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# Pre-vaccination prevalence of anogenital and oral human papillomavirus in young HIV-infected men who have sex with men☆,☆☆

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ABSTRACT

The aims of this study were to: 1) determine prevalence of anogenital and oral HPV, 2) determine concordance between HPV at anal, perianal, scrotal/penile, and oral sites; and 3) describe factors associated with anogenital HPV types targeted by the 9-valent vaccine. Data were collected from 2012 to 2015 among men who have sex with men 18–26 years of age enrolled in a vaccine trial (N = 145). Penile/scrotal, perianal, anal, and oral samples were tested for 61 HPV types. Logistic regression was used to identify factors associated with types in the 9-valent vaccine. Participants' mean age was 23.0 years, 55.2% were African-American, and 26.2% were Hispanic; 93% had anal, 40% penile, and 6% oral HPV. Among those with anogenital infection, 18% had HPV16. Concordance was low between anogenital and oral sites. Factors independently associated with a 9-valent vaccine-type HPV were: race (African-American vs. White, OR = 2.67, 95% CI = 1.11–6.42), current smoking (yes vs. no, OR = 2.37, 95% CI = 1.03–5.48), and number of recent receptive anal sex partners (2+ vs. 0, OR = 3.47,

☆ An AIDS Malignancy Consortium (AMC-072) and Adolescent Trials Network for HIV/AIDS (ATN) Study.
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95% CI = 1.16–10.4). Most MSM were not infected with HPV16 or HPV18, suggesting that they may still benefit from HPV vaccination, but anogenital HPV was very common, highlighting the importance of vaccinating men before sexual initiation.
*Clinical trial number:* NCT01209325

## 1. Introduction

Human papillomavirus (HPV) infection causes anogenital and oropharyngeal cancers in both men and women. HIV-infected individuals are at substantially higher risk for HPV-associated cancers than HIV-uninfected individuals, and HIV-infected men who have sex with men (MSM) are at particularly high risk for anal cancer [6,31,33]. Colon-Lopez et al. reported that among 447,953 people with HIV infection in the U.S., anal cancer incidence was markedly higher than in the general population (standardized incidence ratio 19.1, 95% CI 18.1–20.0) and was highest among MSM [3].

Three prophylactic HPV vaccines that target HPV16 and HPV18, the types most likely to cause anal cancer, have been licensed for use: a 2-valent (HPV16, 18), 4-valent (HPV6, 11, 16, 18) and 9-valent (HPV6, 11, 16, 18, 31, 33, 45, 52, 58) vaccine. Only the latter is currently available in the U.S. The U.S. Advisory Committee on Immunization Practices (ACIP) recommends routine HPV vaccination of men at age 11–12 years, with catch-up vaccination for all men 13–21 years of age and for men at high risk for HPV up to 26 years of age [20,32]. However, vaccination rates in men are relatively low [36]. In one U.S. study conducted in 2011, only 4.9% of MSM between 18 and 26 years of age had received at least one HPV vaccine dose [21]. Low vaccination rates may be due in part to inadequate awareness and understanding, among both clinicians and MSM, of the epidemiology of HPV in MSM and assumptions that the HPV vaccine will not be effective in men who are already sexually active [25].

Recent studies have examined the prevalence and risk factors for HPV in HIV-infected MSM [4,10,13,14,17–19,22,24,27,34,35,37,38,41]. However, few of these studies have recruited only young HIV-infected men, and little is known about HPV infection in this high-risk population. Characterization of type-specific HPV prevalence in young HIV-infected MSM is critical in order determine whether vaccination is likely to be effective. In addition, few previous studies have determined concordance between multiple anogenital and oral sites and examined HPV genotype variants among HIV-infected MSM. Information about concordance has implications for understanding the accuracy of sampling at only one site for anogenital HPV, the extent of self-inoculation between sites, and susceptibility of different anatomic areas to specific HPV types [41]. Information about sequence variation within HPV types is important in that it has been shown to be associated with differences in viral persistence and the risk of cervical cancer [26,29,39,45]. Genotype variants may also contribute to racial and ethnic differences in the prevalence of HPV-associated cancers. We therefore conducted a study to examine the epidemiology of HPV at anogenital and oral sites in young, unvaccinated HIV-infected MSM participating in an HPV vaccine clinical trial. The aims of this study were to: 1) determine prevalence of anogenital (anal, perianal, and scrotal/penile) and oral HPV, 2) describe HPV16, HPV18, and HPV31 genotype variants, 3) determine concordance between HPV at anal, perianal, scrotal/penile, and oral sites; and 4) describe factors (demographic, behavioral, immunologic, and virologic) associated with anogenital HPV types targeted by the 9-valent vaccine, including HPV16/18, in this population.

## 2. Material and methods

We conducted a phase II, open-label, multi-center trial of the quadrivalent HPV (HPV6, 11, 16, 18) vaccine in 13- to 26-year-old HIV-infected MSM. Additional inclusion criteria included: if receiving antiretroviral therapy, receipt of therapy for at least 3 months and no change in the prior 30 days; if not receiving antiretroviral therapy, CD4 count > 350 cells/mm$^3$ prior to study entry; normal anal cytology within 90 days and no HSIL on biopsy; absolute neutrophil count > 750 cells/mm$^3$, hemoglobin $\geq$ 9.0 g/dL, platelet count $\geq$ 100,000/mm$^3$, liver function tests less than 3 times the upper limit of normal, creatinine clearance $\geq$ 60 mL/min, and Karnofsky performance score $\geq$ 70 within 45 days prior to entry. Data from the baseline visit were analyzed for this study. This trial was conducted by the AIDS Malignancy Consortium (AMC-072, NCT01209325) in collaboration with the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN). Participants were recruited between 2012 and 2015 from 15 U.S. sites.

Participants underwent screening with anal cytology and high-resolution anoscopy by trained clinicians. Visible suspicious lesions were biopsied. Those positive for high-grade squamous intraepithelial lesions (HSIL) on biopsy at baseline were excluded from participation in the trial and were not included in this analysis. Participants who completed the first study visit (N = 145) completed a survey instrument at the first visit assessing demographic characteristics, knowledge about HPV and HPV vaccines, smoking and sexual behaviors. Recent CD4 + count and HIV viral load data were collected and participants were tested at baseline for gonorrhea and chlamydia using a urine specimen (tested using a nucleic acid amplification test performed locally at sites). Written informed consent was obtained, and the Institutional Review Board for each participating site approved the study.

Penile/scrotal, perianal and anal samples for HPV DNA testing were collected as follows. The penis (shaft, glans and corona), scrotal skin, and perianal skin were gently abraded with 600 grit emery paper and then swabbed with a Dacron swab moistened with sterile saline. The intra-anal HPV sample was collected using a Dacron swab after a swab for cytology testing. All swabs were placed into a container of STM (Specimen Transport Medium, DIGENE, Gaithersburg MD) and stored at −80 °C until shipment and testing. Throat wash samples (participant swished/gargled with 10 mL of Scope mouthwash) were collected for oral HPV testing. Samples were centrifuged, and the pellet and supernatant were stored at −80 °C until shipment and testing. HPV DNA extraction was performed on all samples. Briefly, the anogenital samples were heat-inactivated followed by addition of Proteinase K and an ammonium acetate/ethanol mixture. They were frozen at −20 °C overnight and then centrifuged to obtain the pellet. The samples were eluted in Tris-EDTA buffer. DNA from oral samples was extracted using a modified Puregene (Qiagen) assay [5].

MY09/MY11 L1 consensus primers were used to amplify HPV sequences as described previously [30]. Beta-globin primers were used as an internal control to test for adequacy of DNA. Samples were dot-blotted onto a membrane and probed for HPV DNA using a chemiluminescent procedure with a consensus probe mixture. Samples were then analyzed for the presence of 33 individual HPV types, and a mix of 28 additional types. Samples that were negative for beta-globin were excluded from analysis.

Finally, we determined the prevalence of anogenital HPV16, 18, and 31 genotype variants. Variant classification was determined by sequencing of the E6 regions of HPV16, 18, and 31. The E6 gene of HPV 16 and HPV 18 were amplified using a previously described protocol and primer set [40,44]. The HPV31 E6 region was amplified by single-tube nested PCR using the outer primers GGAGTGACCGAAAGTGGT GAA (forward) and CTTGTCCAGCTGGACTGTCTA (reverse), and inner primers ACGGTTGGTATATAAAG (forward) and TCGGGTAATTGCT

CAT (reverse). PCR products were then visualized by gel electrophoresis to confirm a single band. The PCR product was cleaned with MCMag Beads (MCLabs, South San Francisco) and sequenced in both directions using the internal primers of the nested PCR. Sequences were aligned to the reference sequence for each type and variant groups determined by previous published groupings.

We first examined participant characteristics and prevalence of anogenital and oral HPV using descriptive statistics. HPV infection was analyzed by site (anal, perianal, scrotal/penile, and oral) and by type: any HPV (positive for at least one HPV type); HPV types in the 2-valent (HPV16, 18), 4-valent (HPV6, 11, 16, 18), and 9-valent (HPV6, 11, 16, 18, 31, 33, 35, 45, 52) vaccines; high-risk HPV (positive for at least one high-risk type), and individual HPV types. We then determined concordance between anogenital sites for those participants who had evaluable HPV results at all three sites, and between any anogenital site and the oral site for those participants who had evaluable results for all four of those sites. We also examined associations between HPV genotype variants and race/ethnicity using a Fisher's exact test. Using univariable logistic regression analysis, we examined associations between the following factors and positivity for one of the types in the 9-valent HPV vaccine, as well as positivity for HPV16 and/or HPV18, by anogenital site: age, race, ethnicity, smoking, sexual behaviors, concurrent chlamydia or gonorrhea infection, CD4 + T-cell count, and HIV viral load. Variables associated with HPV in univariable analyses at $p < .10$ were entered into separate multivariable models by HPV detection site (anal, perianal, scrotal/penile, any site): variables associated with HPV at $p \geq 0.10$ after adjusting for other variables were removed from the multivariable model. Analyses were conducted using SAS version 9.4.

## 3. Results

The median age of participants (N = 145) was 23 years (range 18–26 years). Although 13–26 year-olds were eligible, no one under age 18 years was enrolled. HIV transmission was through homosexual contact in 137 (94.5%), homosexual and heterosexual contact in 5 (3.4%), any sexual contact and IV drug use in 2 (1.4%) and perinatal infection in 1 (0.7%). Of the original 260 HIV-infected MSM screened, 94 (36%) were excluded from enrollment because of a diagnosis of anal HSIL and an additional 21 did not meet other inclusion criteria or did not enroll for other reasons. Of the 145 who were enrolled, just over half (55.2%) were African-American, 26.2% were Hispanic, and 45.3% reported current smoking (Table 1). More than 90% of participants reported having had sexual intercourse with a male partner in the past 6 months: 55.5% reported at least 2 receptive male partners during this time. Urine specimens were positive for gonorrhea or chlamydia in 6 (4.3%) of participants: 1 was positive for both and 5 for chlamydia only. Fewer than 10% of participants had a CD4 + T-cell count of ≤350 cells/mm$^3$ and 91% had an HIV viral load of < 400 copies/mL.

Almost all participants (95%) were infected with at least one HPV type at an anogenital site: 93% at the anal canal, 76% at the perianus,

**Table 1**
Baseline characteristics of the study sample (n = 145).

| Variable | Total[a] | Categories | N (%) | Median (range) |
|---|---|---|---|---|
| Age (years) | 145 | | | 23 (18–26) |
| | | 22–26 | 115 (79.3) | |
| | | 18–21 | 30 (20.7) | |
| Race | 145 | White | 47 (32.4) | |
| | | African-American | 80 (55.2) | |
| | | Other | 18 (12.4) | |
| Ethnicity | 145 | Non-Hispanic | 107 (73.8) | |
| | | Hispanic | 38 (26.2) | |
| Current smoking | 137 | No (not at all) | 75 (54.7) | |
| | | Yes (some days/every day) | 62 (45.3) | |
| Last receptive anal intercourse | 135 | Over 6 months ago | 25 (18.5) | |
| | | 1–6 months ago | 36 (26.7) | |
| | | Within the past month | 74 (54.8) | |
| Sexual intercourse with male partner, past 6 months | 137 | No | 13 (9.5) | |
| | | Yes | 124 (90.5) | |
| Number of male sexual partners, past 6 months | 137 | 0 | 13 (9.5) | |
| | | 1 | 48 (35.0) | |
| | | 2 + | 76 (55.5) | |
| Number of receptive anal male sexual partners, past 6 months | 127 | 0 | 16 (12.6) | |
| | | 1 | 53 (41.7) | |
| | | 2 + | 58 (45.7) | |
| Frequency of condom use during receptive anal sex with male partner, past 6 months | 128 | No anal sex past 6 months | 16 (12.5) | |
| | | Every time | 51 (39.8) | |
| | | Sometimes/never | 61 (47.7) | |
| Number of male oral sexual partners, past 6 months[b] | 136 | 0 | 15 (11.0) | |
| | | 1 | 54 (39.7) | |
| | | 2 + | 67 (49.3) | |
| Frequency of condom use during oral sex, past 6 months | 137 | No oral sex past 6 months | 15 (10.9) | |
| | | Sometimes/always | 36 (26.3) | |
| | | Never | 86 (62.8) | |
| Had sexual intercourse with female partner, past 6 months | 137 | Yes | 8 (5.8) | |
| | | No | 129 (94.2) | |
| Chlamydia and/or gonorrhea (urethral) infection at baseline | 141 | Yes | 6 (4.3) | |
| | | No | 135 (95.7) | |
| CD4 + count (cells/mm3) | 144 | | | 594 (237–1520) |
| | | ≤ 350 | 14 (9.7) | |
| | | > 350 | 130 (90.3) | |
| HIV viral load (copies/mL) | 144 | | | 0 (0–63,000) |
| | | < 400 | 131 (91.0) | |
| | | ≥ 400 | 13 (9.0) | |

[a] Not all N = 145 due to missing data and skip patterns.
[b] Defined as number of men to whom the participant gave oral sex.

**Table 2**
Prevalence of anogenital HPV types (at any anogenital site and stratified by site) and oral HPV types.

| | Any Anogenital Site[a] (n = 141) | Anal[b] (n = 137) | Perianal[c] (n = 136) | Penile/Scrotal[d] (n = 133) | Oral (n = 139) |
|---|---|---|---|---|---|
| **HPV type** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** |
| Any HPV type[e] | 134 (95) | 128 (93) | 104 (76) | 53 (40) | 9 (6) |
| 2-valent vaccine types (16, 18) | 35 (25) | 34 (25) | 15 (11) | 2 (2) | 0 (0) |
| 4-valent vaccine types (6, 11, 16, 18) | 81 (57) | 73 (53) | 46 (34) | 14 (11) | 0 (0) |
| 9-valent vaccine types (6, 11, 16, 18, 31, 33, 45, 52, 58) | 99 (70) | 93 (68) | 59 (43) | 16 (12) | 0 (0) |
| High-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82) | 98 (70) | 95 (69) | 51 (38) | 11 (8) | 3 (2) |
| HPV6[f] | 55 (39) | 49 (36) | 26 (19) | 8 (6) | 0 (0) |
| HPV11[f] | 24 (17) | 17 (12) | 15 (11) | 6 (5) | 0 (0) |
| HPV16[f] | 26 (18) | 25 (18) | 9 (7) | 2 (2) | 0 (0) |
| HPV18[f] | 15 (11) | 14 (10) | 6 (4) | 0 (0) | 0 (0) |
| HPV31[g] | 12 (9) | 12 (9) | 2 (1) | 0 (0) | 0 (0) |
| HPV33[g] | 12 (9) | 12 (9) | 5 (4) | 0 (0) | 0 (0) |
| HPV35 | 19 (13) | 18 (13) | 5 (4) | 0 (0) | 2 (1) |
| HPV39 | 11 (8) | 10 (7) | 3 (2) | 1 (1) | 1 (1) |
| HPV45[g] | 14 (10) | 13 (9) | 6 (4) | 0 (0) | 0 (0) |
| HPV51 | 21 (15) | 19 (14) | 8 (6) | 4 (3) | 0 (0) |
| HPV52[g] | 14 (10) | 13 (9) | 7 (5) | 1 (1) | 0 (0) |
| HPV56 | 8 (6) | 7 (5) | 3 (2) | 1 (1) | 0 (0) |
| HPV58[g] | 22 (16) | 19 (14) | 7 (5) | 1 (1) | 0 (0) |
| HPV59 | 13 (9) | 13 (9) | 7 (5) | 1 (1) | 0 (0) |
| HPV68 | 13 (9) | 12 (9) | 4 (3) | 2 (2) | 0 (0) |
| HPV73 | 6 (4) | 6 (4) | 1 (1) | 1 (1) | 0 (0) |
| HPV82 | 15 (11) | 9 (7) | 5 (4) | 3 (2) | 0 (0) |
| HPV26/69[h] | 6 (4) | 6 (4) | 1 (1) | 0 (0) | 0 (0) |
| HPV30 | 8 (6) | 7 (5) | 3 (2) | 0 (0) | 0 (0) |
| HPV32/42 | 13 (9) | 11 (8) | 4 (3) | 1 (1) | 3 (2) |
| HPV34 | 4 (3) | 3 (2) | 0 (0) | 1 (1) | 0 (0) |
| HPV53 | 20 (14) | 19 (14) | 7 (5) | 1 (1) | 0 (0) |
| HPV54 | 10 (7) | 10 (7) | 7 (5) | 1 (1) | 0 (0) |
| HPV57/2/27 | 1 (1) | 0 (0) | 0 (0) | 1 (1) | 0 (0) |
| HPV61 | 12 (9) | 12 (9) | 7 (5) | 0 (0) | 0 (0) |
| HPV62 | 19 (13) | 17 (12) | 11 (8) | 4 (3) | 0 (0) |
| HPV66 | 4 (3) | 2 (1) | 2 (1) | 0 (0) | 0 (0) |
| HPV67 | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| HPV70 | 7 (5) | 6 (4) | 3 (2) | 0 (0) | 0 (0) |
| HPV71 | 2 (1) | 1 (1) | 1 (1) | 0 (0) | 1 (1) |
| HPV72 | 8 (6) | 6 (4) | 1 (1) | 1 (1) | 1 (1) |
| HPV81 | 12 (9) | 11 (8) | 9 (7) | 0 (0) | 0 (0) |
| HPV83 | 14 (10) | 11 (8) | 7 (5) | 2 (2) | 1 (1) |
| HPV84 | 21 (15) | 17 (12) | 12 (9) | 3 (2) | 0 (0) |
| HPV85 | 3 (2) | 3 (2) | 0 (0) | 0 (0) | 0 (0) |
| HPV86/87 | 14 (10) | 10 (7) | 10 (7) | 1 (1) | 0 (0) |
| HPV90/106 | 18 (13) | 14 (10) | 10 (7) | 1 (1) | 0 (0) |
| HPV97 | 1 (1) | 1 (1) | 1 (1) | 0 (0) | 0 (0) |
| HPV102/89 | 6 (4) | 3 (2) | 3 (2) | 1 (1) | 0 (0) |

[a] Any anogenital site includes participants with samples from 1 to 3 anogenital sites.
[b] Anal only, anal + perianal, anal + penile/scrotal.
[c] Perianal only, perianal + anal, perianal + penile/scrotal.
[d] Penile/scrotal only, penile/scrotal + anal, penile/scrotal + perianal.
[e] Positive for ≥1 HPV type.
[f] Indicates types in the quadrivalent vaccine and nine-valent vaccine.
[g] Indicates types only in the nine-valent vaccine.
[h] We tested for 33 types individually (6, 11, 16, 18, 30, 31, 33, 34, 35, 39, 45, 51, 52, 53, 54, 56, 58, 59, 61, 62, 66, 67, 68, 70, 71, 72, 73, 81, 82, 83, 84, 85, and 97), and 8 mixtures of 2–8 types (32/42, 26/69, 57/2/27, 86/87, 90/106, 102/89, Mix1 containing 7, 13, 40, 43, 44, 55, 74, and 91, and Mix2 containing 3, 10, 28, 29, 77, 78, and 94).

and 40% at the penis/scrotum (Table 2). The most commonly identified type at any site was HPV6, present in 39% of young men; HPV11 was present in 17%. The most common high-risk type was HPV16, identified in 20%; HPV18 was identified in 11%. Fifty-seven percent of participants were infected with at least one HPV type targeted by the 4-valent vaccine, 70% with a type targeted by the 9-valent vaccine, and 70% with at least one high-risk type. Oral HPV was identified in 6% of participants: 3 were infected with high-risk types (2 with HPV35, 1 with HPV39), 3 with HPV32/42, and none with HPV16.

HPV16, HPV18, and HPV31 genotype variants were detected with different frequencies by race, though differences were not statistically significant (Table 3). Among African-American men, 9/24 (38%) known HPV16 variants were of African lineage and 14/24 (58%) were of European lineage. Among White men, 1/10 (10%) of HPV16 variants were of the African lineage and 9/10 (90%) were of the European lineage. Among African-American men, 5/13 (38%) HPV18 variants were of African lineage and 6/13 (46%) were of European lineage, while among White men, 1/5 (20%) were of African lineage and 2/5 (40%) were of European lineage. Finally, among African-American men, 3/9 (33%) HPV31 genotype variants were type A, 4/9 (44%) were type B, and 1/9 (11%) was type C, while among White men, 5/6 (83%) were type A, 0 were type B, and 1/6 (17%) was type C: the A lineage is found worldwide while the B and C lineages are found primarily in Africa [2].

**Table 3**
HPV16, HPV18, and HPV31 genotype variants, by race[a].

| **HPV16 genotype variants (N = 37)**[b] | | **African** | | **European** | | **Unknown** | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **N** | **%**[c] | **N** | **%**[c] | **N** | **%**[c] | | |
| Race | White | 1 | 10 | 9 | 90 | 0 | 0 | | |
| | African-American | 9 | 38 | 14 | 58 | 1 | 4 | | |
| | Other | 0 | 0 | 2 | 100 | 0 | 0 | | |
| | Unknown | 1 | 100 | 0 | 0 | 0 | 0 | | |
| **HPV18 genotype variants (N = 21)**[d] | | **Asian Amerindian** | | **African** | | **European** | | | |
| | | **N** | **%** | **N** | **%** | **N** | **%** | | |
| Race | White | 2 | 40 | 1 | 20 | 2 | 40 | | |
| | African-American | 2 | 15 | 5 | 38 | 6 | 46 | | |
| | Other | 2 | 100 | 0 | 0 | 0 | 0 | | |
| | Unknown | 0 | 0 | 0 | 0 | 1 | 100 | | |
| **HPV31 genotype variants (N = 16)**[e] | | **A** | | **B** | | **C** | | **Unknown** | |
| | | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** |
| Race | White | 5 | 83 | 0 | 0 | 1 | 17 | 0 | 0 |
| | African-American | 3 | 33 | 4 | 44 | 1 | 11 | 1 | 11 |
| | Other | 1 | 100 | 0 | 0 | 0 | 0 | 0 | 0 |

[a] Only enrolled participants having strain variant data were included. P values were calculated for the association between race and variant using Fisher's exact test; all were > .05. The A lineage is found worldwide while the B and C lineages are found primarily in Africa.
[b] Six observations belonging to five participants who were screened but not enrolled into the study were excluded in the table.
[c] Row percentage.
[d] One participant who was screened but not enrolled into the study was excluded in the table.
[e] Five observations belonged to four participants who were screened but not enrolled into the study were excluded in the table.

HPV type concordance between sites was relatively low (Table 4). HPV16 was identified in 20% of young men at any site, but in only 6% at both the anal and perianal sites, 2% at the anal and penile/scrotal sites, 1% at the perianal and penile/scrotal sites, and 1% at the anal, perianal and penile/scrotal sites. In each of the 4 cases in which HPV16 or HPV18 were identified at more than one site and genotype variant results were available, analysis revealed the same variant at both sites. There was no concordance between anogenital and oral HPV types. Generally, the highest concordance for all types was between the contiguous anal and perianal sites.

Multivariable logistic regression models identified participant characteristics independently associated with infection with at least one HPV type targeted by the 9-valent vaccine (Table 5). Separate models assessed HPV infection at each anogenital site and any site. After adjusting for race and current smoking, younger age (18–21 years vs. 22–26 years) was significantly associated with 9-valent anal HPV infection (odds ratio [OR] = 3.46). Number of receptive anal sex partners in the past 6 months was associated with perianal HPV infection (OR = 4.51 for 2 + vs. 0 partners). Current smoking was the only factor associated with penile/scrotal HPV infection (OR = 9.82). The numbers of oral sex partners (defined as giving oral sex) and receptive anal partners (defined as receiving anal sex) in the past 6 months were highly correlated; therefore, for the outcome variable HPV infection at any site, separate models were estimated that included either number of anal or number of oral sex partners. In the multivariable model that included receptive anal sex partners (i.e. number of partners from whom the participant has received anal sex) but not oral sex partners, the following characteristics were associated with HPV infection at any site: African-American vs. White race (OR = 2.67), current smoking (OR = 2.37), and number of receptive anal sex partners in the past 6 months (OR = 3.47 for 2 + vs. 0 partners). In the model that included oral sex partners but not receptive anal sex partners, the following characteristics were associated with HPV infection at any site: African-American vs. White rate (OR = 2.97), current smoking (OR = 2.52), and number of male oral sex partners in the past 6 months (OR = 4.10 for 2 + vs. 0 partners). Multivariable logistic regression models also assessed participant characteristics independently associated with infection with HPV16 and/or HPV18 (Table 5). Younger age (18–21 vs. 22–26 years) was associated with perianal HPV infection (OR = 4.42); chlamydia and/or gonorrhea infection with penile/scrotal HPV

**Table 4**
HPV types in the 9-valent vaccine by site and concordance between sites (n = 127)[a].

| | **Any site**[b] | **Anal only** | **Perianal only** | **Penile /scrotal only** | **Anal + perianal** | **Anal + penile/ scrotal** | **Perianal + penile/ scrotal** | **Anal + perianal + penile/ scrotal** | **Oral + any anogenital site** |
|---|---|---|---|---|---|---|---|---|---|
| **Individual HPV types** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | |
| HPV6 | 55 (43) | 22 (17) | 3 (2) | 2 (2) | 22 (17) | 5 (4) | 5 (4) | 4 (3) | 0 (0) |
| HPV11 | 24 (19) | 6 (5) | 3 (2) | 2 (2) | 10 (8) | 3 (2) | 3 (2) | 2 (2) | 0 (0) |
| HPV16 | 26 (20) | 15 (12) | 1 (1) | 0 (0) | 8 (6) | 2 (2) | 1 (1) | 1 (1) | 0 (0) |
| HPV18 | 15 (12) | 7 (6) | 1 (1) | 0 (0) | 5 (4) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| HPV31 | 12 (9) | 9 (7) | 0 (0) | 0 (0) | 2 (2) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| HPV33 | 12 (9) | 7 (6) | 0 (0) | 0 (0) | 5 (4) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| HPV45 | 14 (11) | 7 (6) | 0 (0) | 0 (0) | 5 (4) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| HPV52 | 14 (11) | 6 (5) | 1 (1) | 0 (0) | 6 (5) | 1 (1) | 1 (1) | 1 (1) | 0 (0) |
| HPV58 | 22 (17) | 11 (9) | 2 (2) | 1 (1) | 5 (4) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **Any 9-valent type** | 99 (80) | 30 (24) | 3 (2) | 1 (1) | 54 (43) | 14 (11) | 13 (10) | 12 (9) | 0 (0) |

[a] Analyses only include participants who had evaluable HPV results at all 4 anatomical sites (anal, perianal, penile/scrotal, oral).
[b] Type was detected at any site.

**Table 5**
Results of univariable and multivariable logistic regression models: unadjusted and adjusted (for participant characteristics) odds of infection with HPV types included in the 9-valent HPV vaccine (Model 1) and infection with HPV16/18 (Model 2), at the anal, perianal, penile/scrotal, and any site[a].

| Participant characteristics | Categories | Total participants in category (N) | Type-specific HPV positive (%) | Unadjusted OR[b] (95% CI[c]) | Adjusted OR[d] (95% CI) | |
|---|---|---|---|---|---|---|
| **Model 1: Outcome variable is infection with HPV types included in the 9-valent vaccine** | | | | | | |
| **Anal site (N = 137)** | | | | | | |
| Age (years) | 18–21 | 27 | 85 | 3.29 (1.06–10.18) | **3.46 (1.08–11.11)** | |
| | 22–26 | 110 | 64 | 1.0 | – | |
| Race | African-American | 77 | 75 | 1.88 (0.84–4.22) | 1.80 (0.76–4.27) | |
| | Other | 18 | 50 | 0.62 (0.20–1.88) | 0.54 (0.16–1.77) | |
| | White | 42 | 62 | 1.0 | – | |
| Smoking (current) | Yes | 60 | 75 | 2.0 (0.94–4.26) | 2.17 (0.97–4.85) | |
| | No | 70 | 60 | 1.0 | – | |
| Number of receptive anal male sex partners, past 6 months | 2+ | 55 | 78 | 2.56 (0.91–7.19) | | |
| | 1 | 51 | 61 | 1.11 (0.41–2.97) | | |
| | 0 | 24 | 58 | 1.0 | – | |
| **Perianal site (N = 136)** | | | | | | |
| Age (years) | 18–21 | 27 | 59 | 2.23 (0.95–5.27) | | |
| | 22–26 | 109 | 39 | 1.0 | – | |
| Number of receptive anal male sex partners, past 6 months | 2+ | 57 | 61 | 4.51 (1.54–13.18) | **4.51 (1.54–13.18)** | |
| | 1 | 49 | 35 | 1.51 (0.50–4.53) | 1.51 (0.50–4.53) | |
| | 0 | 23 | 26 | 1.0 | – | |
| **Penile/scrotal site (N = 133)** | | | | | | |
| Smoking (current) | Yes | 58 | 22 | 9.82 (2.12–45.61) | **9.82 (2.12–45.61)** | |
| | No | 70 | 3 | 1.0 | – | |
| **Any site (N = 141)** | | | | | **Model 1a** | **Model 1b** |
| Age (years) | 18–21 | 28 | 86 | 3.04 (0.98–9.39) | | |
| | 22–26 | 113 | 66 | 1.0 | | |
| Race | African-American | 78 | 81 | 2.80 (1.23–6.36) | **2.67 (1.11–6.42)** | **2.97 (1.22–7.22)** |
| | Other | 18 | 50 | 0.67 (0.22–2.0) | 0.57 (0.16–2.0) | 0.58 (0.16–2.04) |
| | White | 45 | 60 | 1.0 | | |
| Smoking (current) | Yes | 62 | 79 | 2.40 (1.11–5.20) | **2.37 (1.03–5.48)** | **2.52 (1.06–5.97)** |
| | No | 72 | 61 | 1.0 | | |
| Number of receptive anal male sex partners, past 6 months | 2+ | 57 | 82 | 3.69 (1.30–10.49) | **3.47 (1.16–10.37)** | |
| | 1 | 52 | 62 | 1.26 (0.48–3.31) | 1.29 (0.46–3.64) | |
| | 0 | 25 | 56 | 1.0 | | |
| Number of male oral sex partners in past 6 months | 2+ | 66 | 80 | 2.72 (0.82–9.01) | | **4.10 (1.13–14.91)** |
| | 1 | 52 | 60 | 0.98 (0.31–3.18) | | 1.53 (0.43–5.53) |
| | 0 | 15 | 60 | 1.0 | | |
| **Model 2: Outcome variable is infection with HPV16/18** | | | | | | |
| **Anal site (N = 137)** | | | | | | |
| Number of receptive anal male sex partners, past 6 months | 2+ | 55 | 36 | 4.0 (1.06–15.10) | 6.66 (0.93–47.69) | |
| | 1 | 51 | 18 | 1.50 (0.37–6.13) | 2.87 (0.39–21.09) | |
| | 0 | 24 | 13 | 1.0 | – | |
| Frequency of condom use during oral sex, past 6 months | Never | 80 | 24 | 2.03 (0.42–9.78) | 0.51 (0.05–5.02) | |
| | Mostly/Half/ Occasionally | 23 | 17 | 1.37 (0.22–8.6) | 0.39 (0.03–4.66) | |
| | Every time | 12 | 58 | 9.1 (1.39–59.62) | 2.85 (0.28–28.60) | |
| | No oral sex | 15 | 13 | 1.0 | – | |
| **Perianal site (N = 136)** | | | | | | |
| Age (years) | 18–21 | 27 | 26 | 4.42 (1.44–13.57) | **4.42 (1.44–13.57)** | |
| | 22–26 | 109 | 7 | 1.0 | 1.0 | |
| **Penile/scrotal site (N = 130)** | | | | | | |
| Sexual intercourse with a male partner, past 6 months | Yes | 117 | 1 | 0.09 (0.01–1.48) | | |
| | No | 11 | 9 | 1.0 | – | |
| Chlamydia and/or gonorrhea infection (current) | Yes | 6 | 17 | 22.46 (1.78–282.72) | **22.46 (1.78–282.72)** | |
| | No | 124 | 1 | 1.0 | 1.0 | |
| CD4+ T-cell count | ≤350 | 12 | 8 | 10.91 (0.64–186.67) | | |
| | > 350 | 121 | 1 | 1.0 | – | |
| **Any site (N = 141)** | | | | | **Model 2a** | **Model 2b** |
| Age (years) | 18–21 | 28 | 39 | 2.40 (0.99–5.80) | | 2.29 (0.90–5.79) |
| | 22–26 | 113 | 21 | 1.0 | – | – |
| Number of receptive anal male sex partners, past 6 months | 2+ | 57 | 37 | 4.28 (1.14–16.03) | **7.27 (1.04–50.59)** | 3.76 (0.99–14.29) |
| | 1 | 52 | 17 | 1.54 (0.38–6.25) | 2.97 (0.41–21.26) | 1.33 (0.32–5.52) |
| | 0 | 25 | 12 | 1.0 | – | – |

(*continued on next page*)

**Table 5** (*continued*)

| Participant characteristics | Categories | Total participants in category (N) | Type-specific HPV positive (%) | Unadjusted OR[b] (95% CI[c]) | Adjusted OR[d] (95% CI) |
|---|---|---|---|---|---|
| **Model 1: Outcome variable is infection with HPV types included in the 9-valent vaccine Anal site (N = 137)** | | | | | |
| Frequency of condom use during oral sex, past 6 months | Never | 83 | 24 | 2.06 (0.43–9.93) | 0.49 (0.05–4.75) |
| | Mostly/Half/ Occasionally | 24 | 17 | 1.30 (0.21–8.15) | 0.34 (0.03–4.00) |
| | Every time | 12 | 58 | 9.1 (1.39–59.62) | 2.71 (0.27–27.08) |
| | No oral sex | 15 | 13 | 1.0 | – |

[a] Only those variables associated with the outcome variable at $p < .10$ in univariable analyses are included in the table. Variables included in univariable analyses for both Model 1 and Model 2 included: age, race, Hispanic ethnicity, last receptive anal intercourse, current smoking, last anal sexual intercourse with a male partner, last sexual intercourse with a male partner, number of male sexual partners in the past six months, number of anal male sexual partners in the past 6 months, frequency of condom use during receptive anal intercourse, number of oral male sex partners in the past six months (to whom the participant gave oral sex), frequency of condom use during oral sex, sex with a female partner in the past six months, current Chlamydia or gonorrhea infection, CD4+ T-cell count, and HIV viral load.

[b] OR = odds ratio.

[c] CI = confidence interval.

[d] **Model 1** (outcome variable 9-valent HPV infection): The final model for anal HPV included age, race and smoking, as the number of anal sex partners in past 6 months was not significant at $p < 0.10$ in the multivariable model after adjusting for age, race, and smoking. The final model for perianal HPV included number of anal sex partners in past 6 months, as age was not significant at $p < 0.10$ in the multivariable model after adjusting for the number of anal sex partners. The final models for any site included the following variables. Model 1a included race, smoking, and the number of anal sex partners in past 6 months, as age was not significant at $p < 0.10$ in the multivariable model after adjusting for race, smoking, and the number of anal sex partners. Model 1b included race, smoking, and the number of oral sex partners in past 6 months, as age was not significant at $p < 0.10$ in the multivariable model after adjusting for race, smoking, and the number of anal sex partners. The reason two models were estimated is that number of anal sex partners in the past 6 months and number of oral sex partners in the past 6 months were highly correlated; therefore, separate multivariable logistic regression models were estimated that included either number of anal sex partners (Model 1a) or number of oral sex partners in the past 6 months (Model 1b). In a multivariable model including both anal and oral sex partners, neither was significantly associated with HPV. **Model 2** (outcome variable HPV16/18): The final model for penile/scrotal HPV 16/18 included current Chlamydia or gonorrhea infection, as last sexual intercourse with a male partner was not significant at $p < 0.10$ in the multivariable model after adjusting for current Chlamydia or gonorrhea infection and/or CD4 cell count; also, CD4 cell count was not significant at $p < 0.10$ in the multivariable model after adjusting for last sexual intercourse with a male partner and/or current Chlamydia or gonorrhea infection. In the model predicting HPV16/18 at any site that contained all variables associated with the outcome at $p < .10$ (age, number of anal male sexual partners in the past 6 months, and frequency of condom use during oral sex), none of the variables were associated with the outcome at $p < .05$ but the p value was borderline significant ($p = .055$) for number of anal sexual partners. Therefore, we estimated two separate models, both of which included number of anal sexual partners. Model 2a included number of anal sexual partners in the past 6 months and frequency of condom use during oral sex. Model 2b included number of anal male sexual partners in the past 6 months and age.

infection (OR = 22.46); and number of receptive anal sex partners in the past 6 months at any site (OR = 7.27 for 2 + vs. 0 partners), but was no longer significant in a second model adjusting for age instead of condom use. No variables were associated with anal HPV.

## 4. Discussion

In this study, we examined anogenital and oral HPV DNA detection in young HIV-infected MSM without HSIL, prior to HPV vaccination. The study is novel in that we not only determined the prevalence of anogenital HPV at multiple sites in a unique population of young HIV-infected MSM at high risk for HPV, but also determined the prevalence of oral HPV and HPV genotype variants; examined concordance between HPV at anogenital and oral sites; and determined demographic, behavioral, immunologic, virologic factors associated with having one or more HPV types in the 9-valent HPV vaccine and HPV16/18.

Almost all young men in this study sample were infected with at least one HPV type at any anogenital site. The high prevalence rate is especially notable since men with biopsy-proven HSIL at baseline were excluded. Most previous studies assessing anogenital HPV in HIV-infected MSM were conducted in older men, and demonstrated an HPV prevalence of greater than 90% [1,10,11,16,17,19,24,27,38]. Prevalence rates of anogenital HPV are lower in HIV-uninfected MSM, yet most studies demonstrate anal HPV infection rates that are still high; typically 65–70% [1,16,19,22,24,27,37,41]. Furthermore, 57% of participants were infected with at least one 4-valent vaccine type, and 70% with at least one 9-valent vaccine type. These findings all highlight the importance of educating clinicians and parents about the urgency of vaccinating boys in the target age range of 11–12 years, prior to HPV exposure, to decrease anal cancer incidence and mortality.

Despite the high overall HPV prevalence, 82% of young men in this study were not infected with HPV16 and 89% were not infected with HPV18, the types that cause most anal cancers in MSM [8]. Since this was a vaccine efficacy study, MSM with HSIL were excluded from participation (and offered vaccination outside the study); therefore, the prevalence of anogenital HPV16 or 18 infection may have been even higher in this population of young HIV-infected MSM had they been included in the analysis. However, these data suggest that many young HIV-infected MSM would still likely benefit from vaccination and should be targeted for vaccination, despite their high risk for infection with non-vaccine HPV types. Effective public health messaging is needed to ensure that clinicians, parents, and young men understand that vaccination may be beneficial for young MSM regardless of HIV status and sexual experience. However, vaccinating prior to HPV exposure is expected to be far more effective in preventing HPV-related cancers; therefore, the approach of vaccinating sexually active MSM should not take precedent over a gender neutral vaccination program and a focus on vaccinating children prior to sexual initiation.

Oral HPV prevalence was low in this study sample: 6% of participants were positive for at least one oral HPV type, and none were positive for a 9-valent vaccine type including HPV16. In a recent meta-analysis of oral HPV infection in MSM, the pooled prevalence of oral

HPV16 was 3.0% in HIV-negative and 4.7% in HIV-positive MSM [15]: it is unclear why oral HPV16 prevalence was lower in our population. Although the efficacy of HPV vaccines in preventing oral HPV has not been studied prospectively in clinical trials, the vaccine is expected to be effective in preventing oral HPV [12]. A recent study conducted in a national sample of young adults demonstrated that from 2001 to 2014, the prevalence of oral vaccine-type HPV infections was significantly reduced in vaccinated vs. unvaccinated individuals, corresponding to an estimated 88.2% reduction in prevalence, despite relatively low vaccination rates [9].

Concordance between anogenital sites and between anogenital and oral sites was relatively low in this study. Previous studies similarly have demonstrated low concordance [15,34,41] or no concordance [14] between anogenital and oral sites in MSM. The findings suggest that self-inoculation between anogenital sites or between oral and anogenital sites may be uncommon, that different anogenital sites may vary in terms of their susceptibility to HPV infection, or that the ability to detect the same HPV type from different sampling sites may vary [41]. Conversely, genotype variant analysis showed that the same variants were present when the same HPV type was found at more than one site. Our findings are difficult to interpret given the small number of individuals with concordant type infection at multiple sites, and the fact that individuals with the highest risk for multisite disease (those with HSIL) were excluded, but this finding could be consistent with exposure to a given HPV genotype variant from the same partner at multiple anatomic sites. The prevalence of oral HPV was lower than in some previous studies, which may indicate an issue with detection.

Since HPV16, HPV18, and HPV31 genotype variants were identified in a relatively small number of participants, our ability is limited to draw conclusions about the prevalence of genotype variants in HIV-infected MSM and their association with race. However, we did find that genotype variants tended to differ by race; e.g. African HPV16 variants were found more commonly among African-American vs. other participants. Few studies have examined HPV16 genotype variants in HIV-infected MSM but these have demonstrated that European variants are the most common [23,42,43]. Further study is needed to examine genotype variants in HIV-infected MSM, given their possible association with HPV persistence and the increased risk of cancer with non-European variants [7,26,29,39,45]. Factors associated with anogenital vaccine-type HPV differed by site, but included younger age, African-American race, recent smoking, concurrent urethral chlamydia or gonorrhea infection, and number of recent receptive anal and oral sex partners. These findings are consistent with risk factors for anogenital HPV identified in previous studies. The main outcome variable in this study, 9-valent vaccine-type HPV, differed from previous studies conducted prior to 9-valent HPV vaccine introduction; however, number of receptive anal sex partners is one of the factors most consistently associated with anal HPV across studies, regardless of the outcome variable [11,17,24,28,41]. The implications are that education of young HIV-infected MSM should include counseling about the importance of avoiding smoking or smoking cessation, and practicing safer sexual behaviors including limiting the number of partners with whom they have receptive anal sex.

This study has several limitations. Although participants were recruited from sites across the U.S., the overall study sample was small which limits the power to detect associations between risk factors and HPV outcomes. Self-reported behaviors are subject to bias. Participants were HIV-infected MSM without anal HSIL who also generally had low HIV viral load and high CD4 + T-cell count and who were willing to participate in a clinical trial. Study participants with these characteristics may represent a group at lower risk for STIs than the general population of HIV-infected young MSM.

## 5. Conclusions

This study of pre-vaccination exposure to anogenital and oral HPV in young HIV-infected MSM without HSIL demonstrated that while the prevalence of any HPV type was high, most young HIV-infected MSM who did not have HSIL were negative for HPV16 and HPV18. Our data not only suggest that this group would potentially benefit from HPV vaccination and should be aggressively targeted for vaccination, but also that vaccination of 11–12 year-old boys prior to sexual initiation should be a priority. Although this study focused on HIV-infected MSM without HSIL at screening, all HIV-infected men age 26 and under should be vaccinated since the vaccine may prevent incident HSIL caused by HPV types to which they have not yet been exposed. Young HIV-infected MSM should also be educated about the importance of avoiding smoking and the risks associated with engaging in receptive anal sex with multiple partners.

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## Potential conflicts of interest

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