Immunogenicity and Safety of the Quadrivalent Human Papillomavirus Vaccine in HIV-1–Infected Women

Erna Milunka Kojic,[1] Minhee Kang,[2] Michelle S. Cespedes,[3] Triin Umbleja,[2] Catherine Godfrey,[4] Reena T. Allen,[5] Cynthia Firnhaber,[6] Beatriz Grinsztejn,[7] Joel M. Palefsky,[8] Jennifer Y. Webster-Cyriaque,[9] Alfred Saah,[10] Judith A. Aberg,[3] and Susan Cu-Uvin[1]

[1]Department of Infectious Disease, Brown University, Providence, Rhode Island; [2]Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, Massachusetts; [3]Division of Infectious Diseases, Icahn School of Medicine at Mount Sinai, New York, New York; [4]HIV Research Branch, Therapeutics Research Program, Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, and [5]AIDS Clinical Trials Group Network Coordinating Center, Silver Spring, Maryland; [6]Clinical HIV Research Unit, Department of Internal Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [7]Infectious Diseases Department, Instituto de Pesquisa Clinica Evandro Chagas Fiocruz, Rio de Janeiro, Brazil; [8]Department of Medicine, University of California at San Francisco; [9]Oral HIV/AIDS Research Alliance (OHARA), Virology, Microbiology and Immunology, Dental Ecology, University of North Carolina, Chapel Hill; and [10]Merck Research Labs, North Wales, Pennsylvania

Background. Women infected with human immunodeficiency virus (HIV) are disproportionately affected by human papillomavirus (HPV)–related anogenital disease, particularly with increased immunosuppression. AIDS Clinical Trials Group protocol A5240 was a trial of 319 HIV-infected women in the United States, Brazil, and South Africa to determine immunogenicity and safety of the quadrivalent HPV vaccine in 3 strata based on screening CD4 count: >350 (stratum A), 201–350 (stratum B), and ≤200 cells/μL (stratum C).

Methods. Safety and serostatus of HPV types 6, 11, 16, and 18 were examined. HPV serological testing was performed using competitive Luminex immunoassay (HPV-4 cLIA). HPV type-specific seroconversion analysis was done for participants who were seronegative for the given type at baseline.

Results. Median age of patients was 36 years; 11% were white, 56% black, and 31% Hispanic. Median CD4 count was 310 cells/μL, and 40% had undetectable HIV-1 load. No safety issues were identified. Seroconversion proportions among women at week 28 for HPV types 6, 11,16, and 18 were 96%, 98%, 99%, and 91%, respectively, for stratum A; 100%, 98%, 98%, and 85%, respectively, for stratum B, and 84%, 92%, 93%, and 75%, respectively, for stratum C.

Conclusions. The quadrivalent HPV vaccine targeted at types 6, 11, 16, and 18 was safe and immunogenic in HIV-infected women aged 13–45 years. Women with HIV RNA load >10 000 copies/mL and/or CD4 count <200 cells/μL had lower rates of seroconversion rates.

Clinical Trials Registration. NCT00604175.

Keywords. HPV vaccine; HIV-infected women; immunogenicity; vaccine safety; anogenital disease.

Persistent infection with oncogenic human papillomavirus (HPV) can cause anal and cervical intraepithelial neoplasia and cancer [1, 2]. Human immunodeficiency virus (HIV)–infected women are disproportionately affected by HPV-related anogenital disease, compared with HIV-uninfected women [3, 4]. Despite the immunologic reconstitution associated with the use of combination antiretroviral therapy (cART), the prevalence of anogenital HPV infections and diseases remains high [5–7]. Current cervical cancer prevention strategies are aimed at secondary preventions with early detection and treatment of intraepithelial lesions due to HPV infection, and to date there is no consensus in the

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Correspondence: Erna Milunka Kojic, MD, Brown University, 1125 N Main St, Providence, RI 02906 (ekojic@lifespan.org).

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literature on how to implement anal cancer prevention among women. These measures may not be accessible to women living in countries with limited medical resources, areas that carry a disproportionate mortality burden from cervical cancer [8]. Primary prevention of HPV infection is therefore critically needed.

The quadrivalent HPV vaccine was designed to prevent 4 types of HPV infection, types 16 and 18 (the causative agents of most cervical and anal cancers) and types 6 and 11 (which cause most anogenital warts). The vaccine consists of virus-like particles generated by the expression of the major capsid protein L1 from HPV types 6, 11, 16, and 18 with an aluminum adjuvant. When given to HIV-uninfected women without prior exposure to HPV-16 or -18, the HPV vaccine demonstrated 98% efficacy in preventing cervical intraepithelial neoplasia related to the vaccine types [9] and 100% of anogenital warts [10]. In a trial of healthy boys and men 16–26 years of age, the efficacy of the vaccine was 90.4% in preventing external genital lesions due to the vaccine types [11]; among 602 men who have sex with men, the efficacy against anal intraepithelial neoplasia associated with the vaccine types was 77.5% [12]. The use of the vaccine among 700 black women prevented 100% of cervical and vulvar disease [13]. To our knowledge, no vaccine efficacy studies have been published to date on HIV-infected persons.

HIV-infected persons have been documented to have poor responses to standard vaccination series such as hepatitis A and B [14–16]. Data on predictors of immunogenic responses to vaccinations have been inconsistent, but both HIV viremia and CD4 cell counts can affect responses [14, 17]. In a study designed to assess the immunogenicity of the quadrivalent HPV vaccine among HIV-infected men with CD4 cell counts >200 cells/μL, 95% exhibited seroconversion and no relationship between CD4 cell counts and HPV antibody concentrations were observed, but higher anti–HPV-16 and -18 antibody concentrations were noted in those receiving cART [18]. Similar results were found among 99 HIV-infected young women aged 16–23 years [19]. Neither study included participants with CD4 cell counts <200 cells/μL. Here we present data on the first 28 weeks on study from an international multicenter clinical trial that aimed to assess the immunogenicity and safety of the quadrivalent HPV vaccine among HIV-infected women aged 13–45 years with different levels of CD4 cell counts.

METHODS

Study Design

AIDS Clinical Trials Group (ACTG) Protocol 5240 (see Appendix for group members) was an international phase 2, open-label, single-arm study with stratification by $CD4^+$ cell count to assess the immunogenicity and safety of the quadrivalent HPV recombinant vaccine (Gardasil) directed against HPV types 6, 11, 16, and 18. CD4 cell strata were defined as stratum A: >350 cells/μL; stratum B: 201–350 cells/μL, and stratum C: ≤200 cells/μL. The 3 strata opened simultaneously. The study initially had HIV RNA stratification to balance the number of participants with ≤10 000 copies/mL in each CD4 stratum. This stratification was subsequently removed due to enrollment delay as it was not a part of the primary study analysis. We planned to analyze data using both the 10 000 and 400 copies/mL cutoffs, as the latter may be clinically more meaningful. The primary endpoint of the study was type-specific HPV antibody development 1 month after the completion of the HPV vaccination series (week 28) in participants negative for the type-specific antibodies at baseline. Seroconversion from seronegative to seropositive status was defined as the development of antibody levels above the serostatus cutoffs for HPV types 6, 11, 16, and 18 as determined by the assay developer: ≥20, ≥16, ≥20, and ≥24 milli-Merck units (mMU)/mL, respectively. The planned sample size was 134 women in each of the 3 CD4 cell count strata. Participants were enrolled at ACTG sites in the United States; Fiocruz, Brazil; and Johannesburg, South Africa. Institutional review boards of the participating institutions approved the study, and each participant gave written informed consent.

The protocol was amended as new data emerged and to improve feasibility. The sample size was adjusted to 94 participants in each stratum based on seroconversion rates from external HPV vaccine studies. Other changes to the protocol included allowing women with prior cervical low-grade cytology results to enroll and removal of ART duration requirement prior to the study.

Enrollment Criteria

Inclusion criteria were follows: women aged 13–45 years; documentation of HIV type 1 (HIV-1) infection, hemoglobin level ≥8.0 g/dL, platelet count ≥100 000/μL, aspartate and alanine aminotransferase levels ≤3 times the upper limit of normal (ULN), direct bilirubin level of <2.5 × ULN, and a Karnofsky score ≥70. Participants of reproductive potential were required to use contraception for the duration of the study.

Individuals were excluded if they had high-grade cervical intraepithelial neoplasia (CIN II or III), vaginal intraepithelial neoplasia (VIN II or III), or genital warts within 180 days prior to study entry. Recent or expected use of systemic antineoplastic agents, immunomodulatory treatments, or investigational vaccines was excluded. Women with known hypersensitivity to components of the vaccine, currently pregnant or breastfeeding, hemophilia, prior hysterectomy, or prior receipt of HPV vaccines were excluded.

Study Treatment

At entry, week 8, and week 24, participants received the quadrivalent HPV vaccine 0.5 mL intramuscularly. The primary

immunogenicity endpoint was determined 4 weeks after the third vaccination.

Study Evaluations

We report on clinical assessments made at each vaccination and at weeks 4, 12, and 28. CD4 cell count was assessed at entry and weeks 4, 8, 12, 24, and 28. Plasma HIV-1 RNA and routine laboratory monitoring were assessed at entry and weeks 4, 12, and 28. Participants were contacted 24–48 hours after each vaccination to assess for vaccine-related symptoms. All laboratory abnormalities, signs, and symptoms were graded using the Division of AIDS Adverse Event Grading Table, Version 1.0.

Laboratory Testing

HPV serological testing was performed using competitive Luminex immunoassay (HPV-4 cLIA; Merck Research Laboratories). Anal and cervical HPV DNA polymerase chain reaction (PCR) testing was performed with MY09/MY11 primers and L1 consensus and type-specific probing as described elsewhere [20]. HIV RNA testing was performed locally, using Roche Ultra-Sensitive HIV Real-time (RT) PCR, Roche COBAS AmpliPrep/TaqMan HIV-1, or Roche Amplicor Monitor HIV RT PCR.

Statistical Methods

The initial target sample size of 134 in each CD4 stratum was based on the assumption of at least 70% true seroconversion proportion for each HPV type, where the proportion greater than the null of 50% was to be considered success in the study population. With emerging results from completed HPV vaccine studies in the literature, the sample size was subsequently adjusted to 94 in each stratum, now assuming at least 90% true seroconversion proportion and to conclude proportion greater than the revised null of 70% as success. These sample sizes accounted for loss to follow-up and exclusion of individuals seropositive for all 4 HPV types at study entry who would not contribute to the primary analysis.

The primary immunogenicity analysis was on participants who had completed the vaccination series per protocol, had HPV-negative antibody results at baseline, and available week 28 results. Analysis on all participants who received any vaccines was conducted as an intention-to-treat, secondary analysis.

The proportion of type-specific antibody seroconversion within each CD4 stratum was estimated with a 2-sided 95% confidence interval (CI) using exact Clopper-Pearson method, without adjustment for multiple CIs. The CIs around geometric mean titers (GMTs) were calculated assuming t distribution of $\log_{10}$-transformed antibody titer. Fisher exact tests were used to compare binary or categorical variables among groups. A joint model that includes all observed antibody results from each individual who was seronegative for all 4 HPV types at baseline was developed, to assess the effects of HPV type, baseline CD4 cell count (>200 or ≤200 cells/μL), baseline HIV RNA level (>10 000 or ≤10 000 copies/mL), and age (>35 or ≤35 years) on seroconversion. The generalized estimating equation (GEE) approach using a logit link function was taken as a method of analyzing correlated antibody data on 4 HPV types from each individual.

RESULTS

Study Participants

Three hundred nineteen participants were enrolled from March 2008 to July 2011 (130 participants in stratum A, 95 in stratum B, and 94 in stratum C). Accrual to strata A and B was completed prior to the sample size adjustment with enrollment exceeding 94. There were 29 participants enrolled from Brazil and 25 from South Africa. One participant in stratum A was found to be ineligible after enrollment; 2 participants in stratum A and 1 participant in stratum C were not able to start vaccination series within 72 hours of entry and were removed from the study and excluded from the analysis. Therefore, the total number of participants in this analysis was 315, with 127 in stratum A, 95 in stratum B, and 93 in stratum C. Baseline participant characteristics are shown in Table 1. Baseline seropositivity for each of the 4 HPV vaccine types is presented in Table 2. It ranged between 13% and 45%; only 4% of women were seropositive for all 4 types, with no difference among women with high or low baseline CD4 counts. We did not find an association between age and baseline seropositivity except for HPV type 18 in the highest and lowest CD4 strata ($P = .041$ and .027, respectively). There were no statistically significant differences in seroprevalences in the US sites and non-US sites across the 3 CD4 strata. Cervical and/or anal HPV DNA results on types 6/11 (combined), 16, and 18 were available for 287 subjects (115 in CD4 stratum A, 86 each in B and C). Of the 146 subjects who were seronegative for types 6/11 at baseline, 2 (1.4%) were DNA positive. Of the 175 who were seronegative for type 16 at baseline, 14 (8.6%) were DNA positive, and of the 209 such subjects for type 18, 14 (6.7%) were DNA positive (data not shown).

Immunogenicity Analyses

Per-protocol immunogenicity analysis results are shown in Table 3. The seroconversion proportion was close to 100% for HPV types 6, 11, and 16 in strata A and B, and for type 18, 91% in stratum A and 85% in stratum B. In stratum C, the proportion of responders was 84%, 92%, 93%, and 75% for types 6, 11, 16, and 18, respectively. For all 4 types in both strata A and B, and for HPV types 6, 11, and 16 in stratum C, the lower bounds of the CIs were >70%. The CI for type 18 in stratum C includes 70%. Week 28 serostatus among all study participants who received at least 1 vaccine and were seronegative for the respective HPV type at baseline, regardless of the number of vaccines

Table 1. Baseline Characteristics

Characteristic	Total	CD4 Stratum		
		A (>350 Cells/μL)	B (201–350 Cells/μL)	C (≤200 Cells/μL)
No. of participants	315	127	95	93
Age, y, median (Q1, Q3)	36 (30, 41)	35 (29, 40)	38 (33, 42)	36 (31, 40)
Race/ethnicity				
White non-Hispanic	11%	15%	9%	9%
Black non-Hispanic	56%	53%	62%	55%
Hispanic	31%	31%	26%	34%
Other/unknown	2%	1%	2%	2%
CD4, cells/μL, median (Q1, Q3)	310 (197, 498)	519 (418, 664)	287 (246, 344)	154 (86, 188)
Nadir CD4, cells/μL, median (Q1, Q3)	179 (47, 314)	368 (234, 482)	176 (64, 261)	41 (20, 108)
Undetectable plasma HIV-1 RNA	40%	38%	45%	38%
Detectable plasma HIV-1 RNA[a]	60%	62%	54%	62%
Missing	<1%	0%	1%	0%
Plasma HIV-1 RNA				
≤10 000 copies/mL	64%	56%	73%	66%
>10 000 copies/mL	36%	44%	26%	34%
Missing	<1%	0%	1%	0%
Plasma HIV-1 RNA				
≤400 copies/mL	50%	43%	58%	51%
>400 copies/mL	50%	57%	41%	49%
Missing	<1%	0%	1%	0%
No antiretrovirals	34%	54%	25%	14%

Abbreviations: HIV-1, human immunodeficiency virus type 1; Q1, 1st quartile; Q3, 3rd quartile.

[a] Lower limit of quantitation of the HIV RNA assay is 1.4 $\log_{10}$ copies/mL.

received, was also analyzed, and the results were similar. Table 3 presents HPV antibody concentrations at week 28 in participants who were seronegative at baseline, and Table 4 presents results in participants who were seropositive at baseline.

Predictors of Seroconversion

Week 28 seroconversion was compared pairwise among the 3 CD4 cell count strata on participants who received at least 1 vaccine and who were seronegative to at least 1 of the 4 HPV

Table 2. Baseline Seropositivity for Human Papillomavirus Vaccine Types

HPV Type	Total	CD4 Stratum		
		A (>350 Cells/μL)	B (201–350 Cells/μL)	C (≤200 Cells/μL)
No.[a]	308	120	95	93
Seropositivity for type 6	126 (41%)	54 (45%)	35 (37%)	37 (40%)
Seropositivity for type 11	64 (21%)	22 (18%)	23 (24%)	19 (20%)
Seropositivity for type 16	100 (32%)	44 (36%)	30 (32%)	26 (28%)
Seropositivity for type 18	61 (20%)	29 (24%)	12 (13%)	20 (21%)
Seronegative for all 4 types	121 (39%)	44 (37%)	42 (44%)	35 (38%)
Seropositive for any 1 type	86 (28%)	33 (27%)	24 (25%)	29 (31%)
Seropositive for any 2 types	53 (17%)	20 (17%)	15 (16%)	18 (19%)
Seropositive for any 3 types	35 (11%)	18 (15%)	10 (11%)	7 (7%)
Seropositive for all 4 types	13 (4%)	5 (4%)	4 (4%)	4 (4%)

Abbreviation: HPV, human papillomavirus.

[a] No. of participants with results for all 4 HPV vaccine types available.

Table 3. Human Papillomavirus Antibody Concentrations at Week 28 in Participants Seronegative for a Given Type at Baseline

	Participants Seronegative for HPV Type at Baseline						
	Per-Protocol Analysis[a]			Intention-to-Treat Analysis[b]			
HPV type and CD4 Stratum	No.[c]	No. Seropositive at Week 28	% Seropositive at Week 28 (95% CI)	No.[c]	No. Seropositive at Week 28	GMTs at Week 28, mMU/mL (95% CI)	Median Titer at Week 28, $\log_{10}$ mMU/mL (Q1, Q3)
Type 6							
A	54	52	96.3 (87.3–99.5)	60	58	462 (321–667)	2.70 (2.37, 3.11)
B	50	50	100.0 (92.9–100.0)	58	57	349 (242–504)	2.50 (2.12, 2.96)
C	45	38	84.4 (70.5–93.5)	52	42	137 (82–229)	2.35 (1.41, 2.84)
Type 11							
A	86	84	97.7 (91.9–99.7)	93	91	477 (362–627)	2.76 (2.41, 3.08)
B	59	58	98.3 (90.9–100.0)	70	67	417 (287–607)	2.64 (2.26, 3.05)
C	62	57	91.9 (82.2–97.3)	71	62	205 (129–327)	2.51 (1.79, 2.93)
Type 16							
A	67	66	98.5 (92.0–100.0)	73	72	1200 (871–1654)	3.14 (2.80, 3.49)
B	56	55	98.2 (90.4–100.0)	63	61	1117 (746–1672)	3.12 (2.79, 3.46)
C	56	52	92.9 (82.7–98.0)	64	57	571 (328–994)	3.03 (2.26, 3.39)
Type 18							
A	78	71	91.0 (82.4–96.3)	86	78	175 (126–243)	2.25 (2.01, 2.66)
B	71	60	84.5 (74.0–92.0)	80	66	171 (115–255)	2.34 (1.74, 2.82)
C	61	46	75.4 (62.7–85.5)	69	50	94 (59–149)	2.09 (1.15, 2.62)

Abbreviations: CI, confidence interval; GMT, geometric mean titer of HPV antibodies; HPV, human papillomavirus; mMU/mL, milli-Merck units/mL; Q1, 1st quartile; Q3, 3rd quartile.

[a] Participants seronegative for a given type at baseline who completed the vaccination series per protocol with HPV antibody results at week 28 study visit.

[b] Participants who had HPV antibody results available at both baseline and week 28 study visits and who had received either partial or complete vaccination series.

[c] No. of participants in the analysis.

types at baseline. There was a numerical trend of lower seroconversion in stratum C compared with stratum A (92% vs 98%, $P = .080$) and compared with stratum B (92% vs 98%, $P = .096$). Seroconversion proportions were too high for HPV types 6, 11, and 16 in strata A and B to discern differences between HIV RNA groups. In stratum C, seroconversion proportion for HPV types 6, 11, 16, and 18 were 89%, 97%, 100%, and 91%, respectively, among women with a viral load <400 copies/mL compared with 73%, 77%, 81%, and 56% among women with a viral load >400 copies/mL ($P = .29$, .01, .01, and .001, respectively). Similar results were found for all types using the viral cutoff of 10 000 copies/mL except for HPV-16, for which the result was only statistically significant when using the viral cutoff of 400 copies/mL. In the GEE model, the odds of seroconversion in HPV types 6, 11, and 16 were higher compared with type 18, with corresponding OR estimates of 3.45, 3.45, and 4.53 for types 6, 11, and 16 ($P = .0005$, .0001, and <.0001, respectively). The GEE model also showed that seroconversion was higher with CD4 cell count >200 μL (odds ratio [OR], 3.31; $P = .01$) and lower with HIV RNA >10 000 copies/mL (OR, 0.26; $P = .005$). Age effect was not statistically significant.

Safety Issues

There were no significant safety issues identified by the study monitoring committee. There were 2 deaths, both from stratum A (1 from lymphoma and 1 from meningitis), neither related to the vaccine. One participant in stratum B had an allergic reaction; 1 participant from stratum C developed a grade 3 fever. Sixteen participants had grade 1 or higher fever reported during the postvaccination follow-up (n = 5, 4, and 7 in strata A, B, and C, respectively). Three participants from stratum C experienced grade 2 injection site reactions. Overall, 17% of participants experienced grade 3 or higher adverse events, 11% grade 3 or higher signs and symptoms, and 8% grade 3 or higher laboratory abnormalities. Laboratory abnormalities were more common in individuals who were more immune compromised. The most common adverse event was pain; other common events were neurological, gastrointestinal, and skin related.

DISCUSSION

The quadrivalent HPV vaccine is safe and immunogenic among HIV infected women aged 13–45 years who were seronegative

Table 4. Human Papillomavirus Antibody Concentrations at Week 28 in Participants Seropositive for a Given Type at Baseline

	Subjects Seropositive for HPV Type at Baseline						
HPV Type and CD4 Stratum	No.[a] (ITT)[b]	Baseline GMT, mMU/mL (95% CI)	Baseline Median Titer, $\log_{10}$ mMU/mL (Q1, Q3)	No.[a] (ITT)	Week 28 GMT, mMU/mL (95% CI)	Week 28 Median Titer, $\log_{10}$ mMU/mL (Q1, Q3)	Week 28 Median Change in Titer, $\log_{10}$ mMU/mL (Q1, Q3)
Type 6							
A	54	69 (55–87)	1.89 (1.54, 2.07)	52	770 (479–1238)	2.96 (2.53, 3.50)	1.12 (0.59, 1.54)
B	35	68 (50–91)	1.88 (1.45, 2.16)	33	651 (369–1151)	2.84 (2.55, 3.27)	1.10 (0.61, 1.52)
C	37	85 (66–109)	1.98 (1.63, 2.10)	36	725 (499–1055)	2.84 (2.51, 3.12)	0.97 (0.55, 1.29)
Type 11							
A	22	67 (42–108)	1.75 (1.52, 2.05)	20	1253 (737–2131)	3.19 (2.75, 3.37)	1.32 (1.07, 1.71)
B	23	70 (43–115)	1.81 (1.45, 2.01)	21	951 (399–2268)	2.99 (2.42, 3.40)	1.42 (0.86, 1.59)
C	19	96 (46–200)	1.85 (1.38, 2.61)	17	704 (407–1217)	3.00 (2.59, 3.11)	0.60 (0.28, 1.25)
Type 16							
A	44	91 (66–127)	1.85 (1.59, 2.29)	40	3027 (1920–4771)	3.56 (3.31, 3.83)	1.65 (1.26, 1.93)
B	30	136 (74–249)	1.88 (1.52, 2.76)	28	2208 (1037–4702)	3.59 (2.91, 3.80)	1.29 (0.84, 1.86)
C	26	83 (43–160)	1.67 (1.46, 2.09)	24	1252 (685–2287)	3.04 (2.65, 3.53)	1.06 (0.62, 1.79)
Type 18							
A	29	68 (49–95)	1.72 (1.56, 2.05)	27	771 (403–1475)	3.02 (2.37, 3.46)	1.02 (0.48, 1.51)
B	12	93 (41–212)	1.82 (1.51, 2.22)	11	487 (166–1424)	2.74 (2.12, 3.09)	0.89 (0.50, 1.53)
C	20	85 (54–132)	1.88 (1.60, 2.15)	19	458 (250–838)	2.66 (2.18, 3.02)	0.85 (0.04, 1.22)

Abbreviations: CI, confidence interval; GMT, geometric mean titer of HPV antibodies; HPV, human papillomavirus; ITT, intention-to-treat; mMU/mL, milli-Merck units/mL; Q1, 1st quartile; Q3, 3rd quartile.

[a] No. of participants in the analysis.

[b] Participants who received any vaccines with HPV antibody results at both baseline and week 28 study visits.

for the HPV types included in the vaccine, with observed seroconversion proportions >75% for all 4 HPV types. For women seropositive for the given HPV types prior to the vaccination series, the vaccine induced a significant increase in antibody levels.

Seroconversion proportions were higher among women with baseline CD4 cell counts >200 cells/μL compared with ≤200 cells/μL. This is consistent with observations from immunogenicity studies of other vaccines (eg, hepatitis A and B) but is a new finding for the HPV vaccine. Prior immunogenicity studies of the quadrivalent HPV vaccine among HIV- infected men, children, and young women did not include participants with low CD4 cell counts.

The effects of HIV RNA load on seroconversion were evaluated. Among women with CD4 counts ≤200 cells/μL, women with HIV RNA load <400 copies/mL at baseline had better seroconversion proportions for HPV types 11, 16, and 18 compared with women with viral loads ≥400 copies/mL. Women with CD4 counts >200 cells/μL had seroconversion proportions >90% for all HPV types, so we were unable to discern differences between HIV RNA groups, a finding similar to prior studies of relatively immunocompetent HIV-infected men and young women. We did not observe a relationship between age and seroconversion rates.

The odds of seroconversion were significantly higher for HPV types 6, 11, and 16 compared with type 18 as measured by cLIA. This finding is consistent with other studies and may be related to the assay used and not due to an inherent difference in immunogenicity between HPV types [21–23]. The cLIA is a type-specific assay that measures antibody binding to a single epitope. Immunoglobulin G (IgG) LIA is an antibody direct binding assay that measures all IgG with an increased sensitivity over the cLIA [24]. Brown et al assessed the antibody responses of young women to the quadrivalent HPV vaccine by both assays on the same sera and found that after 4 years, the seropositivity for HPV type 18 remained high at 97% when measured by the total IgG LIA but declined to 65% using cLIA and remained similar by both assays for HPV types 6, 11, and 16 [24]. The antibody concentrations or GMTs induced by the quadrivalent HPV vaccine were significantly higher than those induced by natural HPV infection. The GMT levels among the women with CD4 cell counts >200 cells/μL were similar to those found in HIV-infected men with comparable CD4 cell counts. Among women with CD4 cell counts <200 cells/μL, however, we found a trend for lower titers compared with higher CD4 cell counts, with a statistical significance noted for only HPV-6. When compared with published data on HIV-uninfected women, the anti–HPV-16 and -18 GMT

in our HIV-infected cohort was almost half that of HIV uninfected women in similar age groups (GMT range, 571–1200 mMU/mL for HPV-16 in our study vs 2134 mMU/mL in the literature) [25]. The clinical significance of this finding is unclear as the protective titers of HPV antibodies are not defined. Our definition of seroconversion is likely to be higher than the titers required for clinical protection.

The quadrivalent HPV vaccine has been shown to be highly effective in preventing HPV acquisition and disease due to the vaccine types in healthy women, especially if administered prior to HPV exposure. In the current study, only 4% of women were seropositive for all 4 vaccine types, either due to lack of prior HPV exposure or due to loss of serum HPV antibodies. This suggests that the majority of HIV-infected women, regardless of immune status, would benefit from the vaccination series. Future studies are needed to determine the duration of immunogenicity as well as an assessment of the effect of anogenital and oral HPV infection on vaccine responses.

In conclusion, data from this multicenter study show that the quadrivalent HPV vaccine directed against HPV types 6, 11, 16, and 18 is safe and immunogenic in HIV-infected women aged 13–45 years supporting the recommendations of the Advisory Committee on Immunization Practices and the World Health Organization to vaccinate HIV-infected persons. Women with HIV RNA load >10 000 copies/mL and/or CD4 count <200 cells/μL had lower seroconversion, and there was a tendency for lower HPV titers in the more immunosuppressed group of vaccinated women.

Notes

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APPENDIX

AIDS Clinical Trials Group (ACTG) Protocol 5240 members. Sandra Wagner Cardoso and Ruth Khalili Friedman, Instituto de Pesquisa Clinica Evandro Chagas (IPEC), Fiocruz (Site 12101) Site ID 60554, Grant 10U01AI069476-01. Lorraine Sanchez-Keeland, PA-C, and Hannah Edmondson, RN, MPH, University of Southern California (Site 1201) CTU Grant AI069428. Dr Sharlaa Badal-Faesen and Sibongile Ramotshela, WITS HIV CRS (Site 11101) CTU Grant AI069463. Karen T. Tashima, MD, and Deborah Perez, RN, The Miriam Hospital (Site 2951) CTU Grant AI069412-08. Mark Rodriguez, RN, BSN, and Ge-Youl Kim, RN, Washington University CRS (Site 2101) CTU Grant AI069495. Donna McGregor, NP, and Sarah Sutton, MD, Northwestern University (Site 2701) CTU Grant AI069471. Dr Princy Kumar and Dr Mary Young, Georgetown University (Site 1008). Susan Blevins RN, MS, ANP-C, and Donna Pittard, BSN, UNC AIDS Clinical Trials Unit (Site 3201) CTU Grant 5-U01 AI069423; Texas Childrens Hospital CRS (Site 3801). Pablo Tebas, MD, and Aleshia Thomas BSN, RN, University of Pennsylvania (Site 6201) CTU Grant AI-069467-07; CFAR Grant 5-P30-AI-045008-15. Shobha Swaminathan, MD, and Christie Lyn Costanza, BA, MPH, New Jersey Medical School Adult Clinical Research Center (Site 31477) CPCRA CTU, Fred Gordin PI, Grant 5 UO1 AI69503-03; UNC Clinical Trials Research Center of the Clinical and Translational Science Award RR 025747; UNC Center for AIDS Research AI050410. Annie Luetkemeyer, MD, and Mary Payne, RN, UCSF AIDS CRS (Site 801) CTU Grant 5UO1 AI069502-07. Dr Timothy Lane and Dr Cornelius Van Dam, Regional Center for Infectious Disease (Site 3203) CTU Grant AI069423. Wayne State University Detroit (Site 5048).

University of Florida Jacksonville (Site 5051). Roberto C. Arduino, MD, and Francisco Mora, MD, HART (Site 31473) CTU Grant 5UM1 AI069503. Karen Cavanagh, RN, and Janet Forcht, RN, New York University/NYC HHC at Bellevue Hospital (Site 401) CTU Grant Al069532.

Jenifer Baer, RN, BSN, and Carl J. Fichtenbaum, MD, University of Cincinnati (Site 2401) NIAID Grant AI-069513; refunded through a consortium with Case Western. Kimberly Smith MD, MPH, and Tondria Green, RN, Rush University Medical Center (Site 2702) CTU Grant 1U01 AI069471. Rush University Cook County Hospital Chicago, NICHD CRS (Site 5083).

Miller Children's Hospital Long Beach CA (Site 5093). Dorothy Sawo, FNP, PhD, and Madeline Torres, RN, Columbia University HPTR (Site 30329) CTU Grant 5U01 AI069470-01; GCRC Grant 5 UL1 RR021456-07. Michelle Mba and Lauren Rogers, Trinity Health & Wellness Center (Site 31443) CTU Grant U01 AI069471. Dr Norman Markowitz, MD, and Dr Indira Brar, MD, Henry Ford Hospital (Site 31472). Amita Gupta, MD, and Ilene Wiggins, RN, Johns Hopkins University AIDS Clinical Trials Unit (Site 201) CTU Grant NIAID 5UM1-AI069465; NCATS Grant UL1TR001079. Joanne Santangelo, NP, and Susan Cahill, RN, UCSD (Site 701) CTU Grant AI69432. Margaret A. Fischl, MD, and Hector Bolivar, MD, University of Miami HIV/AIDS Clinical Trials Unit (Site 901) CTU Grant 1U01AI069477; Grant P30 AI073961 (Miami Center for AIDS Research). Mary Adams, RN, and Christine Hurley, RN, University of Rochester (Site 1101), Trillium Health (Site 1108) CTU Grant UMI AI069511. Shelia Dunaway, MD, and Jane Hitti, MD, MPH, University of Washington ACTU (Site 1401) CTU Grant UM1 AI069481. Vicki Bailey and Husamettin Erdem, Vanderbilt Therapeutics Clinical Research (Site 3652) CTU Grant U01AI069439. Charles E. Davis Jr, MD, and Gregory Taylor, MD, Institute of Human Virology Baltimore Treatment (Site 4651) CTU Grant 1U01AI069447. Tulane University New Orleans NICHD CRS (Site 5095). Jorge L. Santana Bagur, MD, and Olga I. Méndez Flores, MD, Puerto Rico-ACTU (Site 5401) CTU Grant 5UM1AI069415-07. Elizabeth Lindsey, RN, and Truus Delfos-Broner, CRNP, Alabama Therapeutics CRS (Site 5801) CTU Grant U01 AI069452. Clifford Gunthel, MD, and Dale Maddox, RN, The Ponce de Leon Center CRS (Site 5802). John Baxter, MD, and Pola de la Torre, MD, Cooper University Hospital (Site 31476). Teri Flynn, ANP, and Amy Sbrolla RN, Massachusetts General Hospital (Site 101) CTU Grant IUOIAI69472. Debbie Slamowitz, RN, and Sandra Valle, PA-C, Stanford University (Site 501) CTU Grant AI069556. Ardis Moe, MD, and Vanessa Cajahuaringa, UCLA CARE Center (Site 601) CTU Grant UM AI069424; Grant UL1RR033176. Deborah McMahon, MD, and Carol Oriss, BSN, University of Pittsburgh CRS (Site 1001) Grant # AI 069494. Michael F. Para, MD, and Kathy J. Watson, RN, The Ohio State University (Site 2301) CTU Grant AI069474.

Traci Davis, RN, and Kim Whitely, RN, MetroHealth CRS (Site 2503) CTU Grant AI-69501.

South Florida CDTC Ft Lauderdale NICHD CRS (Site 5055). Christina Megill, PA-C, and Valery Hughes, NP, Cornell CTU (Site 7804) CTU Grant AI069419m CTSC Grant TR000457.

Dr David Cohn, MD, and Diane States, RN, BSN, Denver Public Health (Site 31470) CTU Grant AI 069503. Vicky Watson, RN, and Carol Clark, RN, Virginia Commonwealth University CRS (Site 31475) CTU Grant 5UM1AI069503; VCU CCTR (GCRC) Grant UL1TR000058. Charlene Gaca, RN, and Ioana Bica, MD, Boston Medical Center (Site 104).

UCSD Maternal, Child, and Adolescent HIV CRS (Site 4601). Howard University Washington DC NICHD CRS (Site 5044).

University of Puerto Rico Pediatric HIV/AIDS Research Program CRS (Site 6601). Mary Albrecht, MD, and Andrea Kershaw, NP, Beth Israel Deaconess (Partners/Harvard) CRS (Site 103) CTU Grant U01 AI069472-07. Elizabeth Livingston, MD, and Joan Riddle, RN, Duke University Medical Center CRS (Site 1601) CTU Grant 5UM1- AI069484-07. Patricia Walton, RN, and Jane Baum, RN, Case CRS (Site 2501) CTU Grant AI69501. Womens and Childrens HIV Program (Site 4005). Columbia IMPAACT CRS (Site 4101). University of Miami Pediatric/Perinatal HIV/AIDS (Site 4201). San Juan City Hospital (Site 5031). Graham Ray and Cathi Basler, University of Colorado Hospital Clinical Research (Site 6101) CTU Grant AI69450; Grant RR025780. The Research and Education Group, Portland CRS (Site 31474) CTU Grant 1U01AI069503. Thomas Jefferson University Med. Ctr. CRS (Site 31482) CTU Grant 1U01AI069464. James H. Sampson, MD, and Norma Martinez, RN, BSN, The Research and Education Group, Portland CRS (Site 31474) CTU Grant 1U01AI069503.