MAJOR ARTICLE

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

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Background. Human immunodeficiency virus type 1 (HIV-1)-infected men are at increased risk for anal cancer. Human papillomavirus (HPV) vaccination may prevent anal cancer caused by vaccine types.

Methods. AIDS Malignancy Consortium Protocol 052 is a single-arm, open-label, multicenter clinical trial to assess the safety and immunogenicity of the quadrivalent HPV (types 6, 11, 16, and 18) vaccine in HIV-1–infected men. Men with high-grade anal intraepithelial neoplasia or anal cancer by history or by screening cytology or histology were excluded. Men received 0.5 mL intramuscularly at entry, week 8, and week 24. The primary end points were seroconversion to vaccine types at week 28, in men who were seronegative and without anal infection with the relevant HPV type at entry, and grade 3 or higher adverse events related to vaccination.

Results. There were no grade 3 or greater adverse events attributable to vaccination among the 109 men who received at least 1 vaccine dose. Seroconversion was observed for all 4 types: type 6 (59 [98%] of 60), type 11 (67 [99%] of 68), type 16 (62 [100%] of 62), and type 18 (74 [95%] of 78). No adverse effects on CD4 counts and plasma HIV-1 RNA levels were observed.

Conclusions. The quadrivalent HPV vaccine appears safe and highly immunogenic in HIV-1–infected men. Efficacy studies in HIV-1–infected men are warranted.

Clinical trials registration. NCT 00513526.

Anal cancer is caused by persistent infection with high-risk types of human papillomavirus (HPV) [1]. Approximately 66% of anal cancers are caused by HPV type 16 and 5% by HPV type 18 [2]. Human immunodeficiency virus type 1 (HIV-1)-infected men who have sex with men are at increased risk for anal cancer [3], and the incidence may have increased further in the era of antiretroviral therapy (ART) [4–8]. Anal cancer prevention strategies have emerged that screen for high-grade anal intraepithelial neoplasia (HGAIN)

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through an algorithm of cytology and high resolution anoscopy–directed biopsies, prompting removal or destruction of HGAIN lesions [9]. Options for primary prevention are currently limited.

The use of the quadrivalent HPV vaccine has been shown to prevent persistent cervical HPV infection caused by vaccine types (6, 11, 16, and 18) in women and to prevent nearly 100% of high-grade cervical, vaginal, and vulvar intraepithelial neoplasia associated with vaccine types, the precursor lesions to invasive cancers at these sites, in women who were not infected at baseline [10, 11]. This vaccine prevented 93% of persistent anal infections with vaccine types in young HIV-1–uninfected men who have sex with men [12].

The quadrivalent HPV vaccine is a recombinant protein virus-like particle vaccine with a proprietary adjuvant, amorphous aluminum hydroxyphosphate sulfate [13]. HIV-1–infected individuals have lower rates of antibody conversion to similar vaccine constructs, such as the hepatitis A vaccine and hepatitis B vaccine, compared with HIV-1–uninfected individuals [14–16]. This study was designed to test the hypothesis that the quadrivalent HPV vaccine is safe and immunogenic in HIV-1–infected men.

METHODS

Study sites. AIDS Malignancy Consortium Protocol 052 was a multicenter, single-arm, open-label, pilot trial conducted at 8 clinical trial sites (Boston University Medical Center, Boston, MA; Denver Public Health, Denver, CO; Laser Surgery Care, New York, NY; Montefiore Medical Center, Bronx, NY; University of California, Los Angeles, CA; University of California, San Francisco, CA; Virginia Mason Medical Center, Seattle, WA; Weill-Cornell Medical College, New York, NY). Data collection and follow-up for 18 months after entry are ongoing. Institutional review boards of the participating institutions approved the study, and each patient gave written informed consent.

Enrollment criteria. Inclusion criteria were as follows: men aged $\geq$18 years; laboratory documentation of HIV-1 infection; if receiving ART, receipt of ART for at least 6 months prior to entry and no change in ART within 30 days of entry, CD4 count $\geq$200 cells/μL, and plasma HIV-1 RNA level <200 copies/mL; if not receiving ART, CD4 count >350 cells/μL and no plans to start ART within 28 weeks of entry; anal cytology result that was normal, atypical squamous cells of uncertain significance, or low-grade squamous intraepithelial lesions; having an absolute neutrophil count >750 cells/μL, hemoglobin level $\geq$9.0 g/dL, platelet count $\geq$100,000 platelets/μL, and aspartate and alanine aminotransferase levels $\leq$3 times the upper limit of normal; total or conjugated bilirubin <2.5 times the upper limit of normal; calculated creatinine clearance by Cockcroft-Gault equation $\geq$60 mL/min; and a Karnofsky performance score $\geq$70.

Participants were excluded if they had anal or perianal carcinoma, high-grade squamous intraepithelial lesions (HSILs), atypical squamous cells suggestive of HSILs or invasive carcinoma on cytology, or HGAIN on high resolution anoscopy–guided biopsy, at any point prior to entry. Participants were excluded if polymerase chain reaction (PCR) testing of anal swabs detected DNA for both HPV 16 and 18. Participants with recent or expected use of systemic antineoplastic agents, immunomodulatory treatments, or investigational vaccines were excluded. Participants with hemophilia, prior splenectomy, or prior receipt of HPV vaccines were excluded.

Study treatment. At entry, week 8, and week 24, participants received the quadrivalent HPV (types 6, 11, 16, and 18) recombinant vaccine (0.5 mL) intramuscularly. The primary immunogenicity end point was determined 4 weeks after the third vaccination.

Study monitoring. Clinical assessments were made at each vaccination and at week 4, week 12, and week 28. Plasma HIV-1 RNA level, CD4 cell count, and routine safety laboratory monitoring were assessed at entry, week 4, week 12, and week 28. Participants were provided with a diary to report targeted symptoms occurring within 5 days of vaccination. Participants were contacted 24–48 h after each vaccination by study personnel to assess for vaccine-related symptoms. All laboratory abnormalities, signs, and symptoms were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0 [17]. Anal swabs for cytology and high resolution anoscopy with directed anal biopsies of lesions consistent with anal intraepithelial neoplasia were performed to assess eligibility and at week 28. Briefly, high resolution anoscopy is visualization of the anal canal and perianal skin using a colposcope after application of 3% acetic acid [18]. Criteria analogous to those used in cervical colposcopy are used to identify areas suspicious for anal intraepithelial neoplasia [19]. Biopsies of these areas are obtained using standard biopsy forceps. A questionnaire to assess tobacco use and sexual behavior was administered at entry and week 28. Oropharyngeal samples for HPV DNA PCR and anti-HPV immunoglobulin A were collected but were not available for analysis at the time of publication.

Laboratory testing. Anal swabs for HPV DNA PCR testing were obtained to assess eligibility and at entry and week 28, as described elsewhere [20]. This testing was performed at a central laboratory. Specimens negative for β-globin gene amplification were excluded from analysis. The results of PCR were recorded on a scale from 0 to 5 on the basis of the intensity of the signal on the dot-blots, as described elsewhere [21]. Anal swab specimens to assess eligibility were assayed for HPV types 16 and 18 only. However, 4 participants were missing anal swab specimens from entry, or the specimen was unsatisfactory. Stored anal swab specimens obtained within 45 days of entry

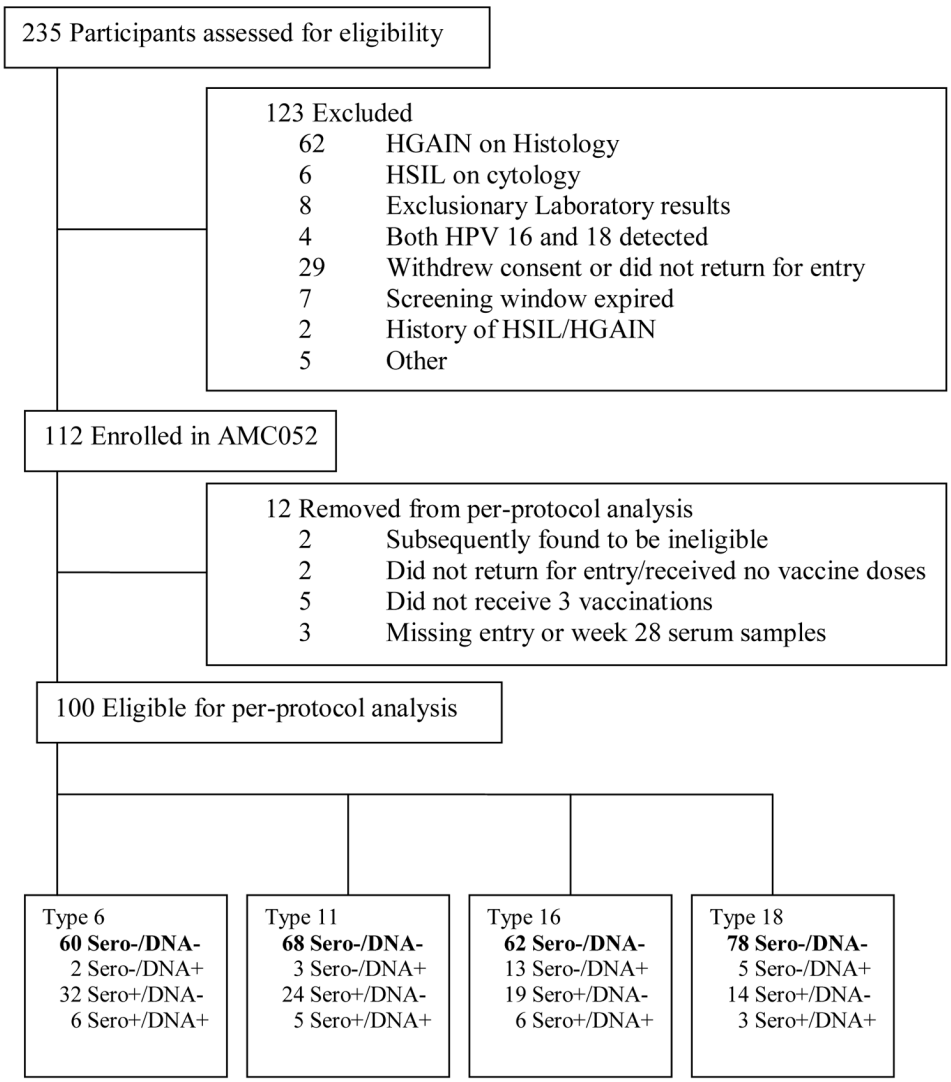

Figure 1. AIDS Malignancy Consortium (AMC) Protocol 052 study flow for all participants who provided informed consent. DNA, detection of type-specific anal HPV DNA by polymerase chain reaction; HGAIN, high-grade anal intraepithelial neoplasia; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; Sero, detection of type-specific serum anti-HPV antibodies above the assay cut-off.

to assess eligibility were reassayed for the full panel of HPV infections.

Serum samples were collected for assessment of antibody responses at entry and week 28. We analyzed vaccine type epitope-specific neutralizing anti-HPV antibodies with a competitive Luminex-based immunoassay (Merck Research Laboratories), as described elsewhere [22, 23]. These assays were performed under the direction of Merck Research Laboratories at PPD Vaccines and Biologics Laboratory.

Statistical considerations. Separate analyses were conducted for HPV types 6, 11, 16, and 18. The primary end point was seroconversion at week 28. This was defined as being seronegative at entry (ie, having no detectable type-specific anti-HPV antibodies or detectable antibodies below the prespecified cut-off for the assay) and seropositive at week 28 (ie, antibody concentrations above the assay cut-off). For inclusion in the primary per-protocol analysis for a given HPV type, participants were required to be seronegative for that type and to have no HPV DNA detected for that type by PCR of the anal swab at entry and screening. Participants were also required to have received 3 vaccine doses. The proportion of participants experiencing seroconversion and the accompanying exact binomial lower 1-sided 95% confidence interval (CI) were reported for types 6, 11, 16, and 18.

The study was designed so that using a 1-sided alternative type 1 error rate of 5%, a sample size of 40 eligible participants in the per-protocol analysis for a given type would provide ~80% power to exclude a seroconversion rate of ⩽45%, assuming that the seroconversion rate was 65%. Because this was a single-group pilot trial, the type-specific antibody responses

Table 1. Baseline Participant Characteristics

Characteristic	Participants (n = 112)
Race/ethnicity	
White, not Hispanic	70 (63)
Black, not Hispanic	14 (13)
Hispanic	20 (18)
Asian/Pacific Islander	6 (5)
>1 race	2 (2)
Age	
Median years (IQR)	44 (37–51)
Minimum years	22
Maximum years	61
CD4 count[a]	
⩾Median cells/μL (IQR)	517 (423–680)
Minimum cells/μL	144
Maximum cells/μL	1645
Nadir CD4 cell count[a]	
⩾Median cells/μL (IQR)	226 (143–337)
Minimum cells/μL	0
Maximum cells/μL	848
ART	
Current use	94 (84)
No current use	18 (16)
Plasma HIV-1 RNA level[a]	
<200 copies/mL	90 (83)
200–9,999 copies/mL	10 (9)
⩾10,000 copies/mL	9 (8)
Receptive anal sex[a]	
Never	4 (4)
0 partners within 6 months of entry[b]	34 (30)
1 partner within 6 months of entry	39 (36)
⩾2 partners within 6 months of entry	32 (29)
AIDS-defining illness	
History	14 (13)
No history	95 (87)

NOTE. Data are no. (%) of participants, unless otherwise indicated. ART, antiretroviral therapy; HIV-1, human immunodeficiency virus type 1.

[a] Data are missing for 3 participants who did not return for entry visit. An additional participant is missing a CD4 cell count from entry.

[b] One participant reported a history of recent anal sex but chose not to answer questions about recent sexual activity. This was imputed as 0 partners in the past 6 months.

were reported with 1-sided 95% CIs with precision for the lower bound of efficacy. Very few data existed on the rate of seropositivity in this population at the time of AIDS Malignancy Consortium Protocol 052 design [24, 25]. We assumed that 50% of participants would be excluded from the primary analysis because of seropositivity prior to vaccination, and 10% would have detectable HPV DNA for a given type at entry. The sample size was increased an additional 10% to account for attrition, for a planned sample size of 110 participants.

All 109 participants who received at least 1 vaccine dose were included in the safety analyses. The primary safety end point was occurrence of grade 3, 4, or 5 adverse events that were possibly, probably, or definitely related to vaccination, as determined by the site investigator. The proportion of participants experiencing such adverse events and corresponding 1-sided 95% CI were reported. Preplanned secondary safety analyses were to report the proportion of participants experiencing a grade ⩾2 adverse event related to vaccination and to report changes in plasma HIV-1 RNA level and CD4 cell count stratified by ART use.

The geometric mean concentration of anti-HPV antibodies and the accompanying 95% CI were calculated for the primary per-protocol population for each type as a prespecified secondary end point. Participants with undetectable antibody concentrations were nominally assigned a value of 50% of the detection limit for the assay. The plan in the protocol was to assess predictors of seroconversion using logistic regression. Because the number of participants without seroconversion was smaller than hypothesized by the protocol, the logistic regression analysis was not performed. In a post hoc analysis, we analyzed the relationship of CD4 cell count at entry, nadir CD4 count, ART use, age, and antibody concentration at entry, and HPV DNA detection to log-transformed antibody concentrations at week 28 was assessed using multivariable linear regression.

RESULTS

Study participants. One hundred twelve participants were enrolled from 9 January 2008 through 24 November 2008. The flow of study participants who gave informed consent for study participation is shown in Figure 1. Of note, of 123 participants excluded, 50% had HGAIN by histology and 5% had HSILs by cytology. Baseline characteristics of the 112 participants who entered the study are shown in Table 1. Anal cytology results were normal in 48%, atypical squamous cells of uncertain significance were present in 35%, and low-grade squamous intraepithelial lesions were detected in 17%. No anal intraepithelial neoplasia was found on high resolution anoscopy in 71% of participants, and 29% had low-grade anal intraepithelial neoplasia.

Twelve participants were not included in the per-protocol immunogenicity analyses; 2 did not receive any vaccine, 2 were subsequently found to be ineligible (1 did not receive any vaccine doses and 1 received all 3 vaccine doses), 4 received 1 vaccine dose but did not complete study follow-up, and 1 did not receive the third vaccine dose per protocol and remained in study follow-up. Three additional participants were missing either the baseline or week 28 serum samples.

Immunogenicity end points. Immunogenicity end points are shown in Table 2. The observed proportion of participants with seroconversion at week 28 in the primary per-protocol

Table 2. Geometric Mean Antibody Concentrations according to Baseline Seropositivity and Anal Human Papillomavirus (HPV) DNA Detection

HPV type, anti-HPV serology	Anal HPV DNA detection	No. of participants	No. (%) of participants seropositive at week 28	Baseline GMC, mMU/mL	Week 28 GMC, mMU/mL (95% CI)
Type 6					
Negative	Negative	60	59 (98)	6	357 (256–497)
Negative	Positive	2	2 (100)	7	47[a]
Positive	Negative	32	30 (94)	75	1050 (514–2143)
Positive	Positive	6	6 (100)	86	531 (351–804)
Type 11					
Negative	Negative	68	67 (99)	5	525 (412–669)
Negative	Positive	3	2 (67)	6	177[a]
Positive	Negative	24	24 (100)	46	1804 (1263–2576)
Positive	Positive	5	5 (100)	90	617 (154–2472)
Type 16					
Negative	Negative	62	62 (100)	6	1139 (849–1529)
Negative	Positive	13	12 (92)	6	504 (177–1434)
Positive	Negative	19	19 (100)	74	2067 (1145–3733)
Positive	Positive	6	6 (100)	117	1480 (280–7831)
Type 18					
Negative	Negative	78	74 (95)	5	181 (136–241)
Negative	Positive	5	5 (100)	5	183 (27–1248)
Positive	Negative	14	14 (100)	54	819 (413–1623)
Positive	Positive	3	3 (100)	63	840[a]

NOTE. CI, confidence interval; GMC, geometric mean concentration of anti-HPV antibodies; mMU/mL, milli-Merck units/mL.

[a] CIs not reported for subgroups with <5 participants.

analysis were for type 6 (98% [1-sided 95% CI, 92%]), type 11 (99% [1-sided 95% CI, 93%]), type 16 (100% [1-sided 95% CI, 95%]), and type 18 (95% [1-sided 95% CI, 89%]). All of these CIs excluded the 45% threshold and, thus, supported the primary hypothesis. When including all 100 participants in the per-protocol analysis without regard to baseline seropositivity or HPV DNA detection, 97%, 98%, 99%, and 96% had detectable antibodies at week 28 to types 6, 11, 16, and 18, respectively.

In a post hoc analysis, we analyzed the baseline predictors of antibody concentrations at week 28. For all types, higher baseline concentrations were significantly associated with higher concentrations at week 28. Current ART use at baseline was associated with higher anti-HPV 16 (0.38 $\log_{10}$ mMU/mL [95% CI, 0.05–0.72]) and anti-HPV 18 concentrations (0.36 $\log_{10}$ mMU/mL [95% CI, 0.03-.69]). Type-specific DNA detection on anal swab at entry was associated with lower anti-HPV 11 concentrations (-0.48 $\log_{10}$ mMU/mL [95% CI, -0.86 to -0.10]), lower anti-HPV 16 concentrations (-0.39 $\log_{10}$ mMU/mL [95% CI, -0.68 to -0.09]), and marginally with lower anti-HPV 6 concentrations (-0.46 $\log_{10}$ mMU/mL [95% CI, -0.95 to 0.02). CD4 cell counts, nadir CD4 count, and age were not associated with antibody concentrations after adjusting for the other variables in the model.

Anal cytology, histology, and HPV detection at week 28. Anal cytology and histology results were available for 105 participants at week 28. Cytology results were normal in 50 participants (48%) and unevaluable in 2 (2%) and indicated atypical squamous cells of uncertain significance in 33 (32%), low-grade squamous intraepithelial lesions in 16 (15%), and HSILs in 3 (3%). Twelve participants (11%) were found to have HGAIN on histology. HGAIN or HSILs was found at week 28 in 3 of 21 participants with HPV 16 detected at entry and in 1 of 8 participants with HPV 18 detected at entry. Table 3 summarizes incident and persistent HPV infection and progression to HGAIN from baseline to week 28.

Safety. There were no grade 3, 4, or 5 events that were related to vaccination among the 109 participants who received at least 1 vaccine dose (0% [1-sided 95% CI, 2.7%]). One subject died 22 weeks after the third vaccination because of a ruptured hepatocellular carcinoma caused by hepatitis C infection. This was reported to be unrelated to vaccination. Four other participants experienced grade 3 events not related to vaccination, including cholecystitis (with concomitant grade 4

Table 3. Week 28 Human Papillomavirus (HPV) DNA and High-Grade Anal Intraepithelial Neoplasia (HGAIN) at Week 28, According to Baseline Results

Week 28 result	Proportion (%) of participants
HPV 6 DNA detected at week 28	
All	9/100 (9)
Persistent infection	4/9 (44)
Incident infection	5/91 (5)
HPV 11 DNA detected at week 28	
All	9/100 (9)
Persistent infection	6/8 (75)
Incident infection	3/92 (3)
HPV 16 DNA detected at week 28	
All	13/100 (13)
Persistent infection	11/19 (58)
Incident infection	2/81 (2)
HPV 18 DNA detected at week 28	
All	3/100 (3)
Persistent infection	2/7 (29)
Incident infection	1/93 (1)
HGAIN or HSILs at week 28	
All	13/105 (12)
Progression from no AIN	6/73 (10)
Progression from low-grade AIN	7/32 (22)

NOTE. No week 28 results are available on 7 participants who were no longer in study follow-up. Five HPV DNA results were either missing or unsatisfactory. Persistent infection is the number with DNA detected at week 28 among those with DNA of the same HPV type detected at entry. Incident infection is the number with DNA detected at week 28 among those with DNA of that type not detected at entry. Progression from no AIN is the number of HGAIN or HSIL among those with no AIN on histology prior to entry. Progression from low-grade AIN is HGAIN or HSIL among others. AIN, anal intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion.

serum glucose and lipase elevations), nonseptic arthritis, headache, and leukopenia. Grade 2 injection site reactions were observed in 9 (8%). Other grade 2 reactions that were related to vaccination were observed in 5 (5%), including 1 participant with recurrent tinnitus possibly related to vaccination, leading to withholding the third vaccine dose. Grade 1 or 2 injection site reactions were observed after the first, second, and third vaccinations in 18%, 17%, and 12% of participants, respectively.

For those receiving ART at baseline, the median CD4 counts at entry, week 4, week 12, and week 28 were 514, 540, 558, and 591 cells/μL, respectively. Plasma HIV-1 RNA levels in this subgroup were <200 copies/mL in 96%, 97%, 97%, and 93% of participants, respectively. For those not receiving ART, the CD4 cell counts were 544, 528, 517, and 513 cells/μL, respectively, and the geometric mean plasma HIV-1 RNA levels in this subgroup were 3.6, 3.4, 3.4, and 3.4 $\log_{10}$ copies/mL, respectively.

DISCUSSION

In this pilot study, the data suggest that the quadrivalent HPV vaccine is safe and elicits anti-HPV antibodies in a high proportion of HIV-1–infected men. The proportion of men exhibiting seroconversion was 95% or greater for each of the HPV types included in the vaccine. For those with preexisting anti-HPV antibodies, the vaccine induced a marked increase in antibody concentrations (Table 2). No serious adverse events attributable to vaccination were observed. The injection site reactions were mild or moderate and were similar to other commonly administered vaccines for HIV-1–infected adults. There were no obvious effects on CD4 cell counts or HIV-1 levels. The CD4 cell counts increased slightly for those receiving ART and decreased slightly for those not receiving ART.

The proportion of participants exhibiting seroconversion was higher than hypothesized during the study design. Approximately 65% of HIV-1–infected subjects experience antibody conversion after hepatitis A vaccination [14], and 18%–71% experience conversion after hepatitis B vaccination [15, 16]. The markedly higher antibody conversion to the quadrivalent HPV vaccine may be attributable to differences in the populations studied; AIDS Malignancy Consortium Protocol 052 participants had a median CD4 count of 517 cells/L, and 92% had a plasma HIV-1 RNA level <10,000 copies/mL. We also excluded patients with current or past HGAIN at study entry. Alternatively, these apparent differences may be attributable to differences in assay sensitivity or the inherent immunogenicity of the vaccines.

The antibody concentrations induced by this vaccine in the primary per-protocol population were lower than those reported in other studies. For example, the anti-HPV 16 antibody concentrations are ~50% those of HIV-1–uninfected women aged 34–45 years [26], and 40% of those reported for HIV-1–uninfected men and women aged 16–26 years [27]. The clinical significance of lower antibody concentrations is unknown because there is no established threshold correlating with efficacy in any population studied to date. Interestingly, the concentrations were similar to those of HIV-1–uninfected men who have sex with men aged 18–26 years [12], suggesting that the lower antibody concentrations were not a direct effect of HIV-1 infection. We did not observe a relationship between age, CD4 cell counts, or nadir CD4 cell counts and antibody concentrations at week 28, but we did observe higher anti-HPV 16 and anti-HPV 18 antibody concentrations in those receiving ART. Further study is clearly needed to determine the role of HIV-1 status, sexual behavior, and other potentially unmeasured factors that may determine immune response to the quadrivalent HPV vaccine. These regression results should be interpreted with caution because this was a post hoc analysis and these results were not controlled for multiple comparisons.

The quadrivalent HPV vaccine is known to be a preventive vaccine and does not treat or prevent disease from prevalent infection with vaccine types [10, 11]. For a given vaccine type, 60%–78% of the per-protocol population were both seronegative and HPV DNA negative in the anal canal. This implies that a high proportion of men may potentially benefit from an HPV preventive vaccine despite being older than previously studied populations and despite having significant prior exposure to HPV infections through receptive anal sex and multiple sexual partners [12, 27]. However, efficacy would need to be confirmed by clinical trials.

This study has several limitations. The clinical significance of these findings is unknown. This study was not designed to establish the efficacy of this vaccine for preventing HPV infection or HGAIN in this population. This study had entry criteria that limit the generalizability of these results. For example, this study did not enroll patients with low CD4 counts or many participants with high plasma HIV-1 RNA levels. Nearly 30% of men entering screening were excluded because of HGAIN or HSILs found during screening, and many others were likely not approached for participation because of prior HGAIN. Further studies are needed to establish the safety and immunogenicity of the vaccine in these groups.

Anal cancer and its precursor, HGAIN, are relatively common problems in HIV-1–infected men. In this multicenter, single-arm pilot study, the quadrivalent HPV vaccine was safe and highly immunogenic in HIV-1–infected men. These data support further study of HPV vaccination in HIV-1–infected men in conjunction with anal cancer screening as measures to reduce the incidence of anal cancer.

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