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High grade anal intraepithelial neoplasia among HIV-1-infected men screening for a multi-center clinical trial of a human papillomavirus vaccine

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Abstract

Purpose—High-grade anal intraepithelial neoplasia (HGAIN) is the precursor lesion to invasive anal cancer. HPV vaccination holds great promise for preventing anal cancer.

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Trial registrations: clinicaltrials.gov [NCT 00513526]

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Methods—We examined 235 HIV-1-infected men screening for participation in a multi-site clinical trial of a quadrivalent HPV vaccine. All participants had anal swabs obtained for HPV testing and cytology, and high resolution anoscopy with biopsies of visible lesions to assess for HGAIN.

Results—HPV 16 and 18 were detected in 23% and 10%, respectively; abnormal anal cytology was found in 56% and HGAIN in 30%. HGAIN prevalence was significantly higher in those with HPV 16 detection compared to those without (38% vs. 17%, P=.01). Use of antiretroviral therapy, nadir and current CD4+ cell count were not associated with abnormal anal cytology or HGAIN.

Conclusion—HGAIN is highly prevalent in HIV-infected men. Further studies are needed on treatment and prevention of HGAIN.

Keywords

human papillomavirus; HIV-1 infection; male; anal intraepithelial neoplasia; anal infection

Introduction

Anal cancer is caused by persistent infection with high-risk types of human papillomavirus (HPV) [1]. HPV type 16 and 18 are responsible for approximately 66% and 5% of invasive anal cancers, respectively [2]. The risk of anal cancer is substantially higher for HIV-1-infected men who have sex with men (MSM) compared with the general population, and the incidence appears to have increased further in the era of effective antiretroviral therapy (ART) [3–7]. Anal cancer prevention programs include screening for the anal cancer precursor, high-grade anal intraepithelial neoplasia (HGAIN), through an algorithm of cytology and high resolution anoscopy (HRA)-directed biopsies [8]. Areas of HGAIN are then excised or ablated in an attempt to prevent progression to invasive anal cancer. In this report, we describe the high prevalence of HGAIN in a sample of HIV-infected MSM screening for a clinical trial of the quadrivalent HPV vaccine.

Methods

Study Sites

AIDS Malignancy Consortium (AMC) Protocol 052 was a multi-center single arm open-label, pilot trial of the safety and immunogenicity of the quadrivalent HPV vaccine in HIV-1-infected adult men. This study was conducted at eight clinical trial sites and has been previously described in detail [9]. Institutional review boards of the participating institutions approved the study, and each patient gave written informed consent.

Inclusion in screening analysis

All participants who signed the consent form were included in this analysis. The original informed consent document did not specify that clinical data (CD4+ cell count, nadir CD4+ cell count and plasma HIV-1 RNA) from subjects not entering the study would be used for the purposes of research. The protocol was modified, with regulatory approvals, to contact these subjects and obtain verbal consent for use of these data for this analysis.

Enrollment criteria for prospective trial

Inclusion criteria have been previously described [9]. To assess eligibility for AMC052, all participants had anal swabs for HPV DNA PCR testing and cytology obtained and HRA (with directed biopsies) performed. Selected inclusion criteria for enrollment in AMC052 and receipt of study vaccination were as follows: HIV-1-infected men aged 18 years or older; if receiving ART, receipt of ART for at least 6 months prior to entry and no change in

ART within 30 days of entry, CD4+ count ≥200 cells/μL and plasma HIV-1 RNA level <200 copies/mL; if not receiving ART, CD4+ count >350 cells/μL and no plans to start ART within 28 weeks of entry. Participants were not eligible if they had a history of anal or perianal carcinoma, HGAIN on HRA-guided biopsy, or high grade squamous intraepithelial lesions (HSIL) or atypical squamous cells suggestive of HSIL on anal cytology, at any point prior to entry.

Laboratory Testing

HPV DNA testing was performed at a central laboratory. Specimens negative for beta-globin gene amplification were excluded from analysis. The results of PCR were recorded on a scale from 0 to 5 based on the intensity of the signal on the dot-blots, as previously described [10]. Anal swab specimens were assayed for HPV types 16 and 18 only. Anal cytology and histology were interpreted locally at the individual study sites.

Statistical Considerations

Multivariable logistic models were constructed to examine predictors of HPV 16, abnormal anal cytological results and HGAIN. Cytology results were dichotomized as normal vs. abnormal (atypical squamous cells, low-grade squamous intraepithelial lesions, or HSIL). HGAIN was defined as at least one biopsy showing HGAIN vs. no biopsies with HGAIN or no biopsies performed. All subject characteristics were included in the multivariable models, except plasma HIV-1 RNA because of the strong association with ART.

Results

Study participants

Two hundred thirty five men gave informed consent and entered the screening process, and 123 were excluded. Verbal consent for use of additional data (e.g. CD4+ cell count, nadir CD4+ count and plasma HIV-1 RNA level) was obtained from 82 (67%) of those who were excluded. The characteristics of the 235 men who were screened were: 142 (60%) were non-Hispanic Whites; the median age was 44 years [IQR 37, 50]; the median CD4+ count was 512 cells/μL [IQR 413, 678]; the median nadir CD4+ count was 240 cells/μL [IQR 148, 330]; 201 participants (86%) were on ART. Plasma HIV-1 RNA levels were available for 187 men; 157 (84%) were less than 200 copies/mL.

HPV 16, HPV 18, anal cytology and histology results are shown in Table 1. There was variation in these results across sites with the proportion of subjects with HPV 16 at each site varying from 0% to 48%, and abnormal cytology varying from 26% to 82%. The proportion of participants with HGAIN was similar at 7 of the sites with a range of 25%–38%. At one site HGAIN was identified in only 2 of 25 participants (8%). Overall the prevalence of HGAIN among those with abnormal anal cytology was 38%, and 20% among those with normal cytology.

The sensitivity, specificity, positive predictive value and negative predictive value of HPV 16 detection for presence of HGAIN were 35%, 84%, 37%, and 82% respectively. The sensitivity, specificity, positive predictive value and negative predictive value of abnormal anal cytology for presence of HGAIN were 71%, 50%, 38%, and 80% respectively. Of the 212 participants with HRA results, 59 (28%) did not have any biopsies obtained. The prevalence of HPV 16 and abnormal anal cytology was similar among those with a biopsy obtained and those without a biopsy obtained.

We examined the relationship of race/ethnicity, age, CD4+ count, nadir CD4+ count, and ART use with detection of HPV 16, abnormal anal cytology and HGAIN. We also examined

the relationship of HPV 16 and HPV 18 detection to abnormal cytology and HGAIN. Non-Hispanic Whites had a marginally higher HPV 16 prevalence compared with non-Hispanic Blacks, Hispanics, and others (30% vs. 9%, 15%, and 20%, P=.05). The prevalence of HGAIN was higher among those with HPV16 compared with those who were HPV 16-negative (38% vs.17%, P=.01). This significant relationship persisted in the multivariable analysis (data not shown). There was no association of ART use, current CD4+ count and nadir CD4+ count with abnormal anal cytology or HGAIN.

Discussion

This multi-center study demonstrates a high prevalence of HGAIN (30%) among HIV-1-infected men from diverse clinical research sites in the United States. This may be an underestimate given that patients with a known history of HGAIN were excluded per protocol and not approached for study participation. This estimate is somewhat lower than prior single-site studies that found a HGAIN prevalence of 52% and 43% in HIV-infected MSM [11,12]. Only 7% had both HPV 16 and 18 detected by HPV DNA PCR. This indicates that the majority of HIV-1-infected men without a prior history of HGAIN may potentially benefit from HPV vaccination despite being highly HPV-exposed. AMC052 established the safety and immunogenicity of the vaccine [9]. However, since we did not measure antibodies to these HPV types in these men, we cannot determine the proportion that had not been exposed to these types. Randomized clinical trials are needed to test the efficacy of this vaccine in the setting of HIV-1 infection.

We found that HPV 16 was the most significant factor associated with HGAIN. However, this study also demonstrates a high prevalence of HGAIN without detectable infection with HPV 16 or HPV 18, and supports the study of HPV vaccines that protect against high-risk HPV types in addition to those found in the currently-available quadrivalent or bivalent vaccines in the setting of HIV. We found that HPV 16 was marginally higher in non-Hispanic whites. We did not expect this finding and it should be confirmed in other studies. This may have been related to the significant regional variation of HPV 16 (0–48%) among the 8 clinical trial sites.

This study has several limitations. The widely varying prevalence of abnormal anal cytology (18% to 74%) and HPV 16 (0% to 48%) suggests that the screening populations varied from site-to-site. This may reflect variations in the referral populations from the sites, and regional variations of HPV16/18 infections in the anal canal in MSM. We did not have sexual history data on participants who screened out of the study and could not examine the relationship of sexual activity to these outcomes. The population studied is not necessarily generalizable to the population of all HIV-infected men because of entry criteria such as prohibiting those with a known history of HGAIN. We did not implement a central pathology review to standardize interpretation across clinical sites. Also, not all subjects consented to have additional information used for this analysis and this missing data restricted the number of subjects included in the multivariable analyses.

In conclusion, this multicenter study of HIV-infected men entering an HPV vaccine clinical trial found a substantial prevalence of HGAIN, a precursor lesion to invasive cancer. These data highlight the necessity of conducting multicenter studies of anal cancer screening and HPV prevention with treatment of HGAIN in order to reduce the growing incidence of invasive anal cancer, particularly in the setting of HIV.

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Table 1

HPV, Cytology, and HRA results for all Screened Subjects

Characteristic	N (%)
Anal HPV detection (N=203)	
HPV16+ / HPV18+	7 (3%)
HPV16+ /HPV18−	40 (20%)
HPV16− /HPV 18+	14 (7%)
HPV 16− /HPV 18−	142 (70%)
Anal cytology (N=231)	
Normal	102 (45%)
ASCUS	72 (31%)
LSIL	45 (19%)
HSIL or ASC-H	12 (5%)
High resolution anoscopy (N=212)	
No biopsy performed	58 (27%)
All biopsies normal	38 (18%)
LGAIN/condyloma	54 (25%)
HGAIN	63 (30%)