Clinical Infectious Diseases

MAJOR ARTICLE

A Randomized, Placebo-Controlled Trial of the Quadrivalent Human Papillomavirus Vaccine in Human Immunodeficiency Virus-Infected Adults Aged 27 Years or Older: AIDS Clinical Trials Group Protocol A5298

Timothy J. Wilkin,[1] Huichao Chen,[2] Michelle S. Cespedes,[3] Jorge T. Leon-Cruz,[2] Catherine Godfrey,[4] Elizabeth Y. Chiao,[5] Barbara Bastow,[6] Jennifer Webster-Cyriaque,[7] Qinghua Feng,[8] Joan Dragavon,[9] Robert W. Coombs,[9,10] Rachel M. Presti,[11] Alfred Saah,[12] and Ross D. Cranston[13]

[1]Division of Infectious Diseases, Weill Cornell Medicine, New York, New York; [2]Center for Biostatistics in AIDS Research, Harvard T.H. Chan School of Public Health, Boston, Massachusetts; [3]Division of Infectious Disease, Icahn School of Medicine at Mount Sinai, New York, New York; [4]Division of AIDS, National Institutes of Allergy and Infectious Diseases, Rockville, Maryland; [5]Department of Medicine, Baylor College of Medicine, Houston, Texas; [6]Social & Scientific Systems, Inc., Silver Spring, Maryland; [7]Department of Dental Ecology, School of Dentistry, University of North Carolina at Chapel Hill; [8]Department of Pathology, [9]Department of Laboratory Medicine, and [10]Department of Medicine, University of Washington, Seattle; [11]Department of Medicine, Washington University School of Medicine, St. Louis, Missouri; and [12]Merck and Company, Inc., West Point, and [13]Department of Medicine, University of Pittsburgh, Pennsylvania

Background. Adults living with human immunodeficiency virus (HIV) are at increased risk for anal and oropharyngeal cancer caused by human papillomavirus (HPV). The efficacy of HPV vaccines in this population is unknown.

Methods. In this phase 3, double-blind, randomized, controlled trial, we assigned HIV-infected adults aged ≥27 years to the quadrivalent HPV (types 6, 11, 16, 18) vaccine or placebo (1:1) stratified by sex and presence of anal high-grade squamous intraepithelial lesions on biopsy (bHSIL). The primary endpoint was vaccine efficacy against incident persistent anal infection with quadrivalent vaccine types or single detection at the final visit that were not present at baseline. Secondary endpoints included vaccine efficacy for anal bHSIL after week 52, persistent oral HPV infection.

Results. A total of 575 participants were randomized. The Data and Safety Monitoring Board stopped the study early due to futility. Vaccine efficacy was 22% (95.1% confidence interval [CI], −31%, 53%) for prevention of persistent anal infection or single detection at the final visit, 0% (95% CI −44%, 31%) for improving bHSIL outcomes and 88% (95.1% CI 2%, 98%) for preventing persistent oral HPV infection, but was 32% (95.1% CI −80%, 74%) for 6-month persistent oral HPV infection or single detection at the final visit.

Conclusions. These results do not support HPV vaccination of HIV-infected adults aged ≥27 years to prevent new anal HPV infections or to improve anal HSIL outcomes. However, our data suggest a role for prevention of oral HPV infections, but this finding should be confirmed in future studies.

Clinical Trials Registration. NCT01461096.

Keywords. human papillomavirus; HIV-1 infection; anal dysplasia; HPV vaccination; oral HPV infection.

Anal cancer is caused by infection with high-risk types of human papillomavirus (HPV) and is a common non-AIDS-defining cancer in human immunodeficiency virus (HIV)–infected adults [1–5]. A metaanalysis of HIV-infected men estimated the anal cancer rate at 45.9/100 000 person-years [6]. Two recent studies have estimated the rate of anal cancer in HIV-infected women to be 30 and 37 per 100 000 person-years [7, 8].

Anal cancer is preceded by high-grade squamous intraepithelial lesions (HSIL) [6]. Some groups recommend preventing anal cancer by screening for HSIL through cytology and high-resolution anoscopy (HRA) with histology sampling [9]. HSIL is treated with targeted ablation [10] or topical therapies such as 5% 5-fluorouracil or trichloroacetic acid to reduce the risk of anal cancer [11, 12]. Some reports suggest that patients who have received an HPV vaccine respond better to treatments of anal HSIL [13] and cervical HSIL [14].

Approximately 50 000 US adults are diagnosed annually with oropharyngeal cancer, with an estimated 5-year survival of 64% [15]. HPV causes 72% of oropharyngeal cancer [16], 84% by HPV 16 and 94% by 9-valent HPV vaccine types [17]. There are no prospective data on the efficacy of HPV vaccination to prevent oropharyngeal cancer. A cross-sectional examination of women exiting a randomized HPV vaccine trial detected a lower prevalence of oral infection with vaccine types among vaccine recipients [18].

The quadrivalent HPV vaccine (qHPV) is a prophylactic vaccine that is safe and highly immunogenic in HIV-infected

Received 12 January 2018; editorial decision 22 March 2018; accepted 3 April 2018; published online April 5, 2018.

Correspondence: T. J. Wilkin, Division of Infectious Diseases, Weill Cornell Medicine, 53 W. 23rd St, 6th Floor, New York, NY 10010 (tiw2001@med.cornell.edu).

Clinical Infectious Diseases® 2018;67(9):1339–46

© The Author(s) 2018. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com.

DOI: 10.1093/cid/ciy274

Downloaded from https://academic.oup.com/cid/article/67/9/1339/4961357 by guest on 24 April 2025

adults [19, 20]. In a randomized clinical trial enrolling 598 HIV-uninfected men who have sex with men (MSM) age 18–26 years, qHPV prevented 95% of persistent anal infections with vaccine types (95% confidence interval [CI], 80% to 99%) in the per-protocol analysis [21]. The vaccine also prevented 75% of anal HSIL due to vaccine types in the per-protocol analysis (95% CI, 9.9% to 95%). The US Advisory Committee on Immunization Practices recommends HPV vaccination for HIV-infected people up to age 26 years [22].

Prior HPV vaccine clinical trials have enrolled participants with a low exposure to HPV based on age and other enrollment criteria. The efficacy of HPV vaccination in populations with high levels of current and prior HPV infection is unknown. Adult Clinical Trials Group (ACTG) A5298 was conducted to test the hypothesis that qHPV prevents persistent anal infection with vaccine types not detected at study entry in HIV-infected men and women aged ≥27 years, a population with high levels of prevalent and prior HPV infections.

METHODS

Study Design and Participants

ACTG A5298 was a randomized, double-blinded, placebo-controlled, phase 3 clinical trial conducted at 24 sites in the United States and Brazil. The protocol was designed to enroll 464 HIV-infected MSM. A protocol modification added 100 HIV-infected women. Follow-up was planned for 3 years after the last participant was enrolled to a maximum of 4 years participation for an individual participant. Each site's institutional review board or ethics committee approved the trial. All participants provided written informed consent.

Entry Criteria

Participants met the following criteria: HIV-1 infection; age ≥27 years; safety laboratory tests; for men, receptive penile–anal sex or oral–anal sex with another man within 1 year; and ability to provide informed consent. Thirty percent of male participants and 50% of female participants were required to have HSIL on histologic analysis of anal biopsies (bHSIL).

Participants were excluded for history of HPV-related cancer, anal HSIL or condyloma treatment within 6 months, prior HPV vaccination, anticoagulant use, allergy to vaccine components, active drug or alcohol use or other condition that would interfere with study requirements, bleeding diatheses, systemic antineoplastic or immunomodulatory treatment, and pregnancy or breastfeeding.

Randomization and Masking

Participants were randomly assigned 1:1 to either HPV quadrivalent (types 6, 11, 16, and 18) vaccine (Merck and Co. Inc., Kenilworth, New Jersey) or matched placebo at baseline, week 8, and week 24. The placebo for male participants was the vaccine adjuvant with no viral-like particles; female participants received 0.9% saline because placebo was no longer available from Merck. Permuted-block randomization was balanced by site and stratified by sex and presence of bHSIL at study screening. The treatment assignment was provided electronically to local study pharmacists who prepared identical prefilled vaccine syringes. Investigators, participants, and study staff were masked to treatment allocation.

Procedures

Participants underwent 2 prevaccination samplings with anal swabs, as well as oral mouthwash rinse for HPV DNA typing [23, 24], anal swab for cytology, HRA with directed anal biopsies, and blood draw for CD4+ T-cell count, HIV-1 viral load, and HPV antibodies. Post-randomization, anal swabs for cytology and HPV testing, and oral mouthwash rinse were collected at week 28, week 52, and every 26 weeks thereafter. HPV antibodies were collected at week 28. The local treating provider determined treatment of anal bHSIL and additional HRA. A sexual activity questionnaire was obtained at baseline, week 28, week 52, and every 26 weeks thereafter.

Anal and oral HPV DNA polymerase chain reaction (PCR) testing was performed using L1 consensus primers MY09/MY11/HMB01 and B-globin primers PC04/GH20. Specimen adequacy was determined by dot blot hybridization and probed with biotin-labeled B-globin and generic HPV probes. B-globin/HPV-positive samples were then genotyped using a liquid bead microarray assay (LBMA) based on Luminex technology as described [25, 26]. The typing test is a semiquantitative assay used to detect 37 HPV types.

Cytology specimens were interpreted using the Bethesda classification [27]. Anal histology results were classified as no evidence of intraepithelial lesion or malignancy, low-grade squamous intraepithelial lesions (condyloma, intraepithelial neoplasia grade 1, or atypia), bHSIL (intraepithelial neoplasia grade 2 and/or 3 or carcinoma in situ), or invasive cancer.

Serum samples were analyzed using vaccine-type epitope-specific neutralizing anti-HPV antibodies with a competitive Luminex-based immunoassay (Merck Research Laboratories, Kenilworth, New Jersey), as described elsewhere [28, 29]. These assays were performed under the direction of Merck Research Laboratories at PPD Vaccines and Biologics Laboratory.

Outcomes

The primary outcome was time to first new persistent infection of any qHPV type. Persistent infection was defined as qHPV-type infection confirmed by PCR at 2 consecutive 6-month assessments. Participants with baseline HPV infection were evaluable for the primary outcome if they developed new persistent infection with a different qHPV type. A single detection at the final visit was included as an endpoint for the primary outcome; the endpoint of persistent infection only was reported for comparison. Secondary outcomes included persistent oral

Downloaded from https://academic.oup.com/cid/article/67/9/1339/4961357 by guest on 24 April 2025

HPV infection, detection of bHSIL at week 52 or later, anal cytological outcomes, and grade 3 or 4 adverse events related to vaccination. Adverse events were solicited during clinical assessments and graded using Division of AIDS Table for Grading the Severity of Adult Adverse Events Version 1.0, December 2004 [30].

Statistical Analyses

We targeted 90% power to detect 65% vaccine efficacy for the primary endpoint. Sample size calculations were based on a study of MSM [31], with 370 MSM required. We inflated the sample size by 25% (N = 464 MSM) to account for enlarged intervals, missing measurements, and loss to follow-up. The addition of 100 women (50 with anal bHSIL) was done upon the suggestion of the Data and Safety Monitoring Board (DSMB), and the sample size of 100 (50 with bHSIL) was chosen to provide adequate power for the secondary objectives of examining the effect of qHPV in preventing anal bHSIL.

Efficacy analyses for prevention of anal and oral HPV infections were done using a modified intention-to-treat (mITT) approach that included all participants who received at least 1 study vaccine and all new persistent infections that occurred after the first vaccination. A generalized log-rank test compared the survival functions of qHPV vs placebo [32]. Estimated hazard ratios were computed using the Cox proportional hazards model for interval-censored data. The Haybittle-Peto use function was used; the interim efficacy evaluation was performed with a 2-sided 0.001 level test, and the final analysis used an alpha of 0.0495 with 95.1% CIs. The per-protocol approach (mimicking pivotal phase 3 HPV vaccine analyses) excluded participants who did not complete the vaccine series and endpoints from participants with baseline seropositivity to that HPV type and infections that occurred during the vaccine series. The full ITT approach included all participants and all infections without regard to baseline detection of HPV infections or baseline seropositivity but did require at least 1 negative result post-randomization in those with a baseline infection.

We used the mITT approach for the analysis of anal bHSIL and anal cytological outcomes. The Cochran-Mantel-Haenszel method was used to compare qHPV vs placebo with respect to cytologic outcomes and anal bHSIL detection at week 52 or later stratified by baseline anal bHSIL and sex. The Fisher exact test was used for safety comparison. All analyses were done with SAS version 9.4.

Study Monitoring

An independent DSMB constituted by the National Institutes of Allergy and Infectious Diseases reviewed this study annually. The first efficacy review occurred on 2 September 2015 after 50% follow-up time for the primary endpoint of persistent anal HPV infection. Preset futility rules were met for time to persistent anal HPV infection and bHSIL after week 52. Study personnel were given 3 months to conduct HRA if clinically indicated. Other assessments were suspended.

RESULTS

Of 738 participants assessed for eligibility, 575 were eligible and randomized: 288 randomized to qHPV and 287 to placebo. Participant characteristics were balanced between treatment groups (Table 1). Randomizations occurred between 8 March 2012 and 23 August 2013. One placebo participant withdrew consent prior to the first study vaccine and was. In total, 278 (97%) qHPV participants and 280 (98%) placebo recipients received all 3 study vaccinations. One participant randomized to placebo received a dose of qHPV at week 24 in error. The median length of follow-up was 3.4 years, and the median number of post-randomization anal and oral HPV assessments per participant was 6. Figure 1 shows the flow of participants.

Anal HPV

In the mITT analysis that included single detection of HPV at the final visit, 27 qHPV and 33 placebo participants experienced persistent anal HPV infection with vaccine types with a vaccine efficacy of 22% (95.1% CI, −31% to 53%; P = .35). When only those with documented persistent infection were included, 14 qHPV and 17 placebo participants experienced persistent anal HPV infection with a vaccine efficacy of 21% (95% CI, −61% to 61%; P = .53). The per-protocol and full ITT are presented in Table 2.

Anal bHSIL

Among 186 participants with bHSIL at baseline, 120 (65%) received topical or surgical treatment for bHSIL prior to week 52 and 137 (74%) received 1 treatment prior to study completion, including 66% who received surgical procedures and 17% who received topical therapies. Fifty-five (30%) underwent post-randomization anal biopsies prior to week 52 and 94 (51%) after week 52. Among 388 without anal bHSIL at baseline, 32 (8%) had post-randomization anal biopsies obtained prior to week 52 and 128 (33%) after week 52. Prior to week 52, 19 (7%) were found to have anal bHSIL in the qHPV arm compared to 31 (11%) in the placebo group. After week 52 through study completion, 46 (16%) qHPV participants and 45 (16%) placebo participants were found to have anal bHSIL at some point, with an estimated vaccine efficacy of 0% (95.1% CI, −44% to 31%). Among the 91 bHSIL endpoints that occurred after week 52, 56 (62%) occurred in participants with bHSIL at baseline.

In a post hoc analysis, we restricted the analysis to those with bHSIL at baseline who underwent at least 1 treatment for bHSIL and had at least 1 anal biopsy after the treatment, with 43 in the qHPV group and 47 in placebo included. Among these participants, 27 (63%) in qHPV and 27 (57%) in placebo were diagnosed with recurrent bHSIL, respectively.

Downloaded from https://academic.oup.com/cid/article/67/9/1339/4961357 by guest on 24 April 2025

Table 1. Baseline Participant Demographics, Human Immunodeficiency Virus Disease Parameters, Recent Sexual Activity, Smoking Status, Anal and Oral Human Papillomavirus Infections, Anal High-Grade Squamous Intraepithelial Lesions, and Abnormal Anal Cytology

Characteristic	qHPV	Placebo
Median age (years)	47 (40, 52)	48 (42, 53)
Sex		
Male	236 (82%)	236 (82%)
Female	52 (18%)	51 (18%)
Race/ethnicity		
White non-Hispanic	125 (43%)	136 (47%)
Black non-Hispanic	91 (32%)	89 (31%)
Hispanic	63 (22%)	54 (19%)
Asian, Pacific Islander	5 (2%)	7 (2%)
Other	4 (1%)	1 (0%)
Antiretroviral therapy		
None	7 (2%)	10 (3%)
Current use	281 (98%)	277 (97%)
Plasma human immunodeficiency virus type 1 RNA (copies/mL)		
<200	249 (86%)	259 (90%)
200 to <1000	16 (6%)	8 (3%)
≥1000	17 (6%)	15 (5%)
Missing	6 (2%)	5 (2%)
Median current CD4 count (cells/mm^3)	598 (438, 761)	614 (435, 803)
Missing	3 (1%)	3 (1%)
Median nadir CD4 (cells/mm^3)	254 (105, 373)	259 (119, 419)
Missing	28 (10%)	32 (11%)
Number of male sex partners in the prior 6 months (male participants)		
0	21 (9%)	22 (9%)
1	79 (33%)	95 (40%)
2–5	101 (43%)	82 (35%)
>5	33 (14%)	35 (15%)
Missing	2 (1%)	2 (1%)
Number of anal sex partners (receptive) in the prior 6 months (male participants)		
0	56 (24%)	63 (27%)
1	107 (45%)	97 (41%)
2–5	56 (24%)	63 (27%)
>5	15 (6%)	11 (5%)
Missing	2 (1%)	2 (1%)
Number of male sex partners in the prior 6 months (female participants)		
0	19 (37%)	18 (35%)
1	26 (50%)	32 (63%)
>1	5 (10%)	0 (0%)
Missing	2 (4%)	1 (2%)
Number of anal sex partners (receptive) in the prior 6 months (female participants)		
0	41 (79%)	42 (82%)
1	8 (15%)	7 (14%)
Missing	3 (6%)	2 (4%)
Smoking status		
Current smoker	97 (34%)	84 (29%)
Ex-smoker	94 (33%)	99 (34%)
Non-smoker	96 (33%)	103 (36%)
Missing	1 (0%)	1 (0%)
Anal HPV infection		
HPV 6 DNA detected	71 (25%)	70 (24%)
HPV 11 DNA detected	38 (13%)	37 (13%)
HPV 16 DNA detected	89 (31%)	95 (33%)
HPV 18 DNA detected	54 (19%)	49 (17%)
Missing	1 (0%)	0 (0%)
HPV antibody status		
HPV 6 seropositive	182 (64%)	174 (61%)
HPV 11 seropositive	128 (45%)	110 (38%)
HPV 16 seropositive	135 (47%)	135 (47%)
HPV 18 seropositive	89 (31%)	94 (33%)
Missing	3 (1%)	1 (0%)
Oral HPV infection		
HPV 6 DNA detected	7 (2%)	7 (2%)
HPV 11 DNA detected	6 (2%)	7 (2%)
HPV 16 DNA detected	18 (6%)	11 (4%)
HPV 18 DNA detected	10 (3%)	4 (1%)
Anal HSIL		
bHSIL not detected	193 (67%)	195 (68%)
bHSIL detected	95 (33%)	92 (32%)
Anal cytology results		
Normal	103 (36%)	96 (34%)
Abnormal	182 (63%)	188 (66%)
Missing/unsatisfactory	3 (1%)	3(1%)

Abbreviations: HPV, human papillomavirus; bHSIL, high-grade squamous intraepithelial lesions on anal biopsy; qHPV, quadrivalent HPV vaccine.

Oral HPV

In the mITT analysis, which included persistent HPV infection or single detection of HPV at the final visit, 7 qHPV and 10 placebo participants experienced persistent oral HPV infection with vaccine types, with a vaccine efficacy of 32% (95.1% CI, −80% to 74%; $P = .44$). When only those with documented persistent infection were included, 1 qHPV and 8 placebo participants experienced persistent oral HPV infection with vaccine types, vaccine efficacy 88% (95.1% CI, 2% to 98%; $P = .02$). All 9 of the participants who experienced these endpoints were male. The per-protocol and full ITT are presented in Table 2.

Cytology Analyses

Baseline anal cytological results were available from 569 (99%) participants. Abnormal anal cytology results were found in 182 (63%) qHPV and 188 (66%) placebo participants. The proportion with abnormal anal cytology was not statistically different between arms at any follow-up visit. At the final 2 study visits, abnormal anal cytology was nominally lower in the qHPV group: week 130, 44% vs 52%, $P = .16$; week 156, 45% vs. 55%, $P = .11$.

Immunogenicity

There were 535 participants with HPV serology data available from baseline and week 28. In the qHPV group, seropositivity increased to 98.9%, 100%, 99.6%, and 97.4% for HPV 6, 11, 16, and 18, respectively, at week 28. Seropositivity did not change appreciably in the placebo group.

Downloaded from https://academic.oup.com/cid/article/67/9/1339/4961357 by guest on 24 April 2025

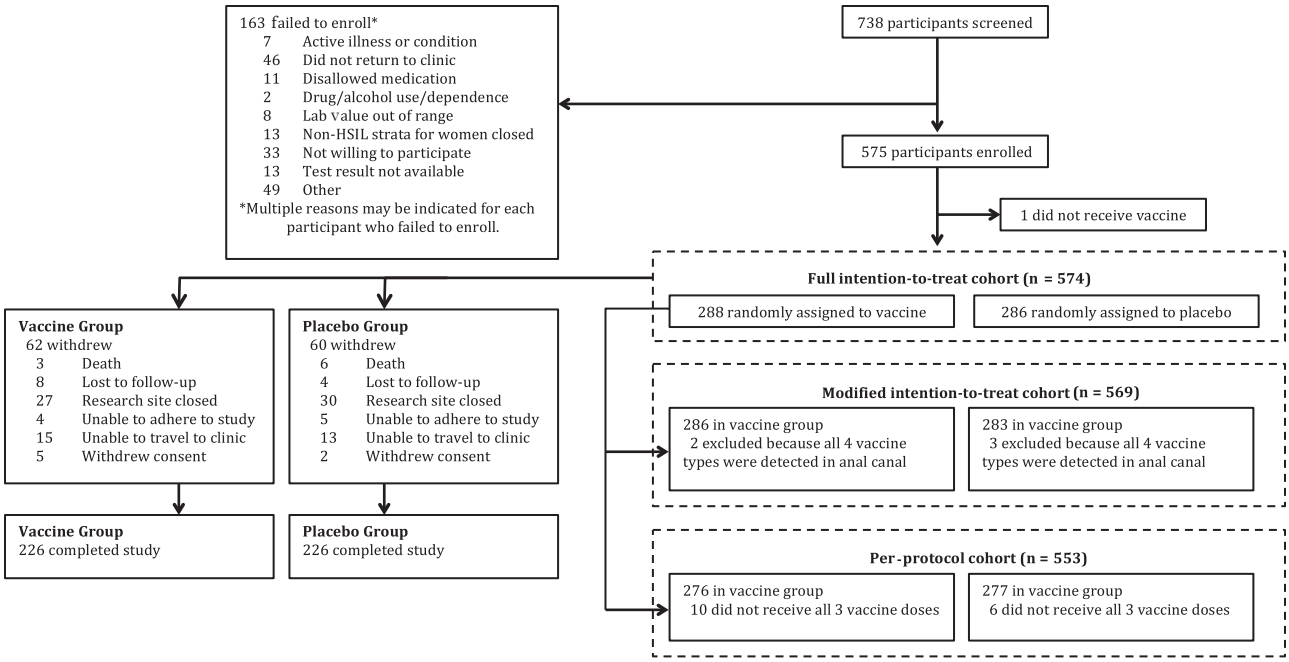

Figure 1. Participant disposition. Abbreviation: HSIL, high-grade squamous intraepithelial lesions.

Safety Analyses

There were no grade 3 or greater events attributable to study vaccination. Three participants (all placebo) did not complete the vaccine series due to adverse events (2 deaths and 1 transient ischemic attack). Within 48 weeks of randomization, 8 qHPV and 23 placebo participants experienced serious adverse events, $P = .006$. After week 48, 20 qHPV and 27 placebo participants experienced serious adverse events. Three qHPV participants (none within 48 weeks of randomization) and 6 placebo recipients (4 within 48 weeks of randomization) died while in the study. None of the deaths were deemed related to study vaccination or study procedures.

DISCUSSION

While HPV vaccination was safe and highly immunogenic consistent with prior studies [19, 20], we did not find evidence for HPV vaccine efficacy for prevention of anal infection with vaccine types in HIV-infected men and women aged ≥27 years with high rates of prevalent and prior HPV infection. There was a trend in the full ITT analyses for partial efficacy (35%, 95.1% CI, −5% to 60%; $P = .08$); however, this estimate is much lower than our hypothesized estimate of 65% and much lower than the efficacy of 95% (95% CI, 80% to 99%) observed in young MSM in the per-protocol population and lower than the efficacy of 59% (95% CI, 43% to 71%) in the ITT population [21]. We found no evidence to support an adjunctive role for HPV vaccination to improve outcomes to treatment of anal bHSIL.

There are issues that impacted our ability to show efficacy. Our observed event rate of persistent anal HPV infection excluding single detection at the final visit (2.7 events per 100 person-years) was lower than the protocol assumed rate (7.3 events per 100 person-years). Even though we obtained 2 pre-vaccination HPV samples, it is possible that we did not detect ongoing HPV infection at baseline either because of inadequate sampling or low-level infection. Also, high baseline seropositivity suggests ongoing or latent infection that may not have been detected by HPV DNA PCR. Prior studies have shown that HPV vaccination does not improve clearance of prevalent HPV types [33]. A study of the bivalent HPV vaccine in women aged >26 years detected a lower vaccine efficacy in women with prior HPV infection or disease [34].

Unlike anal and cervical cancer, there is no premalignant lesion for HPV-associated oropharyngeal cancer that is a viable surrogate in HPV vaccine trials. Persistent oral infection with HPV of ≥6 months duration was identified as the optimal endpoint for clinical trials assessing efficacy of vaccines for prevention of HPV-associated oropharyngeal cancer by the Primary Endpoints for Prophylactic HPV Vaccine Trials Committee convened by the International Agency for Research on Cancer and the US National Cancer Institute [35]. We did find evidence that qHPV prevents persistent oral HPV infection (1 vaccine group endpoint vs 8 placebo group endpoints, $P = .02$, estimated vaccine efficacy 88%, 95.1% CI, 2% to 98%). However, these results should be interpreted with caution given the wide confidence interval and because this result was not significant when a single detection at the final visit was included.

Our oral HPV results are consistent with a prior cross-sectional study of women exiting a randomized clinical trial of the bivalent vaccine, which found a lower prevalence of oral HPV

Downloaded from https://academic.oup.com/cid/article/67/9/1339/4961357 by guest on 24 April 2025

Table 2. Vaccine Efficacy for Persistent Anal Infection, Persistent Oral Infection, Anal High-Grade Squamous Intraepithelial Lesions on Anal Biopsy, and Abnormal Anal Cytology

Endpoint	Vaccine Group		Control Group		Efficacy (95.1% Confidence Interval)
Persistent anal infection	n	Endpoint	n	Endpoint	
mITT-including single detection at final visit	286	27	283	33	22% (–31% to 53%)
mITT-persistent infection only	286	14	283	17	21% (–61% to 61%)
Per protocol analysis	276	7	277	10	31% (–82% to 74%)
Full ITT	288	28	286	41	35% (–5% to 60%)
Persistent oral infection					
mITT-including single detection at final visit	288	7	286	10	32% (–80% to 74%)
mITT-persistent infection only	288	1	286	8	88% (2% to 98%)
Per-protocol analysis	278	1	280	3	66% (–70% to 96%)
Full ITT	288	6	286	14	58% (–9% to 84%)
Improvement of anal high-grade squamous intraepithelial lesions on anal biopsy outcomes[a]					
Full ITT	288	46	286	45	0% (–44% to 31%)
Abnormal anal cytology					
Week 52	231	123 (53%)	229	121 (53%)	0% (–19% to 16%)
Week 104	199	98 (49%)	198	108 (55%)	9% (–10% to 25%)
Week 156	130	58 (45%)	132	72 (55%)	17% (–6% to 35%)

Abbreviations: ITT, intention-to-treat analysis; mITT, modified ITT analysis.

[a]High-grade squamous intraepithelial lesions on anal biopsy specimens were not tested with human papillomavirus (HPV) DNA polymerase chain reaction to determine the causative HPV type.

infection with vaccine types among vaccinated women [18]. In addition, recent analyses from the US National Health and Nutrition Examination Survey found a lower prevalence of oral HPV infection with vaccine types among men and women who received at least 1 dose of HPV vaccine prior to age 26 years compared to unvaccinated individuals (0.11% vs 1.61%; estimated efficacy 88%; 95.1% CI, 5.7% to 98.5%) [36]. The worldwide standard is to vaccinate girls against HPV, but the majority of countries do not recommend vaccinating boys. This is problematic as HPV-associated oropharyngeal cancer is 4 to 5 times higher in men compared to women [37]. The rate of HPV-associated oropharyngeal cancer is 3 times higher in those with HIV infection compared to HIV-uninfected populations [38]. These data suggest that countries should consider the possible benefit of preventing HPV-associated oropharyngeal cancer when deciding HPV vaccination policy for boys.

There are several limitations to our trial. The study was stopped early by the DSMB per protocol-defined futility rules. This limited the precision of our point estimate and prevented observation of outcomes after 3 years. HPV vaccine trials have shown effects in the full ITT analyses 2–3 years after vaccination [21]. Our protocol did not mandate or provide funding for bHSIL treatment. Many participants did not receive treatment, lowering our power to detect significant differences. However, we observed no efficacy for improving anal bHSIL outcomes overall or within the subset that underwent bHSIL treatments. We did not use a central pathology review for cytology or histology outcomes, and bHSIL were not typed to identify the causative HPV type. Finally, we did not have access to the 9-valent HPV vaccine as it had not been approved by the US Food and Drug Administration at study initiation.

In summary, we did not find evidence for HPV vaccine efficacy for prevention of anal HPV infections among HIV-infected men and women aged ≥27 years with a high level of current and prior HPV infection. This underscores the need to vaccinate boys and girls prior to exposure to HPV infection. We did find evidence for vaccine efficacy for prevention of oral HPV infection with vaccine types. These findings should be confirmed in a randomized, placebo-controlled phase 3 trial of the 9-valent HPV vaccine with an endpoint of persistent oral infection.

Notes

Author contributions. All authors were involved in the design and conduct of the study. T. J. W. and R. D. C. were the study chairs. T. J. W., M. C., C. G., E. C., B. B., J. W., R. P., and R. D. C. drafted the protocol and consent forms. T. J. W., H. C., and R. C. drafted the manuscript with input from other authors. H. C. and J. T. L. C. were responsible for the statistical analyses and interpretation. R. W. C., J. D., and Q. F. were responsible for the HPV genotyping. All authors contributed to writing the manuscript and approved the final version.

Acknowledgments. The authors acknowledge the technical support provided by Donna Kenny, Linda Deng, Lisa Hu, and Glenda Daza at the University of Washington. Also, the authors acknowledge the study participants.

Disclaimer. C. G., a National Institutes of Health (NIH) employee, provided critical review of the manuscript, but the views expressed here do not necessarily represent those of the NIH. The content is solely the responsibility of the authors. Merck Sciences Inc. provided study vaccine, matching placebo, protocol funds to partially support oral HPV DNA PCR testing, and funding for HPV serology assays.

Financial support. This work was supported by the National Institute of Allergy and Infectious Diseases (NIAID) through the AIDS Clinical Trials Group (UM1 AI068634, UM1 AI068636, UM1 AI106701) and the National Institute of Dental and Craniofacial Research (U01 AI068636) at the NIH. This work was also supported by the National Institutes of Health Cooperative Agreement (U01AI068636) from the NIAID and the NIDCR. The research sites received additional NIH funding (P30 AI027757, UM1

Downloaded from https://academic.oup.com/cid/article/67/9/1339/4961357 by guest on 24 April 2025

AI069494, UM1 AI069419, UL1 TR000457, UM1 AI069511, UL1 TR000042, UM1 AI068636, AI 069432, UM1 AI069423, UL1 TR001111, P30 AI50410, UM1 AI069532, U01 AI06947602, UM1 AI069419, U01 AI069503, UM1 AI069470, UL1 TR000040; UM1 AI069432, UL1 TR001082, U01 AI069471, UM1 AI069439, UM1 AI069471, UM1 AI069503; UM1 AI069556, UM1 AI069496, UM1 AI068636, UM1 AI069415, UM1 AI069419, UL1 TR000457, UM1 AI069503, UM1 AI069424, UM1 AI069412, U01 A1069472, UM1 AI069472).

Potential conflicts of interest. T. J. W. has received grant funding paid to Weill Cornell Medicine from Bristol Myers-Squibb, Gilead Sciences, and GlaxoSmithKline/ViiV Healthcare and has received honoraria from GlaxoSmithKline/ViiV Healthcare. M. C. has received institutional grant support from GlaxoSmithKline/ViiV Healthcare and Gilead Sciences and is a paid advisor for Gilead Sciences. A. S. is an employee of Merck Sciences and has ownership interest in Merck. R. D. C. has received institutional grant support from Merck and Co. All remaining authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Bower M, Powles T, Newsom-Davis T, et al. HIV-associated anal cancer: has highly active antiretroviral therapy reduced the incidence or improved the outcome? J Acquir Immune Defic Syndr **2004**; 37:1563–5.
2. Diamond C, Taylor TH, Aboumrad T, Bringman D, Anton-Culver H. Increased incidence of squamous cell anal cancer among men with AIDS in the era of highly active antiretroviral therapy. Sex Transm Dis **2005**; 32:314–20.
3. D'Souza G, Wiley DJ, Li X, et al. Incidence and epidemiology of anal cancer in the multicenter AIDS cohort study. J Acquir Immune Defic Syndr **2008**; 48:491–9.
4. Patel P, Hanson DL, Sullivan PS, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992–2003. Ann Intern Med **2008**; 148:728–36.
5. Piketty C, Selinger-Leneman H, Grabar S, et al; FHDH-ANRS CO 4. Marked increase in the incidence of invasive anal cancer among HIV-infected patients despite treatment with combination antiretroviral therapy. AIDS **2008**; 22:1203–11.
6. Machalek DA, Poynten M, Jin F, et al. Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: a systematic review and meta-analysis. Lancet Oncol **2012**; 13:487–500.
7. Hleyhel M, Belot A, Bouvier AM, et al. Trends in survival after cancer diagnosis among HIV-infected individuals between 1992 and 2009. Results from the FHDH-ANRS CO4 cohort. Int J Cancer **2015**; 137:2443–53.
8. Silverberg MJ, Lau B, Justice AC, et a.; North American AIDS Cohort Collaboration on Research and Design of IeDEA. Risk of anal cancer in HIV-infected and HIV-uninfected individuals in North America. Clin Infect Dis **2012**; 54:1026–34.
9. Aberg JA, Gallant JE, Ghanem KG, Emmanuel P, Zingman BS, Horberg MA; Infectious Diseases Society of America. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis **2014**; 58:e1–34.
10. Marks DK, Goldstone SE. Electrocautery ablation of high-grade anal squamous intraepithelial lesions in HIV-negative and HIV-positive men who have sex with men. J Acquir Immune Defic Syndr **2012**; 59:259–65.
11. Fox PA, Nathan M, Francis N, et al. A double-blind, randomized controlled trial of the use of imiquimod cream for the treatment of anal canal high-grade anal intraepithelial neoplasia in HIV-positive MSM on HAART, with long-term follow-up data including the use of open-label imiquimod. AIDS **2010**; 24:2331–5.
12. Richel O, Wieland U, de Vries HJ, et al. Topical 5-fluorouracil treatment of anal intraepithelial neoplasia in human immunodeficiency virus-positive men. Br J Dermatol **2010**; 163:1301–7.
13. Swedish KA, Factor SH, Goldstone SE. Prevention of recurrent high-grade anal neoplasia with quadrivalent human papillomavirus vaccination of men who have sex with men: a nonconcurrent cohort study. Clin Infect Dis **2012**; 54:891–8.
14. Joura EA, Garland SM, Paavonen J, et al; FUTURE I and II Study Group. Effect of the human papillomavirus (HPV) quadrivalent vaccine in a subgroup of women with cervical and vulvar disease: retrospective pooled analysis of trial data. BMJ **2012**; 344:e1401.
15. ASoC. O. Oral and Oropharyngeal Cancer: Statistics. **2014**. Available at: http://www.cancer.net/cancer-types/oral-and-oropharyngeal-cancer/statistics. Accessed 22 August 2017.
16. Steinau M, Saraiya M, Goodman MT, et al; HPV Typing of Cancers Workgroup. Human papillomavirus prevalence in oropharyngeal cancer before vaccine introduction, United States. Emerg Infect Dis **2014**; 20:822–8.
17. Saraiya M, Unger ER, Thompson TD, et al. US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. J Natl Cancer Inst **2015**; 107:djv086.
18. Herrero R, Quint W, Hildesheim A, et al; CVT Vaccine Group. Reduced prevalence of oral human papillomavirus (HPV) 4 years after bivalent HPV vaccination in a randomized clinical trial in Costa Rica. PLoS One **2013**; 8:e68329.
19. Wilkin T, Lee JY, Lensing SY, et al. Safety and immunogenicity of the quadrivalent human papillomavirus vaccine in HIV-1-infected men. J Infect Dis **2010**; 202:1246–53.
20. Kojic EM, Kang M, Cespedes MS, et al. Immunogenicity and safety of the quadrivalent human papillomavirus vaccine in HIV-1-infected women. Clin Infect Dis **2014**; 59:127–35.
21. Palefsky JM, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. N Engl J Med **2011**; 365:1576–85.
22. Markowitz LE, Dunne EF, Saraiya M, et al; Centers for Disease Control and Prevention. Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep **2014**; 63:1–30.
23. D'Souza G, Sugar E, Ruby W, Gravitt P, Gillison M. Analysis of the effect of DNA purification on detection of human papillomavirus in oral rinse samples by PCR. J Clin Microbiol **2005**; 43:5526–35.
24. Heath EM, Morken NW, Campbell KA, Tkach D, Boyd EA, Strom DA. Use of buccal cells collected in mouthwash as a source of DNA for clinical testing. Arch Pathol Lab Med **2001**; 125:127–33.
25. Feng Q, Cherne S, Winer RL, et al. Development and evaluation of a liquid bead microarray assay for genotyping genital human papillomaviruses. J Clin Microbiol **2009**; 47:547–53.
26. Feng Q, Cherne S, Winer RL, et al. Evaluation of transported dry and wet cervical exfoliated samples for detection of human papillomavirus infection. J Clin Microbiol **2010**; 48:3068–72.
27. Solomon D. The Bethesda system for reporting cervical cytology: definitions, criteria, and explanatory notes. 3rd ed. New York: Springer, **2015**.
28. Opalka D, Lachman CE, MacMullen SA, et al. Simultaneous quantitation of antibodies to neutralizing epitopes on virus-like particles for human papillomavirus types 6, 11, 16, and 18 by a multiplexed Luminex assay. Clin Diagn Lab Immunol **2003**; 10:108–15.
29. Dias D, Van Doren J, Schlottmann S, et al. Optimization and validation of a multiplexed Luminex assay to quantify antibodies to neutralizing epitopes on human papillomaviruses 6, 11, 16, and 18. Clin Diagn Lab Immunol **2005**; 12:959–69.
30. U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS table for grading the severity of adult and pediatric adverse events, version 1.0. [Updated August 2009]. Available at: http://rsc.tech-res.com/docs/default-source/safety/table_for_grading_severity_of_adult_pediatric_adverse_events.pdf
31. de Pokomandy A, Rouleau D, Ghattas G, et al; HIPVIRG Study Group. Prevalence, clearance, and incidence of anal human papillomavirus infection in HIV-infected men: the HIPVIRG cohort study. J Infect Dis **2009**; 199:965–73.
32. Sun J. A non-parametric test for interval-censored failure time data with application to AIDS studies. Stat Med **1996**; 15:1387–95.
33. Haupt RM, Wheeler CM, Brown DR, et al; FUTURE I and II Investigators. Impact of an HPV6/11/16/18 L1 virus-like particle vaccine on progression to cervical intraepithelial neoplasia in seropositive women with HPV16/18 infection. Int J Cancer **2011**; 129:2632–42.
34. Skinner SR, Szarewski A, Romanowski B, et al; VIVIANE Study Group. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 4-year interim follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. Lancet **2014**; 384:2213–27.
35. Lowy DR, Herrero R, Hildesheim A; Participants in the IARC/NCI Workshop on Primary Endpoints for Prophylactic HPV Vaccine Trials. Primary endpoints for future prophylactic human papillomavirus vaccine trials: towards infection and immunobridging. Lancet Oncol **2015**; 16:e226–33.
36. Sonawane K, Suk R, Chiao EY, et al. Oral human papillomavirus infection: differences in prevalence between sexes and concordance with genital human papillomavirus infection, NHANES 2011 to 2014. Ann Intern Med **2017**; 167:714–24.
37. Viens LJ, Henley SJ, Watson M, et al. Human papillomavirus-associated cancers—United States, 2008–2012. Morb Mortal Wkly Rep **2016**; 65:661–6.
38. Beachler DC, Abraham AG, Silverberg MJ, et al; North American AIDS Cohort Collaboration on Research and Design of IeDEA. Incidence and risk factors of HPV-related and HPV-unrelated head and neck squamous cell carcinoma in HIV-infected individuals. Oral Oncol **2014**; 50:1169–76.

Downloaded from https://academic.oup.com/cid/article/67/9/1339/4961357 by guest on 24 April 2025

Members of the study team. Jaime Robertson, Christopher Evans, Amneris Luque, Deepa Reddy, and Theresa Schwartz, investigators; Lei Hua, Janet Andersen, Jeanne Jiang, Anthony Lee, Pawel Paczuski, and Ming Yang, statisticians; William Strain and Karl Shaw, community representatives; Christina Megill, site representative; Jennifer Fiegel, Kevin Buck, Lynne Jones, Margaret Suraf, Ann Wallawander, and Aimee Willett, data managers; Laura Hovind, lab data manager; LuAnn Borowski, Laura Blair, and Brian Clagett, laboratory technologists; Ann Marie Anderson and Daniel Gebhardt, site representatives; Isaac Rodriguez-Chavez, National Institute of Dental and Craniofacial Research (NIDCR) clinical science representative; Scharla Estep and Michelle Wildman, protocol pharmacists; and study staff at the following sites: Sara A. Mattiucci and Renee Weinman, University of Pittsburgh (site 1001); Christina Megill and Todd Stroberg, Weill Cornell Chelsea Clinical Research Site (CRS) (site 7804); Christine Hurley and Emily Cosimano, University of Rochester (site 31787); Amy Sbrolla and Teri Flynn, Massachusetts General Hospital CRS (site 101); Eduardo Cachay and Constance Benson, University of California–San Diego AIDS Vaccine Research Center (site 701); Susan Blevins and Jonathan Oakes, University of North Carolina–Chapel Hill CRS (site 3201); Judith A. Aberg and Karen Cavanagh, New York University/Bellevue AIDS Clinical Trial Unit (site 401); Ruth K Friedman and José Ricardo H. Coutinho, Instituto de Pequisa Clínica Evandro Chagas/Fiocruz (site 12101); Shobha Swaminathan and Susana Rivera, New Jersey Medical School Clinical Research Center CRS (site 31786); Jolene Noel-Connor and Dorothy Sawo, Columbia Physicians and Surgeons CRS (site 30329); Craig Nielsen and Cathi Basler, University of Colorado Hospital CRS (site 6101); Beverly E. Sha and Janice Fritsche, Rush University Medical Center CRS (site 2702); Michael Klebert and Teresa Spitz, Washington University in St. Louis CRS (site 2101); Sherrie Wolfe and Margarita Aguilar, Northwestern University CRS (site 2701); Roberto C. Arduino and Maria Laura Martinez, Houston AIDS Research Team CRS (site 31473); Sandra Valle and Debbie Slamowitz, Stanford CRS (site 501); Annie Luetkemeyer and Jay Dwyer, University of California–San Francisco AIDS CRS (site 801; Clinical Trial Unit grant 5UM1AI069496); Michelle Saemann and Jaime Robertson, University of Cincinnati (site 2401); Jorge L. Santana and Sigrid Perez, University Puerto Rico ACTG CRS (site 5401); Valery Hughes and Julia Wagner, Weill Cornell Uptown CRS (site 7803); David Cohn and Diane States, Denver Public Health (site 31470); Ronald Mitsuyasu and Arezou Sadighi, University of California–Los Angeles Care Center CRS (site 601); Helen Patterson and Karen Tashima, the Miriam Hospital CRS (site 2951); Ioana Bica and Betsy Adams, Boston Medical Center (site 104); and Mary Albrecht and Andrea Kershaw, Beth Israel Deaconess (Partners/Harvard) CRS (site 103).

Downloaded from https://academic.oup.com/cid/article/67/9/1339/4961357 by guest on 24 April 2025