Supplementary material accompanying the manuscript titled "Long-term outcomes of adding HPV to the anal intraepithelial neoplasia treatment regimen in HIV-positive men who have sex with men" by Ashish A. Deshmukh, Jagpreet Chhatwal, Elizabeth Y. Chiao, Alan G. Nyitray, Prajnan Das, Scott B. Cantor

Supplementary Appendix 1. Model parameters

Our cohort-based model was composed of HIV-positive men who have sex with men (MSM) in the US. The baseline cohort of 100 000 HIV-positive MSM was stratified into health states by CD4 count, HPV prevalence, and anal histology. In the model the cohort starts at the age of 27 years. We varied the start age in the range of 27 years to 70 years to evaluate the effect of change in start age on the outcomes of incremental cost-effectiveness ratio and decrease in lifetime risk of invasive cancer. At the baseline, patients were distributed based on the anal histology in HIV-positive MSM (HIV status was defined by the patient's CD4 count, which could be in one of three stratum: >500 cells/mm^3, 200-500 cells/mm^3, or <200 cells/mm^3. The model parameters for the baseline patient characteristics of CD4 count distribution and anal histology are presented in Table T1.1.

We presented natural history parameters including HPV incidence and clearance, HIV progression and regression, and anal disease progression and regression in Table T1.2. At the interval of once a year (i.e., annual cycle length), MSM transitioned from one health state to another based on the annual transition probabilities for moving from one state to another. At the start of the model, all MSM were untreated for HGAIN and unvaccinated. MSM diagnosed with HGAIN were either vaccinated with qHPV vaccine or not. Those who did not receive treatment for HGAIN were presumed to follow the natural history, and progressed to anal cancer or regressed to LGAIN or normal. MSM whose anal histology became normal had a risk of HPV reinfection, and the probability of HPV reinfection was based on the annual incidence of HPV types 16 and 18 in HIV-positive MSM. The men infected with HPV could progress to LGAIN or clear their HPV based on the probability of progression to HGAIN or clearance, respectively. After being infected with LGAIN, these men follow anal cancer natural history and progress to HGAIN or become normal.

In addition to the anal disease progression, HIV progression was contingent on the annual probability of moving from one HIV stratum to another based on the patient's CD4 count. HIV regression (improvement in the CD4 count) was triggered by receipt of antiretroviral therapy. In the model, receipt of antiretroviral therapy triggered improvement in the CD4 counts (for details please see Section S2.1).

Vaccine effectiveness was defined as "the decrease in the hazards (probability that an individual at a given time has an event) of recurrent HGAIN after treatment for initial HGAIN, or decrease in the hazards of consecutive HGAIN recurrences" (Table T1.3). The base case vaccine efficacy of 42% can be defined as within one year of treatment, HIV-positive MSM who received treatment for HGAIN and qHPV vaccination were 58% less likely to experience recurrent HGAIN than those MSM who did not get vaccinated during the treatment for HGAIN. In our sensitivity analysis, we varied the hazard ratio in the range of 0.22 for the first year, 0.26 for the second year, and 0.27 for the third and consecutive years to 0.82 for the first year, 0.98 for the second year, and 1.00 for the third and consecutive years. This means that under the worst case assumption, we assumed that within the first year after vaccination, patients in the vaccination strategy were 18% less likely to experience recurrent HGAIN than MSM in no vaccination strategy; during the second year of treatment, MSM in the vaccination strategy were only 2% less likely to experience recurrent HGAIN than MSM in no vaccination strategy, and after that (i.e., after the third year onwards) qHPV vaccination was not effective, as recurrence rates were similar for both the vaccination and no vaccination strategies.

In Table T1.4, annual mortality probabilities associated with HIV status by CD4 count and anal cancer status, annual HIV treatment costs, HGAIN treatment costs, and anal cancer lifetime treatment costs are presented. In the same table, we also presented data on utilities (i.e., quality of life weights by disease condition and age-related quality of life weights).

Appendix Table T1.1. Baseline characteristics

Model parameters	Values
Population* of *HIV-positive MSM	
Model start age	27 years (range 27 years – 70 years)
CD4 count distribution among HIV-positive MSM [1]	
CD4>500	11.65%
CD4 200-500	29.73%
CD4<200	58.62%
Baseline anal histology [2]	
Normal histology	47.5%
LGAIN	28.6%
HGAIN	23.9%
Anal cancer	0%

Abbreviations: LGAIN, low-grade anal intraepithelial neoplasia; HGAIN, high-grade anal intraepithelial neoplasia

Appendix Table T1.2. Natural history parameters

Model parameters [2]	Values		
Incidence, %/year			
HPV 16	13.0 (95% CI 9.6 – 17.6)		
HPV 18	5.3 (95% CI 3.5 – 8.0)		
Clearance, %/year			
HPV 16	14.6 (95% CI 10.2 – 21.2)		
HPV 18	24.5 (95% CI 16.9 – 35.4)		
Transition probabilities (annual) [2-9]			
HIV progression			
CD4>500 to CD4 200–500	0.175 (0.135-0.215)		
CD4 200–500 to CD4<200	0.252 (0.198-0.307)		
HIV Regression	Appendix Section S2.1.		
Anal cancer progression	CD4>500	CD4 200 - 500	CD4<200
Normal to LGAIN	0.245 (95% CI 0.084-0.406)	0.245 (95% CI 0.084-0.406)	0.598 (95% CI 0.279-0.918)
Normal to HGAIN	0.053 (95% CI 0.016-0.091)	0.053 (95% CI 0.016-0.091)	0.138 (95% CI 0.039-0.238)
LGAIN to HGAIN	0.135 (95% CI 0.015-0.255)	0.167 (95% CI 0.059-0.276)	0.488 (95% CI 0.165-0.812)
HGAIN to cancer	(Range 0.00049-0.1058) Appendix Section S2.4		
Anal cancer regression			
LGAIN to normal	0.066 (95% CI 0.000-0.132)		
HGAIN to LGAIN	(Range 0.027-0.209) Appendix Section S2.3		
HGAIN to normal	(Range 0.011-0.091) Appendix Section S2.3		
HGAIN recurrence, % [7]			
After initial treatment	0.61		
After treatment for recurrence	0.49		
After treatment for second recurrence	0.50		

Abbreviations: HPV, human papillomavirus; LGAIN, low-grade anal intraepithelial neoplasia; HGAIN, high-grade anal intraepithelial neoplasia

Appendix Table T1.3. Vaccine effectiveness

Vaccine effectiveness for reducing recurrent HGAIN, HR [10]	
First year	0.42 (95% CI 0.22-0.82)
Second year	0.50 (95% CI 0.26-0.98)
Third year	0.52 (95% CI 0.27-1.00)
Lifetime	0.52 (95% CI 0.27-1.00)

Abbreviations: HGAIN, high-grade anal intraepithelial neoplasia**;** HR, hazard ratio

Appendix Table T1.4. Mortality, costs, and utilities (quality of life weights)

Annual mortality probabilities [11, 12]	
HIV+ (CD4>500)	0.0018
HIV+ (CD4 200 to 500)	0.0044
HIV+ (CD4<200)	0.0688
Anal cancer	0.0843
HIV treatment annual cost, $ [13]	
HIV+ (CD4>500)	12 327
HIV+ (CD4 200 to 500)	21 433
HIV+ (CD4<200)	45 114
HGAIN treatment costs, $ [14]	4795
Anal cancer treatment lifetime costs, $	60 913
qHPV vaccination costs, $	500
Utilities (quality of life weights) [3]	
HIV (CD4 > 500)	0.94 (95% CI 0.90 – 0.98)
HIV (CD4 200 – 500)	0.87 (95% CI 0.84 – 0.90)
HIV (CD4 < 200)	0.80 (95% CI 0.76 – 0.84)
HGAIN	0.98 (95% CI 0.95 – 0.99)
Anal cancer	0.58 (95% CI 0.50 – 0.70)
Age-related utilities for men [15]	
Age group	
0–29	0.928
30–39	0.918
40–49	0.887
50–59	0.861
60–69	0.840
70–79	0.802
>80	0.782

Abbreviations: HPV, human papillomavirus; HGAIN, high-grade anal intraepithelial neoplasia

Supplementary Appendix 2. Model parameterization

Section S2.1. Estimation of change in CD4 count after receipt of antiretroviral therapy

We used data from two previously published studies to model change in CD4 count after receipt of antiretroviral therapy [6, 16]. Based on the guidelines of the U.S. Department of Health and Human Services, our model assumes that a patient is eligible to receive antiretroviral therapy when his CD4 count falls below 350 cells/mm^3. To model change in CD4 count, we created four categories—CD4 count >500, between 350-500, between 200-350, and <200. We used the following continuous data on annual change in CD4 count (Appendix Table T2.1) to predict the change in CD4 count within the categories. Based on the evidence in the literature, we further assumed that after 6 years on antiretroviral therapy, patients with baseline CD4 cell counts of 201-350 returned to nearly normal CD4 cell counts of >500; however, patients with CD4 cell counts in the strata <200 did not return to the strata of >500 and remained in the strata of 200-500 [16].

Appendix Table T2.1. Estimation of the change in CD4 count after receipt of antiretroviral therapy

Baseline CD4 count	Change (cells/mm^3)		
	0-1 year	1-4 years	>4 years
< 200	145	36	8.5
201-350	183	34	3.5

Section S2.2. Estimation of age-specific anal cancer incidence in HIV-positive MSM

The incidence of anal cancer was estimated using two multicenter AIDS cohort studies. D'Souza et al (2008) includes incidence from 1984 to 2007 (i.e., pre-HAART and post-HAART) [8]. However, the study does not give person-years data stratified by age and HIV status. We theoretically calculated age-stratified person years and incidence for HIV-positive MSM using the data from D'Souza et al (2008) and Seaberg et al (2010) [8, 9]. Our estimations are presented in the following table:

Appendix Table T2.2. Anal cancer age-specific incidence

Age, y	Incidence [8]	Age-stratified incidence [9]	Person-years approximation	Person-years, adjusted to reflect overall incidence of 17/12 500	Estimated incidence in HIV-positive MSM
<30	5	58/7911 person-years	689 [(5*7991)/58]	5904 [(689*12 500)/1459]	5/5904 (84 per 100 000)
30-39	5	400/27 778 person-years	347	2973	5/2972 (168 per 100 000)
40-49	5	313/26 681 person-years	238	2039	5 per 2039 (245 per 100 000)
≥50	2	162/14 949 person-years	185	1584	2 per 1584 (126 per 100 000)
	Overall incidence post-HAART: 137/100 000 person-years ≈17/12 500		Total person years = 1459 Person years for our cohort from D'Souza et al = 12 500	Total persons years = 12 500	Total age-adjusted incidence = 137 per 100 000

Section S2.3. Estimation of age-specific HGAIN regression in HIV-positive MSM

Appendix Table T2.3. HGAIN age-specific regression

HIV status	**Regression** [4]			
HIV positive	19.2 per 100 person-years			
HIV negative	37.1 per 100 person-years			
Age	**Regression (overall)**	**n (overall)**	**Person-years (overall)**	**Estimated regression (per 100 person-years)**
<35	40.4 per 100 person-years	6	14.8	33·12
35-45	31.4 per 100 person-years	8	25.5	25.63
46-55	21.9 per 100 person-years	9	41.1	17.89
>55	4.8 per 100 person-years	1	20.8	3.92
Overall	23.5 per 100 person-years	24	102	

Section S2.4. Estimation of age-specific HGAIN to anal cancer progression in HIV-positive MSM
We calibrated age-specific progression from HGAIN to anal cancer using a natural history model of anal carcinoma. To calibrate the progression, we used our previously estimated age-specific incidence (Table T2.1) as a calibration target. Using age-specific HGAIN regression (Table T2.2) and age-adjusted other natural history parameters, the model calibrated age-specific HGAIN to anal cancer progression.

Appendix Table T2.4. Model calibrated age-specific HGAIN to anal cancer progression

Age	**Model parameters**	**Calibration target (incidence of anal cancer)**
	HGAIN to anal cancer (calibrated values)	
<30	0.00360	84 per 100 000
30-39	0.00710	164 per 100 000
40-49	0.01058	243 per 100 000
≥50	0.00049	126 per 100 000

Section S2.5. Estimation of lifetime anal cancer-related treatment costs
We estimated the lifetime cost of anal cancer management using the Surveillance Epidemiology and End Results-Medicare linked database for the years 1992-2009 [17]. For this, we matched newly diagnosed anal cancer patients (by age and sex) to non-cancer controls. For both cases and controls, we estimated survival time from the date of diagnosis until death or the end of follow-up, which was defined as the end of the Medicare claims. We used a parametric regression model to estimate median survival time. Lifetime costs were estimated by combining survival data with Medicare claims. Anal cancer-related costs were estimated as the difference between the costs for cases and controls. All costs were adjusted to 2014 US dollars using Center for Medicare and Medicaid Services (CMS) market basket index levels. Future costs were discounted using a 3% discount rate.

Appendix Table T2.5. Life-time anal cancer-related treatment costs

Parameters	**Cost (US, $) [17]**
Average total costs for cases	132 011
Average total costs for controls	71 098
Anal cancer-related costs	60 913
Anal cancer-related costs per year	8025

Supplementary Appendix 3. Model validation

We validated our natural history model by comparing model-predicted 5-year cumulative incidence in HIV-positive 40-year-old MSM to the 5-year cumulative incidence of anal cancer in HIV-infected patients (median age 40 years) from a large US-based cohort study conducted by Cachay et al [18]. The model-predicted incidence rates were within the 95% confidence intervals of the cumulative incidence reported by Cachay et al.

Table T3. Validation of natural history

Year	Model-predicted cumulative incidence of anal cancer (%)	Cumulative incidence of anal cancer from Cachay et al. [18] [% (95% CI)]
1	0.44	0.30 (0.04 – 2.13)
2	0.60	0.65 (0.16 – 2.60)
3	0.79	1.03 (0.33 – 3.17)
4	1.01	1.03 (0.33 – 3.17)
5	1.26	1.65 (0.59 – 4.52)

Supplementary Appendix 4. Additional sensitivity analyses

We conducted additional sensitivity analysis on HPV incidence and clearance, HGAIN progression and regression, probability of receiving treatment for anal cancer, and utilities associated with HGAIN, anal cancer, and HIV status. No significant variation in the ICER was observed after varying these model parameters using 95% CI or their range (HPV incidence and clearance, and utilities were varied using 95% CI and HGAIN progression and regression were varied using range; we varied HGAIN progression and regression under the assumption that the progression and regression remain static across the age).

Table T4. Additional one-way sensitivity analyses

	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[Φ]	372 656	372 237	17.35	17.51	Dominant[¥]	62.98
HPV 16 incidence						
9.6%	372 428	372 032	17.35	17.51	Dominant[¥]	62.94
17.6%	372 906	372 463	17.35	17.50	Dominant[¥]	63.02
HPV 18 incidence						
3.5%	372 541	372 133	17.35	17.51	Dominant[¥]	62.96
8%	372 810	372 376	17.35	17.50	Dominant[¥]	63.02
HPV16/18 clearance						
10%	374 316	373 806	17.32	17.48	Dominant[¥]	63.19
50%	372 354	371 959	17.36	17.51	Dominant[¥]	62.93
HGAIN progression (assuming that the progression remains static across the age)						
0.00360	373 840	372 622	17.12	17.19	Dominant[¥]	58.74
0.01058	372 288	372 121	16.95	17.12	Dominant[¥]	56.26
HGAIN regression (assuming that the regression remains static across the age)						
0.0392	372 656	372 237	17.35	17.51	Dominant[¥]	62.98
0.3312	372 656	372 237	17.35	17.51	Dominant[¥]	62.98
Probability of receiving treatment for anal cancer (compliance)						
25%	371 773	371 933	16.90	17.12	985	63.13
50%	372 295	372 112	17.00	17.15	Dominant[¥]	63.04
75%	372 526	372 192	17.01	17.16	Dominant[¥]	63.00
Utility anal cancer						
0.50	372 656	372 237	17.35	17.50	Dominant[¥]	62.98
0.70	372 656	372 237	17.36	17.51	Dominant[¥]	62.98
Utility HGAIN						
0.95	372 656	372 237	17.29	17.45	Dominant[¥]	62.98
0.99	372 656	372 237	17.37	17.52	Dominant[¥]	62.98
Utility HIV (CD4 >500)						
0.90	372 656	372 237	16.57	16.69	Dominant[¥]	62.98
0.98	372 656	372 237	17.47	17.62	Dominant[¥]	62.98
Utility HIV (CD4 200–500)						
0.84	372 656	372 237	17.02	17.16	Dominant[¥]	62.98
0.90	372 656	372 237	17.02	17.16	Dominant[¥]	62.98
Utility HIV (CD4 <200)						
0.76	372 656	372 237	16.80	16.93	Dominant[¥]	62.98
0.84	372 656	372 237	17.24	17.39	Dominant[¥]	62.98

Abbreviations: qHPV, quadrivalent human papillomavirus vaccine; ICER, incremental cost-effectiveness ratio

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

***** We used the lower and upper limits of the 95% confidence intervals from Swedish et al [10] to vary vaccine efficacy for best-case and worst-case scenario, respectively.

[¥] Vaccination increases lifetime effectiveness and decreases lifetime cost (i.e., the strategy is cost saving).

References:

1. Center for Disease Control and prevention. Reported CD4+ T-lymphocyte results for adults and adolescents with HIV infection—37 States, 2005–2007: National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, **2009**.
2. 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(5): 487-500.
3. Karnon J, Jones R, Czoski-Murray C, Smith KJ. Cost-utility analysis of screening high-risk groups for anal cancer. J Public Health (Oxf) **2008**; 30(3): 293-304.
4. Tong WW, Jin F, McHugh LC, et al. Progression to and spontaneous regression of high-grade anal squamous intraepithelial lesions in HIV-infected and uninfected men. AIDS **2013**; 27(14): 2233-43.
5. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med **2011**; 365(6): 493-505.
6. Lifson AR, Krantz EM, Eberly LE, et al. Long-term CD4+ lymphocyte response following HAART initiation in a U.S. Military prospective cohort. AIDS Res Ther **2011**; 8(1): 2.
7. Goldstone RN, Goldstone AB, Russ J, Goldstone SE. Long-term follow-up of infrared coagulator ablation of anal high-grade dysplasia in men who have sex with men. Dis Colon Rectum **2011**; 54(10): 1284-92.
8. 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(4): 491-9.
9. Seaberg EC, Wiley D, Martinez-Maza O, et al. Cancer incidence in the multicenter AIDS Cohort Study before and during the HAART era: 1984 to 2007. Cancer **2010**; 116(23): 5507-16.
10. 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(7): 891-8.
11. Phillips AN, Gazzard B, Gilson R, et al. Rate of AIDS diseases or death in HIV-infected antiretroviral therapy-naive individuals with high CD4 cell count. AIDS **2007**; 21(13): 1717-21.
12. Surveillance Epidemiology and End Results Program (SEER). SEER Stat Fact Sheets: Anal Cancer. Available at: http://seer.cancer.gov/statfacts/html/anus.html. Accessed August 2,.
13. Bozzette SA, Joyce G, McCaffrey DF, et al. Expenditures for the care of HIV-infected patients in the era of highly active antiretroviral therapy. N Engl J Med **2001**; 344(11): 817-23.
14. Goldie SJ, Kuntz KM, Weinstein MC, Freedberg KA, Palefsky JM. Cost-effectiveness of screening for anal squamous intraepithelial lesions and anal cancer in human immunodeficiency virus-negative homosexual and bisexual men. Am J Med **2000**; 108(8): 634-41.
15. Hanmer J, Lawrence WF, Anderson JP, Kaplan RM, Fryback DG. Report of nationally representative values for the noninstitutionalized US adult population for 7 health-related quality-of-life scores. Med Decis Making **2006**; 26(4): 391-400.
16. Moore RD, Keruly JC. CD4+ cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. Clin Infect Dis **2007**; 44(3): 441-6.
17. Deshmukh AA, Zhao H, Franzini L, et al. Total lifetime and cancer-related costs for elderly patients diagnosed with anal cancer in the United States. Under review **2015**.
18. Cachay E, Agmas W, Mathews C. Five-year cumulative incidence of invasive anal cancer among HIV-infected patients according to baseline anal cytology results: an inception cohort analysis. HIV Med **2015**; 16(3): 191-5.