MAJOR ARTICLE

Long-Term Outcomes of Adding HPV Vaccine to the Anal Intraepithelial Neoplasia Treatment Regimen in HIV-Positive Men Who Have Sex With Men

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Background. Recent evidence shows that quadrivalent human papillomavirus (qHPV) vaccination in men who have sex with men (MSM) who have a history of high-grade anal intraepithelial neoplasia (HGAIN) was associated with a 50% reduction in the risk of recurrent HGAIN. We evaluated the long-term clinical and economic outcomes of adding the qHPV vaccine to the treatment regimen for HGAIN in human immunodeficiency virus (HIV)–positive MSM aged ≥27 years.

Methods. We constructed a Markov model based on anal histology in HIV-positive MSM comparing qHPV vaccination with no vaccination after treatment for HGAIN, the current practice. The model parameters, including baseline prevalence, disease transitions, costs, and utilities, were either obtained from the literature or calibrated using a natural history model of anal carcinogenesis. The model outputs included lifetime costs, quality-adjusted life years, and lifetime risk of developing anal cancer. We estimated the incremental cost-effectiveness ratio of qHPV vaccination compared to no qHPV vaccination and decrease in lifetime risk of anal cancer. We also conducted deterministic and probabilistic sensitivity analyses to evaluate the robustness of the results.

Results. Use of qHPV vaccination after treatment for HGAIN decreased the lifetime risk of anal cancer by 63% compared with no vaccination. The qHPV vaccination strategy was cost saving; it decreased lifetime costs by $419 and increased quality-adjusted life years by 0.16. Results were robust to the sensitivity analysis.

Conclusions. Vaccinating HIV-positive MSM aged ≥27 years with qHPV vaccine after treatment for HGAIN is a cost-saving strategy. Therefore, expansion of current vaccination guidelines to include this population should be a high priority.

Keywords. human papillomavirus; quadrivalent human papillomavirus vaccine; secondary/adjunct prevention; anal neoplasia; cost-effectiveness analysis.

Human immunodeficiency virus (HIV)–positive men who have sex with men (MSM) are at significantly greater risk for anal intraepithelial neoplasia and anal cancer [1–4]. The risk of anal cancer in these men is 37-fold higher than that in the general population [2–5]. The increased risk is primarily attributed to persistent anal human papillomavirus (HPV) infection, particularly genotypes 16 and 18, which can lead to precancerous lesions that may progress to invasive cancer if untreated [6].

In 2010, the Food and Drug Administration approved the quadrivalent HPV (qHPV) vaccine for the primary prevention of anal cancer and condyloma in boys and young men aged 11–26 years. Subsequently, the Centers for Disease Control and Prevention (CDC)

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Advisory Committee on Immunization Practices recommended the administration of the vaccine in all HIV-infected boys and girls 11 or 12 years of age and in those 13–26 years of age who were not previously vaccinated [7].

The current CDC vaccination guidelines do not recommend qHPV vaccination after age 26 years; however, emerging evidence suggests that the vaccine is beneficial as a secondary/adjuvant prevention strategy for the prevention of recurrent anal neoplasia and recurrent condyloma in older men [8, 9]. For example, qHPV vaccination of older MSM who had a history of high-grade anal intraepithelial neoplasia (HGAIN) was associated with a 50% reduction in the risk of recurrent HGAIN [8]. To further investigate the protective effect of qHPV vaccination for the prevention of occurrence and recurrence of HGAIN in older MSM, multiple clinical trials are underway; however, their results will not be available for several years [10, 11]. The long-term clinical and economic outcomes of the vaccine for the prevention of recurrent HGAIN and invasive cancer in older HIV-positive MSM are unknown. Therefore, the objective of the current study was to evaluate the cost-effectiveness of the qHPV vaccine for the prevention of recurrent HGAIN and to predict the lifetime reduction in the risk of anal cancer in HIV-positive MSM aged ≥27 years.

METHODS

Markov Model

We developed a Markov model to compare the long-term effects of qHPV vaccination with no vaccination after HGAIN treatment in HIV-positive MSM aged ≥27 years. Our model used the following health states: HIV-positive status based on CD4 cell count (ie, >500, 200–500, or <200 cells/mm^3); HPV status (presence or absence of HPV-16/18 positivity); baseline prevalence of anal histology (normal [ie, no low-grade anal intraepithelial neoplasia (LGAIN)], no HGAIN, and no cancer], LGAIN, HGAIN, or invasive cancer); HGAIN recurrence (≤3 recurrences); survivorship; and death (Figure 1).

At the start of the model, all persons in the cohort were considered unvaccinated and untreated for HGAIN, and the cohort was distributed based on the baseline prevalence of anal

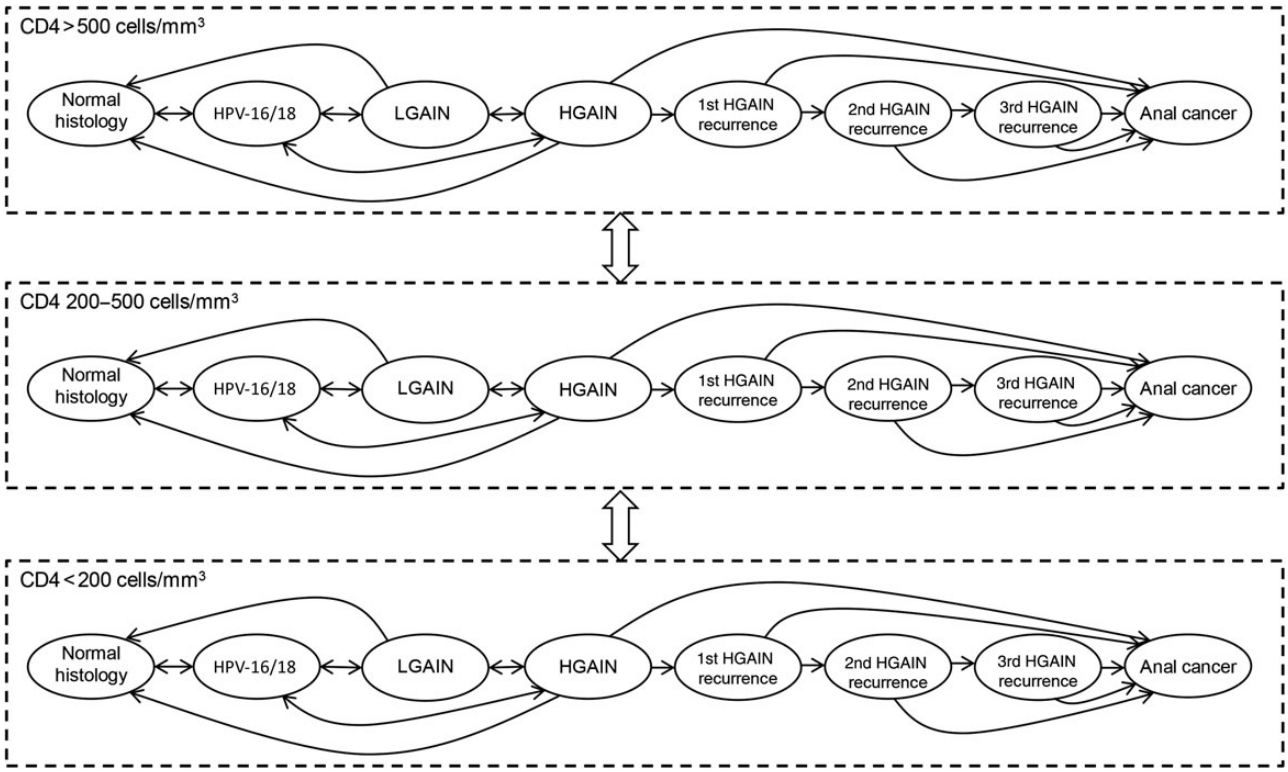

Figure 1. Schematic model depicting health states of clinical and economic significance. At any given time, a patient occupies one of the health states represented by ovals. Arrows between states represent possible transitions based on annual probabilities. Dashed rectangles distinguish anal histology states by CD4 cell count (cells/mm^3). As time progresses, patients can transition to other states and acquire cost and health utilities associated with that state. Anal histology and high-grade anal intraepithelial neoplasia (HGAIN) treatment characteristics were overlaid on the human immunodeficiency virus (HIV) status of the patients; that is, anal disease and HIV disease could concurrently progress or regress with time. The model stops when all patients transition to the death state. Note that a patient could transition to the death state from any of the above states because of background mortality (for the sake of clarity, these transitions are not shown in the figure). Abbreviations: HGAIN, high-grade anal intraepithelial neoplasia; HPV, human papillomavirus; LGAIN, low-grade anal intraepithelial neoplasia.

histology and the distribution of CD4 cell count. The time horizon was divided into cycles of 1-year duration. Within each cycle, persons transitioned from one health state to another based on the transition probabilities. Anal histology and HGAIN treatment characteristics were overlaid on the HIV status of the patients; that is, anal and HIV disease could concurrently progress or regress over time. In the model, MSM treated for HGAIN were either vaccinated with qHPV vaccine or not. After treatment for initial HGAIN, patients may develop recurrent HGAIN. Vaccinated patients had a lower risk of HGAIN recurrence than unvaccinated patients. Recurrent and untreated HGAIN led to anal cancer. Persons could die from HIV-related illness, anal cancer, or other unrelated causes (see Supplementary Appendix 1 for details).

Clinical Data

Incidence of Anal Cancer

We first estimated the age-specific incidence of anal cancer using 2 previously published multicenter studies [3, 12]. D'Souza et al [3] provided the overall incidence of anal cancer in HIV-positive MSM; however, the study did not provide person-time data stratified by age and HIV status. Using person-time data from Seaberg et al [12] and age-specific anal cancer diagnosis and overall (age-adjusted) incidence of anal cancer in HIV-positive MSM from D'Souza et al [3], and assuming that the proportion of the person-time distribution in patients with anal cancer is similar to that in patients with HIV-related cancers, we estimated the incidence of anal cancer in MSM stratified by age and HIV status (see Supplementary Appendix Section 2.2 for details).

Model Parameters

We present all model parameters in Supplementary Appendix 1. The baseline prevalence of anal histology in HIV-positive MSM and baseline CD4 cell count data were obtained from the CDC [13] and a meta-analysis [1]. The incidence and clearance of HPV types 16 and 18 were obtained from Machalek et al [1]. Because the progression from HPV to LGAIN has not been assessed in the literature, we used the progression from normal histology to LGAIN to predict the progression from HPV to LGAIN. We used published study findings to estimate the risks of transitions within precancerous states or between precancerous states and invasive cancer [14]. Regression rates from HGAIN to LGAIN and from HGAIN to normal tissue were estimated from Tong et al [15]. The study by Tong et al does not provide age-specific regression of HGAIN in HIV-positive MSM; therefore, using the data on age-specific regression of HGAIN in both HIV-positive and HIV-negative MSM and age-adjusted data on regression of HGAIN in HIV-positive MSM, we calculated age-specific HGAIN regression in HIV-positive MSM (see Supplementary Appendix Section 2.3 for details).

There are no direct estimates of the progression from HGAIN to anal cancer. We calibrated age-specific progression from HGAIN to anal cancer using a separate natural history Markov model for anal carcinogenesis in HIV-positive MSM. For this, we used our previously estimated age-specific incidence of anal cancer in HIV-positive MSM as the calibration target and the age-adjusted progression rate from HGAIN to anal cancer of 1 case in 377 per year from Machalek et al [1] as a reference point (details in Supplementary Appendix Section 2.4).

Vaccine effectiveness (defined as the reduction in the hazards of developing recurrent HGAIN) data were obtained from Swedish et al [8] (details in Supplementary Appendix Section 1 and Table T1.3). We assumed a constant degree of vaccine protection and lifetime duration of protection for the base-case analysis. Under alternative scenarios, we evaluated the effect of decline in the degree of protection using functions that follow normal and exponential distributions. We used data from Goldstone et al [16] to determine the probability of HGAIN recurrences (Supplementary Appendix Table T1.2). Mortality data were based on CD4 cell count and anal cancer status [17, 18] (Supplementary Appendix Table T1.4).

Modeling Assumptions

We assumed that the incidence of HPV infection is static across all ages. For the base-case analysis, we assumed that all MSM were compliant with treatment for HGAIN and invasive cancer; moreover, all MSM were assumed to be receiving treatment for HIV infection as their CD4 cell counts warrant highly active antiretroviral therapy. The improvement in the CD4 cell count after the inception of antiretroviral therapy was based on data from previously published studies [19, 20] (details in Supplementary Appendix Section 2.1). Finally, those who survived 5 years after treatment for invasive cancer were assumed to be cured; their life expectancy was determined using US life tables and the HIV-related risk of death associated with their CD4 cell count [21].

Costs

The lifetime cancer-related costs were estimated using survival data from the Surveillance, Epidemiology, and End Results (SEER) Medicare database (details in Supplementary Appendix Section 2.5). The cost of HGAIN treatment was obtained from a study published elsewhere [22]. The cost of a 3-dose qHPV vaccination was assumed to be $500. The annual costs of care for patients with HIV stratified by CD4 cell count were obtained from Bozzette et al [23]. We adjusted all costs to 2014 US dollars using consumer price indices for medical care [24].

Health-Related Utilities

Health-related utilities (defined as preference-based valuation of the health states) for HGAIN, anal cancer, and HIV-positive status (based on CD4 cell count) were obtained from

a cost-effectiveness analysis published elsewhere [25] (see Supplementary Appendix Table T1.4). We further adjusted all health-related utilities by age [26].

Analysis

We conducted the analysis from the healthcare perspective. The results are presented as the decrease in lifetime risk of anal cancer, associated lifetime healthcare costs, quality-adjusted life expectancy, and incremental cost-effectiveness ratio (ICER; defined as the additional cost of including a vaccination program to gain an additional quality-adjusted life year [QALY]). All costs and QALYs were discounted at a 3% rate [27]. To determine the robustness of the results, we performed deterministic and probabilistic sensitivity analyses on all model parameters (see Supplementary Appendix 4 for details). We used TreeAge Pro 2014 software (TreeAge Software, Inc.; Williamstown, Massachusetts) for modeling and analysis.

RESULTS

Model Validation

The model-predicted cumulative incidence rates were within 95% confidence intervals of the reported values (see Supplementary Appendix 3 for details).

Model-Predicted Anal Cancer Incidence

The model predicted the incidence of anal cancer per 100 000 persons (Figure 2). The incidence was highest in HIV-positive 48-year-old MSM—325 per 100 000 persons. The natural history model predicted that the lifetime risk of developing invasive anal cancer was 29.56% for a 48-year-old man. If vaccinated, under the assumption that the vaccine degree of protection remains constant throughout the duration of protection, the incidence of invasive anal cancer for a 48-year-old man dropped to 106 per 100 000 persons (an almost 3-fold drop). If the vaccine degree of protection follows a normal or an exponential distribution, the incidence of anal cancer for a 48-year-old man dropped to 100 or 250 per 100 000 persons, respectively. Under all scenarios, vaccination resulted in a drop in the incidence of anal cancer across all ages.

Cost-Effectiveness Analysis

In the base-case analysis, we found that qHPV vaccination after treatment for HGAIN in a 27-year-old HIV-positive MSM decreased the lifetime risk of anal cancer by 63%. Vaccination decreased the lifetime cost by $419 (from $372 656 to $372 237) and increased the QALYs by 0.16 (from 17.35 to 17.51) (Table 1). Therefore, qHPV vaccination strategy was cost saving; that is, it decreased costs and increased QALYs.

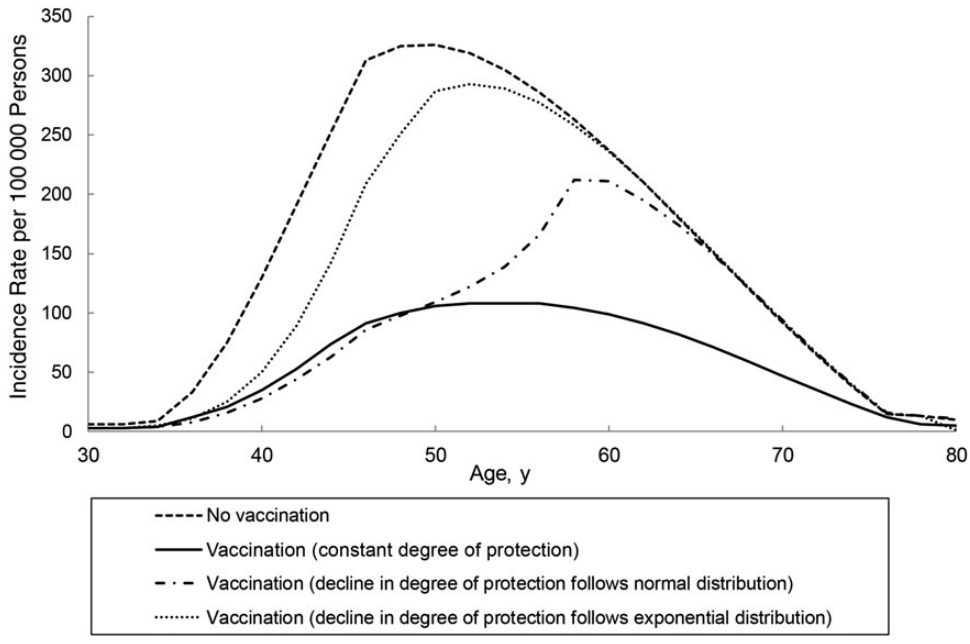

Figure 2. Model-predicted incidence rate of anal cancer per 100 000 person-years with and without quadrivalent human papillomavirus (qHPV) vaccination. The model-predicted incidence of anal cancer is shown under the scenario of (1) no vaccination, (2) a vaccination strategy that assumes a constant degree of protection throughout the duration of protection, (3) vaccination under the assumption that the decrease in degree of protection follows a normal distribution, and (4) vaccination under the assumption that the decrease in degree of protection follows an exponential distribution. We used a constant waning rate of 1/30 per year to predict the decline in degree of protection that follows a normal distribution and a mean and standard deviation of 30 and 5 years, respectively, to predict the decline that follows an exponential distribution.

Table 1. Base-Case Results and Sensitivity Analysis

Variable	Total Cost, $		Total QALYs		ICER, $/QALY	Decrease in Lifetime Risk of Anal Cancer After Vaccination, %
	No qHPV Vaccine and Treatment for HGAIN	qHPV Vaccine and Treatment for HGAIN	No qHPV Vaccine and Treatment for HGAIN	qHPV Vaccine and Treatment for HGAIN		
Base case[a]	372 656	372 237	17.35	17.51	Dominant[c]	62.98
Vaccine effectiveness[b]						
Best-case scenario (high effectiveness)	372 656	370 437	17.35	17.56	Dominant[c]	88.01
Worst-case scenario (low effectiveness)	372 656	372 906	17.35	17.36	36 221	1.99
Age at vaccination, y						
30	364 407	363 754	16.82	16.95	Dominant[c]	64.29
40	330 368	328 922	14.70	14.76	Dominant[c]	67.72
50	287 210	285 401	12.26	12.28	Dominant[c]	70.54
60	236 807	235 016	9.57	9.58	Dominant[c]	70.18
70	179 712	178 269	6.71	6.70	Dominant[c]	71.05
Rate of decline in vaccine degree of protection						
Normal	372 656	372 476	17.35	17.48	Dominant[c]	42.67
Exponential	372 656	372 662	17.35	17.41	113.95	14.68
Probability of being treated for HGAIN and HGAIN recurrences, %						
25	366 311	366 188	17.28	17.35	Dominant[c]	29.24
50	369 842	369 508	17.32	17.43	Dominant[c]	48.00
75	371 614	371 218	17.34	17.47	Dominant[c]	57.64

Abbreviations: HGAIN, high-grade anal intraepithelial neoplasia; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; qHPV, quadrivalent human papillomavirus vaccine.

[a] For the base case, we assume that the degree of protection remains constant throughout the duration of protection (ie, lifetime).

[b] We used the lower and upper limits of the 95% confidence intervals from Swedish et al [8] to vary vaccine effectiveness for best- and worst-case scenarios, respectively.

[c] Dominant means that the vaccination increases lifetime effectiveness and decreases lifetime cost (ie, the strategy is cost saving).

Sensitivity Analysis

We evaluated the sensitivity of model outcomes to vaccine effectiveness. Under the best-case scenario, using the lower limit of the 95% confidence interval for vaccine effectiveness (ie, under the assumption that the qHPV vaccine is highly efficacious for reducing recurrent HGAIN), we found that vaccination decreased the lifetime risk of anal cancer by approximately 88%. Under the worst-case scenario, using the upper limit of the 95% confidence interval for vaccine effectiveness, this decrease was approximately 2%. The corresponding economic outcome varied between cost saving to an ICER of $36 221 per QALY, for the best case and worst case scenarios of vaccine effectiveness.

Under the alternative assumption that the vaccine degree of protection declines at a normal rate, we found that vaccination resulted in a 43% decrease in lifetime risk of anal cancer and was determined to be a cost-saving strategy; however, under the assumption that the vaccine degree of protection declines at an exponential rate, vaccination resulted in an ICER of $114 per QALY and a decrease in lifetime risk of 15% (Table 1). When the probabilities of receiving treatment for HGAIN and HGAIN recurrences were varied in the range of 25% and 75%, the decrease in the lifetime risk of anal cancer changed from 29% and 58%, respectively. Vaccination remained a cost-saving strategy across the range (Table 1).

We also performed a threshold analysis to identify the maximum economically acceptable vaccine effectiveness in terms of the hazard ratio. We found that to be economically unacceptable (ie, to cross the maximum willingness-to-pay threshold of $50 000 per QALY) in HIV-positive MSM, the hazard ratio for the decrease in the risk of recurrent HGAIN should be >0.98 for the first and subsequent years after vaccination.

The age at vaccination and treatment had the highest impact on the ICER, followed by the progression from HGAIN to anal cancer (Figure 3*A*). The top 20 model parameters in the order of their impact on the ICER (from most to least sensitive) are presented using a tornado diagram in Figure 3*A*. For all model parameters, the ICERs remained below $50 000 per QALY. The results of probabilistic sensitivity analysis showed that vaccination was cost-effective with 100% probability at the willingness-to-pay threshold of $12 000 per QALY or more (Figure 3*B*).

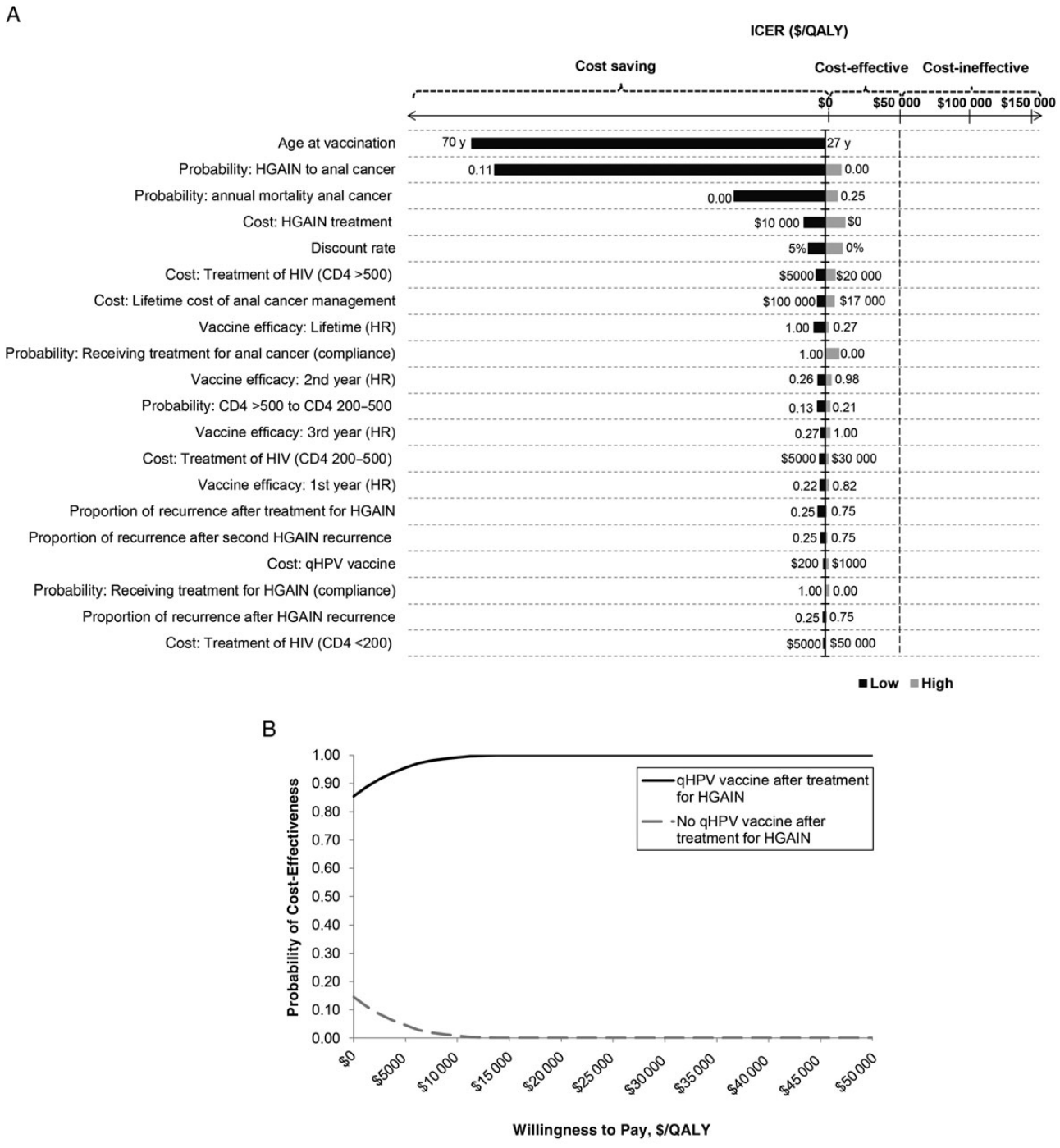

Figure 3. *A*, Tornado diagram displaying the 20 model parameters with the impact on cost-effectiveness in the order of sensitivity. Cost saving means that vaccination decreased lifetime cost and increased quality-adjusted life expectancy; cost-effective means that vaccination increased both lifetime cost and quality-adjusted life expectancy; however, the incremental cost-effectiveness ratio (ICER) was below the societal willingness-to-pay threshold of $50 000/quality-adjusted life year (QALY). The horizontal axis represents outcome in terms of ICER (additional cost of including a vaccination program to gain an additional QALY). Parameters are arrayed along the vertical solid line, which represents the outcome point of base-case ICER. Bars are arranged in descending order of bar width, which represents the degree of uncertainty (longest bar represents parameter generating widest uncertainty). We divided the horizontal axis into 3 regions: regions of cost saving, cost-effectiveness, and cost-ineffectiveness. CD4 represent CD4 cell count (cells/mm^3). *B*, Cost-effectiveness acceptability curves comparing no qHPV vaccination with qHPV vaccination strategy. This plot shows the probability that the vaccination strategy is cost-effective compared with the no-vaccination strategy and the no-vaccination strategy is cost-effective compared with the vaccination strategy for a range of willingness-to-pay thresholds that a decision maker may consider acceptable. Abbreviations: HGAIN, high-grade anal intraepithelial neoplasia; HIV, human immunodeficiency virus; HR, hazard ratio; qHPV, quadrivalent human papillomavirus vaccine.

Additional 1-way sensitivity analyses are presented in Supplementary Appendix 4.

DISCUSSION

Our analysis suggests that qHPV vaccination in HIV-positive MSM aged ≥27 years who have been diagnosed and treated for HGAIN decreases the lifetime risk of anal cancer and is a cost-saving strategy because it decreases lifetime costs and increases quality-adjusted life expectancy. The results were robust irrespective of reasonable changes in vaccine effectiveness and age at vaccination.

We found that even under the worst-case assumption of vaccine effectiveness, in which we assumed that the vaccine essentially becomes ineffective after the third year of treatment, vaccinating older HIV-positive MSM remained a highly cost-effective strategy. Moreover, to be economically unattractive (ie, to cross a conservative willingness-to-pay threshold of $50 000/QALY), the hazard ratio for the vaccination strategy should be >0.98 for the first and subsequent years. Based on data from published observation studies on the prevention of recurrent anal neoplasia and anal condyloma in men [8, 9] and similar findings observed in the prevention of cervical neoplasia in women [28], the qHPV vaccine is expected to prevent recurrent precancerous lesions with moderate to high effectiveness. Therefore, it is unlikely that adjuvant vaccination in HIV-positive MSM will not be cost-effective. This finding is important, because the results from ongoing clinical trials evaluating the efficacy of qHPV vaccine for preventing recurrent HGAIN in older HIV-positive MSM may not change the overall policy conclusion of our study. The results from these trials will not be available for ≥5 years; expanding qHPV vaccination sooner rather than later to the cohort of older HIV-positive MSM who have been diagnosed and treated for HGAIN could reduce the incidence of anal cancer by almost 3-fold in those men and may save health care resources.

To our knowledge this is the first study to evaluate the long-term outcomes of adjuvant qHPV vaccination in HIV-positive MSM. Earlier studies evaluated prophylactic/primary qHPV vaccination in MSM aged <27 years (the current practice), and adjuvant vaccination in HIV-negative MSM previously exposed to HPV types 16 and/or 18, aged ≥27 years, after treatment for HGAIN. Both studies found that prophylactic vaccination of young MSM and adjuvant vaccination of 27 years or older HIV-negative MSM is likely to be cost-effective [29, 30].

Sensitivity analysis showed that our results remained robust to changes in model parameters. Similar to earlier findings [30], the disease-related parameter that had the greatest effect on the cost-effectiveness results was progression from HGAIN to anal cancer. Although data on this progression are not available, we calibrated these values using the best available information from the literature. Future research should be prioritized to estimate this progression.

There is insufficient evidence regarding the duration and degree of protection after qHPV vaccination in HIV-positive MSM aged ≤26 years. According to recently published studies, the vaccine is expected to render protection for at least 6–8 years after primary vaccination [31, 32], and there is no evidence as yet necessitating administration of a booster dose. Nevertheless, short duration of primary protection creates a strong rationale for the sequential use of other secondary prevention strategies (eg, cytologic testing and digital anal examination) for the identification of new lesions or tumor formation and secondary/adjuvant vaccination to reduce the risk of recurrent lesions and invasive cancer in older men.

Previous work and our findings create a strong case for qHPV vaccination of all MSM irrespective of their age and HIV status [29, 30]. However, the challenge lies in getting men to disclose their sexual identity to healthcare providers. A study shows that men are more comfortable disclosing their sexual identity at or after age 20 years (ie, 2 years after the sexual debut) [33], when the potential effectiveness of primary vaccination is likely to have declined [29]; therefore, screening and adjuvant vaccination becomes a priority, particularly in older HIV-positive MSM.

Administration of the qHPV vaccine as an adjuvant prevention strategy after age 26 years should not supplant the role of the vaccine as a primary prevention strategy, nor should it be considered a substitute for screening strategies, such as cytology-based testing or digital anal examination. We believe that a comprehensive anal cancer prevention program that includes both primary prevention (ie, primary vaccination) and secondary prevention (ie, screening and adjuvant vaccination) would be more effective than the status quo of primary vaccination only and would have a distinct role in preventing invasive cancer through the prevention of HPV infection, the identification of anal intraepithelial neoplasia, and the prevention of HGAIN recurrence. However, we acknowledge that anal cancer screening is not widely accepted and implemented because there have been no definitive studies documenting the benefit of routine screening in MSM.

It must be recognized that the current article focuses on patients who already have HGAIN. Although it is true that the prevalence of HGAIN would substantially decrease with more widespread vaccination of adolescent boys, current vaccination rates are only 13.9% [34]. Furthermore, the high prevalence of HGAIN among HIV-positive MSM will remain a major issue given the large percentage of unvaccinated boys. We believe that adjuvant qHPV vaccination could play a large role in decreasing the risk of anal cancer among these men in the future.

Our study has several limitations. The vaccine effectiveness data were based on an observational study in HIV-negative MSM [8]. For the purpose of analysis, we assumed that the vaccine would be equally effective in HIV-positive MSM. Confirmation from a randomized clinical trial evaluating vaccine efficacy in HIV-positive MSM is required. Owing to a lack of data, we assumed that HPV incidence remains static across all

age groups. Indirect vaccine benefits (eg, herd immunity) were not incorporated in our model. We also did not take into account the effectiveness of the vaccine in preventing recurrent condyloma [9]. Therefore, the model underestimated the overall cost-effectiveness of the vaccine, and inclusion of these benefits would further improve cost-effectiveness.

In conclusion, qHPV vaccination is cost saving in HIV-positive MSM aged ≥27 years who are being treated for HGAIN. Given the increasing burden of anal cancer, expansion of a vaccination program to include these men should be a high priority.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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