



## High specific immune response to a bivalent anti-HPV vaccine in HIV-1-infected men in São Paulo, Brazil



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### ABSTRACT

**Introduction:** Infection with Human papillomavirus (HPV) has been reported as one of the most prevalent agent sexually transmitted diseases, but its true prevalence in men is not precisely known, mainly due to the near absence of symptoms. Moreover, few studies evaluating the post-vaccination immune response have been performed to date in men, hence the hypotheses tested in this study can be important to enable a better understanding of both the immunopathogenesis and the response to vaccination in HIV-infected patients, and to help in the elaboration of strategies of vaccination against HPV in the HIV-infected population.

**Objectives:** To analyze the specific response to antigens of HPV vaccine in HIV-infected men.

**Methods:** A total of 25 HIV-infected male patients who met the inclusion criteria during the data collection period were vaccinated; however, six (30%) had anti-HPV at baseline, and were not considered further in the analysis. Therefore, 19 HIV-infected individuals were included in the study, along with five healthy, HPV-seronegative controls.

**Results:** Patients infected with HIV-1 were subdivided into two groups, A and B, according to their T CD4 cells count at the time of vaccination, namely: Group A: CD4 > 500; Group B: CD4 < 500. The proportion of seroconversion after immunization with three doses of a bivalent anti-HPV vaccine was 92%.

**Conclusion:** HIV-infected patients as well as HIV negative controls responded to anti-HPV vaccination, regardless of their T CD4 cells count and HIV plasma viral load. These results demonstrate that anti-HPV immunization in HIV-infected males is effective and should be encouraged, thus helping to decrease the risk of infection, mortality and morbidity of diseases associated with HPV in men.

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### Introduction

Human papillomavirus (HPV) infections rank among the most common virus sexually transmitted diseases worldwide [1]; it is an epitheliotropic virus, characterized by its icosahedral, non-encapsulated form, with a diameter of 50 nm, and includes as its genetic material a molecule of double-stranded circular DNA with approximately eight thousand base pairs [2]. To date, more than 200 types of human HPV have been described and classified into

high and low risk subgroups; there are 45 potentially oncogenic types infecting the anogenital region [3].

HPV escapes recognition by the immune system by not causing cell lysis and not inducing a local inflammation [4]. In its infection cycle there is no viremia, and a very low amount of viral protein is expressed; also, the virus is not cytolytic. Thus, there is no signaling to the immune system to activate the innate response, as well as a delay in the adaptive response [1], leading to an immune dysfunction, with a decrease in the number of antigen-presenting cells (APCs) and T-cell lymphocytes. Immune surveillance is impaired, due both to a deficient presentation of antigens and to a reduced effector phase of T-lymphocyte activation and antibody production [5].

Anti-HPV vaccine was the result of the mastering of the key technologies that are capable of producing virus-like (VLP) particles. Recombinant DNA was used to generate VLPs able to mimic

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the natural virus, causing high titers of neutralizing serum antibodies. Today there are two types of vaccines commercially available: Cervarix<sup>®</sup> (GlaxoSmithKline Biologicals website) containing VLPs (Virus Like Particle) types 16 and 18, Gardasil<sup>®</sup> (Merck Dohme Shape, Whitehouse Station, New Jersey) containing VLPs of types 6, 11, 16 and 18. Both vaccines contain an adjuvant aluminum salt that precipitates VLP allowing a more slowly release of the antigen [6,7]. More recently, a prophylactic non-valent HPV (types 6/11/16/18/31/33/45/52/58) VLP (9vHPV) vaccine in young men 16–26 years of age in comparison to young women 16–26 years of age showed safety and immunogenetic [8].

In women with immunodeficiency, iatrogenic or acquired, the prevalence of HPV-associated lesions is higher than in immunocompetent individuals [9]. HIV-seropositive subjects experience an increased infection rate with a high number of relapse after treatment and an accelerated development of HPV-associated cancer [10,11]. In HIV-infected men, the prevalence of HPV in the genital area is 18.2% while that in the anus is 59.3% [12,13].

Besides the specific response to vaccine antigens, we analyzed the anti-HPV immune response from HIV-1-infected men in different strata of immune deficiency. The hypothesis was tested by stratification according to the number of T CD4<sup>+</sup> lymphocytes, in an attempt to assess the count range with the highest probability of vaccine response. The degree of vaccine response in HIV-infected patients may indicate which patients have a greater potential for in vivo vaccine response.

## Material and methods

In total, 450 HIV-infected individuals have been in follow-up at our outpatient service for the last 25 years. Among them, 300 subjects are males, 56 of whom aged 18–45 years and were seen in the Clinic during the study. These patients underwent a screening to check for the presence of HPV in oral samples, previously published elsewhere [14]; eight tested positive for HPV and 23 had other exclusion criteria and were not vaccinated. Therefore, in this study, 25 patients satisfied the inclusion criteria, were invited and agreed to participate, all of them were men who make sex with men. Five HIV-negative control subjects were tested for HIV infection and submitted to an oral cleansing prior to vaccination. Patients and controls were recruited from October 2012 to February 2013. The Ethical Board of Hospital das Clínicas approved the clinical study; it is registered at the clinical trial identifier (NCT02236234).

### Subject population

HIV-1-infected men aged 18–45 years old were invited to participate, regardless acquisition mode of transmission. We selected two groups according to the updated outpatient records: nine had T-CD4 cells counts above 500 cells/ $\mu$ L whereas 16 had T-CD4 cells counts below 500. Exclusion criteria included other types of immunodeficiencies, such as renal failure or hepatic malignancies, autoimmune diseases, immunosuppressive medications, or other vaccination within the last 2–3 weeks. All patients gave informed consent, which contained information about the study. After agreeing to sign the term, they answered a questionnaire containing information on socio-behavioral, presence or history of sexually transmitted diseases, HIV viral load, CD4+T cells count and time of the first HIV testing.

### Vaccine

Cervarix<sup>®</sup> (GlaxoSmith-Kline, Brentford, England, a bivalent human papillomavirus vaccine (types 16 and 18), is a recombinant

protein virus-like particle. It was administered by intramuscular injection 0.5 mL at 0, 4 and 24 weeks. The primary immunogenicity endpoint was determined three weeks after the third vaccination dose.

### Design study

Twenty-five HIV-infected patients who met the inclusion criteria during data collection period were analyzed and classified as follows: All were vaccinated; however, six (24%) had anti-HPV antibodies at baseline, and were not considered further in the analysis. Therefore, 19 HIV-infected individuals were described in the study (nine patients with T CD4 < 500 cells/mm<sup>3</sup> and 10 patients with CD4  $\geq$  500 cells/mm<sup>3</sup>). Control group was made up of five healthy adults who were negative for HIV and HCV infections.

### Laboratory methods

Samples were collected by venipuncture from the peripheral blood of research subjects and processed in tubes containing 5 mL of gel; the tubes were centrifuged at 2000xg at a room with a temperature of 15 °C for 15 min. Two aliquots of 500  $\mu$ l of serum were stored at –80 °C in order to perform the analysis.

### HPV serology

Presence of IgG antibodies to HPV 16 and 18 in the sera samples was detected using a type specific ELISA using L1VLPs from *S. cerevisiae* (kindly provided by Dr Ian Frazer, Univ of Queensland, Woolongaba, AU). Fifty microliters of 0.03 mg/ml of each VLP were used to coat the ELISA plates overnight at 4 °C. From every two wells coated with VLP, one was coated with PBS, pH 7.2. Plates were then washed once with PBST (0.02% Tween in PBS pH7.2) and blocked with 100 ml of BSA blocking solution (1.5% bovine serum Albumin in PBS) for 2 h. After the blocking step, plates were washed twice with PBST. Sera and control samples, diluted 1:50 with a solution of 5% fat free milk powder, 0.1% BSA in PBST, were tested in duplicate and incubated at 37 °C for one hour. Plates were washed five times with PBST and tested with horseradish peroxidase conjugated with anti-human IgG (TagoImmunobiologicals, USA) at appropriated dilutions. Following 45 min of incubation at 37 °C, the plates were washed 5 times with PBST and 50 microliters of ABTS solution (0.05% 2,2'-Azino Bis Ethylenebenzthiazoline-6-sulfonic acid, Sigma, USA) were added to each well. The reaction was stopped after 4 min by adding 50 ml of 1% Sodium Dodecyl Sulfate. Optical Density (OD) was read at 415 nm in a microplate reader (Biorad, USA). The OD value for each serum was calculated by subtracting the mean OD of wells coated with VLP from the OD of wells coated with PBS. The cut points for seropositivity for HPV 16 and 18 were determined from the positive controls provided by WHO [15].

## Results

Mean age of group A was 30.44 years, and most patients reported having a college degree (66.7%) and being single (77.8%). The average age of group B was 34, 50% reported having completed high school and 80% were single (these characteristics were not different).

Six patients had anti-HPV antibodies before baseline and therefore were excluded from further analysis. The remaining 19 HIV-infected patients and five controls had titers of anti-HPV antibodies below the cut-off of 0.216. Four weeks after the administration of the first dose of vaccine an increase in titers of

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