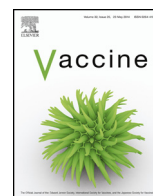




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# Safety and immunogenicity of a quadrivalent human papillomavirus vaccine in HIV-infected and HIV-negative adolescents and young adults

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## ABSTRACT

Human papillomavirus (HPV) infection is highly prevalent and can lead to cancer; the development of safe and efficacious vaccines for HPV is a major public health concern. The two licensed HPV vaccines contain recombinant virus-like particles of HPV 16 and 18; one of such vaccines also protects against HPV types 6 and 11 which cause genital warts. We determined safety and immunogenicity of quadrivalent HPV vaccine in HIV-infected and HIV-negative adolescents and young adults, aged 13–27 years. The seroconversion rate, assessed by antibody titers, 1 month after the administration of the third vaccine dose was 0.85 (95% CI 0.75–0.95) in the HIV-infected group and 0.91 (0.83–0.99) in the HIV-negative subjects ( $p = 0.52$ ). The vaccine was generally safe and well tolerated; the most common side effect was local pain and the most frequent systemic side effect was headache. This is the first report on response to HPV vaccination in both female and male HIV-infected adolescents and young adults and highlights that this population may benefit from HPV immunoprophylaxis. Further studies are needed to examine the long term efficacy of this vaccine in HIV-infected individuals.

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## 1. Introduction

Human papillomavirus (HPV) infection is the most prevalent sexually transmitted infection in the world [1]. The genital HPV family is composed of ~35 distinct types. These HPV types are divided into high risk (associated with the development of anogenital cancer) and low risk (associated with the development of dysplasia and anogenital warts, but rarely cancer). Four HPV types are associated with the majority of HPV related clinical disease. HPV types 16 and 18 cause approximately 70% of cervical cancer, HPV-6 and HPV-11 are responsible for approximately 90% of genital warts in both men and women, and types HPV-6, 11, 16, 18 together cause a significant proportion of cervical intraepithelial neoplasia leading to abnormal Papanicolaou smear [2]. The great majority of HPV infection in immunocompetent

subjects is transient, and persistent infection is rare. In contrast, in immunosuppressed individuals, including transplant recipients or patients with human immunodeficiency virus (HIV) infection, HPV infection often becomes chronic. Higher rates of HPV infection are seen in HIV-infected compared to HIV-negative women [3,4]. Moreover, in the HIV-infected population, HPV infection tends to be more persistent, to involve multiple sites and to progress more frequently into HPV-related abnormalities including squamous intraepithelial lesions, vulvovaginal condyloma acuminata, or anal intraepithelial neoplasia [5,6]. Furthermore, HIV-infected men who have sex with men (MSM) show a 60-fold increase in relative risk for anal intraepithelial neoplasia, and an 8-fold increase for penile cancer compared to HIV-negative men [7–9]. These observations imply that HIV infection increases susceptibility to HPV infection and/or alters the natural history of preexisting or newly acquired HPV infection. Two HPV vaccines have shown to be effective in preventing HPV infection in HIV-negative females and males (>90%) against the serotypes included in the vaccines. One is bivalent and prevents infection from two oncogenic HPV types (HPV 16, 18;

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Cervarix), the other is quadrivalent and prevents infection from two oncogenic HPV types as well as two non-oncogenic HPV types (HPV 6, 11, 16, 18; Gardasil). The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination with three doses of quadrivalent HPV vaccine (QHPV) in women aged 9–26, men aged 13–21 and considers vaccination in men aged 22–26. [10–12].

Several studies on immunogenicity and safety of QHPV have been conducted in both female and male HIV-infected adults [13,14]. A study conducted by AIDS Clinical Trials Group, the ACTG 5240 Trial, showed that QHPV was safe and immunogenic in HIV-infected women aged 13–45 years, with observed seroconversion proportions >75% for all four HPV types. [13]. Wilkin et al. [14] conducted a clinical trial on HIV-infected MSM, vaccinated with three doses of QHPV. Seroconversion was observed for all HPV types. No adverse effects on CD4+ counts and plasma HIV1-RNA were observed. In HIV-infected children and adolescents data on immunogenicity and safety of QHPV is scanty. To date, only few studies have been conducted [15,16]. Levin et al. [15] showed that QHPV was safe, immunogenic and did not alter CD4+ % or plasma HIV-RNA in a cohort of HIV-infected children and adolescents aged 7–12 years. Results from a multicenter trial performed by the Adolescent Medicine Trials Network for HIV/AIDS Interventions, in young women aged 16–23 years ( $n=99$ ), indicated that immune responses to QHPV were robust and the vaccine well tolerated [16]. The safety profile of both vaccines has been assessed in extensively randomized controlled clinical trials prior to licensure and has been further elucidated following licensure from surveillances and specific studies in large population. Both vaccines are associated with relatively high rates of injection site, particularly pain, but this is usually of short duration and resolves spontaneously. Systemic reactions are generally mild and self-limited [17]. The aim of the present study was to evaluate the safety and immunogenicity of QHPV vaccine in adolescents and young adults with HIV infection compared to healthy, HIV-negative subjects matched for age and gender.

## 2. Materials and methods

### 2.1. Study design

This is an ongoing 18 month prospective, non-randomized, controlled, open-label clinical study to assess the long-term immunogenicity of the Quadrivalent human papillomavirus vaccine (QHPV) in HIV-infected adolescents and young adults, results were compared to those obtained from age and sex matched HIV-negative subjects. An interim analysis for safety and immunological outcome in this population was planned at 1 month after completion of vaccine doses. The protocol was approved by the Ethical Committee of the L. Sacco Hospital (Milano, Italy), and the trial was registered at Clinicaltrials.gov with identifier NCT01512784. Written informed consent was obtained from the parents or legal guardians of the adolescents and from patients themselves, prior to study enrolment.

### 2.2. Study population

Forty-six HIV-infected adolescents and young adults followed as outpatients at the pediatric infectious disease clinic of the L. Sacco Hospital, University of Milan, Italy, were consecutively enrolled. Inclusion criteria were: age 13–27 years, females and males, clinically asymptomatic, CD4+ count  $\geq 350$  cells/mm<sup>3</sup>, good compliance to highly active antiretroviral treatment (HAART) and at least two suppressed HIV-RNA (<37 copies/ml) during 6 months prior to enrolment. As a control group 46 HIV-negative subjects matched for age and gender were recruited. Exclusion criteria for

patients and healthy controls were: pregnancy and breastfeeding, prior vaccination with QHPV, history of severe allergic reaction to immunization or hypersensitivity to any vaccine component, any chronic, autoimmune or progressive disease (other than HIV), acute infection requiring therapy or fever at time of enrolment, concomitant therapies (other than HAART), including immunosuppressive, immunomodulating agents or chemotherapy during the 6 months prior to study entry, receipt of blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation prior to study entry, use of investigational agents within 4 weeks prior to study enrolment, current drug or alcohol use or dependence.

### 2.3. Assessment of immunological and virological status

CD4+ T lymphocyte counts and percentage and HIV-RNA viremia were measured in all HIV-infected subjects at baseline and at 1 month after the first, second, third dose of QHPV as well as at 12 and 18 months after the first dose. CD4+ T lymphocytes were measured by flow cytometry using fresh blood sample and a Cytotron Absolute flow cytometer (Ortho Cytometry, Raritan, NJ) with Immunocount II software. HIV viral load was performed locally by the Microbiology Laboratory, at the L. Sacco Hospital, University of Milan. HIV-RNA was measured with a lower detection limit of 37 copies/ml (Quantiplex assay 3.0; Bayer Diagnostics).

### 2.4. QHPV vaccine

QHPV (Types 6, 11, 16 and 18) recombinant vaccine (Gardasil) was given to our Pediatric Department by the Immunization Center of Lombardy region. Vaccine was administered by intramuscular injection in the left or right deltoid muscle. Each subject received QHPV at baseline, after 2 months ( $\pm 10$  days) and after 6 months ( $\pm 10$  days) after the first dose. All subjects remained under observation in clinic for at least 30 min after vaccination.

### 2.5. Evaluation of antibody responses to QHPV vaccination

Serum samples to measure HPV specific antibodies were collected in all HIV-infected and HIV-negative subjects at enrolment (T0), at 1 month following the first (T1), second (T2) and third dose (T3) of QHPV and at 12 (T4) and 18 (T5) months after the first QHPV dose. All samples were kept at  $-80^{\circ}\text{C}$  until further analysis was performed. HPV serology was performed locally by the Immunology Laboratory at the L. Sacco Hospital, University of Milan. Antibody titers against HPV types 6, 11, 16 and 18 were measured using a Human Papillomavirus IgG ELISA kit (Creative Diagnostics, NY, NY, USA) according to manufacturer's instructions. For cut-off calculation, mean OD<sub>450</sub> nm value of the negative control (NC) was determined and the following formulation was applied to calculate the cut-off value:  $\text{NC} + 0.250 = \text{cut-off}$ . Samples with an OD<sub>450</sub> nm lower than the cut-off value were considered not reactive for IgG specific to the HPV antigens present in the vaccine, whilst samples with an OD<sub>450</sub> nm higher than the cut-off value were considered positive for HPV-specific IgG antibodies. Sample concentrations were determined from standard curves, using purified Ig standard human IgG (Sigma–Aldrich, Milan, Italy) assayed in parallel; values were expressed in micrograms per milliliter.

### 2.6. Evaluation of vaccine safety

A detailed clinical history and physical examination were performed at enrolment. All subjects were observed for 30 min after the vaccination. Diaries were provided to each patient to report the occurrence of local (erythema, swelling, induration and pain) or systemic (axillary temperature  $\geq 38^{\circ}\text{C}$ , malaise, headache, myalgia, arthralgia, nausea, shivering or rash) side effects during the

following week after vaccination. Adverse events were defined as injuries or ailments related to or caused by the treatment under study. At each visit, patients or their legal tutors were specifically asked about adverse events, and the first author checked for any association between adverse events and morbidities.

### 2.7. Outcomes

Primary outcome was the assessment of QHPV immunogenicity in HIV-infected subjects by evaluating type specific antibody titers for HPV types 6, 11, 16 and 18 from seronegative status at T0 to seropositive status at 1 month after the completion of QHPV vaccine series (T3) and to compare the same immunogenicity tests with those performed in HIV-negative subjects matched for gender and age.

Secondary outcomes were:

- 1) Assessment of local and systemic side effects during the 7 days after each vaccination dose, in HIV-infected and HIV-negative subjects.
- 2) Evaluation of antibody titers at 1 month after the first two vaccination doses (T1–T2) and at 12 months (T4) and 18 months (T5) after the first vaccination dose in HIV-infected and HIV-negative subjects.
- 3) In HIV-infected patients, longitudinal monitoring of lymphocyte T CD4+ count and HIV viral load, throughout the study period (T0–T1–T2–T3–T4–T5), to assess any effect of QHPV vaccination on HIV viral load or CD4+ count.

### 2.8. Statistical analysis

Continuous variables are reported as means and standard deviations (SD) and categorical variables as counts and percentages. Between-group comparisons of continuous variables were performed using Student's *t*-test and those of categorical variables using Fisher's exact test. Generalized estimating equations (GEE) coupled with fractional polynomials were used to quantify the changes in time of CD4 cells in HIV-infected patients [18]. GEE were also used to quantify the time-specific differences in the anti-HPV IgG titer between HIV-infected and HIV-negative subjects. To this aim, a non-parametric model was used, which employed HIV status (discrete: 0 = no; 1 = yes), time (discrete: 1, 3, 7, 12 and 18 months) and an HIV × time interaction (discrete × discrete). All GEE employed a Gaussian family, a logarithmic link, an exchangeable correlation matrix and robust 95% confidence intervals (95% CI). Bonferroni's correction was applied to 95% CI and *p* values when multiple comparisons were performed. Statistical analysis was performed using Stata 13.1 (Stata Corp., College Station, TX, USA).

## 3. Results

### 3.1. Baseline features

Forty-six HIV-infected patients aged 13–26 years and 46 HIV-negative controls aged 14–27 years were studied. Their baseline measurements are given in Table 1. The two groups had a similar age and a comparable gender and ethnic distribution. The HIV-infected patients had a good immune status as detected by total and percentage CD4+ T lymphocyte cells and 94% had a suppressed HIV-RNA.

### 3.2. Primary outcome

The primary outcome, the seroconversion rate 1 month after the administration of the third vaccine dose, was 0.85 (95% CI

**Table 1**

Baseline measurements of HIV-infected and HIV-negative subjects. Values are means and standard deviations (between parentheses) for continuous variables and counts and percentages (between parentheses) for discrete variables. Percentages may not total 100 due to rounding.

	HIV+ (n=46)	HIV- (n=46)
Caucasians	44 (96%)*	44 (96%)
Males	20 (43%)*	19 (41%)
Age (years)	20 (4)*	20 (4)
CD4+ (count)	715 (280)	–
CD4+ (percentage)	33 (10)	–
CDC stage (A/B/C/N)	19/8/18/1 (41%/17%/39%/2%)	–
HIV-RNA < 37 copies/ml	43 (94%)	–

\**p* > 0.05 vs. HIV- (Student's *t*-test for continuous variables and Fisher's exact test for categorical variables).

**Table 2**

Cumulative incidence of side effects as detected immediately after the administration of the first, second and third vaccine dose in HIV-infected (HIV+) and HIV-negative (HIV-) subjects.

	HIV- N (%)	HIV+ N (%)
Local		
Pain	26 (18.8)	46 (32.6)
Erythema	8 (5.8)	16 (11.3)
Edema	10 (7.2)	11 (7.8)
Induration	14 (10.1)	18 (12.8)
Systemic		
Fever	0 (0)	4 (2.8)
Malaise	2 (1.4)	10 (7.1)
Headache	3 (2.2)	19 (13.5)

0.75–0.95) in HIV-infected and 0.91 (0.83–0.99) in the HIV-negative subjects (*p* = 0.52).

### 3.3. Secondary outcomes

#### 3.3.1. Local and systemic side effects

Table 2 reports the cumulative incidence of side effects detected during the 7 days after the administration of the first, second and third vaccine doses. No formal hypothesis testing was performed on these data due to the expectedly low power to perform between-group comparisons. The most frequent local side effect was pain (32.6% in HIV-infected vs. 18.8% in HIV-negative subjects), followed by induration (12.8% vs. 10.1%), erythema (11.3% vs. 5.8%) and edema (7.8% vs. 7.2%). The most frequent systemic side effect was headache, which occurred in 13.5% of HIV-infected vs. 2.2% of HIV-negative subjects.

**Table 3**

Anti-HPV IgG titers at 1 month after each vaccination dose and at 12 and 18 months after the first dose.

Group	Month	Mean	Lower 95% CI	Upper 95% CI
HIV-	1	10.2	8.1	12.4
HIV+	1	8.0	6.0	9.9
HIV-	3	41.5	36.2	46.8
HIV+	3	42.5	36.4	48.6
HIV-	7	67.1	62.0	72.1
HIV+	7	61.3	55.2	67.4
HIV-	12	42.3	39.4	45.3
HIV+	12	39.7	36.2	43.3
HIV-	18	37.0	32.3	41.8
HIV+	18	31.2	29.3	33.2

Values are means and 95% confidence intervals obtained using generalized estimating equations with Bonferroni's correction for multiple comparisons.

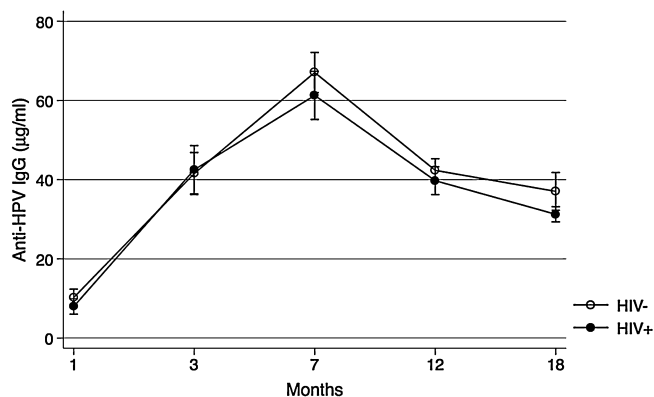


Fig. 1. Anti-HPV IgG titers in HIV-infected (HIV+) and HIV-negative (HIV-) subjects.

3.3.2. Antibody response to QHPV vaccination

Table 3 and Fig. 1 show the changes of the anti-HPV IgG titers at 1 month after each vaccination dose and at 12 and 18 months after the first dose, in HIV-infected and HIV-negative subjects. The mean (Bonferroni's corrected 95% CI) difference of anti-HPV IgG titer between two groups was  $-2.2$  ( $-6.0$  to  $1.5$ ),  $1.0$  ( $-9.7$  to  $11.6$ ),  $-5.8$  ( $-16.2$  to  $4.6$ ),  $-2.6$  ( $-8.6$  to  $3.4$ ) and  $-5.8$  ( $-12.5$  to  $0.9$ )  $\mu\text{g/ml}$  at 1, 3, 7, 12 and 18 months respectively (Bonferroni's corrected  $p$  values  $\geq 0.13$ ).

3.3.3. Changes in CD4+ cells and HIV-RNA

Fig. 2 shows the changes in CD4+ cells and HIV-RNA of HIV-infected patients during the study. The CD4+ count remained stable during the study ( $p=0.9$ ) while the percentage of CD4+ cells increased slightly ( $p=0.01$ ). Most patients maintained undetectable levels of HIV-RNA during the study.

4. Discussion

This study was undertaken in HIV-infected and HIV-negative males and females aged 13–27 years with the assumption that QHPV would be optimally effective in HIV-infected subjects. The HIV-infected subjects included in the study were clinically asymptomatic, had CD4+ lymphocyte T-cell count  $> 350$  cell/ $\text{mm}^3$ , showed good compliance to HAART with at least two suppressed HIV-RNA ( $< 37$  copies/ml) during 6 months prior to enrolment. The rate of seroconversion was 85% in HIV-infected and 91% in HIV-negative subjects. Our data in HIV-infected subjects are similar to those previously reported by Levin et al. [15] in HIV-infected children aged 7–12 years with CD4+  $> 15\%$  on ART or  $> 25\%$  on or off HAART, in whom the vaccine was found to be highly immunogenic with a 96% seroconversion rate. Notably, in our HIV-infected population, HPV antibody titers as a response to QHPV vaccine were slightly lower than those obtain in HIV-negative children [15]. During the study period CD4+ T lymphocytes remained stable, the percentage of CD4+ showed a slight increase and undetectable HIV-RNA characterized the majority of patients. These results are consistent with a previous study showing that administration of QHPV in HIV-infected children did not alter the CD4+ status or HIV viral load [15]. In our study the QHPV was generally safe and well-tolerated, as previously reported in pre and post-licensure clinical trials. No serious or life threatening adverse events were reported, and the most common side effects were local injection site reactions and mild self-limited systemic symptoms [19]. The most common local side effect was pain which occurred in 18.8% of HIV-negative and in 32.6% of HIV-infected subjects; the most common systemic side effect was headache, reported in 13.5% of HIV-infected and in 2.2% of HIV-negative individuals. The side effect rates reported in our study were similar to those showed in previous studies in HIV-infected population and appeared to be lower than the ones reported in studies conducted in HIV-negative population [17,19]. The main limitation of this study is that patients in the HIV-infected group were all relatively immune competent,

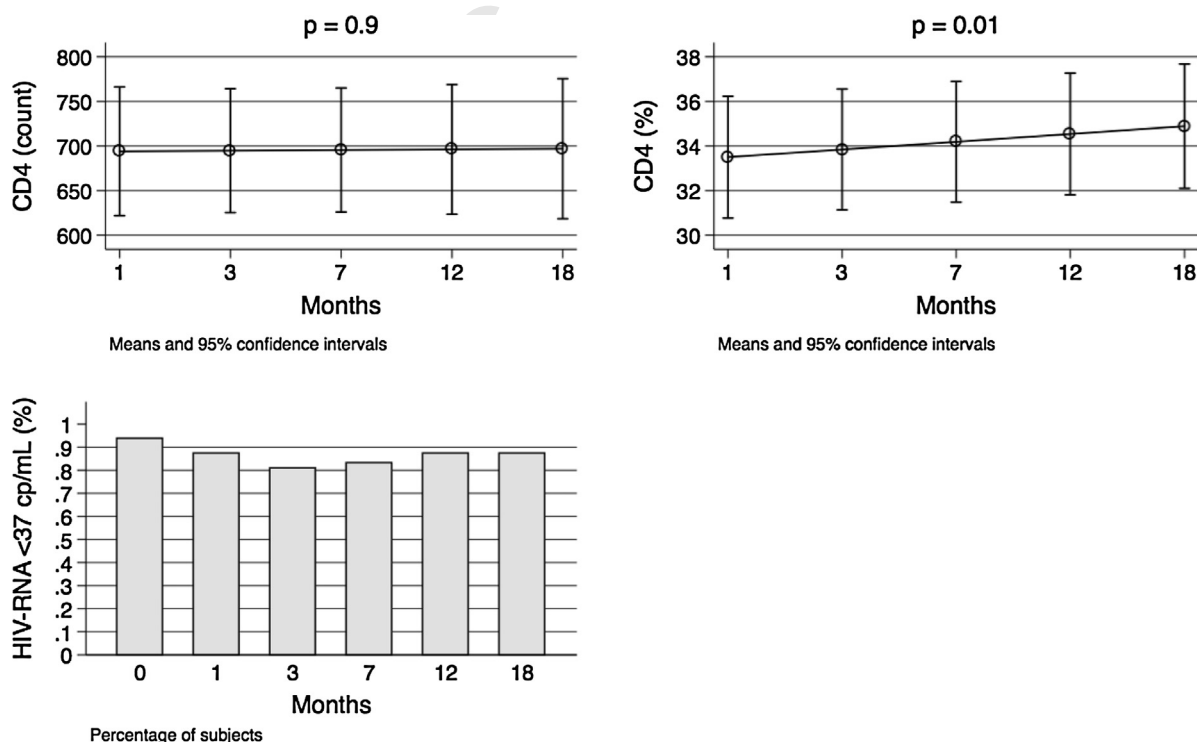


Fig. 2. CD4+ count and HIV-RNA of HIV-infected patients.

with suppressed HIV-RNA levels, relatively normal CD4+ T lymphocyte count and clinically well, making this group very similar to the HIV-negative controls.

In conclusion our data demonstrate that Quadrivalent HPV-vaccine showed a similar immunogenic efficacy in HIV-infected adolescent and young adults and in healthy controls matched for age and gender. Moreover, the vaccine was generally safe and well tolerated; the most common side effect was local pain and the most frequent systemic side effect was headache. This is the first report on response to HPV vaccination in both female and male HIV-infected adolescents and young adults; results herein suggest that this population may benefit from HPV immunoprophylaxis. Further studies are needed to examine the long term efficacy of HPV vaccination in HIV-infected individuals.

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