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Development and calibration of a mathematical model of anal carcinogenesis for high-risk HIV-infected men

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Abstract

Objectives—Men who have sex with men (MSM) who are living with human immunodeficiency virus (HIV) are at highest risk for anal cancer. Our objective was to use empirical data to develop a comprehensive disease simulation model that reflects the most current understanding of anal carcinogenesis, which is uniquely positioned to evaluate future anal cancer screening strategies as well as provide insight on the unobservable course of the disease.

Setting—North America

Methods—The individual-based simulation model was calibrated leveraging primary data from empirical studies, such as a longitudinal HIV-positive MSM cohort study ((HIPVIRG); n=247) and the North American AIDS Cohort Collaboration on Research and Design ((NA-ACCORD); n=13,146). We used the model to infer unobservable progression probabilities from high-grade precancer to invasive anal cancer by CD4+ nadir and HPV genotype.

Results—The calibrated model had good correspondence to data on genotype- and age-specific HPV prevalence; genotype frequency in precancer and cancer; and age- and nadir CD4+-specific cancer incidence. The model-projected progression probabilities differed substantially by HPV genotype and nadir CD4+ status. For example, among individuals with CD4+ nadir <200, the

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median monthly progression probability from a high-grade lesion to invasive cancer was 0.054% (i.e., 6.28% 10-year probability) and 0.004% (i.e., 0.48% 10-year probability) for men with an HPV16 infection versus without an HPV infection, respectively.

Conclusion—We synthesized existing evidence into a state-of-the-art anal cancer disease simulation model that will be used to quantify the tradeoffs of harms and benefits of alternative strategies, understand critical uncertainties, and inform national anal cancer prevention policy.

Keywords

Human papillomavirus (HPV); anal neoplasms; decision analysis; mathematical model

INTRODUCTION

The average population risk of developing anal cancer is less than 2 per 100,000 individuals. However, men who have sex with men (MSM) living with human immunodeficiency virus (HIV) face a 30–70 times greater risk of developing anal cancer[1–4]. Unlike cervical cancer, standardized national or international screening protocols for squamous cell carcinoma of the anus do not yet exist[5] despite the growing evidence that this human papillomavirus (HPV)-related cancer is preceded by premalignant stages, which if detected and removed, may prevent progression to cancer[6]. Several prospective longitudinal natural history studies among high-risk populations have contributed to advancing the biological understanding of anal HPV and precancers[7], while ongoing clinical trials seek to evaluate the efficacy of ablative methods (infrared coagulator or hyfrecation) and topical therapies such as 5-fluorouracil cream to remove anal precursors and prevent progression to anal cancer (Clinical trials identifiers: NCT01164722 and NCT02135419).

Although the role of HIV and antiretroviral therapies (ARTs) in anal carcinogenesis is not entirely understood, recent studies have suggested that the degree of immunosuppression throughout an individual's lifetime reflected by CD4$^+$ nadir rather than current immune status is related to the risk of developing high-grade anal intraepithelial neoplasia (AIN2/3) and invasive cancer[8–14]. In addition, ART does not induce regression of existing AIN2/3[15]. Following ART initiation at low CD4$^+$ nadir, individuals may have incomplete immune reconstitution that does not fully protect against the development of anal cancer. Increases in life expectancy may allow HIV-infected individuals more time to develop anal cancer, which may be especially important among men who delay HIV treatments or who present with lower CD4+ counts at diagnosis[16].

Computer-based simulation models synthesize and extrapolate currently-available evidence from epidemiologic and clinical studies and can be used to evaluate long-term outcomes such as cancer diagnosis and mortality that are not readily observable in existing studies. In addition, the development of a comprehensive natural history model that reflects the current understanding of anal carcinogenesis can be used to estimate the value of cancer control interventions (e.g., screening or vaccination) on current and future trends. Such analyses can provide timely evaluations of forthcoming screening and treatment technologies, improve current understanding of influential natural history parameters, and identify high-value areas of future research (i.e., value of information analyses). Although previous models have been

developed[17–19], no existing models capture the role of nadir CD4$^+$ or explicitly simulate the HPV genotype-specific natural history pathways to invasive cancer. Our objective was to use primary and secondary data to develop a disease simulation model that reflects the most current understanding of anal carcinogenesis, accounting for interactions between HPV genotype-specific infections, nadir CD4$^+$ lymphocyte strata, and ART status.

METHODS

Model description

We developed a natural history microsimulation model that reflects the most recent understanding of anal carcinogenesis, accounting for interactions between HPV genotype-specific infections, CD4$^+$ nadir lymphocyte strata, and ART status in the absence of treatment of anal cancer precursors (Figure 1). Individual HIV-infected MSM enter the model at age 30 years and are randomly assigned to a CD4$^+$ count and categorized in to one of four CD4$^+$ nadir strata: 1) CD4$^+$ >500, 2) CD4$^+$ 350–500, 3) CD4$^+$ 200–349, and 4) CD4$^+$ <200. The selection of CD4$^+$ nadir categories was based on historical cutoffs to initiate ARTs. Conditioned on CD4$^+$ count, men are allocated to an initial HPV-specific non-cancer anal health state: 1) No/latent HPV; 2) HPV without precursors; 3) low-grade (AIN1); and 4) high-grade precursor (AIN2/3). HPV-specific health states are stratified by five HPV genotype categories: 1) HPV-16; 2) HPV-18; 3) HPV hi-5 (including HPV-31, -33, -45, -52, -58); 4) other oncogenic types (i.e., HPV-35, -39, -51, -56, -59, -66, -68, -82); and 5) low-risk types (i.e., HPV-6 and -11). Each month, an individual may acquire, or clear, (an) HPV infection(s), progress or regress between precancerous states, and progress to cancer. Anal health state transitions can be a function of age, nadir CD4$^+$ count, genotype-specific HPV infection, and current health state. Invasive anal cancer may be detected through symptoms (at which point the individual would initiate cancer-directed therapy); if the patient's cancer is not detected in a given month, his disease may or may not progress to a more advanced clinical stage. Each month, an individual also faces a CD4$^+$-specific probability of initiating ART or transitioning to a lower CD4$^+$ count. Death can occur due to HIV-related complications, anal cancer (for those who develop it), or other non-HIV/non-anal cancer causes (**See** Web Appendix **for additional model assumptions**).

Baseline model parameterization

Model parameterization involves the selection of model input parameters from clinical (often natural history) studies to specify the initial model. Parameterization of the natural history anal cancer model involved a multi-disciplinary approach requiring literature reviews, analysis of primary empirical data, expert opinion from epidemiologists and clinicians, and an iterative calibration process to explore plausible ranges of unobserved parameters and structural assumptions (Table 1).

Health states at model start—Upon entering the model, individuals are randomly assigned a nadir CD4$^+$ count following a gamma distribution and categorized into one of four CD4$^+$ categories to reflect the nadir CD4$^+$ counts observed among HIV-infected MSM enrolled in the HIPVIRG (Human Immunodeficiency and Papilloma Virus Research Group) cohort (**see** Web Appendix)[14]. Following CD4$^+$ category assignment, each individual is

stochastically allocated to one or more initial non-cancer anal health states for each independent HPV category, if relevant (Web Appendix Table 1). Starting distributions reflect genotype-specific lesion prevalence derived from the baseline data from the HIPVIRG cohort[14,20].

HPV incidence and clearance—For each participant in the HIPVIRG cohort study, the lowest blood CD4$^+$ cell count prior to ART-initiation was obtained[20]. We derived the age-specific (i.e., 30–39, 40–49, and 50$^+$ years) monthly probabilities of acquiring HPV infection(s) for each HPV genotype category (Table 2). We obtained the baseline input probabilities for HPV clearance from the HIPVIRG cohort as function of nadir CD4+ category and HPV genotype; generally, they increased with higher nadir CD4+ count (Table 2).

Precancerous lesion progression and regression—Using empirical data from HIPVIRG[14], we calculated precancer progression and regression probabilities for each nadir CD4$^+$ category, and adjusted to preserve nadir CD4+ relationships (**see** Web Appendix). We allowed baseline progression and regression probabilities to be the same across HPV genotypes, and relied on the calibration process to adjust the baseline probabilities for each HPV genotype.

Among HIPVIRG participants, two individuals with nadir CD4$^+$<200 (1,345 person-months) who did not receive treatment for AIN2/3 progressed to invasive cancer, resulting in a monthly progression probability of 0.15% (confidence interval: 0.02%–0.54%). We set the baseline probability of progressing to cancer for individuals with a nadir CD4$^+$ 200 to half (reflecting slower progression) of the baseline probability of progressing to cancer for individuals with a nadir CD4$^+$ <200[16].

Anal cancer progression, detection and mortality—Among the men who develop invasive anal cancer, their cancer may progress to more severe stages (classified using AJCC 6th edition staging grouped by Stage I; Stages II/III; and Stage IV), facing an increasing probability of being detected through symptoms in each advanced stage (Table 2)[21]. In addition to background mortality due to HIV and other causes, individuals who develop anal cancer face excess mortality due to anal cancer death. In the ART-era, anal cancer prognosis for an HIV-infected individual is similar to an HIV-negative individual[22–24]; therefore, we used population-based data from the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) program for cancer registries (i.e., not HIV-specific). We extracted the 5-year cancer cause-specific[25] survival probabilities stratified by stage and time since diagnosis (year 1, years 2–3, years 4–20) to derive the monthly probability of dying from anal cancer (Web Appendix Table 2).

HIV-related parameters—HIV-infected individuals face a monthly probability of initiating ART that increases as nadir CD4$^+$ count declines (Web Appendix Table 3). In 2002 at the baseline of the HIPVIRG cohort, 93% of individuals had initiated ARTs. In the absence of ART initiation, individuals may progress to lower CD4 counts over time[26] and face elevated CD4$^+$-specific risks of dying from HIV-related causes (Web Appendix Table 3). Upon initiating ART (to ensure the model simulated cohort corresponds to that of the

HIPVIRG cohort), individuals stay within their CD4^{+} nadir category for their remaining lifetime, but face a lower HIV-related mortality (remains slightly elevated compared with the general population[27]).

Model calibration

Following identification of baseline inputs of the model, we calibrated (or fit) the model for specific model transitions that were unobservable or varied from setting to setting. We identified and allowed key uncertain parameter inputs to vary in order to characterize joint uncertainty in the natural history of anal cancer, and to ensure good-fit to empirical data from HIV-infected MSM study populations in North America. In particular, we relied on calibration to infer HPV genotype-specific variations in age- and CD4^{+} nadir-specific input parameters.

Following a similar calibration approach used for a natural history model of HPV-induced cervical carcinogenesis[28,29], we identified plausible ranges around baseline input parameter values and repeated model simulations by drawing uniformly across the predefined parameter search space for each model run, resulting in unique combinations of natural history parameters. For specific parameters, we constrained the search space to preserve well-understood relationships between HPV genotypes (Table 2; Web Appendix). In order to identify the parameter sets that maximized correspondence between model-projected outcomes and empirical data (i.e., calibration targets), we employed a likelihood-based approach that involved calculating the likelihood score for each unique parameter set using a likelihood ratio test to identify 'good-fitting' parameter sets.

The calibration target data (Web Appendix Table 4) included data formats not directly used as model inputs (e.g., age-, HPV genotype-, and CD4+-specific data). We used genotype-specific prevalence of HPV infection by age, prevalence of AIN1 and AIN2/3 precursors by age, and the frequency of HPV genotypes in AIN1 and AIN2/3 from the HIPVIRG cohort study[14]. To mimic the 6-month detection rate schedule in the HIPVIRG cohort study, we simulated a population similar to the study population; specifically, model detection rates reflected biannual screening visits. Screening, however, did not involve the treatment of precursors or screen detection of anal cancer. In addition, we used data from the most recent meta-analysis evaluating HPV type distribution in anal cancer tissues among HIV-infected men, which showed a lower contribution of HPV-16 to anal cancers among HPV-infected men compared with HPV-uninfected men (i.e., 57% vs. 77%, respectively)[30]. Age- and CD4^{+} nadir-specific anal cancer incidence rates were derived from the Multi-cohort collaboration North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) study (**see** Web Appendix). For calibration, we restricted the analytic cohort to cancers diagnosed among men aged 30 and older between 2000 and 2007 (n=57 cases and 47,366 person-years) in order to correspond with the HIPVIRG longitudinal trial period.

Model outcomes

Following calibration, we selected a sample (i.e., 50) of the 'good-fitting' parameter sets with the highest aggregate likelihood score to capture probabilistic uncertainty in the natural history process. We used the sample of 'good-fitting' sets to assess the face validity and

projective validity of the model fit to external data not used in the calibration process, such as age of cancer diagnosis, life expectancy by CD4+ nadir category, and cumulative risk of precancerous lesions. Model outcomes reflect projections for men diagnosed with HIV prior to 2002, which capture the distribution of nadir CD4+ counts and ART status initiations reported in the HIPVIRG cohort study.

Model outcomes were reported as the median, minimum and maximum values across the top 50 'good-fitting' sets. Lastly, we used the top fitting parameter sets to infer the posterior (i.e. post-calibration process) progression probabilities for the progression from AIN2/3 to invasive anal cancer by CD4+ nadir and HPV genotype.

RESULTS

Calibration results

Among the 200,000 randomly sampled parameter sets, the 50 'good-fitting' sets that produced the highest agreement to our 58 calibration targets, generally yielded reasonable fits to empirical data on age-specific HPV prevalence (Figure 2a); age-specific prevalence of AIN1 and AIN2/3 (Web Appendix Figure 1); genotype distribution of HPV infections in AIN1, AIN2/3 and cancer (Figure 2b); age- and CD4+ nadir-specific anal cancer incidence (Figure 2c); and stage of cancer detection (Web Appendix Figure 2). Cancer incidence rates were three- to five-fold higher among men with CD4+<200 compared to men with CD4+>500. For example, the median cancer incidence peaked at 176 per 100,000 men among individuals aged 45–49 years with CD4+ nadir<200 and 28 per 100,000 men among individuals aged 45–49 years with CD4+ nadir>500.

Model projections

Among these 'good-fitting' sets, the model estimated a lifetime risk of developing detected anal cancer of 2.5% (range: 0.4–5.7%) with a mean age of cancer diagnosis of 46.1 years (range: 44.9–47.3 years) and a median diagnosis of 44.5 years (range: 43.0–46.0 years), which are consistent with empirical data from other HIV-infected MSM cohorts that reported cumulative incidence of 1.7% (2005–2009)[31], and mean ages of 45.4 years[22] and 49 years[21], or a median age of 38 years[1] (Table 3). Using anal cancer survival probabilities derived from SEER registries, we projected anal cancer mortality rates that varied by age; median age-specific rates ranged from 9 to 42 per 100,000 HIV-infected MSM (Web Appendix Figure 4).

Among all men and irrespective of CD4+ nadir, the total (undiscounted) life expectancy was 59.7 years (range: 59.5–59.8), but also varied by CD4+ nadir category. For example, the life expectancy among men with CD4+ nadir <200 was 53.8 years (range: 53.5–54.0), while the life expectancy among men with CD4+ nadir >500 was 72.8 years (range: 72.6–72.9); these projections were generally consistent with life expectancies reported from HIV-infected MSM in NA-ACCORD[32] and Kaiser Permanente[33] prior to 2006.

Progression to anal cancer

Following calibration, the resulting median monthly progression probability across the top-fitting parameter sets differed substantially by HPV genotype and nadir CD4+ status. For example, the median monthly progression probability from an HPV-16 AIN2/3 to invasive cancer was 0.027% (i.e., 3.19% 10-year probability) among individuals with CD4+ nadir >500, and 0.054% (i.e., 6.28% 10-year probability) among individuals with CD4+ nadir <200 (**See** Web Appendix Figure 3). In contrast, the median monthly progression probability from an AIN2/3 to invasive cancer not related to HPV was 0.002% (i.e., 0.24% 10-year probability) among individuals with CD4+ nadir >500, and 0.004% (i.e., 0.48% 10-year probability) among individuals with CD4+ nadir <200.

DISCUSSION

We developed an individual-based natural history simulation model by synthesizing primary and secondary data from the most recent North American studies of anal HPV-related neoplasia in HIV-infected MSM in order to address alternative anal cancer screening approaches in a timely manner. This calibrated model can be used to superimpose various existing and proposed scenarios of anal cancer screening to determine the long-term population-level health and economic consequence, often unavailable from empirical trials, as well as to determine which screening strategies provide the most value for money. Our natural history model, which was consistent with empirical data from other HIV-infected MSM anal cancer studies, also provides important insights on the progression potential of high-grade precancers to invasive disease by HPV genotype and CD4+ nadir, endpoints that are difficult to observe in empirical studies and have not been directly observed to date.

Several groups[17,18,34] have developed disease simulation models to evaluate the value of screening for anal precancers among HIV-infected MSM. Among these studies, the range of recommendations included annual anal Pap screening, which would trigger anoscopy and biopsy if abnormal in the US[17] to no screening in England[18]. However, these studies did not account for independent HPV genotypes, and the potential sustained role of nadir CD4+ following ART initiation on disease progression. In addition, Lam and colleagues[34] did not evaluate long-term outcomes such as cancer or life-expectancy. A recent study by Ong and colleagues[19] developed a Markov model evaluation of the cost-effectiveness of digital anal rectal exam (DARE) every 1–5 years; however, the model did not include precancerous health states and made simplifying assumptions around the age-specific probability of developing anal cancer, ignoring important age differences in cancer risk between the general population and HIV-infected MSM.

To our knowledge, the model we describe here is the first with capabilities to evaluate nuanced screening and vaccination policies that captures complex interactions between anal carcinogenesis and HIV natural history, which are important to capture when evaluating potential anal cancer screening strategies. To date, no other anal cancer models have incorporated HPV-genotype-specific data from large cohort studies, nor utilized the North American cohorts of HIV and anal cancer diagnosis to inform model transition probabilities.

Limitations

There are limitations to our model structure, data availability and calibration approach. Our model is inherently tied to the empirical data that informed it. Similar to many natural history studies, our model used the composite outcome using cytology/histology results as true underlying health state. While cytology-alone may not be highly sensitive, high-resolution anoscopy was performed on all men. In addition, HIV-infected MSM often have multiple AIN lesions, and tracking the status of individual lesions is difficult in clinical practice. For example, a new AIN2/3 diagnosis could either be a previously detected lesion that progressed, or a new lesion that appeared, which may have been truly absent or simply missed at the previous visit. To minimize missing lesions, the HIPVIRG study required chart review where the worst lesion seen was confirmed. In addition, anoscopists completed at each session a diagram to indicate changes in the lesions they previously saw. Similarly, many HIV-infected MSM have multiple HPV infections[7,14], and microdissection to determine the HPV genotype attributable to individual AIN1s and AIN2/3s was not performed. In our model we assumed each HPV type was acquired and progressed independently, driven by the HPV incidence probabilities observed in the HIPVIRG cohort study.

There may be other mechanisms by which ART affects HPV natural history other than through preventing a lower absolute CD4^{+} nadir. For example, ART initiation affects HPV natural history, most notably via immune reconstitution. It is possible that absolute CD4+ nadir, time at CD4+ nadir, timing of this CD4+ nadir in relation to the present, and extent of immune reconstitution (i.e. current CD4+) all impact probability of progression from AIN2/3 to invasive cancer. The Swiss Cohort study[9] suggested that CD4+ nadir, CD4+ count 6–7 years prior to present, and current CD4+ count were each associated with cancer incidence; however, the authors did not present a multivariable analysis, so it is unclear which factors are *independently* associated with cancer incidence, based on their data. Kesselring and colleagues[35] published an adjusted hazard ratio for anal cancer of 1.52 per year of CD4+ count below 200, suggesting that it is not just absolute CD4^{+} nadir, but rather time at CD4+ nadir, that has an impact on anal cancer incidence. Though our model attempts to capture the role CD4^{+} count in risk of developing anal cancer, and does so using what the literature suggests is likely the most robust clinical predictor of progression to invasive cancer, i.e. absolute CD4+ nadir[8,9,11–14,16,35–38], the model is not able to comprehensively integrate the complex – and not fully understood – interplay between CD4^{+} count through time and risk of anal cancer. In addition, we reduced the baseline probability of progressing from AIN2/3 to invasive cancer for individuals with a CD4^{+} nadir 200 by half compared with individuals with a CD4^{+} nadir <200, but acknowledge that the reference group from the multivariable analysis from D'Souza and colleagues (16) was compared to total cancer incidence irrespective of lesion status.

No data are available to inform the progression between stages of cancer and symptom stage detection probabilities. We used a panel of experts from Harvard-affiliated teaching hospitals to inform baseline estimates of the duration between Stage I, Stages II/III and Stage IV cancers, and calibrated these baseline inputs to fit stage distribution observed in SEER among the general population (Web Appendix). Extensive sensitivity analysis will be

performed on all policy analyses to evaluate the robustness of screening policy and cancer progression and detection assumptions. In addition, we assumed that for undetected cancers, progression to later stages was independent of $CD4^+$ nadir. We plan to explore the role of differential cancer progression by $CD4^+$ nadir in future analyses.

Our model does not explicitly capture the dynamic, sexual patterns of HPV acquisition, but relies on age-specific incidence calibrated to observed prevalence to serve as a proxy for sexual behavior. HPV prevalence from the HIPVIRG cohort suggests that the HPV prevalences simulated in our model are representative of other HIV-infected MSM populations[7]. In addition, we assume constant transition probabilities that do not capture the role of persistent HPV infections and lesions. Study cohort size restricted our ability to stratify HPV clearance, and lesion progression and regression by duration; however, ongoing longitudinal studies such as SPANC[39,40] and ANCHOR (Clinical trials identifier: NCT02135419)) may provide insight once trial data are available.

Conclusions

Using primary and secondary data from North American HIV-infected MSM cohorts and registries, we synthesized existing evidence into a single natural history model that reflects the most recent understanding of anal carcinogenesis, accounting for interactions between HPV type-specific infections, $CD4^+$ lymphocyte strata, and ART status. Such models can be used to evaluate the population-level health and economic consequences of complex national screening policies currently on the table in the United States.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations

AIN	Anal intraepithelial neoplasia
ART	Anti-retroviral therapy
ASC-US	atypical squamous cells of undetermined significance
HIPVIRG	Human Immunodeficiency and Papilloma Virus Research Group
HPV	human papillomavirus

MSM	Men who have sex with men
NA-ACCORD	North American AIDS Cohort Collaboration on Research and Design
PCR	polymerase chain reaction
SEER	Surveillance, Epidemiology, and End Results Program.

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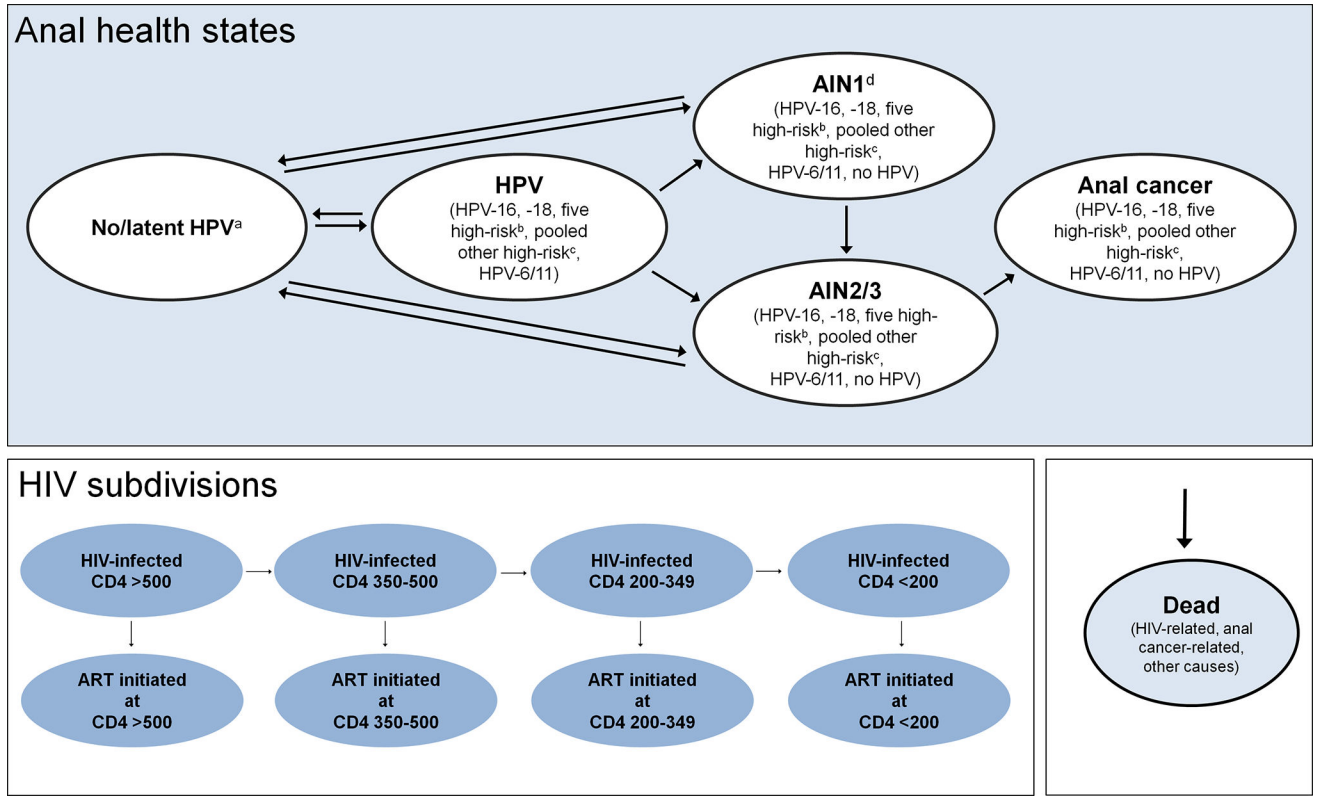
Figure 1.
Model schematic for the natural history of human immunodeficiency (HIV)- and human papillomavirus (HPV)-related anal carcinogenesis. AIN1: Anal intraepithelial neoplasia grate 1, AIN2/3: Anal intraepithelial neoplasia grades 2 and 3, ART: Anti-retroviral treatment, CD4: Cluster of differentiation 4, HIV: Human immunodeficiency virus, HPV: Human papillomavirus. [a]HPV has been completely cleared by the body, or the level of infection is not detectable by laboratory tests, [b]HPV-31, -33, -45, -52 or -58; [c]HPV-35, -39, -51, -56, -59, -66, -68, or -82; [d]AIN1 may not necessarily represent a true precursor state to invasive cancer; the presence of AIN1 may instead increase the probability of having type-specific metachronous AIN2/3.
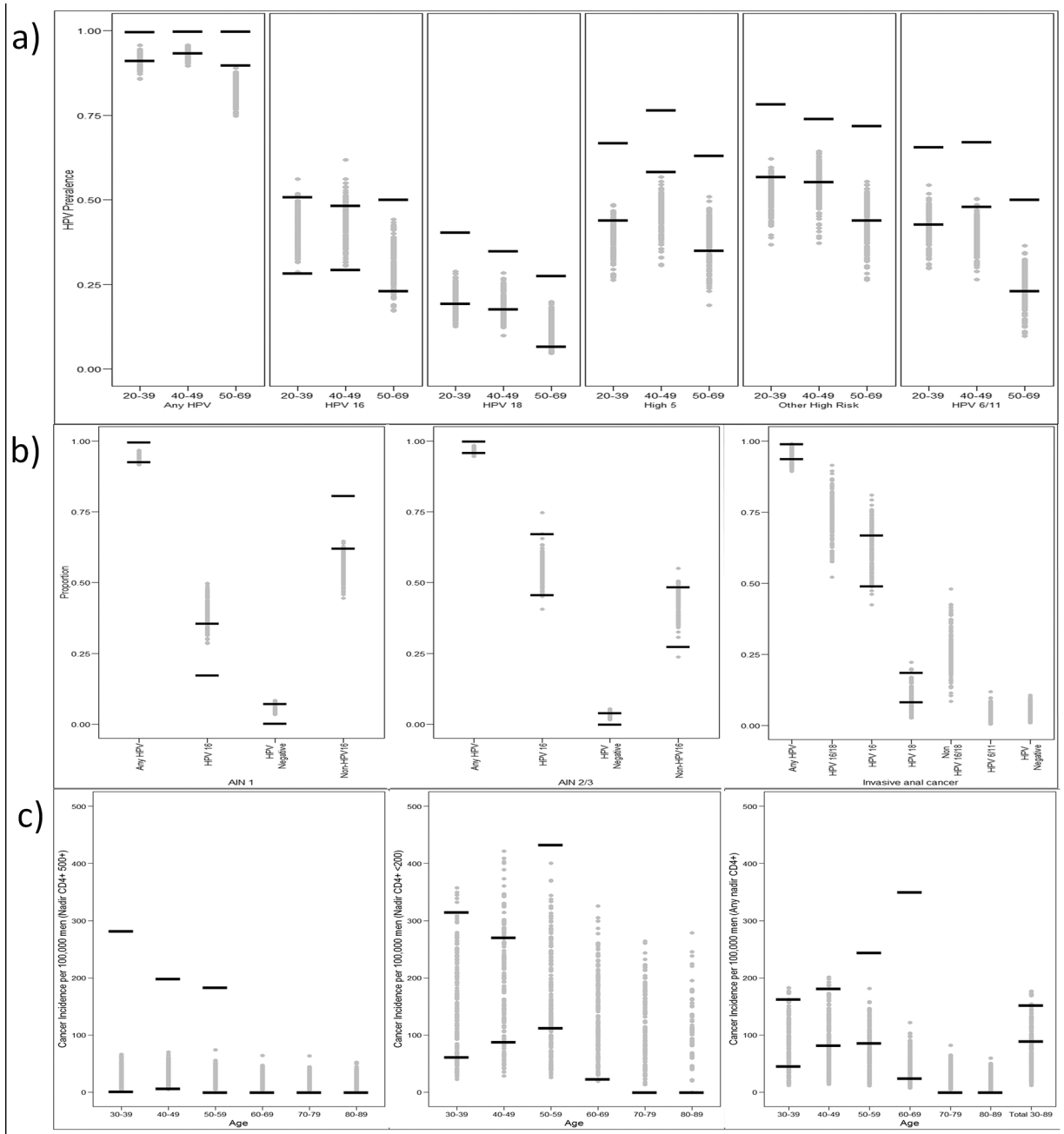
Figure 2.
Model output relative to calibration targets for a) age- and genotype-specific prevalence of human papillomavirus (HPV); b) the proportion of anal intraepithelial neoplasia grade 1 (AIN 1), anal intraepithelial neoplasia grades 2/3 (AIN 2/3), and invasive anal cancers attributed human papillomavirus (HPV) genotypes; and c) anal cancer incidence per 100,000 HIV-infected men who have sex with men (MSM) among those with nadir CD4+ >500 (left panel), nadir CD4+ <200 (middle panel), and any nadir CD4+ levels (right panel). Black bars represent baseline empirical data from: the Human Immunodeficiency and Papilloma Virus Research Group (HIPVIRG) longitudinal cohort (for HPV prevalence and genotypes

in AIN1–3), a systematic review from the International Agency for Research on Cancer (IARC) among HIV-infected men (genotypes in cancer), or the Multi-cohort collaboration North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) study (anal cancer). Upper bounds for some anal cancer empirical targets were >2000 and outside of y-axis range. Grey dots reflect model-projected output among the top 50 'good-fitting' parameter sets identified following likelihood-based calibration. HPV hi-5 includes HPV-31, -33, -45, -52, -58; other oncogenic types include HPV-35, -39, -51, -56, -59, -66, -68, -82. HPV-16/18, non-HPV-16/18, and HPV-6/11 and HPV negative cancers were not included in the likelihood-based scoring algorithm (panel c); however, the comparison was used to assess the predictive validity of the calibrated model for these HPV genotypes.

Table 1

Data Sources Used for Model input and Calibration in the Natural History Model of Anal Carcinogenesis for High-risk HIV-infected Men Who Have Sex with Men (MSM).

First Author, Year	Study design	Model variable	Location	Sample size	Population
Natural history parameters					
de Pokomandy, 2009	Prospective cohort	HPV incidence by age; HPV clearance by CD4+ nadir[a]	Montreal, Canada	241	HIV-infected MSM aged 18–65 years
de Pokomandy, 2011	Prospective cohort	Low- and high-grade progression and regression by CD4+ nadir[a]	Montreal, Canada	243	HIV-infected MSM aged 18–65 years
de Pokomandy (unpublished)	Prospective cohort	High-grade lesion progression to invasive anal cancer	Montreal, Canada	247	HIV-infected MSM aged 18–65 years
Harvard-affiliated oncologists (expert opinion)	NA	Cancer progression; cancer symptom detection by stage	NA	NA	NA
SEER Program, 2014	Population-based registry data	Cancer survival	United States	By stage: Stage I; II/III; IV (AJCC 6th edition)[b]	SEER-18 Registries Research Data + Hurricane Katrina Impacted Louisiana Cases, (diagnosed 2004–2012)
Calibration targets					
de Pokomandy, 2009	Prospective cohort	Age- and type-specific HPV prevalence	Montreal, Canada	236	HIV-infected MSM aged 18–65 years
de Pokomandy, 2011	Prospective cohort	Age-specific prevalence of low- and high-grade lesions	Montreal, Canada	245	HIV-infected MSM aged 18–65 years
de Pokomandy, 2011	Cross-sectional data	HPV genotype frequency in low- and high-grade lesions	Montreal, Canada	185	HIV-infected MSM aged 18–65 years
Clifford, 2017	Meta-analysis	HPV genotype frequency in anal cancer	Worldwide	176	HIV-infected men (majority MSM)
SEER Program, 2014	Population-based registry data	Cancer stage detection	United States	By stage: Stage I; II/III; IV (AJCC 6th edition)[b]	SEER-18 Registries Research Data + Hurricane Katrina Impacted Louisiana Cases, (diagnosed 2004–2012)
NA-ACCORD P2010	22 cohorts	Age-specific anal cancer incidence by CD4+ nadir[c,d]	US and Canada	13,146	HIV-infected MSM with CD4+ nadir status[c]

Abbreviations: CD4+ cluster of differentiation 4; HIV: Human immunodeficiency virus; HPV: Human papillomavirus; MSM: men who have sex with men; NA: not applicable; SEER: Surveillance Epidemiology, and End Results.

[a] Lowest blood CD4+ cell count before the beginning of current HAART were obtained from each patient's medical file;

[b] AJCC 6th edition stages groupings are identical to AJCC 7th edition (which is currently used in clinical practice), and are also consistent with AJCC 8th edition (which goes into effect in clinical practice January 2018);

[c] CD4+ nadir was defined as CD4+ count measurement closest to HAART initiation within window of 6 months prior to 3 months after HAART initiation;

[d] Histology types included: Squamous cell carcinoma, NOS (82.7%); Sq. cell carcinoma, keratinizing, NOS (2.7%); Sq. cell carcinoma, micro-invasive (2.7%); Basaloid carcinoma (1.3%); Basaloid squamous cell carcinoma (4%); Cloacogenic carcinoma, NOS (1.3%); Neoplasm, malignant (1.3%); Unknown (1.3%); Malignant melanoma, NOS (1.3%).

Table 2

Selected Baseline Values, Calibration Search Ranges, and Best-fitting Multipliers from Calibration.

	Base value[a]	Multiplier search range[b]	Median (range of multiplier values among top 50 parameter sets)
Progression parameters			
HPV-16 incidence age < 40	0.011	0.6 — 1.7	1.3 (0.6 — 1.7)
HPV-16 incidence age 40–49	0.013	0.7 — 1.5	1.2 (0.7 — 1.5)
HPV-16 incidence age 50+	0.005	0.4 — 2.4	1.9 (0.7 — 2.4)
HPV-18 incidence age < 40	0.004	0.5 — 2.1	1.4 (0.6 — 2.1)
HPV-18 incidence age 40–49	0.006	0.6 — 1.7	1.3 (0.6 — 1.7)
HPV-18 incidence age 50+	0.002	0.3 — 3.1	1.9 (0.5 — 3.0)
HPV-Hi5 incidence age < 40	0.007	0.5 — 2.1	1.7 (0.5 — 2.1)
HPV-Hi5 incidence age 40–49	0.018	0.6 — 1.7	1.4 (0.6 — 1.7)
HPV-Hi5 incidence age 50+	0.012	0.5 — 1.9	1.4 (0.6 — 1.9)
HPV-HO incidence age < 40	0.018	0.5 — 1.8	1.5 (0.6 — 1.8)
HPV-HO incidence age 40–49	0.027	0.6 — 1.6	1.3 (0.7 — 1.6)
HPV-HO incidence age 50+	0.013	0.5 — 2.1	1.6 (0.7 — 2.1)
HPV-LR incidence age < 40	0.009	0.5 — 1.9	1.5 (0.5 — 1.9)
HPV-LR incidence age 40–49	0.010	0.6 — 1.7	1.4 (0.7 — 1.7)
HPV-LR incidence age 50+	0.003	0.3 — 3.1	2.1 (0.5 — 3.0)
HPV-16 to AIN1	0.011	1.0 — 2.5	1.9 (1.0 — 2.5)
HPV-18 to AIN1	0.011	0.4 — 1.0	0.8 (0.4 — 1.0)
HPV-Hi5 to AIN1	0.011	0.4 — 1.0	0.8 (0.4 — 1.0)
HPV-HO to AIN1	0.011	0.4 — 1.0	0.8 (0.4 — 1.0)
HPV-LR to AIN1	0.011	0.4 — 1.0	0.8 (0.4 — 1.0)
No HPV to AIN1	0.011	0.4 — 1.0	0.5 (0.4 — 0.8)
HPV-16 to AIN2/3	0.007–0.010	1.0 — 2.0	1.6 (1.0 — 2.0)
HPV-18 to AIN2/3	0.007–0.010	0.5 — 1.0	0.8 (0.5 — 1.0)
HPV-Hi5 to AIN2/3	0.007–0.010	0.5 — 1.0	0.7 (0.5 — 1.0)
HPV-HO to AIN2/3	0.007–0.010	0.5 — 1.0	0.7 (0.5 — 1.0)
HPV-LR to AIN2/3	0.007–0.010	0.5 — 1.0	0.7 (0.5 — 1.0)
No HPV to AIN2/3	0.007–0.010	0.5 — 1.0	0.7 (0.5 — 1.0)
HPV-16 AIN1 to AIN2/3	0.010–0.017	1.0 — 1.7	1.4 (1.1 — 1.7)
HPV-18 AIN1 to AIN2/3	0.010–0.017	0.6 — 1.0	0.8 (0.6 — 1.0)
HPV-Hi5 AIN1 to AIN2/3	0.010–0.017	0.6 — 1.0	0.8 (0.6 — 1.0)
HPV-HO AIN1 to AIN2/3	0.010–0.017	0.6 — 1.0	0.9 (0.6 — 1.0)
HPV-LR AIN1 to AIN2/3	0.010–0.017	0.6 — 1.0	0.8 (0.6 — 1.0)
No HPV AIN1 to AIN2/3	0.010–0.017	0.6 — 1.0	0.8 (0.6 — 1.0)
HPV-16 AIN2/3 to CA	0.00075–0.0015	0.0 — 1.5	0.4 (0.0 — 0.9)
HPV-18 AIN2/3 to CA	0.00075–0.0015	0.0 — HPV-16 AIN2/3 to CA	0.21 (0.04 — 0.85)
HPV-Hi5 AIN2/3 to CA	0.00075–0.0015	0.0 — HPV-16 AIN2/3 to CA	0.13 (0.02 — 0.63)
HPV-HO AIN2/3 to CA	0.00075–0.0015	0.0 — HPV-16 AIN2/3 to CA	0.06 (0.02 — 0.31)

	Base value[a]	Multiplier search range[b]	Median (range of multiplier values among top 50 parameter sets)
HPV-LR AIN2/3 to CA	0.00075–0.0015	0.0 — HPV-16 AIN2/3 to CA	0.04 (0.01 — 0.26)
No HPV AIN2/3 to CA	0.00075–0.0015	0.0 — HPV-16 AIN2/3 to CA	0.02 (0.01 — 0.17)
Clearance and regression parameters			
HPV-16 AIN2/3 to NL	0.0031–0.0067	2.0 — 15.0	8.5 (4.1 — 14.9)
HPV-18 AIN2/3 to NL	0.0031–0.0067	HPV-16 AIN2/3 to NL — 23.0	16.8 (7.5 — 22.9)
HPV-Hi5 AIN2/3 to NL	0.0031–0.0067	HPV-16 AIN2/3 to NL — 23.0	15.3 (8.2 — 22.4)
HPV-HO AIN2/3 to NL	0.0031–0.0067	HPV-16 AIN2/3 to NL — 23.0	15.1 (6.5 — 22.9)
HPV-LR AIN2/3 to NL	0.0031–0.0067	HPV-16 AIN2/3 to NL — 23.0	13.6 (5.6 — 22.2)
No HPV AIN2/3 to NL	0.0031–0.0067	HPV-16 AIN2/3 to NL — 23.0	13.9 (6.5 — 23)
HPV-16 AIN1 to NL	0.0021–0.0075	0.3 — 1.0	0.6 (0.3 — 1.0)
HPV-18 AIN1 to NL	0.0021–0.0075	1.0 — 4.0	2.4 (1.0 — 4.0)
HPV-Hi5 AIN1 to NL	0.0021–0.0075	1.0 — 4.0	1.8 (1.1 — 3.8)
HPV-HO AIN1 to NL	0.0021–0.0075	1.0 — 4.0	2.4 (1.1 — 3.9)
HPV-LR AIN1 to NL	0.0021–0.0075	1.0 — 4.0	2.1 (1.0 — 3.9)
No HPV AIN1 to NL	0.0021–0.0075	1.0 — 4.0	2.5 (1.1 — 3.9)
HPV-16 clearance	0.0093–0.0196	1.0 — 2.0	1.2 (1.0 — 1.7)
HPV-18 clearance	0.0121–0.0315	HPV-16 clearance — 2.0	1.5 (1.1 — 1.9)
HPV-Hi5 clearance	0.0174–0.0187	HPV-16 clearance — 2.0	1.5 (1.1 — 2)
HPV-HO clearance	0.0175	HPV-16 clearance — 2.0	1.4 (1.0 — 2.0)
HPV-LR clearance	0.0074–0.0152	HPV-16 clearance — 2.0	1.5 (1.1 — 2.0)
Cancer parameters			
Stage I symptom detected	0.062	0.95 — 1.05	1.01 (0.95 — 1.05)
Stages II/III symptom detected	0.248	0.95 — 1.05	1.02 (0.95 — 1.05)
Stage IV symptom detected	0.588	0.95 — 1.05	1.0 (0.95 — 1.04)
Stage I to Stage II/III	0.080	0.95 — 1.05	0.99 (0.95 — 1.05)
Stage II/III to Stage IV	0.025	0.95 — 1.05	0.99 (0.95 — 1.04)

Abbreviations: AIN1: anal intraepithelial neoplasia grade 1; AIN2/3: anal intraepithelial neoplasia grades 2/3; HPV: human papillomavirus; HPV-Hi5: high-risk HPV types include HPV-31, -33, -45, -52, -58; HPV-HO: high-risk other HPV types (including HPV-35, -39, -51, -56, -59, -66, -68, -82) ; HPV-LR: low-risk HPV types 6 and 11; NL: normal/no lesion.

[a] Ranges reflect age- or nadir CD4+-specific baseline values;

[b] Conditional search ranges restricted relationships between HPV genotypes.

Table 3

Summary of Model-projected Output for HIV-infected Men Who Have Sex with Men (MSM).

Model output	Median (range of multiplier values among top 50 parameter sets)
Total life expectancy	59.7 (59.5–59.8)
Total life expectancy (CD4$^+$ nadir <200)	53.8 (53.5–54.0)
Total life expectancy (CD4$^+$ nadir 200–349)	53.9 (53.9–54.0)
Total life expectancy (CD4$^+$ nadir 350–500)	69.1 (68.9–69.2)
Total life expectancy (CD4$^+$ nadir >500)	72.8 (72.7–72.9)
Lifetime risk of detected anal cancer	2.5% (0.4–5.7%)
Mean age cancer detection	46.1 (44.9–47.3)
Median age cancer detection	44.5 (43.0–46.0)
Proportion diagnosed Stage I anal cancer	23.2% (21.0–25.1%)
Proportion diagnosed Stage II/III anal cancer	66.9% (65.4–69.3%)
Proportion diagnosed Stage IV anal cancer	9.9% (9.1–11%)

Abbreviations: AIN1: anal intraepithelial neoplasia grade 1; AIN2/3: anal intraepithelial neoplasia grades 2/3.