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Description of a Pilot Anal Pap Smear Screening Program Among Individuals Attending a Veteran's Affairs HIV Clinic

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Abstract

Despite the higher risk of anal cancer among HIV-infected individuals currently there are no national or international guidelines for anal dysplasia screening. We assessed acceptance and feasibility of screening for anal intraepithelial neoplasia (AIN), the rate of abnormalities, and relationship between the presence of AIN and a history of receptive anal intercourse. Eighty-two percent of HIV-patients approached during routine clinic visit agreed to participate in the study with anal Pap smear collection; 53% had abnormal cytology results and among those undergoing high-resolution anoscopy with biopsy, 55% had high-grade AIN, including 2 cases of carcinoma *in situ*. Anal cytology was well accepted and it was feasible to be incorporated into HIV primary care practice. Abnormal cytology was not significantly associated with history of anal intercourse ($p = 0.767$). The high rate of abnormal results reinforces the need for further evaluation of the role of systematic anal Pap smear screening for HIV patients.

Introduction

Although highly active antiretroviral therapy (HAART) has dramatically impacted the natural history of HIV disease, the quality of life and the very lives of these individuals is increasingly affected by anal cancer.[1–3] Patel et al.[1] reported trends in anal cancer rates in the HIV-infected population and found incidence rates per 100,000 person–years of 19.0 for 1992–1995, 48.3 for 1996–1999, and 72.2 for 2000–2003. One cohort study showed that as many as 49% of HIV-infected homosexual and bisexual men developed high-grade dysplasia in the course of a 4-year period compared with 17% of HIV-uninfected homosexual and bisexual men.[4] Furthermore, a recent study showed evidence of progression from high-grade anal dysplasia to anal cancer.[5]

Although most available data on anal dysplasia and anal cancer in HIV-infected individuals are derived from studies of men who have sex with men (MSM),[6,7] there is evidence that other HIV-infected individuals are at higher risk as well.[8–14] Cross-sectional studies identified anal dysplasia in 26% of HIV-infected women and 34% of HIV-infected men without a history of anal intercourse.[10,14] Grulich et al found increased rates of anal cancer in HIV-infected individuals who had not yet developed AIDS.[11]

The presentation of anal cancer is usually nonspecific and may cause symptoms such as pain, bleeding, and the development of a mass lesion. The prognosis of anal cancer like that of many other cancers is associated with the stage of disease at diagnosis. Analysis of anal cancer outcomes in the United States from 1973 through 2000 showed that survival was significantly improved for patients who received a diagnosis of local disease compared to those receiving a diagnosis of regional disease or distant disease (5-year survival rates: 78%, 56%, and 18%, respectively).[12] In a retrospective review Wexler et al.[13] reported 32 HIV-infected patients treated for anal squamous cell carcinoma, showing that locoregional recurrence, cancer-specific survival, and overall survival were all significantly associated with tumor size at the time of diagnosis.

Anal cancer resembles cervical cancer in anatomy and histology, and both cancers are strongly related to oncogenic human papillomavirus (HPV).[8,9,14,15] A recent systematic

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review by Hoots et al.[16] showed that prevalence of HPV 16 and/or 18 in invasive anal cancer cases was similar to that reported in invasive cervical cancer. The incidence of cervical cancer decreased significantly after the introduction of cervical cytology screening.[17] Similar to cervical cancer, screening could potentially impact anal cancer incidence, morbidity, and mortality. A study by Hu and Goldie[18] concluded that the economic burden of noncervical HPV disease in the United states is substantial. A prior cost-effectiveness analysis by Goldie et al.[19] found that screening HIV-infected MSM every 2–3 years for anal squamous intraepithelial lesions with anal cytology would provide life-expectancy benefits comparable to other accepted preventive health measures and would be cost effective.

A recent review of the literature evaluating many aspects of anal Pap smear screening program among HIV-infected individuals was limited by the absence of published randomized clinical trials.[20] However, the burden of anal dysplasia and cancer in HIV-infected individuals is evident. Our team started a pilot anal Pap smear screening program among individuals attending the Miami VA HIV clinic to assess acceptance and feasibility of screening for AIN, the rate of abnormalities, and relationship between the presence of abnormal anal cytology and history of anal intercourse.

Methods

This study was conducted with the approval of the Committee on Human Research of the Miami VA Hospital and all procedures were performed subsequent to obtaining informed consent.

From February to July 2006, patients 18 years and older with HIV infection attending routine clinic visits and having no history of anal cancer or prior anal cytology screening were informed of the study. Individuals who agreed to be enrolled were asked to complete a self-administered questionnaire eliciting information on: demographics, including age, gender, race; sexual practices, including history of anal intercourse (yes/no), and number of sexual partners in the preceding 12 months (0, 1–3, 4 or more); history of sexually transmitted diseases (syphilis, gonorrhea, chlamydia); HIV-related information including years since HIV diagnosis (less than 5 or 5 years or more), and whether currently taking antiretroviral medications (yes/no). Data on CD4 T-cell count and HIV viral load at the time of the anal cytology were abstracted from the medical charts.

Caregivers, two physicians, and two nurse practitioners were trained to perform specimen collection according to the method described by the Johns Hopkins University Local Performance Site of the Pennsylvania/Mid Atlantic AIDS Education and Training Center. Anal Pap smears were collected using the ThinPrep® cytobrush (Hologic, Bedford, MA). The specimens were collected into ThinPrep® (TP) fixative and processed with the TP Processor. Anal cytology was performed and all samples were read by one pathologist and interpreted using the Bethesda criteria. Samples with insufficient cells for analyses were considered unsatisfactory. Results were reported as: negative for dysplasia; atypical cells of unknown significance (AS-CUS); low-grade squamous intraepithelial lesion (LSIL) for AIN-1; and high-grade squamous intraepithelial lesion (HSIL) for AIN-2,3. Patients with abnormal cytology classified as AS-CUS or greater were referred for high-resolution anoscopy (HRA) with biopsy of visible lesions seen by addition of 3% acetic acid. HRAs were performed by proctology surgeons trained in HRA. We used the anal cancer screening protocol proposed by Chin-Hong and Palefsky.[20] Biopsy results were coded as the most severe category, if multiple biopsies were taken. Histology results were reported as AIN 1, AIN 2, and AIN 3, including squamous cell carcinoma *in situ* (SCCIS) in this category.

Statistical analysis

Descriptive statistics such as means, standard deviations, medians, and ranges are reported for continuous variables; and frequencies and percentages for discrete variables. χ^2 tests were used to assess association between discrete variables and cytology results; Mann-Whitney tests were used for the comparison of participants with versus without abnormal cytology with respect to variables with skewed distributions such as CD4 cell counts and HIV viral loads. The later variables were also polychotomized and the resulting categorical variables were used in chi-square analyses. Separate logistic regression models were used with cytology results (abnormal versus normal) as the dependent variable to ascertain the predictive value of each of a series of clinical variables. To avoid duplication of information, results of the logistic regression analyses are presented instead of those of the χ^2 analyses.

Results

A total of 160 HIV-infected patients attending our clinic were approached, and 131 (82%) agreed to participate in the study. Table 1 shows the sociodemographic and clinical characteristics of the study participants. Their age ranged from 29 to 80 years, with a median of 49 years and a mean $\pm$ standard deviation (SD) of 50.5 ± 9.2 years. All participants were males, and included 51.9% blacks, 32.8% whites, and 13.7% Hispanics. Approximately two fifths (39.7%) reported anal intercourse; most of the participants were sexually active and approximately two thirds (59.5%) had 1 to 3 partners and one third (27.5%) had 4 or more partners in the prior 12 months; 51.9% had a history of STD. Most participants (84.7%) had been diagnosed with HIV for 5 or more years and approximately three quarters (75.6%) were currently on antiretroviral therapy. CD4 counts ranged from 5 to 1554 cells/mm^3 with 25th, 50th, and 75th percentiles of 241, 404, and 673 cell/ mm^3, respectively.

Approximately two fifths (43.5%) of participants had a CD4 cell count below 350 cells/mm^3. The viral load distribution was highly skewed: 70 participants (53.4%) had a detectable HIV viral load that ranged from 75 to 156,259 copies per milliliter. The demographic characteristics of the participants reflect those of the clinic population, including the fact that the clinic is predominantly of male patients and by chance all participants enrolled were HIV-infected men.

Of the 131 patients who underwent anal cytology, 33 had insufficient cells on cytology and were excluded from further analysis. Among the 98 subjects with adequate cytology samples, 52 (53%) had abnormal cytology: 30 (58%) AS-CUS; 19 (37%) LSIL; and 3 (5%) HSIL.

Compared to patients with normal cytology, those with abnormal results had significantly lower CD4 counts (Mann-Whitney test p value $= 0.010$), and higher, although not

Table 1. Sociodemographic and Clinical Characteristics of 131 Male Participants

Characteristic	n *(%)*
Age	
< 40 years old	12 (9.2)
40 years old or older	119 (90.8)
Race	
Black	68 (51.9)
White	43 (32.8)
Hispanic	18 (13.7)
Other	2 (1.6)
Anal intercourse	
Yes	52 (39.7)
No	73 (55.7)
Did not answer	6 (4.6)
Number of sex partners in the past 12 months	
0	11 (8.4)
1–3	78 (59.5)
4 or more partners	36 (27.5)
Did not answer	6 (4.6)
History of STD	
Yes	68 (51.9)
No	62 (47.3)
Did not answer	1 (0.8)
Years of HIV diagnosis	
< 5 years	20 (15.3)
5 or more years	111 (84.7)
Currently on ARV therapy	
Yes	99 (75.6)
No	32 (24.4)
CD4 count (cells/mm^3)	
> 500	50 (38.2)
350–500	24 (18.3)
200–350	36 (27.5)
< 200	21 (16.0)
HIV VL (copies/mL)	
< 75	61 (46.6)
75–4000	27 (20.6)
> 4000	43 (32.8)

STD, sexually transmitted diseases; ARV, antiretroviral therapy; VL, viral load.

statistically significant, viral load (Mann-Whitney test p value = 0.311).

Results of separate logistic regression models are shown in Table 2. None of the variables considered were statistically significant predictors of abnormal cytology, except for CD4 counts (p value = 0.026). The odds of abnormal cytology increased with: increasing number of sex partners with odds rations ranging from 2.0 to 3.8; decreasing CD4 cell counts with odds ratios ranging from 1.6 to 4.0; and increasing viral load levels with odds rations ranging from 1.3 to 1.6.

Of the 52 patients with abnormal cytology, 33 (63%) underwent HRA with biopsy of visible lesions. Of the 19 patients with abnormal cytology who did not undergo HRA, 1 died, 1 relocated out of state, and the remaining 17 did not report for their proctology evaluation. For the 33 patients with abnormal cytology who presented for HRA, histology confirmed AIN in all but 2; 1 cytology with one atypical cell had paired histology with no abnormality, and 1cytology with AS-CUS had paired histology with chronic inflammation but no dysplasia, 13 (39%) AIN-1 and 18 (55%) AIN-2,3, including 2 carcinoma *in situ.*

Compared to patients with low grade dysplasia, those with higher grade dysplasia had significantly lower CD4 cell count and higher HIV viral load (p value = 0.03 and p value = 0.005, respectively), however history of anal intercourse, history of STDs, number of sex partners in the last 12 months and currently being on HAART were not significantly predictors of the degree of dysplasia (Table 3).

Discussion

This pilot study shows that anal Pap smear screening as part of routine HIV care visits is feasible. The screening was well accepted and we screened approximately 32% of all HIV patients attending our clinic in a period of 5 months. This included screening a substantial number of HIV-positive men since men represent 95% of the HIV-positive patients in our clinic.

The incidence of anal disease in MSM, including HIV-infected MSM is well recognized[6,21–23] and anal cancer screening is recommended in this population. Little data, however, exist regarding anal dysplasia in HIV-infected men without history of anal intercourse. In our study abnormal anal cytology was as frequent in patients who denied anal intercourse as in patients with history of anal intercourse. And among patients with abnormal cytology who underwent HRA, history of anal intercourse was not predictive of the degree of the dysplasia and the two cases of carcinoma *in situ* were in patients who denied anal intercourse. It is important to notice that these data are based on self-reports. Thus, the reporting of stigmatizing behaviors like practicing anal intercourse may have been underreported.

Nonetheless, our data are consistent with studies of anal HPV disease and anal dysplasia in HIV-positive individuals independent of sexual orientation. Piketty et al.[14] compared HIV-infected men who were intravenous drug users and HIV-infected MSM and the prevalence of high grade anal dysplasia did not differ between the two groups. Drobacheff et al.[24] investigated the prevalence of anal HPV infection in HIV-infected patients (36 men and 14 women) and found no difference in the prevalence of high-risk HPV DNA in homosexual men compared to other HIV-positive patients.

We found that patients with lower CD4 cell count were more likely to have abnormal cytology on anal Pap smear screening and higher grade dysplasia on histology of the anoscopy biopsied lesions. This trend has been reported in other studies.[25,26] However, we did not find a statistically significant correlation with HAART therapy. Results of studies on the impact of HAART on high-grade anal dysplasia are still conflicting mainly due to a limited number of available studies and the fact that most of these are cross-sectional. [6,9,14,27,28] Carefully designed prospective cohort studies are necessary to further evaluate the effect of HAART on anal dysplasia.

Our study had 33 samples (25%) that were unsatisfactory for cytology analysis. Recent anal Pap studies have reported that 4–8.5% of specimens are unsatisfactory.[26,29–32] The utility of anal Pap smear screening depends on the appropriate number of cells in the anal samples. Specimens were collected with a cervical brush in liquid media. Cervical brush and Dacron swabs have been shown to obtain good cellularity and high yield for AIN.[33,34] In our study, factors that could have been related to the elevated number of unsatisfactory results

Table 2. Correlates of Abnormal Cytology

Characteristic	Cytology: Abnormal (n = 52)	Cytology: Normal (n = 46)	OR [95% CI]	p Value
Anal intercourse				0.767
No	28 (50.9)	27 (49.1)	Comparison Group	
Yes	20 (54.1)	17 (45.9)	1.13 [0.49, 2.62]	
History of STD				0.463
No	27 (57.4)	20 (42.6)	Comparison Group	
Yes	25 (50.0)	25 (50.0)	0.74 [0.33, 1.65]	
Number of sex partners in the last 12 months				0.069
0	4 (50.0)	4 (50.0)	Comparison Group	
1–3	24 (44.4)	30 (55.6)	1.95 [0.95, 4.01]	
4 or more partners	21 (70.0)	9 (30.0)	3.81 [0.90, 16.04]	
On ARV therapy				0.416
No	11 (45.8)	13 (54.2)	Comparison Group	
Yes	41 (55.4)	33 (44.6)	1.47 [0.58, 3.70]	
CD4 count (cells/mm^3)				0.026
>500	10 (33.3)	20 (66.7)	Comparison Group	
350–500	10 (50.0)	10 (50.0)	1.59 [1.09, 2.32]	
200–350	21 (72.4)	8 (27.6)	2.50 [1.18, 5.26]	
<200	11 (57.9)	8 (42.1)	4.00 [1.28, 12.5]	
Viral Load (copies/mL)				0.364
<75	19 (45.2)	23 (54.8)	Comparison Group	
75–4000	15 (62.5)	9 (37.5)	1.27 [0.80, 2.02]	
≥ 4000	18 (56.3)	14 (43.8)	1.61 [0.64, 4.07]	

STD, sexually transmitted diseases; ARV, anti-retroviral therapy; OR, odds ratio; CI, confidence interval.

Table 3. Correlates of Abnormal Histology

Characteristic	Histology results: AIN I (n = 13)	Histology results: AIN II-III or SCCIS (n = 18)	p Value
Anal intercourse			0.066
Yes	2 (18.2)	9 (81.8)	
No	9 (52.9)	8 (47.1)	
History of STD			0.833
Yes	6 (40.0)	9 (60.0)	
No	7 (43.8)	9 (56.3)	
Number of sex partners in the last 12 months			0.469
0	1 (33.33)	2 (66.7)	
1–3	9 (50.0)	9 (50.0)	
4 or more partners	2 (25.0)	6 (75.0)	
On ARV therapy			0.069
Yes	13 (48.1)	14 (51.9)	
No	0 (0.0)	4 (100.0)	
CD4 count (cells/mm^3)			0.031
<200	4 (50.0)	4 (50.0)	
200–350	2 (16.7)	10 (83.3)	
350–500	3 (42.9)	4 (57.1)	
>500	4 (100.0)	0 (0.0)	
Viral load (copies/mL)			0.005
<75	9 (81.8)	2 (18.2)	
75–4000	1 (10.0)	9 (90.0)	
>4000	0 (0.0)	2 (100.0)	
>10000	3 (37.5)	5 (62.5)	

STD, sexually transmitted diseases; ARV, antiretroviral therapy; AIN, anal intraepithelial neoplasia; SCCIS, squamous cell carcinoma *in situ*.

are lack of staff expertise in collecting anal Pap smears since the procedure was newly introduced in the clinic, and also the fact some patients may have had anal intercourse or anal manipulation within 24 h prior to the anal sample collection. Nonetheless, the results underscore the necessity of specialized training of clinicians in performing anal Pap smears and of routinely orienting the patients undergoing anal Pap smear screening to avoid anal intercourse, anal manipulation (with finger insertion or sexual aids), anal enemas or anal douche within 24 h prior to sample collection.

Of the 98 (75%) anal Pap smear samples adequate for analysis, more than 50% had abnormal results. For the patients with abnormal cytology who presented for HRA, histology confirmed AIN in all but 2. Although abnormal cytology was predictive of abnormal histology, the grading did not correlate with the histologic findings; the 2 patients with squamous cell carcinoma *in situ* had AS-CUS on cytology analysis. These findings are consistent with other published reports[29,35] and support the recommendation of further evaluation with HRA with biopsy of visible lesions of patients with any abnormal anal cytology, including AS-CUS. High-risk HPV (HR-HPV) testing has improved specificity of cervical cytology and altered colposcopy triage guidelines.[36] In our study HR-HPV testing of anal cytology samples was not performed, however HR-HPV DNA testing Hybrid Capture 2 (HC2; Digene, Gaithersburg, MD) method has been used to triage referral for HRA. Goldstone demonstrated sensitivity of 83% and specificity of 53% with this approach and concluded that whereas this had the potential to reduce referral numbers for HRA, some high-grade dysplasia would be missed.[37] Candidate biomarkers currently being researched have the potential to improve both specificity and sensitivity of anal cytology.[38]

Treatment of visible lesions on HRA was guided by the algorithm suggested by Chin-Hong and Palefsky.[24] Until now the therapy for anal dysplasia has followed the principles of therapy for cervical dysplasia. There are, however, no efficacy studies or randomized clinical trials. The few small case series of treatment outcome in HIV-infected patients showed limited success and high procedure-associated morbidity.[18,39–41] Nonsurgical approaches with infrared coagulation, imiquimod, and therapeutic vaccines are appealing,[42–45] and further work is required. One limitation of our study is the failure of one third of the patients with abnormal cytology to present for follow-up proctology evaluation. It is evident that screening is only effective if patients can be induced to comply with necessary follow-up and treatment. Other studies also illustrate the barrier of noncompliance. In the prospective study by Matthews et al.[29] on a cohort of 1864 HIV-positive patients receiving anal Pap smear as part of routine care within a 3-year period only 40% of their patients had followed through with the additional testing. In a study of routine anal cytology in an urban HIV clinic, Scott et al.[26] reported that in a cohort of 265 HIV-positive patients receiving routine anal Pap smears, only 36% of patients with abnormal anal cytology underwent anoscopy. In this study barriers to anoscopy included patient-centered difficulties such as the perceived intolerability of the anoscopy procedure, fear of cancer diagnosis, and difficult with maintaining clinical appointments. Other major HPV-associated cancers in HIV-infected individuals, including cervical cancer, suffer from poor follow-up screening rates as well.[48,49] One study of barriers to recommended cervical cancer screening in HIV-infected women found that depressive symptoms, substance use, fear of gynecologic examination and simply forgetting the appointment may be barriers to cervical cancer screening in HIV-infected women.[51] Some of those barriers may be applicable to barriers associated with poor anoscopy follow-up. Also the relative novelty of the anoscopy test and the fact that HPV and the risk of anal cancer are still largely unknown among HIV-infected individuals may account for poor follow up. [20,46,47]

Our study is in concordance with other studies[20] showing that anal precancerous lesions are commonly found in HIV-infected individuals. The prospect of primary prevention with HPV vaccine is promising. Although to date there has not been any published studies demonstrating the efficacy of the HPV vaccine in preventing anal cancer, it is plausible the vaccine would be protective and a future tool in anal cancer prevention in men and women. The challenge will be for HIV-infected individuals to be vaccinated before they acquire HPV infection. A recent survey on acceptability of vaccine among MSMs showed that 93% indicated that they would be willing to disclose that they were MSM to a health professional in order to obtain the vaccine for free, but not until on average 2 years after their sexual debut and after a median of 15 sexual partners.[50] While issues on anal cancer primary prevention still evolving, screening for anal dysplasia is a potential available tool, however, to date no national or international guidelines for anal dysplasia screening exist. There is a possibility that the HIV health care providers may be deterred from instituting any form of anal cancer screening for HIV-infected individuals by the perception that screening is time- and resource-consuming. The same could be said regarding the absence of reports of the benefits of such screening. A study such ours demonstrates the feasibility of anal Pap smear screening in routine HIV care that makes possible the early detection of precancerous and even cancerous lesions. Our results indicate the need for authoritative answers regarding anal dysplasia screening which in turn should act as a stimulus for further research. While anal cytology has not yet been proved to be an optimal screening tool, research exploring improved methods of screening should be prioritized as well. HIV-infected individuals benefitting from HAART are living longer and, therefore, anal cancer in this population will likely remain a significant medical challenge. Until there is a consensus regarding anal Pap smear screening, HIV-infected patients need to know they are at risk of anal cancer, and anal health should be an issue of priority for HIV care providers to discuss with their HIV-positive patients.

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References

1. Patel P, Hanson DL, Sullivan PS, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992–2003. Ann Intern Med 2008;148:728–736.
2. Chiao EY, Krown SE, Stier EA, et al. A population-based analysis of temporal trends in the incidence of squamous anal cancer in relation to the HIV epidemic. J Acquir Immun Defic Syndr 2005;40:451–455.
3. Bower M, Powles T, Newson-Davis T, et al. HIV-associated anal cancer: has highly active antiretroviral therapy reduced the incidence or improved the outcome? J Acquir Immune Defic Syndr 2004;37:1563–1565.
4. Palefsky JM, Holly EA, Ralston ML, et al. High incidence of anal high-grade squamous intra-epithelial lesions among HIV-positive and HIV-negative homosexual and bisexual men. AIDS 1998;12:495–503.
5. Berry M, Jay N, Cranston R, et al. Progression of high-grade anal intraepithelial neoplasia to invasive cancer among HIV-positive men who have sex with men. 2009 [Abstract 867]. Montreal, Canada: 16th Conference on Retroviruses and Opportunistic Infections, February 8–11, 2009.
6. Palefsky JM, Holly EA, Efirdc JT, et al. Anal intraepithelial neoplasia in the highly active antiretroviral therapy era among HIV-positive men who have sex with men. AIDS 2005;19:1407–1414.
7. Piketty C, Darragh TM, Heard I, et al. High prevalence of anal squamous intraepithelial lesions in HIV-positive men despite use of highly active antiretroviral therapy. Sex Transm Dis 2004;31:96–99.
8. Frisch M, Biggar RJ, Goedert JJ. Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. J Natl Cancer Inst 2000; 92:1500–1510.
9. Wilkin TJ, Palmer S, Brudney KF, et al. Anal intraepithelial neoplasia in heterosexual and homosexual HIV-positive men with access to antiretroviral therapy. J Infect Dis 2004; 190:1685–1691.

10. Holly EA, Ralston ML, Darragh TM, et al. Prevalence and risk factors for anal squamous intraepithelial lesions in women. J Natl Cancer Inst 2001;93:843–849.
11. Piketty C, Darragh TM, Da Costa M, et al. High prevalence of anal HPV infection and anal cancer precursors among HIV-infected individuals in the absence of anal intercourse. Ann Intern Med 2003;183:453–459.
12. Grulich AE, Li Y, Macdonald A, et al. rates of non-AIDS-defining cancers in people with HIV infection before and after AIDS diagnosis. AIDS 2002;16:1155–1161.
13. Johnson LG, Madeleine MM, Newcomer LM, et al. Anal cancer incidence and survival: The surveillance, epidemiology, and end results experience 1973–2000. Cancer 2004; 101:281–288.
14. Wexler A, Berson AM, Goldstone SE, et al. Invasive anal squamous cell carcinoma in the HIV-positive patient: Outcome in the era of highly active antiretroviral therapy. Dis Colon Rectum 2008;51:73–81.
15. Palefsky JM, Holly EA, Gonzales J, et al. Detection of human papillomavirus in anal intraepithelial neoplasia and anal cancer. Cancer Res 1991;51:1014–1019.
16. Hoots BE, Palefsky JM, Pimenta JM, Smith JS. Human papillomavirus type distribution in anal cancer and anal intraepithelial lesions. Int J Cancer 2009;124:2375–2383.
17. Qualters JR, Lee NC, Smith RA, et al. Breast and cervical cancer surveillance, United States, 1973–1987. MMWR CDC Surveill Summ 1992;41:1–7.
18. Hu D, Goldie S. The economic burden of noncervical human papillomavirus diseases in the United States. Am J Obstet Gynecol 2008;198:500.
19. Goldie SJ, Kuntz KM, Weinstein MC, Freedberg KA, Palefsky JM. Cost-effectiveness of screening for anal squamous intraepithelial lesions and anal cancer in human immunodeficiency virus-negative homosexual and bisexual men. Am J Med 2000;108:634–641.
20. Chiao EY, Giordano TP, Palefsky JM, et al. Screening HIV-infected individuals for anal cancer precursor lesions: A systematic review. Clin Infect Dis 2006;43:223–233.
21. Goedert JJ, Cote TR, Virgo P, et al. Spectrum of AIDS-associated malignant disorders. Lancet 1998;351:1833–1839.
22. Palefsky JM, Holly EA, Hogeboom CJ, et al. Virologic, immunologic, and clinical parameters in the incidence and progression of anal squamous intraephitelial lesions in HIV-positive and HIV-negative homosexual men. J Acquir Immune Defic Synd Hum Retrovirol 1998;7:314–319.
23. Palefsky JM, Holly E, Ralston MR, et al. Prevalence and risk factors for human papillomavirus infection of the anal canal in human immunodeficiency virus (HIV)-positive and HIV-negative homosexual men. J Infect Dis 1998;177:361–367.
24. Drobacheff C, Dupont P, Mougin C, et al. Anal human papillomavirus DNA screening by Hybrid Capture II in human immunodeficiency virus-positive patients with or without anal intercourse. Eur J Dermatol 2003;13:367–371.
25. Chin-Hong PV, Palefsky JM. Natural history and clinical management of anal human papillomavirus diseases in men and women infected with human immunodeficiency virus. Clin Infect Dis 2002;35:1127–1134.
26. Scott H, Khoury J, Moore BA, Weissman S, et al. Routine anal cytology screening for anal squamous intraepithelial lesions in an urban HIV clinic. Sex Transm Dis 2008;35:197–202.
27. Palefsky JM, Holly EA, Ralston ML, et al. Effect of highly active antiretroviral therapy on the natural history of anal squamous intraepithelial lesions and anal human papillomavirus infection. J Acquir Immune Defic Syndr 2001 ;28:422–428.
28. Kiviat NB, Redman M, Hawes S, et al. The effect of HAART on the detection of anal HPV and squamous intraepithelial lesions among HIV infected homosexual men. Bethesda, MD: 6th International Conference on Malignancies in AIDS and Other Immunodeficiencies, 2002.
29. Arain S, Walts AE, Thomas P, Bose S. The anal Pap smear: Cytomorphology of squamous intraepithelial lesions. Cytojournal 2005;2:4.
30. Mathews WC, Sitapati A, Caperna JC, et al. Measurement characteristics of anal cytology, histopathology, and high resolution anoscopic visual impression in an anal dysplasia screening program. J Acquir Immune Defic Syndr 2004;37:1610–1615.
31. Lytwyn A , Salit IE, Raboud J, et al. Interobserver agreement in the interpretation of anal intraepithelial neoplasia. Cancer 2005;103:1447–1456.
32. Cranston RD, Hart SD, Gornbein JA, et al. The prevalence, and predictive value, of abnormal anal cytology to diagnose anal dysplasia in a population of HIV-positive men who have sex with men. Int J STD AIDS 2007;18:77–80.
33. Arain S, Walts AE, Thomas P, Bose S. The anal pap smear: Cytomorphology of squamous intraepithelial lesions. Cytojournal 2005;2:4.
34. Vajdic CM, Anderson JS, Hillman RJ, Medley G, Grulich AE. Blind sampling is superior to anoscope guided sampling for screening for anal intraepithelial neoplasia. Sex Transm Infect 2005;81;415–418.
35. Panther LA, Wagner K, Proper J, et al. High resolution anoscopy for men who have sex with men: Inaccuracy of anal cytology as a predictor of histologic high-grade anal intraepithelial neoplasia and the impact of HIV serostatus. Clin Infect Dis 2004;38:1490–1492.
36. Kulasingam SL, Kim JJ, Lawrence WF, et al. Cost-effectiveness analysis based on the atypical squamous cells of undetermined significance/low-grade squamous intraepithelial lesion Triage Study (ALTS). J Natl Cancer Inst 2006;98:92–100.
37. Goldstone SE, Enyinna CS, Davis TW. Detection of oncogenic human papillomavirus and other predictors of anal high-grade dysplasia in men who have sex with men with abnormal cytology. Dis Colon Rectum 2009;52:31–39.
38. Ho KS, Cranston RD. Anal cytology screening in HIV-positive men who have sex with men: What's new and what's now? Curr Opin Infect Dis 2010;23:21–25.
39. Chang GJ, Berry JM, Jay N, Palefsky JM, Welton ML. Surgical treatment of high-grade anal squamous intraepithelial lesions: A prospective study. Dis Colon Rectum 2002;45:453–458.
40. Nadal SR, Manzione CR, Galvao VM, et al. healing after anal fistulotomy: A comparative study between HIV+ and HIV− patients. Dis Colon Rectum 1998;41:177–179.
41. Abbasakoor F, Boulos PB. Anal intraepithelial neoplasia. Br J Surg 2005;92:277–290.
42. Goldstone SE, Kawalek AZ, Huyett JW. Infrared coagulator: A useful tool for the treatment of anal squamous intraepithelial lesions. Dis Colon Rectum 2005;48:1042–1054.
43. Kreuter A, Hochdorfer B, Stucker M, et al. Treatment of anal intraepithelial neoplasia in patients with acquired HIV with imiquimod 5% cream. J Am Dermatol 2004;50:980–981.
44. Klencke B, Matijevic M, Urban RG, et al. Encapsulated plasmid DNA treatment for human papillomavirus 16-associated anal dysplasia: a phase I study of ZYC101. Clin Cancer Res 2002; 8:1028–1037.

45. Palefsky JM, Berry JM, Jay N, et al. A trial of SGN-00101 (HspE7) to treat high-grade anal intraepithelial neoplasia in HIV-positive individuals. AIDS 2006;20:1151–1155.
46. Logan JL, Khambaty MQ, D'Souza KM, Menezes LJ. Cervical cancer screening among HIV-infected women in a health department setting. AIDS Patient Care STDs 2010; 24:471–475.
47. Beckmann CA, Beckmann CRB, Lipscomb GH, King RE, Steere E. Pap smear screening: Determinants of patient compliance. J Womens Health (Larchmt) 1995;4:663–668.
48. Tello MA, Jenckes M, Gaver J, Anderson JR, Moore RD, Chander D. Barriers to Recommended Gynecologic Care in an Urban United States HIV Clinic. J Womens Health (Larchmt) 2010;19:1511–1518.
49. Tiro JA, Meissner HI, Kobrin S, Chollette V. What do women in U.S. know about human papillomavirus and cervical cancer? Cancer Epidemiol Biomarkers Prev 2007; 16:288–294.
50. Pitts MK, Fox C, Willis J, Anderson J. What do gay men know about human papillomavirus? Australian gay men's knowledge and experience of anal cancer screening and human papillomavirus. Sex Transm Dis 2007;34:170–173.
51. Simatherai D, Bradshaw CS, Fairley CK, Bush M, Heley S, Chen MY. What men who have sex with men think about the human papillomavirus vaccine. Sex Transm Infect 2009;85:148–149.

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