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High Prevalence of High Grade Anal Intraepithelial Neoplasia in HIV-infected Women Screened for Anal Cancer

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Abstract:

There is no consensus on optimal screening for anal cancer (AC) in HIV+ women. 715 unique asymptomatic women in a high-prevalence HIV+ community were screened for AC with anal cytology and triage to high-resolution anoscopy (HRA) after routine screening was implemented in a large urban hospital system. Of these, 75(10.5%) had an abnormal anal cytology and 29(38.7%) with an abnormality had high grade AIN. Women with poorly-controlled HIV were significantly more likely to have high grade AIN (p=0.03). Given the high rate of AIN in screened HIV-infected women, routine AC screening in all HIV-infected women should be strongly considered.

Key Words:

Anal cancer screening; Anal cytology; high resolution anoscopy; HPV-associated disease

Introduction:

The incidence of anal carcinoma (AC) has been increasing despite the implementation of ART, which has not been shown to consistently alter the course of HPV-associated anogenital disease[1]. Anal cancer in specific populations, such as people living with HIV/AIDS, has been increasing at alarming rates.[2] This is likely due to the fact that HIV promotes HPV persistence and consequently, HIV-infected individuals are also at increased risk for the development of HPV-associated neoplasms [1, 3,4,5]. Across all strata of HIV control, HPV rates and abnormal anal cytology are exceedingly high[6]. In fact, studies in HIV-infected women show that HPV prevalence in the anal canal is higher than in the cervical-vaginal tract [1,6, 3]. The incidence of AC in HIV+ men who have sex with men (MSM) is 10-50 times that of the general population, and comparable to cervical cancer incidence rates prior to implementation of cervical cancer screening (40-50/100,000)[7]. Similar to the cervix, the anus is susceptible to neoplastic transformation as a result of persistent HPV at the anal dentate line between squamous and columnar cells. In women with HIV/AIDS, the incidence of AC is 7-28 times greater than the general population[6, 8]. This relatively recent phenomenon was probably masked in the pre-ART era, when HIV-infected patients typically succumbed to an AIDS-defining illness soon after initial HIV infection. Now that they are living longer with ART, these patients are at risk for non-AIDS-defining malignancies such as AC. Treatment for AC is usually associated with significant morbidity and mortality in advanced disease, which highlights the importance of improving screening strategies for its precursor lesions[9].

Unlike cervical cancer, there are currently no large prospective natural history studies for AIN, and it is difficult to determine the optimal screening strategy and the impact of routine AC screening on AC prevention. Consequently, consensus is lacking between national and local public health organization guidelines on anal cancer screening in HIV-infected patients. Since 2007, the New York State Department of Health (NYS DOH) has recommended annual anal cytology in HIV-infected subjects with a history of anogenital condylomata or with abnormal cervical/vulvar histology, along with referral for high resolution anoscopy (HRA) [10] in those with abnormal anal cytology or abnormal findings on anal exam[11, 12-14]. In contrast, the Department of Health and Human Services guidelines discourage screening and treatment programs for AIN due to a lack of complete understanding of the relative harms and benefits of anal cytology screening[15].

Bronx County has one of the highest HIV prevalence rates in the US with 1.8% of the population known to be HIV infected, representing 3% of the total US HIV burden. Montefiore Medical Center is the largest provider of medical services for people with HIV in the Bronx and has adopted routine screening for AC with annual anal cytology in all HIV-infected patients. In the ART era, little data exists regarding the prevalence of anal HPV and AIN among HIV-infected women[3,6,16,17]. Most prior studies are in MSM with HIV. Therefore, extrapolation of anal cytology prevalence to HIV-infected women is likely inaccurate given the lower disease prevalence rates. The purpose of this study is to determine the prevalence of high grade AIN in asymptomatic, HIV-infected women during the implementation period of routine AC screening in an urban hospital system.

Methods:

At Montefiore Medical Center, annual screening with an anal cytology was initiated in HIV-infected patients by primary care providers in infectious disease clinics starting in March, 2008. Adoption of this recommended practice was incremental, so not all providers began screening on this date. Anal cytology results were tracked throughout this implementation period beginning in March, 2008 until December, 2010 and then retrospectively reviewed. Providers screened all HIV-infected women with anal cytology at the time of a routine visit using a Dacron swab that was inserted into the anal canal and rotated as previously described[18,19], then sent in liquid-based media (SurePath™, BD, NJ) to the hospital-based cytopathology laboratories for analysis. As part of the adoption and tracking during implementation, when patients reported anogenital warts or providers identified obvious anogenital warts, this was noted in patient charts. These patients were not 'asymptomatic' screens and as such were not included in the analysis. Anal cytology results were categorized according to the Bethesda system for cervical cytology: normal; atypical squamous cells; low-grade squamous intraepithelial lesions (LSIL); and high-grade squamous intraepithelial lesions (HSIL). Women with unsatisfactory anal cytology results were excluded from classification. Anal histological results were categorized as normal, condyloma, AIN1, AIN2, and AIN3. All women with abnormal anal cytology were referred for HRA and subsequent biopsy of abnormal lesions by one of two trained surgical providers (ME and DS). In cases where a patient had more than one anal cytology during this time period, subject information was counted only once. In these cases, the highest grade AIN from HRA-directed biopsy from any of the visits was used for this analysis.

Baseline clinical and HIV-related data were obtained from chart review after IRB approval. HIV control was defined for each patient as poor, moderate, or well-controlled based on their CD4 T-cell count and viral load (VL). In brief, those with CD4>500 cells/mm^3 and undetectable VL were characterized as well-controlled. Those with CD4 <250 and detectable VL were defined as poorly-controlled. All other patients are defined as moderately-controlled. The association of high grade anal dysplasia with HIV status was performed using Fisher's exact test. A Kappa coefficient was calculated to determine the agreement between anal cytology and HRA-directed biopsy.

Results:

Screening with anal cytology was performed on 715 unique HIV-infected women from March 2008 until December 2010. Symptomatic patients were those in whom anogenital condylomata was noted in patient charts. Symptomatic patients were excluded from this analysis since an anal cytology in this setting would not be considered screening. Also, many subjects with anogenital condylomata have an abnormal anal cytology, thus inclusion of these patients would falsely increase the disease prevalence and specificity. During this time period, 479 HIV-infected women had one anal cytology and 236 had 2 or more. Of these, a total of 75 patients (75/715, 10.5%) had an abnormal cytology (atypical, ASCUS, LSIL, or HSIL), and were referred for HRA.

The clinical and demographic characteristics of patients undergoing HRA (Table 1) is typical for the HIV population in Bronx, NY, in that they were ethnically and racially diverse. Sixty-one percent smoked, and 79% had a diagnosis of AIDS. The median

CD4 count around the time of screening was 290 (range 7-1551 cell/mm^3). At the time of screening anal cytology, 41.3% had a CD4<250 cell/mm^3, and 45 patients (60%) had an undetectable VL.

Results of the HRA directed biopsy(ies) stratified by anal cytology are provided in Table 2. Of 75 women referred for HRA, 20 (26.7%) had atypical or ASCUS cytology, 51(68%) had LSIL, and 4 (5.4%) had HSIL. The sensitivity of an abnormal anal cytology for detecting anal disease was 72%. Despite the small number of patients with HSIL diagnosed from the anal cytology, 38.7% (29/75) of all HRA-directed anal biopsies performed on this screening population had a final diagnosis of high grade AIN (AIN2 or 3), and 21/75 (28%) had HRA-directed biopsy results that was normal. There was no significant association between the degree of abnormality on anal cytology and HRA-directed biopsy histology (κ=0.11); however, this could be due, in part, to the small sample size. As expected, HIV status significantly associates with the presence of high grade AIN (distribution of results in Table 2). For example, 11/18 (61%) with poorly controlled HIV infection had high grade AIN, but only 1/20 (5%) with well-controlled HIV had high grade AIN (p=0.03).

Discussion:

In this contemporary cohort of asymptomatic HIV+ women, the rate of abnormal anal cytology is very high (10.5%). However, this is lower than what has previously been reported in the literature, with rates between 17-33% [3,6,16,17]. This might be attributable to the variation in cytopathological interpretation [20]. In women with abnormal cytology, we found an impressively high rate of high-grade AIN determined by

HRA-directed biopsy (38.3%). This is significantly higher than results previously reported, ranging from 6.7% for all AIN in a study by Abramowitz et al. to 21.4%.[21, 6, 17] Additionally, although most of this cohort was maintained on ART, the rate was not as high as the general HIV clinic population and compared to previous reports[22,17,16] ,our study includes a higher percentage of poorly-controlled HIV+ subjects, with 34.7% having a CD4 T-cell count <200 cells/mm^3. The high proportion of poorly-controlled relative to well-controlled HIV-infected women in our anal cytology positive group may have contributed to the high rate of high-grade AIN.

Unlike Pap tests for cervical cancer screening, the correlation between abnormal anal cytology and HRA-directed biopsy in our analysis is extremely poor. This finding is important, and suggests a number of potential problems with current AC screening in women. First, sampling of the anal canal is different than sampling in the cervix and as such, sloughing or performance of collection of abnormal cells might be different. Second, anal cytology performance has been shown to vary depending on the level of HIV virologic suppression and extent of the disease[18,19]. Given the relatively poor performance of identification of high grade AIN with anal cytology, other strategies that may improve screening performance should be explored, including innovative sampling devices or use of molecular testing strategies in combination with cytology. Considering the lower disease prevalence and anal HPV prevalence in HIV-infected women when compared to HIV-infected MSM[6], inclusion of HPV testing in a triage algorithm for well-defined clinical groups of HIV-infected women might be a more optimal strategy for triage to HRA. There are a number of trials in the planning stages in the US to assess such alternative strategies in women.

Our study has multiple limitations. HRA-directed biopsies were only performed on those patients with abnormal anal cytology. There are likely false-negative anal cytology tests in this population, which likely underestimated the disease prevalence and affects the sensitivity of anal cytology. Also, because this study was done soon after the adoption of AC screening, and before the practice became more universally adopted in our population, the screened population may differ from the general population of HIV-infected patients. Providers may have been more likely to screen patients they consider at higher risk for HPV infection. This point is reinforced with the lower rate of ART use in this cohort than in the general HIV population. Nearly 10% of patients refused to have biopsies. Since the analysis was done only in those who had HRA-directed biopsies, this may have impacted sensitivity calculations and univariate associations with clinical and demographic characteristics. In those who underwent biopsy, some of these subjects had delays (up to 9 months) from time of initial anal cytology to HRA. During this time, the disease might have worsened, with a minority potentially regressing, falsely increasing our prevalence of high grade AIN. As part of tracking, providers were asked to document patient complaints and objective findings of obvious anogenital warts. Despite this, the prevalence of condyloma in this group is probably underestimated, given the high prevalence of asymptomatic condylomata detected with HRA. Also, there was limited information regarding the prior AC screening histories of this patient population. However, given that this population is community-based and their care has been provided by the same team of providers since their HIV diagnosis, the vast majority of these patients were AC screening naïve. HPV testing was not performed in these patients because it is not currently recommended.

Therefore, the utility of HPV testing could not be assessed with regards to disease risk stratification. Larger comprehensive prospective screening studies for AC prevention in the setting of HIV for both women and men are clearly needed.

In conclusion, until we have validated, optimized screening strategies for AC in the setting of HIV, we recommend that all HIV+ women who have any abnormal anal cytology be referred for HRA, particularly those with poorly controlled HIV who are significantly at even higher risk for harboring a high grade AIN than women who are well-controlled. Given the lower high grade AIN disease prevalence in women with well-controlled HIV, other strategies to improve disease ascertainment, such as inclusion of HPV testing might be found to be useful for AC screening optimization in prospective studies. This risk stratification might prove to be different for women than it is for men, and particularly MSM, where prevalence rates appear to be considerably higher. Given the high rate of high grade AIN in screened HIV-infected women, as well as an aging population of HIV-infected patients, measures to increase routine AC screening should be strongly considered.

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Table 1: Population characteristics

		N	Percent
Mean age, years (± SD)		48.7 (±10.1)	
Median CD4 cells/mm^3 (range)		290 (IQR* 144,507)	
Race	White	10	13.3
	Black	36	48.0
	Mixed	13	17.3
	Unknown	16	21.4
Current tobacco use			
	Yes	46	61.3
	No	20	26.7
	Unknown	9	12.0
History of sexually-transmitted disease			
	Yes	30	40.0
	No	35	46.7
	Unknown	10	13.3
Diagnosis of AIDS			
	Yes	59	78.7
	No	16	21.3

*IQR=inter-quartile range

	HRA-Directed Biopsy Results		
Preceding Anal Cytology	**Normal (%)**	**AIN1 and Warts (%)**	**AIN2/3 (%)**
Atypical	0 (0)	1 (1.3)	3 (4.0)
ASCUS	4 (5.3)	5 (6.7)	7 (9.3)
LSIL	16 (21.4)	19 (25.3)	16 (21.4)
HSIL	1 (1.3)	0 (0)	3 (4.0)
TOTAL	**21 (28)**	**25 (33.3)**	**29 (38.7)**
HIV Control			
Good	11 (14.7)	8 (10.7)	1 (1.3)
Moderate	10 (13.3)	10 (13.3)	17 (22.7)
Poor	1 (1.3)	6 (8.0)	11 (14.7)
TOTAL	**22 (29.3)**	**24 (32.0)**	**29 (38.7)**