Committee on Immunization Practices to vaccinate HIV-infected individuals.” Even women not taking antiretrovirals, the researchers noted, almost always had immune responses shown in previous studies to protect against persistent HPV infection and development of HPV-related genital lesions.
Another quadrivalent vaccine trial, ACTG 5240, involved 315 HIV-positive women in the United States (83% of participants), Brazil, and South Africa. Women in this trial were older than in the just-described US study, with a median age of 36 years (IQR 30 to 41), and the investigators divided them into three groups: (1) stratum A, 127 women with a CD4 count above 350 cells/mm³ when they entered the trial, (2) stratum B, 95 women with a CD4 count of 201 to 350 cells/mm³ at study entry, and (3) stratum C, 93 women with a baseline CD4 count at or below 200 cells/mm³. Researchers presented results on the first two strata at the 2012 International AIDS Conference, and results for all three strata appear on ClinicalTrials.gov.

More than half of the 315 women (56%) were black, 30% Hispanic, and 11% white. Median nadir CD4 count stood at 179 cells/mm³. Two thirds of women (66%) were taking antiretroviral therapy, and 64% had a viral load below 10,000 copies/mL. Baseline seronegativity rates for HPV-6, 11, 16, and 18 were 52%, 72%, 61%, and 72% in stratum A, 63%, 76%, 68%, and 87% in stratum B, and 60%, 79%, 72%, and 78% in stratum C.

Geometric mean titers against each genotype and seroconversion rates for women negative at entry were generally high in all three groups (Table 4), though lower than in the US study of younger women (Table 3) and lower in stratum C than in stratum A or B. The somewhat lower response rates in stratum C—women who started the study with a CD4 count below 201 cells/mm³—provide the first such evidence in people with HIV. The vaccine had a good safety profile in these 315 women, with 3 serious adverse events in stratum A (2.4%), 1 in stratum B (1.05%), and 2 in stratum C (2.15%).

### Table 4. Geometric mean titers and seroconversion rates with quadrivalent vaccine in 315 women with HIV

<table>
<thead>
<tr>
<th>Geometric mean titer (mMu/mL)</th>
<th>Seroconversion rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stratum A</td>
</tr>
<tr>
<td></td>
<td>CD4s &gt; 350</td>
</tr>
<tr>
<td>HPV-6</td>
<td>462.3</td>
</tr>
<tr>
<td>HPV-11</td>
<td>476.5</td>
</tr>
<tr>
<td>HPV-16</td>
<td>1199.9</td>
</tr>
<tr>
<td>HPV-18</td>
<td>175.0</td>
</tr>
</tbody>
</table>

Source: ClinicalTrial.gov. ACTG 5240.
A completed phase 2 trial of the bivalent vaccine in 54 HIV-positive women and 24 HIV-negative women from 18 to 25 years old also found good HPV-16 and 18 seroconversion rates and geometric mean titers.\textsuperscript{31} HPV vaccination began in late 2006 in the United States, and a large survey of girls and women suggests a significant impact among 14- to 19-year-olds.\textsuperscript{32} CDC researchers compared prevalence of HPV-6, 11, 16, or 18 in 2003-2006 (the prevaccine era) and 2007-2010 (the vaccine era) in more than 8000 girls and women from 14 to 59 years old. By 2010 only 32\% of 13- to 17-year-olds, a prime target group, had been vaccinated. Nevertheless, among 14- to 19-year-olds, cervicovaginal prevalence of one of the four HPV types fell from 11.5\% (95\% CI 9.2 to 14.4) in 2003-2006 to 5.1\% (95\% CI 3.8 to 6.6) in 2007-2010, a 56\% drop. HPV prevalence did not drop from one period to the next in older women.

### HPV vaccine studies in men

For boys and men 9 to 26 years old, Gardasil, the quadrivalent HPV vaccine, is licensed for prevention of (1) anal cancer caused by HPV-16 and 18, (2) genital warts caused by HPV-6 and 11, and (3) grades 1 to 3 AIN caused by HPV-6, 11, 16, and 18.\textsuperscript{27} Those indications rest on results of a placebo-controlled trial involving 4065 healthy boys and men 16 to 26 years old, 602 of whom (15\%) were MSM and none of whom had HIV infection.\textsuperscript{33} Although this 18-country study excluded men with HIV, US vaccine advice specifically recommends the quadrivalent vaccine for “men and women with compromised immune systems (including HIV/AIDS), though age 26,”\textsuperscript{3} because of other findings reviewed below.

The 4065-person placebo-controlled trial had a per-protocol population (in which participants got all three vaccine doses and none had HPV-6, 11, 16, or 18 at study entry) and an intention-to-treat population (in which participants got one or more doses and could have one or more of the vaccine-targeted HPV types).\textsuperscript{33} In the intention-to-treat population, vaccine efficacy in preventing external genital lesions measured 60.2\% (65.5\% for lesions related to one of the four HPV types targeted by the vaccine). In the per-protocol population, vaccine efficacy in preventing external genital lesions related to one of the four vaccine-targeted HPV types was 90.4\%.

These investigators conducted a substudy of the 602 MSM to see if the quadrivalent vaccine prevented anal HPV infection, AIN, and anal cancer.\textsuperscript{34} Again they scrutinized results by intention-to-treat and per-protocol analyses, as defined in the preceding paragraph. Study participants gave serum specimens for HPV serology testing and sequential anal swabs for anal cytology analysis and HPV DNA testing.

All study participants were 16 to 26 years old, and none of these MSM had HIV infection. The men lived in Australia, Brazil, Canada, Croatia, Germany, Spain, and the United States. They had 5 or fewer lifetime sex partners but had anal intercourse with another boy or man in the past year. None had a history of anogenital warts or AIN.

At the baseline visit, only 27.4\% of men were seropositive or HPV DNA positive for HPV-6 or 11, only 16.4\% were positive for HPV-16, and only 11.3\% were positive for HPV-18. Almost three quarters of men (71.8\%) had completed the planned 36 months of follow-up when the investigators ended the study.
In 598 men included in the intention-to-treat and per-protocol analyses, vaccine efficacy was usually significant for AIN by HPV type and lesion type (Table 5). No cases of anal cancer developed during the study in this young population.

Table 5. Quadrivalent vaccine efficacy against AIN in 598 HIV-negative MSM

<table>
<thead>
<tr>
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<th>Events/100 p-y with vaccine</th>
<th>Events/100 p-y with placebo</th>
<th>Efficacy (95% CI)</th>
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<tr>
<td><strong>Intention-to-treat analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIN due to any HPV type</td>
<td>13.0</td>
<td>17.5</td>
<td>25.7% (–1.1 to 45.6), not significant</td>
</tr>
<tr>
<td>AIN due to HPV-6, 11, 16, or 18</td>
<td>6.3</td>
<td>12.6</td>
<td>50.3% (25.7 to 67.2)</td>
</tr>
<tr>
<td>AIN due to HPV-16 or 18</td>
<td>1.8</td>
<td>4.0</td>
<td>55.2% (8.5 to 79.3)</td>
</tr>
<tr>
<td>AIN grade 1</td>
<td>5.0</td>
<td>9.9</td>
<td>49.6% (21.2 to 68.4)</td>
</tr>
<tr>
<td>AIN grade 2 or 3</td>
<td>2.7</td>
<td>6.0</td>
<td>54.2% (18.0 to 75.3)</td>
</tr>
<tr>
<td>AIN grade 2</td>
<td>1.6</td>
<td>4.3</td>
<td>61.9% (21.4 to 82.8)</td>
</tr>
<tr>
<td>AIN grade 3</td>
<td>1.5</td>
<td>2.8</td>
<td>46.8% (–20.2 to 77.9) not significant</td>
</tr>
<tr>
<td><strong>Per-protocol analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIN due to any HPV type</td>
<td>4.0</td>
<td>8.9</td>
<td>54.9% (8.4 to 79.1)</td>
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<tr>
<td>AIN due to HPV-6, 11, 16, or 18</td>
<td>1.3</td>
<td>5.8</td>
<td>77.5% (39.6 to 93.3)</td>
</tr>
<tr>
<td>AIN due to HPV-16 or 18</td>
<td>0.5</td>
<td>2.4</td>
<td>78.6% (–0.4 to 97.7) not significant</td>
</tr>
<tr>
<td>AIN grade 1</td>
<td>1.0</td>
<td>3.9</td>
<td>73.0% (16.3 to 93.4)</td>
</tr>
<tr>
<td>AIN grade 2 or 3</td>
<td>0.8</td>
<td>3.1</td>
<td>74.9% (8.8 to 95.4)</td>
</tr>
<tr>
<td>AIN grade 2</td>
<td>0.5</td>
<td>2.2</td>
<td>75.8% (–16.9 to 97.5) not significant</td>
</tr>
<tr>
<td>AIN grade 3</td>
<td>0.5</td>
<td>1.4</td>
<td>63.7% (–103.0 to 96.4) not significant</td>
</tr>
</tbody>
</table>

*Defined in text.
AIN, anal intraepithelial neoplasia; p-y, person-years.
Source: Palefsky JM et al.34

continued...
Adverse event rates did not differ between the vaccine group and the placebo group. Most study participants (about 58%) in both treatment arms reported injection-site reactions, and fewer than 1.5% in each arm reported a severe injection-site reaction. About 18% in each group had a vaccine-related systemic reaction, and no one had a serious vaccine-related adverse event.

The researchers note that quadrivalent vaccine efficacy would be best if boys got vaccinated before becoming sexually active. They observed that identifying gay or bisexual boys at such an early age is impractical, but all boys would benefit from HPV vaccination if clinicians followed US advice to vaccinate boys at age 11 or 12.

The authors suggest that quadrivalent vaccination could prevent HPV-related disease in men, perhaps even cancer. “Just as the prevention of cervical intraepithelial neoplasia of grade 2 or 3 is expected to reduce the risk of cervical cancer in vaccinated women,” they propose, “prevention of anal intraepithelial neoplasia of grade 2 or 3 is expected to reduce the risk of anal cancer among vaccinees.”

Further analyses of heterosexual men and MSM in this trial showed that immunogenic responses to the quadrivalent vaccine were comparable to those observed in women and that adverse events were usually mild or moderate and comparable in the vaccine group and the placebo group.

A nonrandomized single-center cohort study turned up evidence that the quadrivalent vaccine prevents recurrence of treated high-grade AIN in HIV-negative MSM. Researchers at Mount Sinai School of Medicine in New York City compared 88 vaccinated men with 114 unvaccinated men. Only 16% of these men were younger than 30 years old, and one third of the vaccinated group was 40 or older.

During 340 person-years of follow-up, high-grade AIN developed in 13.6% of vaccinated men versus 30.7% of unvaccinated men. Multivariate analysis determined that vaccination halved the risk of recurrent high-grade AIN 2 years after study entry (hazard ratio 0.50, 95% CI 0.26 to 0.98, P = 0.004). Among men infected with cancer-causing HPV types, the vaccine also halved the rate of recurrent high-grade AIN 2 years after study entry (hazard ratio 0.47, 95% CI 0.22 to 1.00, P = 0.05). Sexually transmitted infection rates after study entry suggested that changing sexual behavior did not explain the differences between vaccinated and unvaccinated men. “If our results are confirmed by a randomized, placebo-controlled trial,” the authors suggested, “then indications for vaccination and the age of the target population should be expanded.”

AIDS Malignancy Consortium Protocol 052 established the safety and immunogenicity of the quadrivalent vaccine in HIV-positive men 22 to 67 years old. This single-arm, open-label trial involved 112 men enrolled in 2008 at eight US sites who were at least 18 years old, had a CD4 count at or above 200 cells/mm³ and a viral load below 200 copies/mL if taking antiretroviral therapy, or above 350 cells/mm³ if not taking antiretrovirals. They could not have high-grade AIN or anal cancer. Men received the quadrivalent vaccine at entry, at week 8, and at week 24. Four weeks after the last dose, the investigators evaluated participants for seroconversion to the four vaccine types and for adverse events.
Median age stood at 44, 63% of men were white, 18% Hispanic, 13% black, and 5% Asian. Median CD4 count measured 517 cells/mm³ (IQR 423 to 680), and 84% of men were taking combination antiretroviral therapy. Among men negative for the four vaccine HPV types at study entry, 59 of 60 seroconverted for type 6, 67 of 68 for type 11, 62 of 62 for type 16, and 74 of 78 for type 18. Antibody titers were about 40% of those measured in young HIV-positive men with no history of sex with other men but were similar to those of young HIV-negative MSM. Among 109 men who got at least one vaccine dose, there were no grade 3 or worse adverse events attributable to vaccination. The vaccine had no substantial impact on CD4 counts or viral load.

An ACTG trial is assessing efficacy of the quadrivalent vaccine in preventing anal HPV infection and high-grade AIN in HIV-positive men and women. NCT01461096 is a phase 3 double-blind placebo-controlled trial currently recruiting HIV-positive men or women at least 27 years old. Participants cannot have any HPV-related cancer or anal, cervical, or vaginal cytological results that may indicate invasive carcinoma at any point before study entry. The primary endpoint is time to first new persistent infection of HPV-6, 11, 16, or 18. Secondary endpoints include biopsy-proved high-grade AIN. Another quadrivalent vaccine trial, NCT01512784, is enrolling HIV-positive and negative youth and young adults from 13 to 27 years old in Italy. The primary endpoint is type-specific antibody titers for the quadrivalent HPV types 1 month after participants take three doses.

More than 96% of vaccinated children and no placebo recipients seroconverted to the four vaccine types at geometric mean titers more than 27 to 262 times greater than seropositivity cutoff values. Those geometric mean titers were 30% to 50% lower against types 6 and 18 than in similarly aged HIV-negative historical controls. But titers were similar to or higher than those of 16-to-26-year-old HIV-negative women, in whom the quadrivalent vaccine is highly efficacious. Safety results in the two study arms were similar to findings in previous trials of the quadrivalent vaccine in children. Some study participants got a fourth dose of the vaccine after 72 weeks. The fourth dose increased antibody responses to HPV-18.

Risk perception, vaccine awareness, vaccine coverage

Research conducted since HPV vaccine licensing in the United States suggests that young US women do not see vaccination as an invitation to riskier sex. Other work shows that few young women and men got vaccinated between 2007 and 2012, even though vaccine acceptance is high among potential recipients and healthcare providers.

A survey of 99 HIV-positive women from 16 to 23 years old entering an HPV vaccine trial found that most of them correctly perceived that they would have a lower risk of HPV infection after vaccination. Almost all of these young women believed continued...
they still had to practice safe sex after vaccination, but a subset of participants thought the quadrivalent vaccine would protect them from other sexually transmitted infections. Patient education clearly must accompany HPV vaccination.

A nationally representative sample of 15-to-24-year-old US women found that those who got vaccinated against HPV had tripled odds of always wearing a condom during sex. This study of 1243 adolescents and young women surveyed in 2007-2008 found no link between getting vaccinated and sexual activity or number of sex partners. Vaccination rates in these years immediately following HPV vaccine approval for girls and young women were low among 15-to-19-year-olds and even lower among 20-to-24-year-olds (30.3% versus 15.9%, \( P < 0.001 \)). Race did not affect vaccine uptake in the younger group, but 20-to-24-year-old non-Hispanic blacks were 85% less likely than non-Hispanic whites to get vaccinated.

Among the 995 unvaccinated young women, only 37.6% of 15-to-19-year-olds and 42% of 20-to-24-year-olds said they planned to get vaccinated in the next 12 months. Women with sexual experience were more than twice as likely to say they intended to get vaccinated. CDC investigators believe their findings “highlight the need to better communicate information regarding lifetime risk for HPV and the importance of receiving HPV vaccine prior to sexual initiation.”

A later CDC report on HPV vaccine coverage among 13-to-17-year-old girls in the United States traced a slowly rising vaccination rate. Whereas 25.1% of girls got one or more vaccine doses in 2007, 53% got one or more anti-HPV shots in 2011 (Figure 4). But that rate barely changed in 2012, inching up to 53.8%. Only one third of these girls got all three HPV vaccine doses in 2012, though that rate rose from a mere 5.9% in 2007 (Figure 4). The CDC team estimated that HPV vaccine coverage would have reached 92.6% if girls got vaccinated during health-care visits when they got another vaccine.

**Figure 4.** A survey of 13-to-17-year-old US girls found that rates of receiving all three doses of an HPV vaccine rose steadily from 2007 through 2010. But the rate plateaued from 2010 through 2012, with only one third of girls getting all three doses. US guidelines recommend HPV vaccination for all girls and young women up to 26 years old, for all boys and men up to age 21, and for MSM and HIV-positive men and boys and men up to age 26.
The quadrivalent HPV vaccine received US licensing approval for 9-to-26-year-old boys and men in 2009. In 2010 a CDC survey of 1741 men 18 to 26 years old found that 51.8% had heard of HPV and 34.8% knew about the vaccine, but only 1.1% got vaccinated. Several factors made HPV vaccination more likely: white race, more education, a US birthplace, more physician contacts, private health insurance, getting other vaccines, and reporting risk behaviors for sexually transmitted infections.

In 2009 a national survey of 247 US MSM found high acceptability of the HPV vaccine in men with or without HIV (78% and 74%), yet relatively few men thought the vaccine worked in men or that physicians could prescribe it for men. A 2010 review of 23 published surveys, half conducted in the United States, found 74% to 78% acceptability of a vaccine that protects against cervical cancer and genital warts among male college students. But acceptability reached only 33% in community samples of men. From 82% of 92% of physicians surveyed said they would vaccinate older adolescent boys, but most parents and healthcare providers stated a preference for vaccinating females versus males. HPV vaccine acceptability among mothers ranged expansively from 12% to 100% in these surveys.

A review of 22 studies involving 8360 men found that an average 50.4% considered HPV vaccination acceptable. In nine studies that reported vaccine acceptability by sexual orientation, 58.4% of MSM and 50.0% of heterosexuals perceived HPV vaccination as acceptable. Taken together, these studies indicate that clinicians could have a big impact on HPV vaccination rates by advising patients to get this vaccine.

Three analyses found that HPV vaccination is generally cost-effective in girls, women, boys, and men. A 29-study analysis determined that routine vaccination of girls and women is cost-effective when compared with cervical cancer screening alone. Another study figured that HPV vaccination of 12-year-old US boys “might potentially be cost-effective,” particularly if vaccine coverage is low in girls and women and if the analysis includes all potential health benefits of HPV vaccination. A study focusing on HPV vaccination of US MSM suggested that vaccination of MSM 26 years old or younger is cost-effective and that cost-effectiveness in HIV-positive MSM rises with higher HIV prevalence.

Which HIV-positive people should get the HPV vaccine—and when?

Guidelines formulated by the CDC’s Advisory Committee on Immunization Practices (ACIP) explicitly recommend HPV vaccination* for people with HIV. The ACIP recommends three vaccine doses for children as young as 9, for young men up to age 21, and for young women up to age 26 who have not had all three doses. The guidelines specifically recommend HPV vaccination for “any man who has sex with a man” and for “men and women with compromised immune systems (including people living with HIV/AIDS) through age 26.”

*The bivalent vaccine and the quadrivalent vaccine are licensed to prevent cervical cancer in women; the quadrivalent vaccine is also licensed to prevent genital warts and cancers of the anus, vagina, and vulva and it is the only vaccine licensed for use in boys and men.

But the guidelines also caution that “the immune response and vaccine efficacy [in immunocompromised people] might be less than that in immunocompetent persons.” And so far two of the three trials that tested
quadrivalent vaccine immunogenicity and safety in HIV-positive women\textsuperscript{29} or men\textsuperscript{38} included only a few participants with a CD4 count below 200 cells/mm\textsuperscript{3}. The trial in men excluded people with fewer than 200 cells/mm\textsuperscript{3}.

The third completed trial of the quadrivalent vaccine included 93 women with a baseline CD4 count of 200 cells/mm\textsuperscript{3} or less.\textsuperscript{29,30} As discussed above under “HPV vaccine studies in women,” ACTG 5240 found that women with a CD4 count below 201 cells/mm\textsuperscript{3} had lower geometric mean titers of antibodies to the four HPV types and lower seroconversion rates than women with higher CD4 counts. But titers were reasonably high and seroconversion rates exceeded 75% for each of the quadrivalent vaccine genotypes (Table 4).

The quadrivalent vaccine trial in 99 HIV-positive US women found lower geometric mean titers of antibodies against HPV-16 and 18 in women not taking antiretrovirals than in a comparison group of HIV-negative women taking the vaccine in another trial (Table 3).\textsuperscript{28} The single-arm study testing the quadrivalent vaccine in 112 HIV-positive men with a median CD4 count of 517 (IQR 423 to 680) found higher anti-HPV-16 and anti-HPV-18 concentrations in men taking antiretrovirals when the study began than in men not taking antiretrovirals.\textsuperscript{38} But these researchers did not see a correlation between CD4 count or nadir CD4 count and antibody concentrations at week 28.

Should clinicians administer the HPV vaccine only after starting ART, boosting low CD4 counts, and stopping HIV replication? With no guidelines addressing that question, providers will have to decide for themselves based on still-meager data, primarily from 93 women in ACTG 5240.\textsuperscript{30} Top HPV/HIV experts disagree. For example, Timothy Wilkin (Weill Cornell Medical College, New York) tells RITA! he thinks “it makes sense to wait 6 months or so until” until people with uncontrolled HIV replication reach an undetectable load on treatment “before HPV vaccination (or any other vaccine other than seasonal influenza vaccine).” But in an interview in this issue of RITA!, Joel Palefsky (University of California, San Francisco) suggests that clinicians don’t have to wait for an undetectable viral load or higher CD4 count because HPV seroconversion rates and titers achieved by people with still compromised immunity are generally high enough to protect them from vaccine-covered HPV genotypes.

References


continued...


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