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Risk factors for anal HPV-16/18 infection in Mexican HIV-infected men who have sex with men

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ABSTRACT

Objective. To describe the prevalence of specific HPV types among HIV-positive men who have sex with men (MSM), particularly the presence of HPV-16 and/or -18, and to determine the factors associated with anal HPV-16/18 infections.

Methods. This is a cross-sectional study from a baseline cohort of 525 HIV-positive MSM, who attended an HIV Clinic in Mexico City. Socio-demographic characteristics, sexual behaviors and HIV-related parameters were assessed. Anal samples were tested for HPV DNA using the Linear Array HPV genotyping assay.

Results. The overall prevalence of any HPV type in the anal canal among 446 participants was 93.1%. At least one oncogenic HPV type was detected in 72.2% of the subjects and HPV-16 and/or18 were detected in 30.7%. Additionally, 76.9% of patients were infected with multiple HPV types. Having more than 10 receptive sexual partners in the last 6 months (OR = 2.30; 95% CI 1.12–4.74) and a CD4 cell count ≤350 cells/μL (OR = 1.97; 95% CI 1.26–3.09) were factors positively associated with HPV-16/18 infection in the anal canal.

Conclusion. Co-infection with HPV-16/18 and other oncogenic types are predominant in this group of HIV-positive MSM. The recognition of infection with specific oncogenic types will be of aid in designing future preventive strategies that target this high-risk population.

Introduction

Anal HPV infections represent a major health burden for HIV-positive men, particularly for men who have sex with men (MSM) (Critchlow et al., 1998; Chin-Hong and Palefsky, 2002; Palefsky, 2007). The prevalence of anal HPV infections in this population is over 90% (de Pokomandy et al., 2009; Palefsky et al., 1998; Salit et al., 2009) including a high frequency of infection with multiple HPV types (Chin-Hong et al., 2008; Goldstone et al., 2009; Hagensee et al., 2004; Parisi et al., 2011; Sirera et al., 2006). HPV-16 is the most prevalent type, followed by HPV-18 (de Pokomandy et al., 2009; Gao et al., 2010; Guimaraes et al., 2011; Palefsky et al., 1998; Parisi et al., 2011). Oncogenic HPV infections, particularly type 16, are characterized by greater persistence, higher risk of progression to high-grade intraepithelial neoplasia (HGAIN) (Schiffman et al., 2005), and are associated with 70-percent of anal carcinomas (Hoots et al., 2009; Wong et al., 2010).

While earlier studies reported the prevalence of HPV in HIV-positive MSM in North America and some countries in Europe and Asia, there is little data on anal HPV infection and related disease among MSM in Latin American countries like Mexico, resulting in a lack of recognition of the health problem and delays in health intervention. Since HIV-positive men in Mexico have high coverage of antiretroviral treatment, anal cancer morbidity may pose a significant problem for this population. This is the case in the US, where anal cancer incidence rates have increased in the post-highly active antiretroviral therapy (HAART) era (ranging from 75/100,000 to 137/100,000) compared to the pre-HAART era (D'Souza et al., 2008; Patel et al., 2008; Piketty et al., 2008).

Researchers are currently evaluating quadrivalent vaccine immunization to prevent HPV infections in HIV-positive MSM. Recent results have demonstrated the safety and immunogenicity of this vaccine in said population (Wilkin et al., 2010), and a clinical phase III trial is being developed to evaluate the vaccine's efficacy in preventing anal HPV

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infections (ClinicalTrials.gov: NCT01461096). The rate reduction of anal intraepithelial neoplasia (AIN) with the quadrivalent HPV-vaccine has been only demonstrated in a subpopulation of HIV-negative MSM (Palefsky et al., 2011). If similar results are found for HIV + MSM, HPV infections must be characterized in order to assess the cost-effectiveness of this preventative strategy.

The present analysis derives from baseline information of a HIV + MSM cohort in Mexico City. The objective is to describe the prevalence of specific HPV types in this population, particularly HPV-16/18, and to determine factors associated with these infections in the anal canal. This information will be useful in designing prevention strategies and care services for HIV-infected MSM in Mexico.

Materials and methods

Study population

This cross-sectional study is based on baseline information from a cohort of HIV-positive MSM recruited at Condesa Clinic, which provides free HIV care in Mexico City. Men were eligible for participation if they were 18 years or older and had any type of sexual intercourse at least once with another male.

To be included in the study, men needed to be HIV seropositive; whether they were currently or not yet receiving HAART did not affect their eligibility. HAART initiation criteria were: CD4 cell count ≤350 cell/μL, AIDS-defining condition, presence of HIV-associated nephropathy, or need for hepatitis B treatment. All participants voluntarily signed consent forms. Participants enrolled from December 2009 through October 2011 were included in the present analysis. The Ethics and Biosafety Committees of the Instituto Nacional de Salud Pública (INSP), Cuernavaca, Mexico approved the study procedures.

Study procedures

Recruitment

Condesa Clinic medical personnel recruited subjects during their routine clinical visits. Before the baseline visit, participants were instructed not to shower and to abstain from sexual intercourse for 24 hours before sample collection. A total of 740 HIV + MSM were invited to participate in the study, of whom 82 declined, and 133 did not return for the baseline visit. Therefore, at the time of this analysis we had data available for 525 enrolled subjects, representing an acceptance rate of 70.9%.

Risk factors assessment

Interviewers confidentially administered a standardized questionnaire to each participant to record socio-demographic characteristics, sexual behavior, condom use, STI history, smoking history, history of illegal drug use and medical history. Participants' medical records were reviewed to assess information on the number of years since HIV diagnosis, CD4 cell count and HIV viral load (measurements taken closest to enrollment), HAART history, and specific drug regimen. At the Condesa Clinic, CD4 and viral load levels are assessed biannually.

Anal canal sampling for HPV testing

The intra-anal sample was collected by inserting a dacron swab 3–4 cm into the anal canal and rotating it in a 360-degree circle while pressing against the anal wall. Samples were placed in a vial with 20 mL of PreservCyt® solution, and stored at room temperature. Samples were delivered weekly to the INSP HPV laboratory facilities for genotyping.

HPV genotyping

DNA was extracted using an AmpliLute liquid medium extraction kit (Roche Molecular System). HPV DNA genotyping was then conducted using the reverse line-blot detection system following manufacturer's protocol (Linear Array HPV genotyping test, Roche Molecular Diagnostics, Branchburg, NJ, USA). This test is based on the principle of PCR amplification of the L1 consensus HPV PGMY09/11 pool primer system (450 pb). Amplification was performed using the Applied Biosystems' GeneAmp PCR System 9700 and amplified products were hybridized with a master mix of 37 individual HPV probe genotypes. An additional β-globin gene was amplified with the primers PC04/GH20 as a control.

Statistical analysis

We performed a descriptive analysis of continuous and categorical variables, using parametric and non-parametric summary measures as suitable.

Missing data because of non-response or absent clinical data from medical records (such as date of HIV diagnosis) were treated as missing observations. The present analysis included only the 446 participants (85% of enrolled subjects) whose anal canal samples were β-globin positive at baseline. The characteristics of the participants with samples negative for beta-globin (n = 79) did not differ from those of the rest of the study subjects (data not shown).

The HPV types identified by Linear Array genotyping were classified as follows: 1) Any HPV, if the test was positive for any of the 37 HPV types; 2) oncogenic HPV, if the test was positive for any of HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68; 3) non-oncogenic HPV, if the test was positive only for any of HPV types 6, 11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 66, 67, 69, 70, 71, 72, 73, 81, 82, 83, 84, CP6108, and IS39; and 4) HPV 16/18, if the test was positive for HPV 16 and/or 18, regardless of positivity for other HPV types. Multiple infections signify positivity for more than one type.

We assessed the association among certain variables of interest with the presence of HPV 16/18 using logistic regression. We also performed analysis for infection with HPV-16 and 18 separately. Odds ratios (OR) with 95% confidence intervals (CIs) were estimated to evaluate these associations. Multivariate models were adjusted for potential confounders reported in the literature. Data analysis was performed using the statistical software program STATA version 12.0.

Results

Participant characteristics

The median age of the study population was 33 years (range, 18–69 years). The median age at which participants first had sexual intercourse (anal or oral) with a man was 17 years (range, 4–45 years). Most participants were single (85.1%), and 40.9% reported never having used illegal drugs. Thirty-eight percent reported having had sexual intercourse with a female at least once, but only 12 men reported doing so in the last 6 months. Sixty nine percent of participants reported using condoms over half of the times they had sex with men, although only 12.6% always did so, and 2.3% never used condoms. Most participants had casual male sexual partners in their lifetimes (85.7%), defined as partners with whom they had sex the first time they met (data not shown).

Table 1 shows the socio-demographic, sexual behavior and clinical characteristics of study participants.

HPV prevalence

Overall HPV prevalence was 93.1% with oncogenic HPV infections accounting for 72.2% of cases (Table 2). The prevalence of HPV-16/18 infection was 33% among HPV-positive participants. 51.1% of the HPV-16/18 positive cases had HPV-16 while 29.2% had HPV-18 and 19.7% had concurrent infection with both types.

HPV 16/18 prevalence (35.4%) was higher among participants whose first sexual intercourse occurred before age 18 and slightly lower (24.6%) among men with a later sexual debut with a man. Among men with 25 or more male sexual partners per year, 83.0% had at least one oncogenic HPV infection and almost half of them had HPV 16/18. Also, HPV 16/18 was detected in 40.3% of men with ≤350 CD4 cells/μL, compared to 26.0% of those with higher CD4 counts (Table 2).

Type-specific prevalence of 37 HPV types was analyzed by categories of single or multiple infections among all participants, and in HPV-16/18 anal canal cases (Table 3). The most prevalent oncogenic HPV type in the anal canal was HPV-16 (21.7%) followed by types HPV-58 (16.4%), HPV-59 (15.9%), HPV-39 (15.5%), HPV-18 (15%) and HPV-52 (15%). The most common non-oncogenic types were HPV-6 and -11 (21.4% and 21.1%, respectively). Concomitant infection with other oncogenic HPV types, especially HPV-39 and -58 (both with a 21.9% prevalence), was common among participants with HPV-16/18 (Table 3). 76.9% of participants had two or more HPV types in the anal canal. 19.7% of all