Published in final edited form as:
J Acquir Immune Defic Syndr. 2010 October ; 55(2): 197–204. doi:10.1097/QAI.0b013e3181de8d26.

Safety and Immunogenicity of a Quadrivalent Human Papillomavirus (Types 6, 11, 16, and 18) Vaccine in HIV-Infected Children 7 to 12 Years Old

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Abstract

Background—Quadrivalent human papillomavirus vaccine (QHPV) is >95% effective in preventing infection with vaccine-type human papillomavirus. The safety and immunogenicity of QHPV are unknown in HIV-infected children.

Methods—HIV-infected children (N = 126)—age >7 to <12 years, with a CD4% ≥15—and on stable antiretroviral therapy if CD4% was <25—were blindly assigned to receive a dose of QHPV or placebo (3:1 ratio) at 0, 8, and 24 weeks. Adverse events were evaluated after each dose. Serum antibody against QHPV antigens was measured by a competitive Luminex immunoassay 1 month after the third QHPV dose.

Results—The safety profile of QHPV was similar in the 2 study arms and to that previously reported for QHPV recipients. QHPV did not alter the CD4% or plasma HIV RNA. Seroconversion to all 4 antigens occurred in >96% of QHPV recipients and in no placebo

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A portion of this information was presented at the 15th Conference on Retroviruses and Opportunistic Infections, February 3–6, 2008, Boston, MA, and at the 25th International Papillomavirus Conference, May 8–14, 2009, Malmo, Sweden.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions this article on the journal's Web site (www.jaids.com).

recipients. Geometric mean titer was >27 to 262 times greater than the seropositivity cutoff value, depending on the antigen, but was 30%–50% lower against types 6 and 18 than those of age-similar historical controls.

Conclusions—QHPV was safe and immunogenic in this cohort of HIV-infected children. Efficacy trials are warranted.

Keywords

HPV vaccine; HIV infection; HPV antibody response

Introduction

Human papillomavirus (HPV) is the primary cause of cervical cancer and is responsible for 40%–90% of anal, vulvar, vaginal, penile, and oropharyngeal cancers.[1] The oncogenic potential of HPV is type specific; approximately 70% of cervical cancers are caused by HPV types 16 and 18,[2] which are also the predominant types associated with anogenital and oropharyngeal cancers.[1–3] In contrast, HPV types 6 and 11 are associated with 90% of genital warts and rarely cause anogenital cancers.[4]

A woman's lifetime risk of acquiring HPV infection is >80%; most infections occur within 3–4 years after sexual debut.[5,6] Most HPV infections are transient. However, persistence of HPV 16 and 18 is essential for the development of cervical dysplasia, including cervical intraepithelial neoplasia (CIN) 3 and cancer.[7,8] The prevalence of HPV and CIN 2/3 is severalfold higher in HIV-infected women than in uninfected women.[9] HPV infections persist longer in HIV-infected women.[10] Low-grade squamous intraepithelial lesions in HIV-infected adolescents are likely to persist longer than in HIV-uninfected girls, and HIV-infected girls are 3-fold more likely to develop high-grade squamous intraepithelial lesion.[11] Because this high rate of high-grade squamous intraepithelial lesion has not been demonstrated in adults, these findings suggest that HIV-infected girls are particularly vulnerable.[12]

HPV infection also leads to a 7-fold increase in penile cancer and a 60-fold increase in anal cancer in HIV-infected men compared with uninfected men.[13] HIV-infected adults also have high rates of genital warts, which are often recalcitrant to conventional therapies.[14,15]

Two HPV preventive vaccines (Gardasil; Merck and Co, Inc, Whitehouse Station, NJ; Cervarix; GlaxoSmithKline, Rixensart, Belgium) are licensed. Both vaccines contain viruslike particles (VLP) of HPV types 16 and 18 that stimulate type-specific neutralizing antibodies, which are thought to prevent HPV infection.[16,17] Gardasil also contains HPV types 6 and 11 VLPs.[16] In immunocompetent women, Gardasil is 98%–100% effective in preventing precancerous lesions of the cervix, vulva, and vagina and is very effective in preventing genital warts in men and women.[18–22]

The immunologic response to Gardasil in HIV-infected patients is unknown. This study was undertaken to evaluate the safety and immunogenicity of Gardasil in preadolescent girls and boys with HIV infection.

Methods

Subject Population

Children >7 to <12 years with HIV infection could enroll if their baseline CD4% was ≥15. At least 3 months of highly active antiretroviral therapy (HAART) was required for subjects with a CD4% <25. Exclusion criteria included other immunosuppressive diseases or

medications, other significant acute or chronic illness, other vaccinations within 2–3 weeks (depending on vaccine type) before or after study vaccine, significant abnormalities in hematologic or chemistry tests, and receipt of blood-derived products within 6 months before or during the study. The protocol was approved by the local ethical review committees. Parents or guardians of subjects provided written informed consent.

Vaccine

Quadrivalent human papillomavirus vaccine (QHPV) (types 6, 11, 16, and 18) recombinant vaccine (Gardasil) or identical placebo, 0.5 mL, was administered by intramuscular injection.

Design

Subjects were stratified by their CD4% nadir and CD4% at screening into 3 groups: group 1: CD4% nadir < 15 and CD4% ≥ 15 at screening; group 2: CD4% nadir ≥ 15 and CD4% between ≥15 and <25 at screening; and group 3: CD4% nadir ≥ 25 and CD4% ≥ 25 at screening. Nadir was defined as the lowest CD4% ever recorded for the subject. QHPV or placebo was assigned randomly, in a double-blinded fashion, in a 3:1 ratio, to 40 subjects in each group at entry (90 receive QHPV; 30 receive placebo). Each subject received the same assigned study vaccine 8 and 24 weeks later.

Safety Assessment

Clinical—Subjects were observed in clinic for 30 minutes post vaccination. A report card of relevant signs and symptoms was maintained by the caregiver for 15 days after each injection. Body temperature was recorded for 5 days beginning after the injection. Telephone contact with the caregiver was made on the third day after each injection to inquire about reactions. The caregiver was instructed to immediately report unusual injection site reactions. A clinic visit was required within 24 hours whenever the study coordinator considered that a reaction might be ≥grade 3 (Division of AIDS Table for Grading the Severity of Adverse Events: http://rcc.tech-res.com/safetyandpharmacyvigilance).

Clinical Laboratory—Routine hematologic and chemistry screens were performed at the study site's laboratory at entry, 4 weeks after the first dose, and just before and 4 weeks after the next 2 doses. CD4% and CD4 number were determined at entry, 8 weeks after the first dose, 4 weeks after the second dose, and just before and 4 weeks after the third dose.

Immunologic Assessment

Serum antibody against the HPV antigens[6,11,16,18] was determined at entry and 4 weeks after the third dose of vaccine. Antibody response in the postvaccination sample was the predefined primary immunologic endpoint.

Laboratory Determinations

Assay for Serum Antibody Against HPV Antigens—Serum anti-HPV 6, 11, 16, and 18 antibody was measured using a competitive Luminex immunoassay (cLIA; reported in milli-Merck Units [mMU]/mL).[6,11,16,18,23,24] Seropositivity was defined as an anti-HPV titer ≥20, 16, 20, and 24 mMU/mL, for HPV types 6, 11, 16, and 18, respectively.[24]

CD4 Number and Percent—Analysis of CD4 lymphocyte phenotypes (CD3/4, CD3/8, and CD19) was performed at the participating sites in laboratories that were certified by the Division of AIDS Immunology Quality Assurance Program.

HIV RNA in Plasma—The plasma HIV RNA concentration was determined by the standard or ultrasensitive AMPLICOR HIV-1 MONITOR Test (version 1.5 RNA polymerase chain reaction assay; Roche Diagnostics, Indianapolis, IN).

Statistics

Safety—Graded adverse events (AEs) (≥1 for injection reactions; ≥2 for all others) that occurred within 14 days of each vaccination were grouped into 5 defined toxicity categories. Within each category, the AE with the worst grade for each subject was counted. The worst grade of AEs for each subject within 14 days of any vaccination was calculated for comparisons between groups and between treatment arms. Ungraded diagnoses were described separately.

Immunogenicity—For QHPV cLIA titers lower than the detection limit, the values 3.5, 4, 5.5, and 5 were assigned for HPV types 6, 11, 16, and 18, respectively. Seroconversion was defined as change from seronegative results at baseline to seropositive results at week 28. The QHPV cLIA geometric mean titers (GMTs) were summarized by treatment group, and 95% confidence intervals (CIs) were calculated. Univariate linear regression analyses were performed to identify predictors of week 28 QHPV cLIA titers. For categorical variables having >2 categories, Tukey–Kramer simulation-based adjusted P values were used for pairwise comparisons when F tests were significant ($P < 0.05$). Variables identified as at least marginally significant ($P < 0.1$) predictors of week 28 QHPV cLIA titer were included in the multivariate linear regression analyses.

Results

Safety

The age, gender, and ethnicity of 126 vaccinated subjects (Table 1) were similar between groups (except black, non-Hispanics in group 2) and between treatment arms within groups. CD4% was highest in group 3, in accordance with the stratification. CD4 count and CD4% were similar between treatment arms when all the groups were combined, as was plasma HIV viral load.

Table 2 indicates the type and frequency of AEs reported within 14 days after the first dose of QHPV. AEs were infrequent and their occurrence was similar in QHPV and placebo recipients, except for more frequent ($P = 0.19$) injection site reactions in QHPV recipients. Injection site reactions were mainly grade 1 and not more frequent after the second or third dose. AEs not differ between groups. The AE profile was very similar after each vaccine dose, except for an increase in indirect bilirubin values after the last 2 doses, which was attributed by the site investigators to antiretroviral treatment with atazanavir.

Table 3 indicates the worst grade for signs, symptoms, and laboratory abnormalities in each subject summed over all 3 doses of vaccine or placebo. There were minor, generally nonsignificant, differences in frequency or severity of events between the arms when the data were combined, except for grade 1 events, which were largely due to injection site reactions. Within in each group, AEs were similar in frequency in each arm. The number of grade 2 and 3 AEs was greater after the second dose, but these were almost entirely due to preanalytic artifact (delay before serum separation for glucose determination) or indirect hyperbilirubinemia attributed to atazanavir therapy. Injection site reactions were not more common or severe after the second or third vaccination. There were 7 subjects with only grade 3 events; one subject had only a grade 4 event; and 1 subject had a grade 3 and grade 4 event. No grade 3 or 4 events were considered by the investigators to be treatment related. Fifteen AEs could not be graded (10 received QHPV; 5 received placebo). All were either

preexisting (eg, attention-deficit/hyperactivity disorder) or were common childhood diseases (eg, otitis, urinary tract infection).

The plasma HIV viral load did not trend in any clinically significant manner above the baseline after any vaccine dose in any group in either treatment arm and was similar between treatment arms at all time points (data not shown). The CD4% after each dose of QHPV did not differ significantly between treatment arms (see **Figure 1, Supplemental Digital Content 1,** http://links.lww.com/QAI/A53, which demonstrates that CD4% is not altered by QHPV administration).

Immunogenicity

Four subjects had HPV-specific antibody at baseline; only one had an antibody level that was 2-fold higher than the cutoff value. These 4 subjects were excluded from analysis of their immune response to these antigens. Seroconversion occurred in all the QHPV recipients, except for 3 subjects in group 1 who failed to seroconvert to HPV type 18 [seroconversion by QHPV recipients was 354 of 357 type-specific determinations (99%), whereas 1 of 27 placebo recipients (4%) seroconverted to HPV type 16; seroconversion by placebo recipients was 1 of 108 type-specific determinations (<1%)] (Table 4). The baseline GMT for any antibody type was below the cutoff value. The GMTs in vaccine recipients at 28 days after the third dose of vaccine, for all groups combined, were at least 27, 85, 262, and 38 times greater than seropositivity cutoffs for HPV types 6, 11, 16, and 18, respectively (Table 5). There was no statistically significant difference between groups for GMT against any antigen.

Table 6 displays the GMTs from all groups combined, together with published information on GMTs achieved after vaccinating HIV-uninfected children of the same age.[25,26] The GMTs achieved by vaccinating HIV-infected children were 30%–50% lower for vaccine types 6 and 18 than those achieved in the comparator group, and the 95% CIs around the response estimates of these 2 groups did not overlap on either of these 2 antigens.

Univariate Linear Regression Analysis

This considered the effects of the following on the primary endpoint antibody level: age, immunologic group, gender, ethnicity, and nadir CD4%. Also evaluated were parameters measured at the time of each dose: CD4%, CD4 count, CD8%, CD8 count, and viral load. There were significant correlations across HPV serotypes of higher HPV type-specific antibody level with lower HIV viral load (<5000 copies/mL vs >5000 copies/mL) and lower CD8% and number ($P = 0.01–0.04$, depending on HPV type). There were no consistent correlations with CD4% at the time of vaccination. Hispanic subjects had lower antibody levels against types 16 and 18 than black subjects and lower antibody levels against all 4 serotypes than non-Hispanic white subjects.

Multivariate Linear Regression Analysis

Factors of at least borderline significance across all serotypes (HIV viral load, CD8%, and ethnicity) in the univariate analysis were incorporated into the multivariate linear regression analysis. After adjustment, Hispanic subjects had significantly lower levels for type 18 than black subjects and also had lower levels against types 6, 11, and 18 than the non-Hispanic white subjects.

Discussion

The safety profile of QHPV administered to HIV-infected children was excellent. AEs were similar between vaccine and placebo recipients, regardless of immunologic group or

administration of multiple sequential doses of QHPV. The safety of QHPV in HIV-infected children was very similar to that reported for HIV-uninfected children who were 9–15 years of age.[25,26] Administration of this vaccine—which is the first VLP-based vaccine studied in HIV-infected individuals—did not alter the CD4 status or HIV viral load of the vaccinee.

This study was undertaken in girls and boys younger than 12 years with the assumption that QHPV would be optimally utilized in HIV-infected girls (and possibly boys) before sexual debut. As expected, less than 4% of subjects had detectable HPV antibody to any vaccine HPV type at baseline, and only 1 of 30 placebo recipients developed antibody to a single type during the study.

The rate of seroconversion in this HIV-infected cohort was excellent and consistent with previous reports in young HIV-uninfected children.[25,26] Although the GMTs achieved were >27 to >262-fold higher than the seropositivity cutoff, depending on HPV type, antibody levels achieved against HPV types 6 and 18 in these HIV-infected children were 30%–50% lower than those achieved in historical controls. However, the level of HPV type 6 antibody achieved after QHPV vaccination in HIV-infected children equaled that achieved in HIV-uninfected women 16–26 years old, in whom the vaccine is very efficacious, and antibody levels against the other 3 vaccine types were approximately 2-fold higher than in older healthy vaccine recipients.[27]

The magnitude of the HPV type–specific antibody responses is important because vaccine-induced protection is thought to be mediated primarily through neutralizing antibodies that reach mucosal and external genital surfaces. Because these antibodies at these locations are explained in part by transudation of HPV type–specific antibody from serum,[28–31] it is likely that the higher the serum levels of HPV-specific antibody, the greater the amount of antibody present in the genital mucosa. Although there is some decline in antibody levels measured by cLIA in immune competent women within the first 2 years after vaccination, levels subsequently stabilized for HPV 11 and 16 up to an additional 3 years.[27] HPV 6 and 18 antibody levels continue to decline with time after vaccination. However, there is no evidence that efficacy through 5 years of follow-up has waned among those with declining levels,[32] and no minimum level of protective antibody has been defined. An anamnestic response was shown at 5 years post vaccination.[33] Nevertheless, it is uncertain if vaccine-induced immunity will be lifelong. There is some evidence suggesting that naturally acquired HPV-specific antibodies might decline to a level that will permit reinfection or allow reactivation.[34] As this is the first study in HIV-infected persons, the vaccinees in this study will receive a fourth dose of QHPV at 72 weeks after their third dose of vaccine to determine the magnitude of any anamnestic response.

The information obtained from this and a follow-up study will inform future strategies for preventing HPV infection in HIV-infected children. It is important to note that any strategy is likely to be defined by the clinical status of vaccinees. The subjects in this study were receiving HAART if their CD4% was <25% at entry; the mean CD4% at entry was 29 for group 1, which was the most immune compromised. The extent of immune reconstitution in all study groups probably explains the similar results between the study groups and why the regression analyses did not indicate a correlation of immune response to CD4 status. Recent trials of childhood vaccines in HIV-infected children indicate that immune responses are readily detected in vaccinees who are receiving HAART, although, as shown here, they are not always normal. Apparently, the nature of immune reconstitution after HAART for HIV infection does not ensure a normal immune system. We previously documented in children strong associations between plasma HIV viral load and primary responses to the live attenuated varicella-zoster vaccine[35] and to live attenuated or inactivated seasonal influenza vaccines.[36] Other investigators correlated deficient antibody production in HIV-infected

individuals with overrepresentation of transitional/immature B-cell subpopulations expressing low CD21 and/or CD27[37,38] or underrepresentation of memory B cells expressing adequate levels of CD21, CD27, or immunoglobulins on their surface.[39–41] Despite the lower responses, our results with QHPV add to the evidence obtained with other vaccines that children on HAART with >15%CD4 cells, and children with >25%CD4 cells, irrespective of HAART, will develop strong responses to vaccine immunogens.[35,36,42,43]

This trial confirms the safety and immunogenicity of QHPV in HIV-infected persons and is supportive of an efficacy trial in HIV-infected children in resource-poor countries where QHPV is not yet standard of care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The following clinical sites and personnel are acknowledged for their contribution to IMPAACT trial P1047: Children's National Med. Ctr. Washington, DC (Deidre Thompson; Jennifer Sween; Steven Zeichner); Children's Hospital of Michigan (Ellen C. Moore, MD; Chokechai Rongkavilit, MD; Elizabeth Secord, MD; Ulyssa Hancock, RN, BSN); SUNY Stony Brook, NY (Denise Ferraro, RN; Erin Infanzon; Michele Kelly, PNP); St. Jude/UTHSC (Jill Utech, MSN; Sandra Jones, PNP; Nehali Patel, MD; Lennie Lott, RN); Tulane/LSU Maternal/Child (Russell B. Van Dyke, MD; Margarita Silio, MD; Cheryl Borne, RN; Sheila Bradford, RN); NYU NY NICHD (Sandra Deygoo, MS; William Borkowsky, MD; Siham Akleh, RN; Sulachni Chandwani, MD); Duke University MC Ped (Margaret Donnelly, PA; Mary Jo Hasseett, RN; Joan Wilson, RN; Kareema Whitfield, BS); Rush Univ. Cook County Hosp. Chicago (James B. McAuley, MD, MPH; Nike Mourikes, MD; Maureen Haak, RN, MSN; Kenneth Boyer, MD); USC LA (LaShonda Spencer, MD; James Homans, MD; Michael Neely, MD; Andrea Kovacs, MD); Miller Children's Hospital Long Beach, CA (Audra Deveikis, MD; Jagmohan Batra, MD; Susan Marks, RN; Janielle Jackson-Alvarez, RN); Chicago Children's (Jennifer Armstrong; Ruth Williams; Eric Cagwin); Children's Hospital of Orange County (Stephanie Osborne, BS, RN, CCRC; Antonio Arrieta, MD); Bronx-Lebanon Hosp. (Mavis Dummit, RN; Caroline Nubel, RN; Stefan Hagmann, MD; Murli Purswani, MD); Texas Children's Hosptial (Faith Minglana, RN, BSN; Chivon McMullen-Jackson, RN, BSN; Mary E. Paul, MD; William T. Shearer, MD, PhD); San Juan City Hosp. PR (Midnela Acevedo-Flores, MT, MD; Milagros Gonzáles-Diaz, MD; Lizbeth Fabrega, BS, MS; Wanda Marrero, RN); University of Florida Jacksonville (Mobeen Rathore, MD; Ayesha Mirza, MD; Kathy Thoma, MA; Chas Griggs, Med); University of Colorado Denver (Mark Abzug; Emily Barr; Megan Canon; Carol Salbenblatt); Seattle Children's Hospital (Lisa Frenkel, MD; Ann Melvin, MD, MPH; Joycelyn Thomas, BS, RN); 5057: Strong Memorial Hospital Rochester, NY (Geoffrey A. Weinberg, MD; Barbra Murante, RN, MS, PNP; Susan Laverty, RN; Francis Gigliotti, MD); Howard University Washington, DC (Helga Finke-Castro, MD; Sohail Rana, MD; Connie Nguyen, RPh; Patricia Houston, MS); UCSD Maternal, Child, and Adolescent (Stephen A. Spector, MD; Rolando Viani, MD, MTP; Kimberly Norris, RN; Jeanne Manning, RN); Boston Medical Center Ped. HIV (Ellen R. Cooper, MD; Diana Clarke, PharmD; Laureen Kay, RN); SUNY Downstate Med. Ctr., Children's Hosp (HJ Moallem; JM Kaye; D. Swindel); South Florida CDC Ft. Lauderdale (Ana Puga, MD; Kathleen Graham, PharmD; Lisa Bridges, RN; Richard Sellars, RN); NJ Med. School; UCLA–Los Angeles/Brazil AIDS Consortium; Mt. Sinai Hosp Med Ctr; Chicago, Women's and Children's HIV; University of Miami Pediatric Perinatal HIV/AIDS; Jacobi Med. Ctr. Bronx; University of California San Francisco; University of Puerto Rico Pediatric HIV/AIDS Research Program; WNE Maternal Pediatric Adolescent AIDS; Connecticut Children's Med. Ctr; Jacobi Medical Center, Bronx, NY (Marlene Burey, RN, MSHS; Raphaelle Auguste, RN, BSN; Elaine Perez, RN, MS; Francisco Reinoso, RN, BSN).

Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) [U01 AI068632], the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Institute of Mental Health (NIMH) [AI068632]. Supported by the Statistical and Data Analysis Center at Harvard School of Public Health, under the National Institute of Allergy and Infectious Diseases cooperative agreement #5 U01 AI41110 with the Pediatric AIDS Clinical Trials Group (PACTG) and #1 U01 AI068616 with the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) Group.

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TABLE 1

Characteristics of HIV-Infected Children Receiving QHPV

	Group 1		Group 2	
Parameters (Categorical Levels)	**QHPV (95% CI)**	**Placebo (95% CI)**	**QHPV (95% CI)**	**Placebo (95% CI)**
n	31	10	32	11
Age (y)	10.4 (9.9 to 10.9)	9.8 (8.7 to 10.9)	10.3 (9.8 to 10.7)	9.9 (9 to 10.8)
CD4 count	719 (622 to 815)	1035 (651 to 1418)	954 (796 to 1112)	1012 (679 to 1345)
CD4%	29.1 (26.5 to 31.6)	35.7 (26.9 to 44.6)	33.6 (30.7 to 36.4)	34.6 (30.2 to 39)
Ethnicity (%)				
White, non-Hispanic	1 (3)	0 (0)	0 (0)	2 (18)
Black, non-Hispanic	17 (55)	4 (40)	19 (59)	3 (27)
Hispanic	13 (42)	6 (60)	12 (38)	5 (45)
Others	0 (0)	0 (0)	1 (3)	1 (9)
Gender (%)				
Male	19 (61)	4 (40)	12 (38)	5 (45)
Female	12 (39)	6 (60)	20 (63)	6 (55)
Log_{10} (RNA)	2.6 (2.3 to 2.9)	2.5 (2 to 3.1)	2.7 (2.4 to 3)	2.5 (2 to 3)
RNA group (%)				
≤400 copies/mL	21 (68)	7 (70)	26 (81)	8 (73)
401 to ≤5000 copies/mL	6 (19)	3 (30)	2 (6)	2 (18)
>5000 copies/mL	4 (13)	0 (0)	4 (13)	1 (9)

	Group 3		All Groups	
Parameters (Categorical Levels)	**QHPV (95% CI)**	**Placebo (95% CI)**	**QHPV (95% CI)**	**Placebo (95% CI)**
n	33	9	96	30
Age (y)	9.4 (8.9 to 9.9)	9.9 (8.9 to 10.9)	10 (9.7 to 10.3)	9.9 (9.4 to 10.4)
CD4 count	925 (804 to 1046)	990 (727 to 1254)	868 (794 to 942)	1013 (843 to 1183)
CD4%	38.7 (36.6 to 40.8)	37.3 (32.4 to 42.3)	33.9 (32.3 to 35.5)	35.8 (32.6 to 39)
Ethnicity (%)				
White, non-Hispanic	3 (9)	0 (0)	4 (4)	2 (7)
Black, non-Hispanic	18 (55)	4 (44)	54 (56)	11 (37)

	Group 3		All Groups	
Parameters (Categorical Levels)	**QHPV (95% CI)**	**Placebo (95% CI)**	**QHPV (95% CI)**	**Placebo (95% CI)**
Hispanic	12 (36)	3 (33)	37 (39)	14 (47)
Others	0 (0)	2 (22)	1 (1)	3 (10)
Gender (%)				
Male	12 (36)	3 (33)	43 (45)	12 (40)
Female	21 (64)	6 (67)	53 (55)	18 (60)
Log_{10} (RNA)	2.8 (2.5 to 3.1)	2.8 (2 to 3.7)	2.7 (2.5 to 2.9)	2.6 (2.3 to 2.9)
RNA group (%)				
≤400 copies/mL	18 (55)	7 (78)	65 (68)	22 (73)
401 to ≤5000 copies/mL	8 (24)	0 (0)	16 (17)	5 (17)
>5000 copies/mL	7 (21)	2 (22)	15 (16)	3 (10)

n indicates number of subjects in each column.

RNA indicates plasma HIV RNA.

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TABLE 2

AEs Within 14 Days After First Vaccination: QHPV Vs Placebo

		Group 1		Group 2		Group 3		All Groups	
	AE Category	**QHPV**	**Placebo**	**QHPV**	**Placebo**	**QHPV**	**Placebo**	**QHPV**	**Placebo**
1	Ear and eye and respiratory system	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	1 (11%)	1 (1%)	1 (3%)
2	Injection site reactions	6 (19%)	1 (10%)	7 (22%)	1 (9%)	8 (24%)	1 (11%)	21 (22%)	3 (10%)
3	Laboratory abnormality	2 (6%)	0 (0%)	1 (3%)	1 (9%)	0 (0%)	0 (0%)	3 (3%)	1 (3%)
4	Systemic reactions	2 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (11%)	2 (2%)	1 (3%)
5	Other	0 (0%)	1 (10%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (3%)
	No. of subjects	31	10	32	11	33	9	96	30

All toxicities were counted per subject.

Categories = 1, otitis, pharyngitis, sinusitis, conjunctivitis, cough/wheezing, nasal congestion, pneumonitis; 2, local pain, swelling, tenderness, erythema; 3, abnormalities in neutrophil/platelet count, serum glucose, bilirubin, creatinine, amylase, transaminase; 4, fever, myalgia, weight loss, headache; 5, abdominal pain, chest pain, urinary tract infection, joint pain, gastritis, dental pain, herpes simplex infection, rash, lipodystrophy, attention deficit disorder, pyogenic skin infection.

TABLE 3

Grade of Signs, Symptoms, and Laboratory Abnormalities 14 Days After All Vaccinations: QHPV Vs Placebo

	Group 1		Group 2		Group 3		All Groups	
AEs*	QHPV	Placebo	QHPV	Placebo	QHPV	Placebo	QHPV	Placebo
No. of event (%)	11 (35)	5 (50)	8 (25)	5 (45)	16 (48)	5 (56)	35 (36)	15 (50)
Grade 1 (%)	7 (23)	1 (10)	10 (31)	1 (9)	8 (24)	1 (11)	25 (26)	3 (10)
Grade 2 (%)	12 (39)	4 (40)	9 (28)	4 (36)	8 (24)	2 (22)	29 (30)	10 (33)
Grade 3 (%)	0 (0)	0 (0)	4 (13)	1 (9)	1 (3)	1 (11)	5 (5)	2 (7)
Grade 4 (%)	1 (3)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)
Total subjects	31	10	32	11	33	9	96	30

*The worst grade is counted for each subject, summed over all 3 doses of vaccine or placebo.

Grade 3 or 4 reactions: QHPV [indirect hyperbilirubinemia in subjects receiving atazanavir (4); one of these had hypoglycemia; chronic neutropenia (2); hyperamylasemia (1)]; placebo [fever (1); chronic neutropenia (1)].

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TABLE 4

HPV Type–Specific Seroconversion: QHPV Vs Placebo*

	Group 1		Group 2		Group 3		All Groups†	
Serotype	**QHPV**	**Placebo**	**QHPV**	**Placebo**	**QHPV**	**Placebo**	**QHPV**	**Placebo**
6	100% (29/29)	0% (0/9)	100% (29/29)	0% (0/10)	100% (29/29)	0% (0/8)	100% (87/87)	0% (0/27)
11	100% (30/30)	0% (0/9)	100% (30/30)	0% (0/10)	100% (30/30)	0% (0/8)	100% (90/90)	0% (0/27)
16	100% (29/29)	0% (0/9)	100% (30/30)	10% (1/10)	100% (31/31)	0% (0/8)	100% (90/90)	4% (1/27)
18	90% (27/30)	0% (0/9)	100% (30/30)	0% (0/10)	100% (30/30)	0% (0/8)	97% (87/90)	0% (0/27)

*Seroconversion was measured at week 28 after beginning the vaccination series.

†The type-specific results shown in Table 4 represent the remaining subjects after exclusion of those with protocol violations, unevaluable specimens, or the presence of type-specific antibody at baseline.

TABLE 5

HPV Type–Specific Antibody Titer (GMT) by Groups: QHPV Vs Placebo at 28 Days After Full Immunization

		Group 1		Group 2		Group 3		All Groups	
Serotype	**TRT**	**n**	**GMT (95% CI)**	**n**	**GMT (95% CI)**	**n**	**GMT (95% CI)**	**n**	**GMT (95% CI)**
6	Placebo	9	4 (3 to 6)	10	5 (3 to 7)	8	4 (3 to 6)	27	4 (4 to 5)
	QHPV	29	798 (497 to 1279)	29	404 (235 to 695)	29	522 (344 to 793)	87	552 (421 to 725)
11	Placebo	9	4 (4 to 4)	10	5 (4 to 7)	8	4 (4 to 4)	27	4 (4 to 5)
	QHPV	30	1720 (1199 to 2468)	30	1149 (779 to 1695)	30	1304 (930 to 1829)	90	1371 (1118 to 1682)
16	Placebo	9	6 (6 to 6)	10	7 (5 to 12)	8	6 (6 to 6)	27	6 (5 to 7)
	QHPV	29	5984 (3617 to 9900)	30	5129 (3224 to 8161)	31	4700 (3394 to 6508)	90	5231 (4108 to 6660)
18	Placebo	9	5 (5 to 5)	10	5 (5 to 5)	8	5 (5 to 5)	27	5 (5 to 5)
	QHPV	30	1078 (506 to 2300)	30	984 (544 to 1779)	30	759 (455 to 1268)	90	931 (656 to 1321)

n = number of subjects in the adjacent segment of each row.

TRT = QHPV or placebo arm.

TABLE 6

Antibody Responses to QHPV in HIV-Infected Children Compared With HIV-Uninfected Historical Controls

	HIV Infected		HIV Uninfected	
	Age 9–12, Present Study		Age 9–12, Published	
Serotype	n	GMT (95% CI)	n	GMT (95% CI)
6	63	535 (387 to 739)	563	1053 (974 to 1138)
11	65	1321 (1025 to 1702)	563	1587 (1469 to 1715)
16	65	4987 (3685 to 6751)	560	6444 (5840 to 7110)
18	65	845 (547 to 1306)	565	1558 (1416 to 1716)

Published data are from Block et al[25] and Reisinger et al.[26]

n indicates subjects in each of the comparator groups.