High Prevalence of Anal High-Grade Squamous Intraepithelial Lesions, and Prevention Through Human Papillomavirus Vaccination, in Young Men Who Have Sex With Men Living With Human Immunodeficiency Virus

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Background. Men who have sex with men (MSM) are at high risk for human papillomavirus (HPV)–related anal cancer. Little is known about the prevalence of low-grade squamous intraepithelial lesions (LSILs) and the anal cancer precursor, high-grade squamous intraepithelial lesions (HSILs), among young MSM with HIV (MSMLWH). HPV vaccination is recommended in this group, but its safety, immunogenicity, and protection against vaccine-type HPV infection and associated LSILs/HSILs have not been studied.

Methods. Two hundred and sixty MSMLWH aged 18–26 years were screened at 17 US sites for a clinical trial of the quadrivalent (HPV6,11,16,18) HPV (qHPV) vaccine. Those without HSILs were vaccinated at 0, 2, and 6 months. Cytology, high-resolution anoscopy with biopsies of lesions, serology, and HPV testing of the mouth/penis/scrotum/anus/perianus were performed at screening/month 0 and months 7, 12, and 24.

Results. Among 260 MSMLWH screened, the most common reason for exclusion was detection of HSILs in 88/260 (34%). 144 MSMLWH were enrolled. 47% of enrollees were previously exposed to HPV16. No incident qHPV type–associated anal LSILs/HSILs were detected among men naive to that type, compared with 11.1, 2.2, 4.5, and 2.8 cases/100 person-years for HPV6,11,16,18–associated LSILs/HSILs, respectively, among those previously exposed to that type. qHPV was immunogenic and safe with no vaccine-associated serious adverse events.

Conclusions. 18–26-year-old MSMLWH naive to qHPV vaccine types were protected against incident qHPV type–associated LSILs/HSILs. Given their high prevalence of HSILs, there is an urgent need to vaccinate young MSMLWH before exposure to vaccine HPV types, before initiating sexual activity, and to perform catch-up vaccination.

Keywords. anal human papillomavirus infection; quadrivalent HPV vaccine; anal squamous intraepithelial lesions; men who have sex with men; human immunodeficiency virus.

People living with human immunodeficiency virus (HIV; PLWH) are at elevated risk of anogenital human papillomavirus (HPV) infection and related cancers [1, 2]. Men who have sex

with men living with HIV (MSMLWH) are at particularly high risk of anal cancer [3]. We previously reported that more than 95% of 18–26-year-old MSMLWH had anal HPV infection [4]. However, no previous studies have characterized the prevalence of histologic high-grade squamous intraepithelial lesions (hHSILs), the anal cancer precursor, in young MSMLWH.

HPV vaccination is routinely recommended for the prevention of HPV-associated cancers and genital warts in males and females with a target age of 11–12 years and catch-up vaccination to 26 years. Licensed HPV vaccines are effective in preventing HPV infection prior to exposure and vaccination prior to initiating sexual activity optimizes vaccine efficacy

[5–9]. Given the risk of anal cancer in MSMLWH, HPV vaccination has been strongly recommended in men up to 26 years of age [10]. While HPV vaccination has been shown to be safe, well tolerated, and immunogenic in PLWH [11–19], some studies have demonstrated lower titers in PLWH compared with similarly aged individuals without HIV [14, 18]. No studies have examined vaccine efficacy as measured by the prevention of incident-persistent HPV infection or incident vaccine type–associated HSILs in PLWH younger than 26 years of age. One study of MSMLWH older than 26 years failed to show efficacy in the prevention of anal HPV infection and incident HSILs [12], likely reflecting a high degree of prior sexual exposure to vaccine HPV types. Given their high risk of anal HPV infection, it is critical to understand the prevalence of anal HSILs and the ability of the vaccine to prevent anal HPV infection and HSILs among young MSMLWH.

METHODS

We performed a phase II, open-label, multicenter trial of the quadrivalent HPV (qHPV; (HPV6,11,16,18) vaccine (Merck and Company, Kenilworth, NJ) in 13- to 26-year-old MSMLWH. For ethical reasons, we did not have a placebo control arm in this study. Our primary objectives were as follows (1) to compare incident HPV 6,11,16,18 infection and HPV 6,11,16,18–associated perianal/anal disease among young MSMLWH with or without exposure to these HPV types prior to vaccination and (2) to compare the data among MSMLWH without evidence of prior HPV exposure to similarly aged HIV-negative men who have sex with men (MSM) in the placebo arm of the Merck V503-020 protocol (NCT00090285) [5] without evidence of prior exposure. The study was conducted by the AIDS Malignancy Consortium (AMC) in collaboration with the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN). Participants were recruited between 2012 and 2015 from 15 US sites. The institutional review board for each site approved the study. Inclusion criteria included male at birth, documented HIV-1 infection, age 13 to 26 years, and at least 1 male sexual partner. We excluded those with cytologic HSIL (cHSIL), atypical squamous cells–cannot rule out HSIL (ASC-H), or histologic HSIL (hHSIL) on screening biopsy. These individuals were referred for treatment and offered the qHPV vaccine.

At screening, participants had a complete medical history and physical examination. We collected separate swabs from the anal canal, perianus, and penis/scrotum for HPV DNA testing. We performed high-resolution anoscopy (HRA) with biopsy of suspected lesions. We enrolled eligible participants within 45 days of screening and administered a questionnaire assessing lifestyle habits. We obtained blood to measure CD4/CD8 levels, HIV viral load, and HPV serology; collected oral

Scope (Procter & Gamble) swish/gargle mouthwash specimens for HPV testing and administered the qHPV vaccine at 0, 2, and 6 months. After each injection, participants completed a vaccine report card documenting signs and symptoms and had telephone follow-up to assess for adverse events (AEs). At month 7, we collected blood for CD4/CD8 levels and HIV viral load (VL). At months 7, 12, 18, and 24, we collected blood for HPV serology; anal, perianal, and penile/scrotal swabs; and oral gargles for HPV testing, and performed HRA with biopsy of suspected lesions.

HPV Testing
HPV testing was performed on swabs and rinses with MY09/MY11 L1 consensus primers, as described previously [4]. HPV testing was performed on formalin-fixed paraffin-embedded (FFPE) biopsy samples using sterile technique to avoid cross-contamination, including changing gloves and blades between samples. The first section (4 µm) was set aside and the next 20-µm section was placed into a sterile Eppendorf tube. For DNA preparation we used the Invitrogen by Thermo Fisher Scientific RecoverAll Total Nucleic Acid Isolation Kit (AM1975; Vilnius, Lithuania) following the manufacturer's instructions. Forty amplification cycles were performed, followed by dot-blotting and probing of amplification mixtures as described previously [4]. Overall, 483 of 690 (70%) anal biopsies collected were retrieved and tested for HPV DNA.

HPV Serology
Sera were tested for antibodies to HPV6,11,16,18 using a competitive Luminex immunoassay [5]. Results were expressed as milliMerck units (mMU)/mL, with positivity cutoffs of 11/8/11/10 mMU/mL, respectively.

Statistical Analysis
We defined being naive to a specified HPV type as seronegative at baseline and DNA-negative at baseline and month 7 at all anatomic locations. We analyzed 2 groups: (1) naive, per-protocol (completed the vaccination series per protocol) and (2) previously exposed (seropositive at baseline or DNA-positive at any anatomic site at either baseline or month 7), per protocol. We compared incident-persistent qHPV type infection and incident qHPV type–associated hLSILs/hHSILs between naive and previously exposed participants. We also compared them with similarly aged naive per-protocol HIV-negative MSM participating in the placebo arm of the Merck V503-020 study (NCT00090285) [5].

Case counting for incident hLSIL/hHSIL analysis occurred at months 12, 18, or 24. Analyses were restricted to those with both a histology and anal biopsy HPV DNA result at a given visit. Cases were considered to be qHPV type–related if HPV6,11,16,18 were detected in the FFPE specimen.

Incident-persistent HPV infection was defined as having a positive HPV test at the same anatomic site at 2 consecutive visits after month 7. For this analysis, the previously exposed category only included those who were seropositive and DNA-negative for the specific HPV type. Participants could be in more than 1 HPV type–specific exposure category.

We computed HPV type–specific event rates for incident HPV and lesion endpoints with corresponding 95% confidence intervals (CIs) using Poisson calculations (sample size calculations are found in the Supplementary Material). Given the number of 0 event rates, we compared exposure groups using exact Poisson calculations. *P* values were 2-sided for comparisons of naive groups with previously exposed groups, whereas comparisons to historical controls were a priori selected to be 1-sided.

RESULTS

Although MSMLWH as young as 13 years old could enroll, all participants were 18–26 years old. We enrolled participants at 17 ATN and AMC study sites. A total of 260 MSMLWH were screened and 111 MSMLWH failed screening, mostly due to ASC-H on cytology, cHSILs, or hHSILs (n = 93). Overall, 34% were excluded for cHSILs or hHSILs at baseline. The cytology and histology results of the screened population are shown in Supplementary Table 1.

A total of 149 MSMLWH were enrolled (Figure 1): one withdrew prior to treatment, 4 were ineligible, 144 received the first vaccine injection, 141 received the first 2 injections, and 138 received all 3 injections. Adherence to the visit schedule was 85–100%. Of the 38 MSMLWH who received at least 1 injection but did not attend the month 24 visit, 24 were lost to follow-up, 8 withdrew consent, 3 relocated, 2 were incarcerated, and 1 experienced an AE (grade 3 rectal pain) that led to study withdrawal.

Most participants were aged 22–26 years (mean, 23 years), 60% were African-American, and 45% were smokers. Eighty-two percent reported receptive anal intercourse within the last 6 months, of whom 46% reported consistent condom use (Table 1). The median nadir CD4 count was 309 cells/mL, median enrollment CD4 level was 594 cells/mL, and 9% had an HIV VL of more than 400 copies/mL.

A high proportion of enrollees had LSILs: 35% had cLSILs and 58% had histologic LSILs (hLSILs). Baseline serology and DNA status are shown in Table 2. The proportions who were naive to HPV6,11,16,18 were 22%, 48%, 53%, and 66%, respectively. We examined the impact of testing for HPV DNA at sites other than the anal canal on classification of participants as being naive. HPV6,11,16,18 DNA were detected in the penile or oral sample, but not the anus, in 2 of 132 (1.5%), 1 of 131 (0.8%), 3 of 131 (2.3%), and 1 of 132 participants (0.8%), respectively.
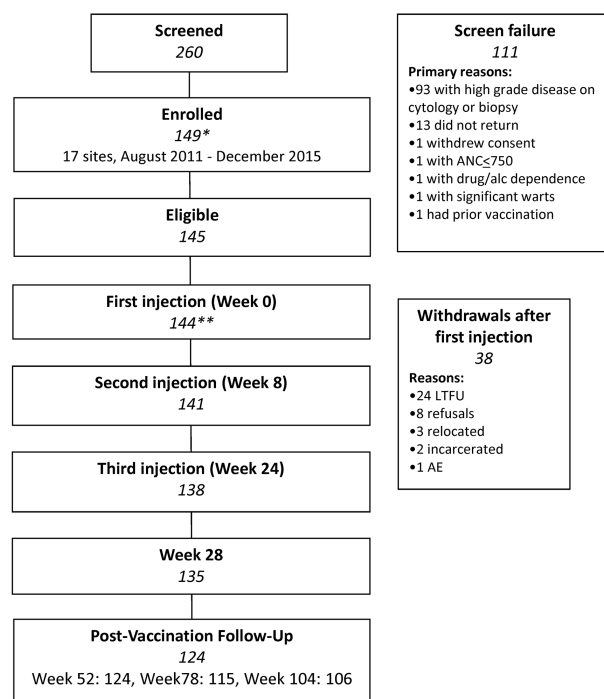

Figure 1. Participant flow in AMC-072. *Four patients were enrolled in error: No treatment per protocol criteria (n = 1), HPV vaccine prior to screening (n = 1), AIN 3 on screening (n = 1), not on HAART for 90 days prior to entry (n = 1). **One patient withdrew/refused prior to beginning protocol therapy. Abbreviations: AE, adverse event; alc, alcohol; AMC, AIDS Malignancy Consortium; AIN, Anal intraepithelial neoplasia; ANC, Absolute neutrophil count; HAART, highly active antiretroviral therapy; HPV, human papillomavirus; LTFU, lost to follow-up.

Geometric mean titers generated by qHPV among naive and previously exposed participants at months 7, 12, 18 and 24 are shown in Figure 2. All seroconverted at month 7 to HPV6, 11, and 16, and 99% seroconverted to HPV18. We compared month 7 and month 24 titers with HPV6,11,16,18 by age (<24, ≥24 years), nadir CD4 (≤350, >350 cells/mm^3), current CD4 (≤500, >500 cells/mm^3), and HIV VL. For baseline seronegative participants, there was a significant difference in titers for HPV18 at month 7 for those with an HIV VL of 75 or less versus more than 75 copies/mL (median, 333 vs 123; *P* = .011), but there were no other significant differences. Titers were higher for all vaccine types at months 7, 12, 18, and 24 among previously exposed versus naive participants.

Table 3 demonstrates incident hLSILs or hHSILs combined and incident anal/perianal hHSILs in the naive per-protocol and previously exposed per-protocol groups by qHPV vaccine type. The overall incidence of any hHSIL was 29.5 (95% CI: 20.6–42.2) per 100 person-years (PY) regardless of HPV type, and overall incidence of anal/perianal hHSILs/hLSILs was 61.3 (95% CI: 39.1–96.1) per 100 PY. Among the naive per-protocol group, there were no incident cases of qHPV vaccine–related hLSILs/hHSILs up to month 24. Incident lesions associated with each of the 4 vaccine types were detected in the previously exposed per-protocol groups, but the differences between naive

Table 1. Demographics of Men Who Have Sex With Men With HIV Enrolled Into the qHPV Vaccine Study

Variable	Total N[a]	Values
Age (years)	144	
22–26		115 (80)
18–21		29 (20)
Age, median (range), years	144	23 (18–26)
Race	134	
White		46 (34)
Black		80 (60)
Other		8 (6)
Hispanic ethnicity	144	38 (26)
Current smoking (some days/every day)	137	62 (45)
Last receptive anal sexual intercourse[b]	134	
Over 6 months ago		23 (17)
1–6 months ago		36 (27)
Within the past month		75 (56)
Sexual intercourse with male partner, past 6 months (yes)	137	124 (91)
Number of male sexual partners, past 6 months	137	
0		13 (9)
1		48 (35)
≥2		76 (55)
Number of receptive anal male sexual partners, past 6 months	137	
0		25 (25)
1		54 (54)
≥2		58 (58)
Frequency of condom use during receptive anal sex with male partner, past 6 months	137	
No anal sex past 6 months		25 (18)
Every time		51 (37)
Sometimes/never		61 (45)
Number of oral male sexual partners, past 6 months	136	
0		15 (11)
1		54 (40)
≥2		67 (49)
Frequency of condom use during oral sex, past 6 months	137	
No oral sex past 6 months		15 (11)
Sometimes/always		36 (26)
Never		86 (63)
Had sexual intercourse with female partner, past 6 months (yes)	137	8 (6)
Chlamydia and/or gonorrhea (urethral) infection at baseline (yes)	141	6 (4)
Nadir CD4+ count (cells/mm^3)	144	
≤350		83 (59)
>350		57 (41)
Nadir CD4+ count, median (range), cells/mm^3	140	309 (10–785)
Enrollment CD4+ count (cells/mm^3)	144	
≤350		14 (10)
>350		130 (90)
Enrollment CD4+ count, median (range), cells/mm^3	144	594 (237–1520)
HIV viral load (copies/mL)	144	
<400		131 (91)
≥400		13 (9)
HIV viral load, median (range), copies/mL	144	0 (0–63000)

Data are presented as n (%) unless otherwise indicated. Abbreviations: HIV, human immunodeficiency virus; qHPV, quadrivalent human papillomavirus.

[a]When data are missing, the sample size is <144; 7 participants did not complete the behavioral questionnaire.

[b]Three participants denied ever having receptive anal intercourse and are not included.

per-protocol and previously exposed per-protocol groups were not statistically significant. There was a statistically significant reduction in incident HPV16-associated hHSILs in the naive group compared with the previously exposed group (*P* = .014).

There were no statistically significant differences between the naive per-protocol and previously exposed per-protocol groups (Table 4). There were no incident-persistent infections in the previously exposed per-protocol group. There were 3 cases of

Table 2. Baseline HPV Serostatus and HPV DNA Status

	HPV6	HPV11	HPV16	HPV18	HPV 6, 11, 16, or 18
Seropositive/DNA-positive	51 (35)	15 (10)	15 (10)	4 (3)	111 (77)
Seropositive /DNA-negative	42 (29)	49 (34)	35 (24)	35 (24)	0 (0)
Seronegative/DNA-positive	17 (12)	9 (6)	16 (11)	8 (6)	31 (22)
Seronegative/DNA-negative	32 (22)	69 (48)	76 (53)	95 (66)	0 (0)
Sero-missing/DNA-negative	2 (1)	2 (1)	2 (1)	2 (1)	2 (1)

Data are presented as n (%). "Seropositive" DNA-positive indicates positive for specified HPV type in any of anal, perianal, penile/scrotal, or oral specimens. The denominator for percentages is 144 participants. Abbreviation: HPV, human papillomavirus.

incident-persistent HPV16 infection in the naive per-protocol group: 1 had HPV6 at baseline by biopsy and anal swab and HPV16 detected at visits 5 and 6; 1 participant had no qHPV types at baseline but had HPV16 detected on anal swab at visits 4, 5, and 6; and 1 participant had HPV6 at baseline on anal biopsy and HPV16 detected at visits 4, 5, and 6. None had HPV16-associated lesions. The 1 incident HPV18 infection was penile/scrotal.

Table 5 shows incident-persistent qHPV vaccine type–associated anal/perianal hLSILs/hHSILs in the naive per-protocol, vaccinated AMC-072 group compared with historical data from naive, per-protocol 18–26-year-old HIV-negative MSM randomized to the V501-020 study placebo arm [5]. Type-associated hLSIL/hHSIL was lower in the AMC-072 group compared with the V501-020 group for all 4 qHPV types. The AMC-072 group had lower incident-persistent HPV infection
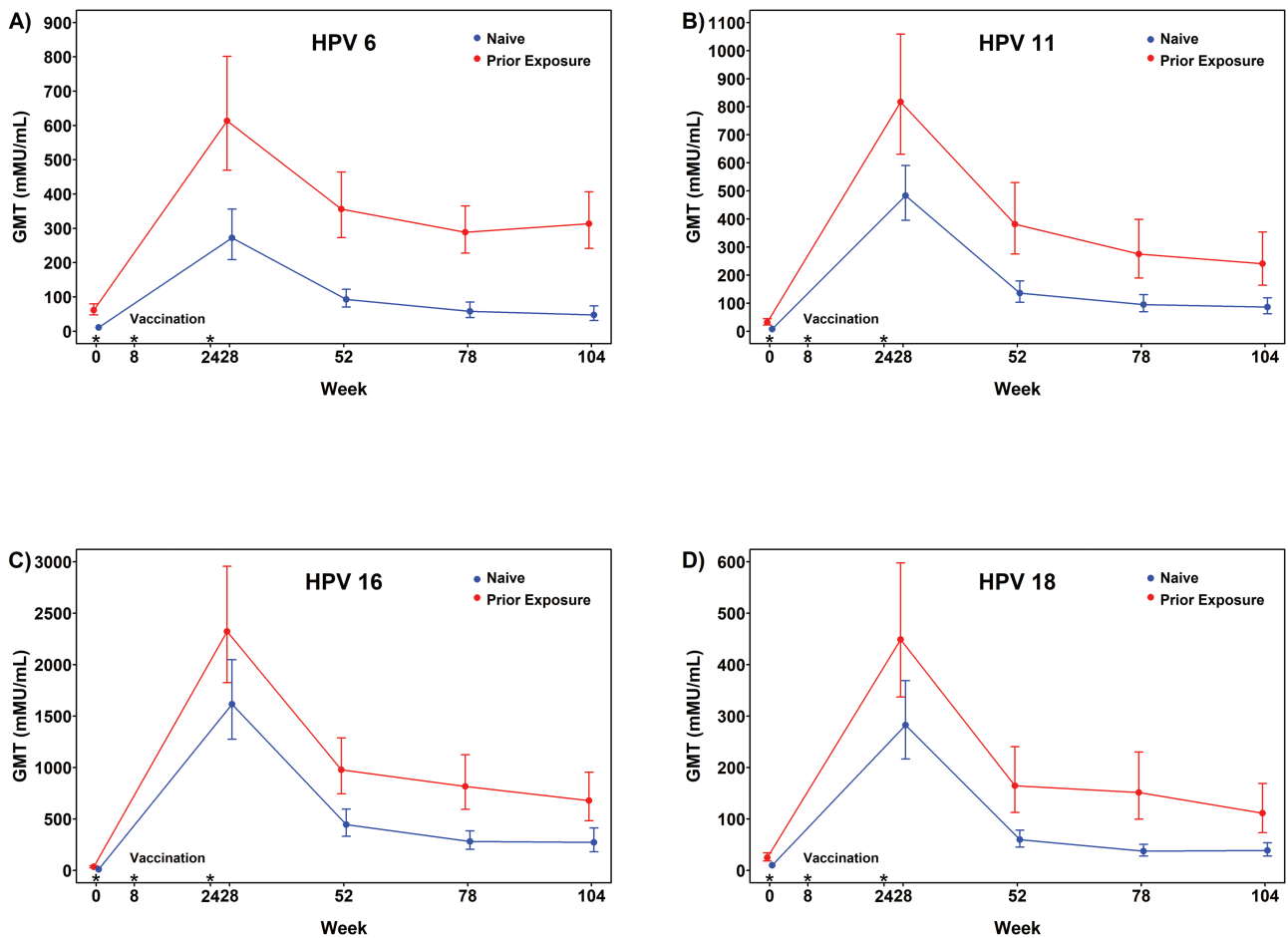

Figure 2. Geometric mean (95% confidence interval) titers to HPV 6 (*A*), 11 (*B*), 16 (*C*), and 18 (*D*) among naive and previously exposed 18–26-year-old men who have sex with men living with HIV, up to 2 years after initiation of vaccination. Titers in participants naive to a qHPV vaccine HPV type are shown in blue. Titers in participants previously exposed to that HPV type are shown in red. Abbreviations: GMT, geometric mean titer; HIV, human immunodeficiency virus; HPV, human papillomavirus; qHPV, quadrivalent human papillomavirus. Asterisks show when vaccine doses were administered.

Table 3. Low-Grade Squamous Intraepithelial Lesions/High-Grade Squamous Intraepithelial Lesions and High-Grade Squamous Intraepithelial Lesions in the Per-Protocol Population Among those Naive at Baseline Compared With Those Already Exposed

Endpoint	Per-Protocol: Naive to Specified HPV Type[a]				Per Protocol: Previously Exposed to Specified HPV Type[a]				P[b]
	No. Included in Analyses	No. of Affected Participants	Person-Years at Risk	Events per 100 Person-Years at Risk	No. Included in Analyses	No. of Affected Participants	Person-Years at Risk	Events per 100 Person-Years at Risk	
Anal/perianal LSILs/ HSILs[c] related to									
HPV6	15	0	25.0	0.0	34	6	53.9	11.1	.112
HPV11	35	0	55.2	0.0	28	1	45.1	2.2	.224
HPV16	39	0	65.3	0.0	29	2	44.0	4.5	.079
HPV18	47	0	75.6	0.0	23	1	36.3	2.8	.162
Any qHPV[d]	9	0	14.7	0.0	34	7	54.4	12.9	.231
Anal/perianal HSILs[e] related to									
HPV6	15	0	25.0	0.0	56	9	86.5	10.4	.064
HPV11	35	0	55.2	0.0	36	1	57.6	1.7	.745
HPV16	39	0	65.3	0.0	32	4	47.4	8.4	.014
HPV18	47	0	75.6	0.0	24	1	37.6	2.7	.166
Any qHPV[d]	9	0	13.4	0.0	63	14	96.2	14.6	.123

Abbreviations: HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; qHPV, quadrivalent human papillomavirus.

[a]Based on serum at baseline and DNA from baseline and month 7 from any anatomical site. Participants could be in >1 exposure category.

[b]Naive and previously exposed group comparison of event rates based on exact Poisson calculations (2-sided test).

[c]Analyses required having both a histologic result and anal biopsy HPV DNA determination at a given visit. Participants with type-specific anal LSILs at baseline were excluded from this analysis, and HSIL at screening was an exclusion criterion. Case counting occurred after month 7 at months 12, 18, and 24.

[d]Analyses required participants to be naive to all 4 types at baseline.

[e]Analyses required having both a histologic result and anal biopsy HPV DNA determination at a given visit. Case counting occurred after month 7 at months 12, 18 and 24.

rates (1.8, 0.0, 2.9, 0.7 per 100 PY for HPV6,11,16,18, respectively) than the V501-020 group (4.5, 1.7, 4.9, 2.7 per 100 PY for HPV6,11,16,18, respectively). There were no statistically significant differences between vaccinated AMC-072 groups and V501-020 groups for incident disease or incident-persistent qHPV type infection associated with each qHPV type, but vaccinated AMC-072 participants had significantly reduced disease in a combined analysis of all 4 qHPV types.

Adverse events were reported by 72% of participants; 92% were grade 1 or 2 and the most common (26%) was injection site reaction (Table 6). Of the 11 serious AEs in 5 participants, none were related to vaccination. The median CD4 level did not decrease and the HIV VL did not increase from baseline to month 7.

DISCUSSION

Consistent with our previous report showing high rates of anal HPV infection in MSMLWH [4], here we report that more than 34% of this population had anal HSILs at screening for this qHPV vaccination study. Further, among those without anal HSILs who were enrolled in the study, 74% had LSILs. The significance of having an HSIL at a young age is unknown because the incidence of anal cancer is low in those younger

Table 4. Incident-Persistent Infection in the Study Population

Endpoint: Persistent Infection[a]	Per-Protocol Naive to Specified HPV Type[b]				Per-Protocol Previously Exposed to Specified HPV Type[b]				P[c]
	No. Included in Analyses	No. of Affected Participants	Person-Years at Risk	Events per 100 Person-Years at Risk	No. Included in Analyses	No. of Affected Participants	Person-Years at Risk	Events per 100 Person-Years at Risk	
HPV6	29	1	55.5	1.8	15	0	29.0	0.0	.671
HPV11	55	0	108.6	0.0	33	0	64.9	0.0	>.999
HPV16	54	3	102.9	2.9	23	0	46.0	0.0	.386
HPV18	74	1	142.9	0.7	23	0	46.1	0.0	.622

No. = number of participants with ≥2 follow-up visits. Abbreviation: HPV, human papillomavirus.

[a]Must have had a positive HPV test at 2 consecutive visits after month 7 (months 12, 18, and 24) at any site (swab DNA anal/perianal, penile/scrotal, oral) and persistent at same site (anal/perianal, penile/scrotal, oral).

[b]Based on serum at baseline and DNA from baseline and month 7 from any anatomical site. By definition, the previously exposed category included only those who were seropositive, DNA-negative for the specific HPV type. Participants could be in >1 exposure category.

[c]Naive and previously exposed group comparison of event rates were based on exact Poisson calculations (2-sided test).

Table 5. Low-Grade Squamous Intraepithelial Lesions or High-Grade Squamous Intraepithelial Lesions in the Merck 020 Per-Protocol Placebo Group Compared With the AMC-072 Per-Protocol Naive Vaccinated Group

Endpoint: Anal/ Perianal LSIL/HSIL[a] Related to	Per-Protocol Merck 020 Placebo Group[b]				Per-Protocol AMC-072 Naive Vaccinated Group				P[c]
	No. Included in Analyses	No. of Affected Participants	Person-Years at Risk	Events per 100 Person-Years at Risk	No. Included in Analyses	No. of Affected Participants	Person-Years at Risk	Events per 100 Person-Years at Risk	
HPV6	144	10	298.5	3.4	15	0	25.0	0.0	.447
HPV11	144	6	298.2	2.0	35	0	55.2	0.0	.361
HPV16	170	6	341.9	1.8	39	0	65.4	0.0	.350
HPV18	193	4	387.4	1.0	47	0	75.6	0.0	.490
HPV6, 11, 16, or 18[d]	208	24	411.6	5.8	58	0	93.0	0.0	.008

Abbreviations: AMC, AIDS Malignancy Consortium; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; qHPV, quadrivalent human papillomavirus.

[a]Analyses required having both histology and anal biopsy HPV DNA determination at a given visit. AMC-072 participants with qHPV type–specific AIN1 or perianal condyloma at baseline were removed (HSIL was an exclusion criteria); "baseline" DNA HPV type based on visits 0 and 3. Case counting occurred after month 7 at visits 4, 5, and/or 6.

[b]The per-protocol Merck 020 placebo group were HIV-negative men who have sex with men, were naive for a given qHPV type, and did not have LSIL or HSIL at baseline.

[c]Merck placebo and AMC-072 naive group comparison of event rates based on exact Poisson calculation (1-sided test).

[d]Consistent with the reported Merck V503-020 combined endpoint, analysis of all participants who were eligible for ≥1 of the individual type-specific analyses. A participant would be counted more than once if multiple lesions of different HPV types developed.

than 26 years and prospective studies of anal HSILs in this group have not been performed. Studies are needed to inform guidelines to recommend screening, such as the Anal Cancer/ HSIL Outcomes Research (ANCHOR) Study, which is designed to determine if screening for and treating anal HSILs is effective in reducing the incidence of anal cancer. Similar to other, older populations [20], anal cytology in young MSMLWH had

limited sensitivity for the detection of HSILs (Supplementary Table 1), unless the threshold for screening included Atypical squamous cells of undetermined significance (ASC-US), and anal cytology underestimated the level of disease detected.

We found that, among participants without anal HSILs detected at screening, a substantial proportion had already been exposed to qHPV vaccine types, particularly HPV6 (78%) and 16 (47%). However, despite the high rate of prior exposure to vaccine HPV types, more than half of young MSMLWH were DNA- and seronegative for HPV16, the type predominantly associated with anal cancer, and therefore could be protected if vaccinated.

Little is known about the performance of the qHPV vaccine in young MSMLWH. Similar to data reported in older women living with HIV [16], our data demonstrate that there were no cases of incident qHPV vaccine type–associated hLSILs or hHSILs among naive vaccinated individuals during the 2-year duration of the study. There was also a statistically significant reduction in HPV16-associated hHSILs among individuals naive to HPV16 compared with previously exposed individuals, a clinically important finding given the dominant role of HPV16 in the pathogenesis of anal cancer. The significance of the 3 cases of incident-persistent HPV16 infection is not clear at this time. Further follow-up would have been needed to determine if this became associated with an incident lesion.

Most of the comparisons between naive and previously exposed populations were not statistically significant. Our ability to demonstrate vaccine efficacy was limited by the small sample size of analyzable participants for each qHPV vaccine type. Factors limiting the size of our analyzable study population included a lower-than-expected number of HPV-naive individuals by type, since the sample size projected 100 naive individuals per type, and a lower-than-expected rate of events among those who had been exposed to each HPV type. Some participants were excluded from infection and disease outcome

Table 6. Adverse Events in Vaccinated Participants in AMC-072

	Affected Participants, n (%)
Adverse events	103 (71.5)
Affecting >5%	
Diarrhea	8 (5.6)
Injection site reaction	37 (25.7)
Infection and infestations—other	9 (6.3)
Neutrophil count decreased	10 (6.9)
Cough	10 (6.9)
Skin and subcutaneous tissue disorders—other	13 (9.0)
Related adverse events[a]	44 (30.6)
Affecting >5%: injection site reaction	37 (25.7)
Any grade 3 adverse event[b]	6 (4.2)
Grade 3 injection site reaction	3 (2.1)
Serious adverse events	5 (3.5)
Full listing	
Skin infection	2 (1.4)
Gum infection	1 (0.7)
Vomiting	1 (0.7)
Nausea	1 (0.7)
Homicidal ideation	1 (0.7)
Suicidal ideation	1 (0.7)
Suicide attempt	1 (0.7)
Potentially related serious adverse events	0 (0)

Abbreviation: AMC, AIDS Malignancy Consortium.

[a]Related adverse events were those that were deemed definitely, probably, or possibly related to vaccine.

[b]Grade 3 was the highest severity for any treatment-related adverse event.

analyses since those with the prevalent endpoint were removed for the incidence calculation and we did not have access to all biopsies for HPV DNA determination.

We also compared our data in the naive vaccinated AMC-072 group with a historical control consisting of the naive placebo group of the V503-020 study. The AMC-072 participants were MSMLWH while the V503-020 participants were HIV-negative MSM. Compared with the vaccinated AMC-072 group, at baseline the V501-020 placebo group was younger, had fewer sexual partners, and had no evidence of any anogenital lesions. The groups also differed by race, with a higher proportion of AMC-072 participants being African-American. Despite being a lower-risk population than our AMC-072 participants, the V501-020 placebo group had a higher incidence of hHSILs associated with all 4 qHPV types than the vaccinated AMC-072 group. These differences were not statistically significant for individual subtypes, primarily due to the size of the study subpopulations, but were significant in a combined analysis of all 4 qHPV types. The level of the titers generated by vaccination among MSMLWH in AMC-072 and the HIV-negative MSM in Merck 020 were similar, and about half of those observed in similarly aged heterosexual men in Merck 020 [5].

The qHPV vaccine was safe and well tolerated by young MSMLWH, and the titers generated suggest that protection should be as long-lasting as in other vaccinated cohorts. There were no differences in titer based on current/nadir CD4 level or HIV VL, other than lower titers to HPV18 among those with a higher HIV VL at month 7. Previously exposed MSMLWH also showed sustained higher titers than naive MSMLWH, consistent with the immunologic memory demonstrated in other populations, including older MSMLWH [21].

Population-based studies among MSM in the United States demonstrate low rates of vaccine initiation, ranging from 13% to 37.6% [22, 23]. It has been estimated that vaccinating 70% of boys will protect 91% of sexual partnerships in MSM [23]. Our findings of no qHPV type–associated LSILs/HSILs among naive vaccinated individuals, that more than half of young MSMLWH were naive to HPV16 at baseline, and the high proportion with HPV infection and disease in the absence of vaccination support recent guidelines for HPV vaccination [10]. These guidelines encourage vaccine initiation at 9–12 years. Catch-up HPV vaccination for all persons through age 26 years, including MSM, is also critical but our data highlight the importance of vaccinating prior to onset of sexual activity whenever possible.

There are several strengths of this study. This was a prospective, phase II multisite study with 2 years of follow-up with rigorous clinical endpoints. The HPV endpoints used to define the naive population and incident-persistent HPV infection included assessment of HPV infection at multiple anatomic locations. The study was performed by clinicians highly experienced in performing HRA and HRA-guided biopsy. There were also several limitations. In addition to sample size limitations, for

ethical reasons we were not able to have a placebo control. Our study excluded those with HSILs at screening, and our results likely overestimate the value of vaccinating the entire population of 18–26-year-old MSMLWH. Our results may therefore not be generalizable to all young MSMLWH. We followed participants for only 24 months and were not able to retrieve all biopsies to perform HPV testing, reducing our analyzable dataset.

In summary, young MSMLWH have a very high risk of HPV-related HSILs and a large proportion have been previously exposed to qHPV types. Our data show that qHPV vaccination is safe, well tolerated, and immunogenic in this population, and prevents incident HPV infection and hHSILs associated with vaccine HPV types to which the individual has not yet been exposed. It is expected that the nonavalent HPV vaccine currently in use should perform similarly to the qHPV vaccine in preventing HPV16 and 18, and to protect against the additional 5 HPV types. Our data confirm the need to continue efforts to vaccinate all boys and young men as early as possible prior to sexual exposure to HPV, and to target young MSMLWH for catch-up vaccination.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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