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Patterns of repeated anal cytology results among HIV-positive and HIV-negative men who have sex with men

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ABSTRACT

Background: Men who have sex with men (MSM) are at increased risk for anal cancer. In cervical cancer screening, patterns of repeated cytology results are used to identify low- and high-risk women, but little is known about these patterns for anal cytology among MSM.

Methods: We analyzed Multicenter AIDS Cohort Study (MACS) data for MSM who were offered anal cytology testing annually (HIV-positive) or every 2 years (HIV-negative) for 4 years.

Results: Following an initial negative (normal) cytology, the frequency of a second negative cytology was lower among HIV-positive MSM with CD4 ≥ 500 (74%) or CD4 < 500 (68%) than HIV-negative MSM (83%) (p < 0.001). After an initial abnormal cytology, the frequency of a second abnormal cytology was highest among HIV-positive MSM with CD4 < 500 (70%) compared to CD4 ≥ 500 (53%) or HIV-negative MSM (46%) (p = 0.003). Among HIV-positive MSM with at least three results, 37% had 3 consecutive negative results; 3 consecutive abnormal results were more frequent among CD4 < 500 (22%) than CD4 ≥ 500 (10%) (p = 0.008).

Conclusions: More than one-third of HIV-positive MSM have consistently negative anal cytology over three years. Following abnormal anal cytology, a repeated cytology is commonly negative in HIV-negative or immunocompetent HIV-positive men, while persistent cytological abnormality is more likely among HIV-positive men with CD4 < 500.

1. Introduction

Anal cancer is rare in the United States general population (1.8 per 100,000) [1,2], though rates are increasing [3]. In contrast, incidence among HIV-seropositive men who have sex with men (HIV-positive MSM) is extremely high, estimated at 131 per 100,000 [4], due to increased human papillomavirus (HPV) prevalence and HIV-associated immunosuppression [5]. During 2001–2005, approximately 28% of U.S. anal cancers in males occurred in men living with HIV, the vast majority in HIV-positive MSM [6]. This burden is likely growing as the HIV-positive population size increases [7,8], though the trend in anal cancer incidence is unclear [9,10]. Anal cancer is also a concern for HIV-negative MSM, who have high prevalence of high-grade anal lesions [11] and 30-fold higher anal cancer incidence than the general population [12,13].

There is an urgent need for effective anal cancer screening methods among MSM. Though no national or international guidelines exist [14], the primary strategy is screening by anal cytology (collected with an anal swab) with referral to high-resolution anoscopy (HRA) for possible biopsy, diagnosis, and treatment of anal precancer/cancer [5,15,16]. This approach is analogous to cervical cancer screening by cytology with referral to colposcopy, but is not as well studied [5,17,18]. Using a threshold of ASC-US (atypical squamous cells of undetermined significance) and higher grades of cellular dysplasia on cytology as a

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positive screen, the sensitivity of both anal and cervical cytology for biopsy-confirmed high-grade dysplasia are estimated at 90%; however, specificity appears lower for anal vs. cervical cytology (33% vs. 53%) [19]. There is some evidence that the sensitivity of anal cytology is higher in HIV-positive vs. HIV-negative MSM, while the specificity may be lower [20–23].

Due to the challenges and uncertainty associated with anal cytology, some have proposed that HIV-positive MSM be referred directly to HRA [24]. However, while anal cytology has high acceptability among MSM [25,26], there are a limited number of trained and experienced HRA providers, a higher cost for the procedure, and uncertain benefits of screening using this diagnostic tool. Thus, evaluating whether using cytology may be appropriate to identify men who do or do not need HRA is an important goal.

At the cervix, the predictive value of repeated cytology results (e.g., low risk after 3 consecutive negative results) is frequently utilized in screening guidelines [27,28]. For anal cytology, however, it is not known what proportion of HIV-positive MSM have consistently negative results. Further, different transition probabilities, such as the likelihood of a negative cytology if the previous cytology was abnormal, have not been described for anal cytology nor compared by HIV or immune status. Such data could inform decisions regarding when and whether to repeat anal cytology or refer MSM to HRA.

2. Methods

2.1. Study population

We analyzed data from the Multicenter AIDS Cohort Study (MACS), a cohort study of HIV-positive and HIV-negative men who have sex with men (MSM). The MACS has 4 United States sites (Baltimore, Chicago, Pittsburgh, and Los Angeles) and has been ongoing since 1984. Visits occur every 6 months and include routine collection of biological and behavioral covariates of interest. For this sub-study, all MACS participants who attended any study visits between June 2010 and July 2011 were offered a free anal cytology test, with collection and testing done as previously described [18]. Men with unsatisfactory cytology results were offered another test at their next visit. By design, over the study period, HIV-positive men were offered annual cytology (up to 4 cytologies total), whereas HIV-negative men were offered a second cytology 2 years later (2 cytologies total). Thus, our analyses including both HIV-positive and HIV-negative MSM describe 2 cytology results typically collected 1 and 2 years apart, respectively. Analyses examining 3 or more cytology results could be performed among HIV-positive MSM only. Information about HRA and treatment of anal dysplasia occurring outside of regular MACS visits was collected using participant questionnaires and subsequent medical record review. This MACS sub-study was approved by the institutional review boards of each participating site.

2.2. Statistical analysis

A substantial proportion of cytology results were classified as being unsatisfactory for evaluation (18% overall, with no substantial changes over time). For the purposes of this analysis (excluding the generation of inverse probability weights described below) we omitted these results and only considered results deemed sufficient for interpretation. Adequate (valid) specimens were classified as negative (normal) or abnormal: ASC-US, low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells cannot exclude HSIL (ASC-H), or high-grade squamous intraepithelial lesion (HSIL). As we stratify by HIV status, we excluded 1 man who acquired HIV after his first cytology. Men who had treatment of anal dysplasia (including imiquimod cream, trichloroacetic acid, cryotherapy, electrocautery, infrared coagulation, or surgery) between their first and second cytology (N = 38) were excluded from all analyses.

A total of 796 HIV-negative and 708 HIV-positive MSM had at least one anal swab collected and evaluated for anal cytology, including inadequate results (Table 1, top portion). In this study, HIV-negative men had up to 2 opportunities to have anal cytology collected while HIV-positive men had up to 4 opportunities. After excluding men with anal dysplasia treatment between their first and second cytology (6 HIV-negative and 32 HIV-positive men), 474/796 (60%) HIV-negative and 502/708 (71%) HIV-positive men had at least 2 valid results and were included in analysis. For analyses considering 3 consecutive cytologies (HIV-positive MSM only), 14 additional men with treatment between the second and third cytology were excluded.

Among men with at least 2 valid cytology tests, and considering only the first 2 valid (consecutive) results, we calculated frequencies of having a negative (vs. abnormal) cytology following a negative or abnormal cytology. We compared these frequencies across HIV-negative MSM and HIV-positive MSM with absolute CD4 + T cell counts (CD4) ≥ 500 cells/μL (immunocompetent) and < 500 cells/μL (potentially immunocompromised) at the first cytology; p-values were calculated using chi-square tests across all three groups. We also present this analysis after dividing abnormal results into more detailed categories (ASC-US, LSIL, ASC-H/HSIL). Among HIV-positive MSM with at least 3 valid results, we also calculated frequencies of having a negative (vs. abnormal) cytology at the third consecutive anal cytology following 2 consecutive negative or 2 consecutive abnormal cytologies, and compared these frequencies by CD4 count at the first cytology; p-values were calculated using chi-square tests across the two HIV-positive groups.

We recognized potential for selection bias in our analysis set of HIV-positive MSM with at least 3 valid results and no anal dysplasia treatment (N = 328), as this group represented less than half of the HIV-positive MSM who originally had at least one anal swab for cytology collected (N = 708). Therefore, we applied inverse probability weights in the analyses of cytology patterns conducted among this group [29]. We generated the weights using a logistic regression model including variables potentially related to consistent participation in cytology testing, including study center, wave of enrollment into cohort, age, race/ethnicity, educational level, first cytology result (including inadequate), HAART status, and number of sexual partners. Weights were stabilized by dividing the overall proportion with complete data by each individual's model-predicted probability of having complete data. We then applied these stabilized weights when calculating the prevalence of cytology patterns among HIV-positive MSM, and when fitting a logistic model comparing characteristics of men with consistently abnormal vs. consistently negative cytology (described below).

Among HIV-positive MSM with at least 3 valid cytologies, we classified men as having different patterns of negative and abnormal results (e.g., negative-abnormal-negative) by considering the first 3 valid results. As a descriptive analysis, we further restricted to HIV-positive MSM with either consistently abnormal results (i.e., 3 consecutive abnormal cytologies) or consistently negative results (i.e., 3 consecutive negative cytologies) and fit a logistic regression model to compare demographic, behavioral, and biological characteristics between these two groups.

3. Results

Among MSM with at least two valid cytology results (Table 1, bottom portion), the median time interval between valid cytologies for HIV-negative MSM was 2.0 years (IQR 1.9–2.2) and for HIV-positive MSM was 1.0 years (IQR 0.96–1.3). The median age was 58 years for HIV-negative MSM and 54 years for HIV-positive MSM. Consistent with the MACS participants overall, most men in this sub-study were non-Hispanic White and had at least a college education. The first valid cytology was more commonly negative for HIV-negative MSM (75%) compared to HIV-positive MSM (64%). Among HIV-positive MSM, the median current CD4 cell count (at the first cytology) was 579 cells/μL,