Journal of Infection (2014) 69, 375–386

BIA
British Infection Association

www.elsevierhealth.com/journals/jinf

No evidence for a protective effect of naturally induced HPV antibodies on subsequent anogenital HPV infection in HIV-negative and HIV-infected MSM

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Accepted 3 June 2014
Available online 12 June 2014

KEYWORDS
HPV;
Antibodies;
Immunology;
Protection;
Anal;
Penile

Summary *Objectives:* To assess whether HPV serum antibodies detected after natural infection protect against subsequent anal or penile infection with the same HPV type in HIV-negative and HIV-infected men who have sex with men (MSM).
Methods: MSM aged ≥18 years were recruited in Amsterdam, the Netherlands (2010–2011), and followed-up semi-annually. Antibodies against 7 high-risk HPV types in baseline serum samples were tested using a multiplex immunoassay; baseline, 6-, and 12-month anal and penile samples were tested for HPV DNA and genotyped using the SPF_{10}-PCR DEIA/$LiPA_{25}$ system (version 1). Statistical analyses were performed using the Wei–Lin–Weissfeld method.

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http://dx.doi.org/10.1016/j.jinf.2014.06.003

Results: 719 MSM (median age 40 years; IQR 35—48) with baseline and follow-up data were included in these analyses; 287 (40%) were HIV-infected. HPV seropositivity at baseline was not significantly associated with subsequent type-specific HPV infection at 6 or 12 months in multivariable analyses (for anal infection adjusted hazard ratio (aHR) 1.2; 95% CI 0.9—1.6; for penile infection aHR 0.8; 95% CI 0.6—1.2). High antibody concentrations showed no protective effect against subsequent infection either.
Conclusions: In a population of highly sexually active, adult MSM, naturally induced HPV antibodies may not protect MSM against subsequent anal or penile HPV infection within one year.

Introduction

Human Papillomavirus (HPV) is one of the most common sexually transmitted infections in the world and the cause of many cancers worldwide, including cervical, anal, penile, and oropharyngeal cancer.[1,2] Most HPV infections are asymptomatic and are cleared by the host immune system within 1 or 2 years, whereby cellular immunity plays a major role.[3] Humoral immune responses are not always observed, and the function of naturally induced serum HPV antibodies is currently unknown.[4,5] In contrast, antibody concentrations after prophylactic HPV vaccination are 1—4 logs higher than those observed after natural HPV infection,[6,7] and have been shown to be very protective against incident and persistent HPV infection and associated diseases in both women[8] and men.[9]

Since 2010 a bivalent HPV vaccine against HPV types 16 and 18 is offered free of charge to young girls in the Netherlands, but boys are not routinely vaccinated. More insight in the function of naturally induced antibodies would be helpful for designing national vaccination programs or targeted prevention strategies. Men who have sex with men (MSM), especially HIV-infected MSM, are more affected by the serious consequences of HPV infection than the general male population, notably with regard to anal cancer.[10] Now that the survival of HIV-infected people in the era of the combination antiretroviral treatment (cART) has increased, an increased incidence rate of anal cancer is observed in HIV-infected MSM.[11] Therefore, HIV-infected individuals are an important target group to take into account when planning HPV prevention strategies.

In this study, we aimed to assess whether naturally induced HPV antibodies confer protection against subsequent type-specific anal and penile HPV infection in HIV-negative and HIV-infected MSM.

Methods

Study population

HIV-negative and HIV-infected MSM were recruited into the HIV & HPV in MSM (H2M) study from July 2010 to July 2011 at three study sites in Amsterdam, the Netherlands: the Amsterdam Cohort Study (ACS) among MSM (Public Health Service of Amsterdam),[12] an outpatient infectious disease clinic (Medical Centre Jan van Goyen), and a Sexually Transmitted Infection (STI) clinic (Public Health Service of Amsterdam).[13] Study methods have been described in detail in earlier reports.[14,15] Inclusion criteria were having had sex with men, being 18 years or older, and in command of English or Dutch. All participants provided written informed consent and the study was approved by the Medical Ethics Committee of the Academic Medical Center (AMC) Amsterdam. Data described in this paper are limited to one year follow-up.

Data collection

At baseline, participants completed an extensive, self-administered questionnaire regarding socio-demographic characteristics, health-related issues, and sexual behavior. Venous blood was drawn for HPV serology. Participants were instructed to self-swab their anus and penile shaft with separate swabs (regular flocked swab with 1 ml UTM medium, Copan, Brescia, Italy) for HPV DNA analyses, as previously described.[14] HIV-related data were obtained from the Dutch Monitoring Foundation's national HIV patients database. Participants were invited for follow-up every 3—6 months. During follow-up visits, anal and penile self-swabs were collected at 6 and 12 months.

HPV serology

Baseline blood samples were taken to the National Institute for Public Health and the Environment (RIVM, Bilthoven, the Netherlands) and stored in −80 °C until analysis. A multiplex immunoassay based on L1 virus-like particles (VLP) (GlaxoSmithKline Biologicals, Rixensart, Belgium) coupled to fluorescent beads (Luminex Corporation, Austin, TX, USA) was used to detect IgG antibodies against HPV types 16, 18, 31, 33, 45, 52, and 58. This assay has been described by Scherpenisse et al.[16] and was shown to measure a broad range of both neutralizing and non-neutralizing HPV-specific epitopes.[17]

Antibodies were analyzed using Bioplex software (Bio-Rad Laboratories, Hercules, CA, USA). Median Fluorescent Intensity (MFI) was converted to Luminex Units (LU) for each analyte. Two controls were used in each plate; one borderline positive and one highly positive. Cut-off values were determined based on sera from children (1—10 years) highly likely to be seronegative, using a one-sided 99% prediction interval method.[18] Cut-off values were determined at ≥9, ≥13, ≥27, ≥11, ≥19, ≥14, and ≥31 LU/mL for HPV types 16, 18, 31, 33, 45, 52, and 58 respectively.