Factors Associated with High-Grade Anal Intraepithelial Lesion in HIV-Positive Men in a Southern U.S. City

Melanie Frank,¹ Cecile D. Lahiri,^{2,3} Minh Ly Nguyen,^{2,3} Cyra Christina Mehta,⁴
Marina Mosunjac,⁵ and Lisa Flowers^{3,6}

Abstract

The incidence of anal cancer is increased in HIV-infected patients compared with the general population. Risk factors associated with the anal cancer precursor, high-grade squamous intraepithelial lesion (HSIL), have not been extensively studied in an urban black population with late-stage HIV disease. We performed a retrospective chart review of HIV-infected men at the Grady Ponce de Leon Center HIV Clinic (Atlanta, GA) referred for high-resolution anoscopy (HRA), a procedure where anal tissue is examined under magnification and abnormal areas are biopsied. Between December 2013 and September 2015, 147 men underwent HRA: 72% were black, and 94% were men who have sex with men. CD4 count closest to time of HRA was a median 325 cells/mm³ (interquartile range 203–473), and 69% had an undetectable HIV viral load. Ninety-four percent had abnormal anal cytology [80% atypical squamous cells of undetermined significance/low-grade squamous intraepithelial lesion (LSIL) and 20% atypical squamous cells, cannot exclude HSIL/HSIL], and 97% had abnormal histology (35% LSIL, 65% HSIL). Statistically significant variables associated with HSIL included number of biopsies [odds ratio (OR) 1.55, 95% confidence interval (CI) 1.13–2.14] and having ≥1 high-grade anal cytology in the last 12 months (OR 3.76, 95% CI 1.38–10.23). No significant association was found between HSIL and CD4, HIV viral load, or recent sexually transmitted infection. In this population, the burden of anal HSIL was extremely high, regardless of most recent anal cytology result. In newly diagnosed HIV-infected men with no history of anal cancer screening, performing HRA as primary anal cancer screening instead of cytology appears to be a viable option.

Keywords: high-grade intraepithelial lesion, anal cancer, men who have sex with men (MSM), HIV

Introduction

THE INCIDENCE OF ANAL squamous cell carcinoma (SCC) has increased in recent years, and it has been suggested that this is directly related to the growing HIV epidemic.^{1,2} In the United States, anal cancer is now the fourth most common malignancy in HIV-positive persons.^{3,4} Incidence rates of anal cancer are significantly increased in HIV-positive compared with HIV-negative persons, particularly in MSM (men who have sex with men), with reported rates ranging from 46 to 128 cases per 100,000 person-years for HIV-positive MSM compared with 5–14 per 100,000 person-years for HIV-negative MSM.^{2,5–7} However, anal cancer research has historically underrepresented black MSM; a recent systematic review on anal

human papilloma virus (HPV) infection, dysplasia, and cancer among black and white MSM found that 64% of studies underrepresented blacks in their study population compared with the general local population, and <10% of these studies were conducted in the southeastern United States,⁸ the epicenter of the current AIDS epidemic.^{9,10}

The majority of SCCs of the anus arise from precursor lesions of the squamocolumnar junction (SCJ) due to persistent HPV infection, particularly types 16 and 18.¹¹ In a meta-analysis of anal HPV infection in HIV-positive MSM, prevalence was noted to be as high as 73.5%.⁶ As persons with HIV have immune systems that are less effective at clearing infections, persistent anal HPV infection leads to dysplasia at the SCJ,¹² making HIV infection a well-

¹Department of Medicine, Emory University School of Medicine, Atlanta, Georgia.

²Department of Medicine, Division of Infectious Diseases, Emory University School of Medicine, Atlanta, Georgia.

³Grady Ponce de Leon Center, Atlanta, Georgia.

⁴Department of Biostatistics and Bioinformatics, Rollins School of Public Health, Atlanta, Georgia.

Departments of ⁵Pathology and ⁶Gynecology and Obstetrics, Emory University School of Medicine, Atlanta, Georgia.

established risk factor for the development of disease at these sites. In addition, HIV-positive men have a higher incidence of high-grade squamous intraepithelial lesion (HSIL) than HIV negative (4-year incidence of 49% vs. 17%, respectively),¹³ and are more likely to progress from low-grade squamous intraepithelial lesion (LSIL) to HSIL over time (62% vs. 36%, respectively).¹⁴ Within the HIV-infected population, other documented risk factors for high-grade anal dysplasia include low CD4 and receptive anal intercourse.^{6,13,15,16} Few studies have examined rates of progression from high-grade anal intraepithelial neoplasia (AIN) to anal SCC in HIV-positive persons, and estimates range between 3.3% and 10% risk per year.^{6,17}

The Infectious Disease Society of America currently has weak recommendation guidelines regarding cytology screening for high-risk patients.¹⁸ Abnormal anal cytology has a high sensitivity but low specificity for detecting biopsy-confirmed high-grade disease.^{19–21} Therefore, when cytology can be combined with histology, more high-grade disease is detected,²² but performing HRA (high-resolution anoscopy) on all patients with any abnormal cytology may not always be feasible, since so few providers are trained in the procedure. In HRA, the perianal and intra-anal canal is examined under magnification, and abnormal areas are biopsied and sent for histological evaluation.

Defining risk factors for the development of HSIL can guide practitioners in establishing the optimal frequency for cytology and subsequent referrals for HRA. The aim of our study was twofold. First, we sought to estimate the prevalence of anal HSIL disease in a predominantly black HIV population referred for HRA within the southern United States, a region disproportionately affected with the highest HIV-related mortality and morbidity rates of any area in the United States.⁹ Second, we aimed to establish predictors of anal HSIL within this high-risk population.

Materials and Methods

We conducted a retrospective chart review of patients at the Grady Ponce de Leon Center (Atlanta, GA). The Ryan White-funded clinic provides comprehensive care for over 6,000 HIV-infected patients annually, predominantly with advanced stages of HIV. We looked specifically at patients who presented for their first HRA between December 1, 2013, and September 30, 2015. We collected demographic data including age, race, sex at birth, sexual practices, and smoking status, as well as clinical data such as number of years since HIV diagnosis, most recent CD4 and viral load, combination antiretroviral therapy (cART) regimens, and recently acquired sexually transmitted infection (STI; syphilis, gonorrhea, chlamydia) diagnosed within 6 months of HRA.

During the HRA visit, all patients underwent an anal cytology collected in liquid media (SurePathTM). Cytology results were reported using the 2001 and 2014 Bethesda terminologies for classifying results of cervical cytology: NILM (negative for intraepithelial lesion and malignancy), ASCUS (atypical squamous cells of undetermined significance), ASC-H (atypical squamous cells, cannot exclude HSIL), LSIL, and HSIL.^{23,24} Abnormal cytology results were dichotomized into low grade (ASCUS or LSIL) and high grade (ASC-H or HSIL). We included ASCUS in the low-grade group, given its low rate of progression to malignancy in the cervix.²⁵

HRA was performed by a single gynecologist trained in anoscopy. Abnormal lesions within the perianus and intra-anal canal identified using 3% acetic acid or Lugol's solution were biopsied. Highest grade biopsy results were classified according to the most recent Lower Anogenital Squamous Terminology (LAST): benign/negative, LSIL (AIN 1), HSIL (AIN 2/AIN 3), and invasive SCC.²⁶

Analyses were conducted using SAS, version 9.3 (SAS Institute, Inc., Cary, NC). Demographic and clinical characteristics of the population were described by counts and percentages for categorical variables and median and first and third quartiles (Q1–Q3) for continuous variables. Logistic regression examined risk factors associated with dichotomized histology. The final multivariate model selection was based on backward selection of covariates ($p=.1$), except for age ≥ 45 years, CD4 count, and recent STI, forced into the model. Model fit was assessed by Hosmer–Lemeshow,

TABLE 1. PATIENT DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Variable	N (%) or median (Q1–Q3)
Age, years	39 (32–48)
Age	
<45 years	100 (68)
≥ 45 years	47 (32)
Race	
Black	106 (72)
White	25 (17)
Hispanic	13 (9)
Other	3 (2)
Smoker	
Never	70 (48)
Current	50 (35)
Past	24 (17)
Sexual practice	
MSM	101 (84)
MSW	7 (6)
MSMW	12 (10)
STI diagnosed in last 6 months	
Yes	40 (27)
No	107 (73)
CD4 (cells/mm ³) closest to HRA	325 (203–473)
Log VL closest to HRA	1.6 (1.6–1.8)
On cART at time of HRA	
Yes	142 (97)
No	5 (3)
cART regimen	
NRTI+ protease inhibitor	68 (47)
NRTI+ NNRTI	25 (17)
NRTI+ integrase inhibitor	39 (27)
Other/combination	12 (8)

Percentages may not total 100 due to rounding.

cART, combination antiretroviral therapy; HRA, high-resolution anoscopy; MSM, men who have sex with men; MSMW, men who have sex with men and women; MSW, men who have sex with women; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; STI, sexually transmitted infection (gonorrhea, chlamydia, or syphilis); VL, viral load.

TABLE 2. PATIENT CYTOLOGY AND HISTOLOGY COLLECTED AT ANOSCOPY VISIT

Cytology result	Histology result			Total
	NILM, n (%)	LSIL (AIN 1), n (%)	HSIL (AIN 2/3), n (%)	
NILM	2 (25)	3 (38)	3 (38)	8
ASCUS	2 (7)	15 (52)	12 (41)	29
ASC-H	0 (0)	4 (22)	14 (78)	18
LSIL	0 (0)	25 (33)	50 (67)	75
HSIL	0 (0)	1 (14)	6 (86)	7
Total	4 (3)	48 (35)	85 (62)	137

Percentages for each row total are shown.

AIN 1, anal intraepithelial neoplasia grade 1; AIN 2/3, anal intraepithelial neoplasia grade 2 or 3; ASC-H, atypical squamous cells, cannot exclude HSIL; ASCUS, atypical squamous cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesion and malignancy.

diagnostic plots, and predictive ability. An alpha of 0.05 was considered significant.

Results

One hundred and fifty-nine referred patients were identified who did not have prior anoscopy. Twelve (8%) were female, 144 (91%) were male, and 3 (2%) were male to female transgender individuals. During this study period, few clinic providers were conducting anal cytology screening in at-risk women, therefore females were excluded from the chart review. Also included were transgender females, as they were genetically male at birth and likely shared risk factors with the men in the study.

The demographics of these 147 patients are presented in Table 1. The median age was 39 years (Q1: 32, Q3: 48), 72% ($n=106$) were black, and 94% ($n=113$) were either MSM or MSMW (men who have sex with men and women). All had a diagnosis of AIDS, and the median CD4 count was 325 cells/mm³ (Q1: 203, Q3: 473). Almost all patients (97%, $n=142$) were on cART at the time of HRA, and 69% had undetectable viral loads (log viral load <1.6 copies/mL). Seventy-eight percent ($n=114$) had the date of HIV diagnosis available, and the median years since diagnosis were 8 (Q1: 2, Q3: 14). Twenty-seven percent ($n=40$) had an STI diagnosis in the 6 months before HRA. Forty-nine percent ($n=70$) never smoked, 17% ($n=24$) were former smokers, and 35% ($n=50$) were current smokers.

Among these 147 patients, 142 were referred for a previous abnormal anal cytology; 51 (35%) ASCUS, 11 (8%) ASC-H, 74 (51%) LSIL, and 6 (4%) HSIL. The remaining five patients were referred to HRA for other reasons: two for anal bleeding, one for anal warts, and two for a remote history of abnormal anal cytology. One hundred and thirty-nine patients had a cytology result concomitant with the HRA: 8 (6%) NILM, 29 (21%) ASCUS, 19 (14%) ASC-H, 76 (55%) LSIL, and 7 (5%) HSIL. Seven patients had results that were either not available in the chart or unsatisfactory, and one patient was unable to tolerate the procedure due to anal warts.

The majority of HRA patients, 143 (97%), had at least one biopsy; 2 were unable to tolerate the procedure, 1 had no visible lesions, and in 1 the practitioner was unable to adequately visualize the SCJ. The median number of biopsies taken was 3 (Q1: 2, Q3: 4). The highest grade biopsy for each patient was recorded: 4 (3%) benign, 49 (34%) LSIL (AIN 1), and 90 (63%) HSIL (AIN 2/3). There were no cases of anal cancer found.

Anal cytology and histology results at time of HRA were concordant, meaning either both low-grade or both high-grade, in 67/137 (49%) patients. The remaining 70 (51%) patients had discordant cytology and histology results: 65 (47%) had a negative or low-grade cytology and high-grade histology and 5 (4%) had a high-grade cytology with negative or low-grade histology. Combined cytology and histology results are shown in Table 2. Regardless of the cytology result at time of HRA, the majority of patients had histologically confirmed high-grade disease.

In multivariate logistic regression analysis with HSIL (AIN 2/3) as the outcome of interest, statistically significant variables associated with HSIL (AIN 2/3) included number of biopsies [odds ratio (OR) 1.55, 95% confidence interval (CI) 1.13–2.14] and having >1 high-grade anal cytology in the previous 12 months (OR 3.76, 95% CI 1.38–10.23), even if cytology from the day of HRA showed low-grade disease. There was no association found between age ≥45 years, race, CD4 count, HIV viral load, or recent STI. These results are depicted in Table 3.

Discussion

We assessed the prevalence and predictors of histological HSIL within an HRA clinic serving an urban, predominantly black population with late-stage HIV disease within the southern United States, the epicenter of the U.S. AIDS epidemic.^{9,10} The rate of high-grade disease found on anal biopsy in 63% of our study patients is much higher compared

TABLE 3. FINAL MULTIVARIATE MODEL FOR PREDICTION OF ANAL HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION, HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION

Covariate	Univariable		Multivariable	
	Odds ratio	95% Confidence limits	Odds ratio	95% Confidence limits
No. of biopsies	1.53	1.15–2.06	1.55	1.13–2.14
≥1 High-grade cytology in last 12 months	3.80	1.45–9.95	3.76	1.38–10.23
Age ≥45 years (Ref.: <45)	0.77	0.37–1.58	0.96	0.42–2.15
CD4 count (per 100 cells)	1.03	0.87–1.21	1.03	0.87–1.23
STI (Ref. No.)	0.56	0.26–1.18	0.59	0.25–1.38

STI (sexually transmitted infection) within 6 months of anoscopy.

with other similar studies evaluating patients with abnormal cytology.^{13,22,27–29} The possibility for this difference could reflect the patient population at the Grady Ponce de Leon Center; the majority of patients were black and had advanced stages of HIV disease with a diagnosis of AIDS. In addition, this high prevalence may be a result of first time surveillance for these patients, as this population had not previously undergone screening with anoscopy or received prior therapy for anal disease. Finally, experience of the anoscopist and the number of biopsies may vary considerably by site and could lead to differences in sampling and capturing all HSIL disease.

We found two significant predictors of HSIL (AIN 2/3); the presence of at least one high-grade cytology in the previous 12 months, even though cytology at time of HRA showed low-grade disease, and number of biopsies taken during HRA. There are several possible explanations for the former. First, anal cytology is a blind procedure (i.e., the practitioner does not directly visualize the SCJ while the cytology is collected) and thus may miss areas of high-grade disease. Second, techniques used for anal cytology may impact sensitivity. Nadal *et al.* suggested that cytology specimens collected with brushes inserted more deeply (2 vs. 4 cm) had a higher percentage of detecting HSIL.³⁰ Finally, compared with cervical lesions, anal SIL can be markedly keratinized, which may result in decreased sensitivity for detecting HSIL on cytology.³¹ Based on our findings, we suggest that any patient with HSIL cytology should be referred to anoscopy and not use repeat cytology for monitoring disease.

This study has limitations. As with all retrospective chart reviews, our analyses were limited to available information in the patient charts. We were not able to gather other information from the patients such as number of sexual partners and receptive versus insertive anal intercourse for MSM. In addition, only patients who are symptomatic or who have a history of abnormal cytology were referred to the HRA clinic, so biopsies were not collected from asymptomatic patients or those without a history of abnormal cytology. Therefore, we were unable to assess the total prevalence of high-grade anal dysplasia or the overall sensitivity and specificity of anal cytology in our clinic population. However, this study was able to assess the prevalence of high-grade dysplasia based on a history of abnormal cytology and confirms the need for follow-up HRA when abnormal cytology is detected.

In our urban Ryan-White-funded clinic that provides care to a medically underserved predominantly black population in the southeastern United States, there is an extremely high burden of high-grade anal dysplasia. Whether these patients should receive treatment or active monitoring is not well established and is currently being investigated with the Phase III randomized clinical trial, ANCHOR (Anal Cancer HSIL Outcome Research). Given the high burden of disease in our population, we propose that HRA is a viable option as a primary anal cancer screening tool, given the poor specificity of cytology for biopsy-proven high-grade disease (17%–39% in two previous studies).^{19,20} While cost of HRA is high with poor reimbursement rates, a prior study showed that HRA alone was the most cost-effective strategy for detecting anal HSIL in HIV-infected MSM due to the high sensitivity and low specificity of anal cytology and HPV testing.³² We acknowledge that primary HRA screening in most settings may not be feasible, given the scarcity of providers trained in the procedure, and therefore, establishing access to a multidisciplinary referral center with the experience and skill set to evaluate and manage anal dysplasia should be a priority for clinics caring for patients at highest risk of anal cancer.

disciplinary referral center with the experience and skill set to evaluate and manage anal dysplasia should be a priority for clinics caring for patients at highest risk of anal cancer.

Acknowledgments

Funding for C.D.L.: NIH/NIAID K23AI124913; ACTSI KL2TR000455 and UL1TR000454; Emory CFAR P30 AI050409.

Data presented at IDWeek, October 2016, New Orleans, LA.

Author Disclosure Statement

No competing financial interests exist.

References

- Shiels MS, Pfeiffer RM, Chaturvedi AK, Kreimer AR, Engels EA: Impact of the HIV epidemic on the incidence rates of anal cancer in the United States. *J Natl Cancer Inst* 2012;104:1591–1598.
- van der Zee RP, Richel O, de Vries HJ, Prins JM: The increasing incidence of anal cancer: Can it be explained by trends in risk groups? *Neth J Med* 2013;71:401–411.
- Shiels MS, Pfeiffer RM, Gail MH, *et al.*: Cancer burden in the HIV-infected population in the United States. *J Natl Cancer Inst* 2011;103:753–762.
- Diamond C, Taylor TH, Aboumradi T, Bringman D, Anton-Culver H: Increased incidence of squamous cell anal cancer among men with AIDS in the era of highly active antiretroviral therapy. *Sex Transm Dis* 2005;32:314–320.
- D'Souza G, Wiley DJ, Li X, *et al.*: Incidence and epidemiology of anal cancer in the multicenter AIDS cohort study. *J Acquir Immune Defic Syndr* 2008;48:491–499.
- Machalek DA, Poynten M, Jin F, *et al.*: Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: A systematic review and meta-analysis. *Lancet Oncol* 2012;13:487–500.
- Crum-Cianflone NF, Hullsiek KH, Marconi VC, *et al.*: Anal cancers among HIV-infected persons: HAART is not slowing rising incidence. *AIDS* 2010;24:535–543.
- Walsh T, Bertozzi-Villa C, Schneider JA: Systematic review of racial disparities in human papillomavirus-associated anal dysplasia and anal cancer among men who have sex with men. *Am J Public Health* 2015;105:e34–e45.
- Reif SS, Whetten K, Wilson ER, *et al.*: HIV/AIDS in the Southern USA: A disproportionate epidemic. *AIDS Care* 2014;26:351–359.
- Centers for Disease Control and Prevention. HIV surveillance report, November 2017. Vol. 29. Available at www.cdc.gov/hiv/library/reports/hiv-surveillance.html accessed March 14, 2018.
- Daling JR, Madeleine MM, Johnson LG, *et al.*: Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. *Cancer* 2004;101:270–280.
- 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.
- Palefsky JM, Holly EA, Ralston ML, Jay N, Berry JM, Darragh TM: 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.
- Palefsky JM, Holly EA, Hogeboom CJ, *et al.*: Virologic, immunologic, and clinical parameters in the incidence and

- progression of anal squamous intraepithelial lesions in HIV-positive and HIV-negative homosexual men. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998;17:314–319.
15. Hillman RJ, van Leeuwen MT, Vajdic CM, *et al.*: Prevalence and predictors of high-grade anal intraepithelial neoplasia in a community-based sample of homosexual men. *Sex Health* 2012;9:574–579.
 16. Wilkin TJ, Palmer S, Brudney KF, Chiasson MA, Wright TC: Anal intraepithelial neoplasia in heterosexual and homosexual HIV-positive men with access to antiretroviral therapy. *J Infect Dis* 2004;190:1685–1691.
 17. Berry JM, Jay N, Cranston RD, *et al.*: Progression of anal high-grade squamous intraepithelial lesions to invasive anal cancer among HIV-infected men who have sex with men. *Int J Cancer* 2014;134:1147–1155.
 18. Aberg JA, Gallant JE, Ghanem KG, Emmanuel P, Zingman BS, Horberg MA: Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis* 2014;58:1–10.
 19. D'Souza G, Wentz A, Wiley D, *et al.*: Anal cancer screening in men who have sex with men in the multicenter AIDS Cohort Study. *J Acquir Immune Defic Syndr* 2016;71:570–576.
 20. Salit IE, Lytwyn A, Raboud J, *et al.*: The role of cytology (Pap tests) and human papillomavirus testing in anal cancer screening. *AIDS* 2010;24:1307–1313.
 21. Johnson GE, Nguyen ML, Krishnamurti U, *et al.*: Cytology as a screening tool for anal squamous intraepithelial lesion for HIV positive men: 10-Year experience in an inner city hospital. *JASC* 2016;5:145–153.
 22. Machalek DA, Poynten IM, Jin F, *et al.*: A composite cytology-histology endpoint allows a more accurate estimate of anal high-grade squamous intraepithelial lesion prevalence. *Cancer Epidemiol Biomarkers Prev* 2016;25:1134–1143.
 23. Solomon D, Davey D, Kurman R, *et al.*: The 2001 Bethesda System: Terminology for reporting results of cervical cytology. *JAMA* 2002;287:2114–2119.
 24. Nayar R, Wilbur DC: The Pap test and Bethesda 2014. *Cancer Cytopathol* 2015;123:271–281.
 25. Melnikow J, Nuovo J, Willan AR, Chan BK, Howell LP: Natural history of cervical squamous intraepithelial lesions: A meta-analysis. *Obstet Gynecol* 1998;92(Pt 2):727–735.
 26. Darragh TM, Colgan TJ, Thomas Cox J, *et al.*: The Lower Anogenital Squamous Terminology standardization project for HPV-associated lesions: Background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *Int J Gynecol Pathol* 2013;32:76–115.
 27. Gaisa M, Sigel K, Hand J, Goldstone S: High rates of anal dysplasia in HIV-infected men who have sex with men, women, and heterosexual men. *AIDS* 2014;28:215–222.
 28. Palefsky JM, Holly EA, Efird 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.
 29. Sendagorta E, Herranz P, Guadalajara H, *et al.*: Prevalence of abnormal anal cytology and high-grade squamous intraepithelial lesions among a cohort of HIV-infected men who have sex with men. *Dis Colon Rectum* 2014;57:475–481.
 30. Nadal SR, Horta SH, Calore EE, Nadal LR, Manzione CR: How far into the anal canal should the brush be introduced for more efficient cytological evaluation? [in Portuguese]. *Rev Assoc Med Bras (1992)* 2009;55:749–751.
 31. ElNaggar AC, Santoso JT, Xie HB: Keratosis reduces sensitivity of anal cytology in detecting anal intraepithelial neoplasia. *Gynecol Oncol* 2012;124:292–295.
 32. Lam JM, Hoch JS, Tinmouth J, Sano M, Raboud J, Salit IE: Cost-effectiveness of screening for anal precancers in HIV-positive men. *AIDS* 2011;25:635–642.

Address correspondence to:

Cecile D. Lahiri, MD, MS

Department of Medicine

Division of Infectious Diseases

Emory University School of Medicine

49 Jesse Hill Jr Drive SE

Atlanta, GA 30303

E-mail: cdelill@emory.edu