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# Impact of Screening and ART on Anal Cancer Incidence in HIV-Positive Men who have Sex with Men:

# Mathematical Modeling Study

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## Abstract

**Background:** The incidence of anal cancer is high in HIV-positive men who have sex with men (MSM). We modeled the impact of screening strategies and combination antiretroviral therapy (cART) coverage on anal cancer incidence in Switzerland.

**Methods:** Individual-based, dynamic simulation model parameterized with Swiss HIV Cohort Study (SHCS) and literature data. We assumed all men to be HPV infected. CD4 cell count trajectories were the main predictors of anal cancer. From 2016 we modeled cART coverage either as below 100% (corresponding to 2010-2015) or as 100%, and the following four screening strategies: (i) no screening, (ii) yearly anal cytology (Pap smears), (iii) yearly anoscopy and (iv) targeted anoscopy five years after CD4 count dropped below 200 cells/µl.

**Results:** Median nadir CD4 cell count of 6,411 MSM increased from 229 cells/µl during 1980-89 to 394 cells/µl during 2010-15; cART coverage increased from 0% to 83.4%. Modeled anal cancer incidence peaked at 81.7/100,000 in 2009, plateaued 2010-2015 and decreased to 58.7 by 2030 with stable cART coverage, and to 52.0 with 100% cART coverage. With yearly cytology, incidence declined to 38.2/100,000 by 2030, with yearly anoscopy to 32.8 and with CD4 count guided anoscopy to 51.3. The numbers needed to screen over 15 years to prevent one anal cancer case (NNS) were 384 for yearly cytology, 313 for yearly anoscopy and 242 for CD4 count dependent screening.

**Conclusions:** Yearly screening of HIV-positive MSM may reduce anal cancer incidence substantially, with a NNS that is comparable to other screening interventions to prevent cancer.

**Keywords:** men who have sex with men (MSM), HIV, AIDS, anal cancer, antiretroviral therapy, Pap screening, mathematical models, cohort studies

## Introduction

Anal cancer is caused by infection with high-risk types of human papillomavirus (HPV) [1–3]. In HIV-negative men who have sex with men (MSM), the incidence of anal cancer is around 5 per 100,000 person-years, which is about 5 times higher than in the general population [1,2]. In HIV-positive MSM, the incidence ranged between 78 and 168/100,000 person-years in studies from the era of combination antiretroviral therapy (cART) [1,4–7]. The main risk factor for anal cancer is a history of infection with high-risk types of human papillomavirus (HPV) which is very frequent in HIV-positive MSM [1–3,8]. Another important risk factor is immunosuppression, characterized by low nadir CD4 counts [4–6,9] or a long duration of exposure to low CD4 counts [10,11]. An analysis of the Swiss HIV Cohort Study (SHCS) found that the strongest predictor was a low CD4 cell count 6-7 years before diagnosis [12]. Other potential risk factors include smoking [2,12] and presence of antibodies against high-risk HPV proteins [12].

Anal intra-epithelial neoplasia (AIN) grades 2 or 3, the precursors of anal cancer [2,3,13], are found in 24% to 50% of HIV-positive MSM [1–3]. The progression from AIN 2/3 to anal cancer is estimated to range from 1.3% to 5.6% over 5 years [1,3,13,14]. Screening for AIN 2/3 and treatment of lesions can prevent progression to anal cancer. Cytology based on Papanicolau (Pap) smears of the anal canal is inexpensive, but with 67% to 90% the sensitivity is low in HIV-positive persons [15]. High-resolution anoscopy and histology requires dedicated equipment and training and is substantially more expensive than cytology, but sensitivity is close to 100% [16]. Electrocautery and infrared coagulation are the most effective treatments for intraanal AIN 2/3 [2]. Burgos *et al.* [17] found that one year after treatment 49% of patients were free of AIN 2/3; other studies showed comparable or better results [18–20]. Although only around half of men

were free of AIN 2/3 after 1 year, the treatment prevented progression to anal cancer in all of them [18–20].

Combination antiretroviral therapy (cART) substantially decreases the risk of opportunistic infections and cancers such as Kaposi sarcoma or Non-Hodgkin lymphoma [8,21], and similar decreases were expected for anal cancer. However, studies suggest that anal cancer incidence increased even after the widespread introduction of cART [4,7–9]. For example, an analysis of 13 cohorts from North America found that the incidence of anal cancer continued to raise during the early years of cART (1996-1999) and plateaued in the 2000s [7]. In the Netherlands, a slight decrease was observed after 2006 [6].

The effectiveness of different screening strategies for anal cancer is unclear and a matter of ongoing debate [1–3,7]. We developed a mathematical model and parameterized it with data from the Swiss HIV Cohort Study (SHCS) and the literature. We used the model to study the impact of increasing the coverage of cART, and of different screening strategies on the incidence of anal cancer.

## Methods

### *Structure of mathematical model*

We developed an individual-based mathematical simulation model to predict anal cancer incidence in HIV-positive MSM in Switzerland, 1980-2030. We assumed that all HIV-positive MSM were HPV-infected and immunodeficiency (measured as trajectories of the CD4 positive lymphocyte cell count per μl) was the main risk factor for anal cancer [12]. The model is a stochastic, dynamic model and consists of a CD4 count layer and an anal cancer layer, which depends on the CD4 count layer (Figure 1).

The CD4 count layer of the model is a Markov model and the anal cancer part is a stochastic compartmental model, where transition probabilities are non-Markovian. In the CD4 count layer, the CD4 trajectories of MSM are modeled across five CD4 count states (<100, 100-199, 200-349, 350-499, and ≥500 cells/μl). The anal cancer layer includes four states of anal cancer progression (no precursor lesion, AIN 1, AIN 2/3, and anal cancer). In the CD4 count layer all transition times are piecewise exponentially distributed. In the anal cancer layer, the rate of progression from no lesion to AIN 1 is a function of the CD4 count ($f(CD4) = \beta_0 * \beta_1^{-CD4/100}$). The hazards of transitions from AIN 1 to AIN 2/3 and from AIN 2/3 to anal cancer are Weibull distributed. The hazard functions are thus of the form $(k/\lambda)(t/\lambda)^{k-1}$, where $k$ is the shape parameter and $\lambda$ the scale parameter. For the MSM who regressed from AIN 2/3 to AIN 1, the time to regression was assumed to be 1 year after detection of AIN 2/3 and successful treatment. We compared the predicted anal cancer incidence with the incidence observed in MSM in the SHCS. For each of the interventions described below, we simulated 10,000,000 HIV-positive MSM who were followed from 1980 to 2030.

We analyzed the Swiss HIV Cohort Study (SHCS) to determine the parameters for the CD4 count layer, including probabilities of transition between CD4 count states and mortality. From 2016 onwards, we used the parameters of 2010-2015. We used published estimates for the anal cancer layer.

### *Analyses of Swiss HIV Cohort Study data*

The SHCS is a prospective longitudinal study that includes about 45% of all HIV-positive adults living in Switzerland, and about 70% of all patients living with AIDS [22]. Socio-demographic, behavioral, clinical, laboratory data and use of cART regimens are recorded at study entry and semi-annual follow-up visits. We included all MSM who had at least three CD4 counts. Follow-

up started at estimated HIV infection date [23]. We split follow-up into periods before cART initiation and on cART. cART was defined as at least three antiretroviral drugs from at least two drug classes. We further split follow-up on cART into periods of successful cART (viral load <1000 copies/ml) and failing cART (viral load ≥1000 copies/ml). Within each calendar period, we monotonically smoothed CD4 trajectories using a general additive model and predicted CD4 cell counts eight times a year. We fit a multistate model with states determined by CD4 cell counts (<100, 100-199, 200-349, 350-499 and ≥500/μl) to six calendar periods (1980-1989, 1990-1994, 1995-1999, 2000-2004, 2005-2009, and 2010-2015). We used the same calendar periods and CD4 count states to parameterize the mortality rates of the MSM in our model.

### *Parameter estimates from literature*

We chose the transition rate from no precursors of anal cancer to AIN 1 in the baseline CD4 category of 100-199 cells/μl so that model simulations corresponded to the anal cancer incidence of 78 per 100,000 person-years reported by Machalek *et al* [1]. We simulated the model 1000 times with 10,000 HIV-positive MSM and used linear regression to identify the rate that matched this incidence best. This rate was 0.15 per person-year ($\beta_0$=0.15 in the equation for the hazard function *f* above). We assumed that the rate of transition from no lesion to AIN 1 increased by 2.04 per 100,000 for every 100/μl decrease in CD4 cell count ($\beta_1$= 2.04), based on estimates from the SHCS [12]. We fit a Weibull distribution to the cumulative incidence observed by Mathews *et al.* [14]: in their study progression from AIN 2/3 to anal cancer was 2.1% (95% CI 1.3-2.8) after 2 years, and 3.9% (95% CI 2.1-5.6) after 5 years. We found no published estimates for the progression from AIN 1 to AIN 2/3. We therefore fit a Weibull distribution to the progression from AIN 1 to AIN 2/3, so that the progression from AIN 1 to anal cancer lasted approximately 6-7 years, in line with observations from the SHCS [12]. The shape parameters (*k*) and scale

parameters ($\lambda$) of these distributions and all other literature derived parameters are shown in Table 1.

### *Interventions*

We examined the effect of 100% cART coverage and screening for AIN 2/3 and treatment on anal cancer incidence in MSM. In the base scenario with cART coverage below 100% and no screening we assumed that the cART coverage achieved in 2010-2015 continued 2016-2030. We implemented the 100% cART coverage scenario by parameterizing the model with the estimates from patients on cART. We considered four different screening strategies, combined with cART below 100%: (i) no screening, (ii) yearly cytology screening, (iii) yearly anoscopy screening and (iv) a CD4 count dependent strategy. In the CD4 count dependent strategy, we assumed that only those MSM were screened who had had a CD4 nadir below 200 cells/µl; they underwent anoscopy five years after their CD4 cell count had dropped below 200 cells/µl. We assumed that cytology had a sensitivity of 81% (95% CI: 69%-93%) based on the study by Chiao *et al* [24], and that anoscopy, including the histological examination of suspicious lesions, was 100% sensitive. We assumed a response rate of 49% one year after treatment initiation for electrocautery or infrared coagulation [17–19,25]. We assumed that treated patients who reverted back to AIN 1 subsequently had the same probability of developing AIN 2/3 as untreated men with AIN 1. For each strategy, we recorded the number of anal cancer diagnoses and the number of screening tests. We then calculated the number of anal cancers prevented compared to the no screening strategy and the number of people who needed to be screened (NNS) to prevent one anal cancer [26]. In all simulations we introduced the screening intervention in 2016.

### *Sensitivity analyses*

We performed a multivariate probabilistic sensitivity analysis. We sampled all model parameters 10,000 times from a log-normal distribution and simulated a population of 10,000 HIV-positive MSM for each sampled parameter set. We used the percentage of anal cancers prevented in each screening scenario as the main outcome variable and calculated Pearson correlation coefficients between all parameter values and outcomes to identify the parameters to which the model was most sensitive. Results are presented as incidence rates per 100,000 person-years, with 95% confidence intervals (95% CI). In an additional sensitivity analysis we tested the assumption of stationary CD4 trajectories. We simulated anal cancer incidence between 1980 and 2015 based on the observed CD4 trajectories in the SHCS.

## Results

We analyzed 6,411 MSM with at least three CD4 counts who were followed in the SHCS between February 1983 and August 2015. Men had between 3 and 170 CD4 counts, totaling 175,827 measurements. Table 2 shows the characteristics of the cohorts of MSM followed in the different calendar periods. Coverage with cART increased from 0% in 1980-1989, to 83.4% in 2010-2015. There were marked increases over time in rates of transition from low to higher CD4 count states (Supplemental Digital Content Table S1, http://links.lww.com/QAD/B109). For example, the rate of transition from CD4 count <100 cells/µl to ≥100 cells/µl increased from 5.3 (95% CI 4.3-6.4) per 100 person-years in 1980-1989 to 122.9 (95% CI 120.8-124.9) per 100 person-years in 2010-2015. As expected, mortality rates increased with decreasing CD4 cell counts and were higher in earlier calendar years than in later years (Supplemental Digital Content Table S2, http://links.lww.com/QAD/B109).

### *Anal cancer incidence*

Under the base scenario of cART coverage remaining at the level reached in the period 2010-2015 (Table 2) and with no screening, the simulated anal cancer incidence rates increased until 2009, plateaued between 2010 and 2015 and decreased from 2015 onwards. The highest rate was simulated for 2009, at 81.7 new cases per 100,000 person-years. The rate declined by 28.2% to 58.7 per 100,000 person-years in 2030 (see Figure 2 and, for a version with 95% CIs, Supplemental Digital Content Figure S1, http://links.lww.com/QAD/B109).

The simulated anal cancer rate was broadly consistent with the incidence rate observed in the SHCS. Between 1997 and 2003, the observed incidence in the SHCS was higher than the simulated rates but estimates were based on small numbers of cases and confidence intervals were wide. The simulated rates matched the observed rates closely from 2003 onwards (Supplemental Digital Content Figure S2, http://links.lww.com/QAD/B109).

### Impact of cART coverage and screening

When modeling anal cancer incidence under the assumption of 100% cART coverage from 2016 onwards, the incidence decreased to 52.0 per 100,000 person-years by 2030, rather than to 58.7 per 100,000 person-years with the base scenario (Figure 2), corresponding to a relative reduction of 11.4% compared to the base scenario. Yearly anoscopy and subsequent treatment decreased anal cancer incidence to 32.8 per 100,000 person-years in 2030, for a reduction of 44.1% compared to the base scenario. Yearly cytology decreased anal cancer incidence to 38.2 per 100,000 person-years in 2030, for a reduction of 34.9%. Finally, CD4 count-dependent anoscopy decreased anal cancer incidence to 51.3 per 100,000 person-years in 2030, for a reduction of 12.6%. The decrease in anal cancer incidence was substantial in the first year after introducing screening. Afterwards the slope was similar to the one observed with the base scenario (Figure 2).

Table 3 shows the number of expected anal cancer cases, the number of screening tests, the number of cancer cases prevented, and the number of MSM needed to screen to prevent one cancer in a hypothetical cohort of 10,000 MSM followed up 2016 to 2030. With yearly Pap screening, 384 MSM would need to be screened for 15 years to prevent one case. Similarly, with the yearly anoscopy strategy, 313 MSM would need to be screened for 15 years to prevent one new case of anal cancer. With CD4 count-dependent screening, 242 MSM would need to be screened once to prevent one anal cancer, but the percent of cases prevented would be smaller than with the other strategies.

### Sensitivity analyses

The results of the sensitivity analyses are shown in Supplemental Digital Content Figures S3 and S4, http://links.lww.com/QAD/B109. All strategies were sensitive to the efficacy of electrocautery or infrared coagulation treatment (Pearson correlation r = 0.46 for yearly anoscopy, r = 0.38 for yearly cytology, and r = 0.20 for CD4-dependent anoscopy). The benefit of the CD4 count-dependent anoscopy screening strategy was most sensitive to the relationship between the risk of transition from AIN 0 to AIN 1 and the CD4 cell count (r = 0.55). The benefit of yearly cytology was also dependent on the sensitivity of cytology screening (r = 0.23). The shape parameter of the Weibull distribution used in the transition from AIN 2/3 to anal cancer correlated with the percentage of anal cancers prevented in all screening strategies (r = 0.13, 0.09, 0.09). Other correlations, including all correlations with transitions between CD4 cell count states (Supplemental Digital Content Figure S4, http://links.lww.com/QAD/B109) were weak, with correlation coefficients below 0.1. In the sensitivity analysis using observed CD4 trajectories the same pattern was evident, with simulated anal cancer incidence rates increasing until 2007 and then plateauing. However, the peak of the incidence was somewhat higher than in the simulation

with stationary CD4 trajectories (Supplemental Digital Content Figure S5, http://links.lww.com/QAD/B109).

## Discussion

This modelling study based on data from the Swiss HIV Cohort Study (SHCS) predicted that anal cancer incidence in HIV-positive MSM peaked in 2009 at around 80 new cases per 100,000, plateaued in subsequent years, and will decrease to about 60 per 100,000 by 2030 in the absence of screening. Universal cART coverage from 2016 onwards would reduce incidence further, to around 50 per 100,000 by 2030. Annual screening with Pap smears or anoscopy would reduce anal cancer incidence substantially, to below 40 per 100,000, and targeted screening of MSM based on the CD4 cell count nadir to about 50 per 100,000. The numbers of MSM needed to screen (NNS) over 15 years to prevent one case were 384 for yearly cytology, 313 for yearly anoscopy and 242 for CD4 count dependent screening.

To our knowledge, this is the first study to predict the incidence of anal cancer in HIV-positive MSM over many years, taking into account cART coverage and individual CD4 cell count trajectories. We used a dynamic stochastic simulation model to estimate anal cancer incidence, based on changes in CD4 trajectories following the introduction of cART and allowing for non-constant rates in progression to anal cancer. Previous studies of the effect of screening for precancerous anal lesions and cancer did not consider the time-dependent effect of CD4 cell count on the risk of anal cancer [27,28]. The CD4 count layer of the model was parameterized with data from the SHCS, one of the longest-running HIV cohort studies worldwide [22,29]. The anal cancer layer was parameterized with data from the literature, but reproduced the incidence observed in the Swiss cohort.

Our findings are consistent with several earlier studies from Europe and the USA which reported that during the first ten years of cART anal cancer incidence continued to rise [4,5,9]. Our results are also in line with an analysis of North American cohorts which found that anal cancer incidence plateaued beyond ten years of cART [7] and with findings from a Dutch cohort that observed a slight decrease after 2006 [6]. Of note, rates of anal cancer were higher in the North American and Dutch cohorts than in our study. In the sensitivity analysis using the observed instead of simulated CD4 trajectories we also noted higher anal cancer incidence rates, but the overall pattern was similar. Our study offers a possible explanation for these trends, namely that during the early study period many HIV-positive MSM initiated cART at very low CD4 cell counts, had already progressed to AIN 1, and then lived long enough to develop anal cancer.

Our study has several limitations. Smoking status was not consistently recorded in the SHCS before the year 2000 and could therefore not be included in the model. Furthermore, although we simulated follow-up of patients until death, we did not explicitly model the effect of ageing. The rate of anal cancer increases with age [2,7,8], but the effect of older age may be less important in HIV-positive MSM where anal cancer is seen at younger ages than in other populations [4,9]. Our model did not take effects of screening and treatment on HPV transmission into account. The applicability of our results to other countries and settings is unclear. It would be of great interest to re-parameterize our model in the context of a different cohort of MSM. The shape of the epidemic curve of anal cancer in HIV-positive MSM will likely be similar in other countries where cART was introduced rapidly, but the peak incidence reached, and the year of the peak might differ. We did not include HPV clearance in the model. Most anal cancers in MSM are caused by HPV type 16 [1] and clearance of HPV type 16 is reduced in HIV-positive individuals [30,31]. Also, integration of HPV into the host genome of squamous cells [32] may happen before HPV clearance.

We did not formally model cost-effectiveness. Goldie *et al* used a state-transition model to estimate the cost-effectiveness of anal Pap screening in HIV-positive MSM in the USA. The authors concluded that with an incremental cost-effectiveness ratio of $13,000 (1997 US dollars, 2-yearly screening in early stage of HIV) per quality-adjusted life year (QALY) gained, such screening offered "quality-adjusted life expectancy benefits at a cost comparable with other accepted clinical preventive interventions" [33]. Czoski-Murray *et al* developed decision-analytical models to evaluate the cost-effectiveness of anal Pap screening in HIV-positive and HIV-negative MSM in the UK [34]. The authors found little evidence that screening "would generate health improvements at a reasonable cost". The incremental cost-effectiveness ratio in MSM, regardless of HIV status, was over £44,000 (2007 pounds sterling) per QALY gained. These discrepant findings are probably due to different assumptions regarding the rate of progression from AIN 2/3 to invasive cancer: the British study [34] assumed that the rate of progression was relatively low, and identical in HIV-positive and HIV-negative persons. Although we did not model this explicitly, it becomes clear from our study that the benefit of a screening program would be greatest now and decrease over time as fewer MSM have low nadir CD4 and more MSM have been vaccinated against HPV.

How does screening for anal cancer in HIV-positive MSM compare to screening for cervical cancer, which is recommended by The United States Preventive Services Task Force (USPSTF) [35] and public health agencies in many other countries? There are no randomized controlled trials of cervical screening in Western countries, and comparisons between women participating and not participating in screening programs are prone to bias [36]. Raffle *et al* [37] analyzed cervical screening in the west of England 1976-1996 and estimated rates of invasive cancer in the absence of screening based on historical data: about 1,800 women were needed to be screened every 5 years during this period to prevent one case of invasive cancer. In rural India, a cluster

randomized trial compared the effectiveness of a single round of screening: the number of women needed to be screened to prevent one cancer (stage II or higher) was 1,258 for cytology and 684 for human papilloma virus (HPV) testing [38]. Little data is available on the effectiveness of screening in HIV-positive women. A cost-effectiveness analysis based on simulated practice in the USA showed that screening with annual Pap smears was cost-effective, and a simulation study of a cohort of HIV-positive women in Cameroon concluded that 262 women will need to be screened at cART initiation to prevent one cervical cancer death [39]. Screening for colorectal cancer and breast cancer is also widely recommended. An Independent UK Panel on Breast Cancer Screening concluded that 180 women would need to be screened every 5 years from age 55 years to age 79 years to prevent one breast cancer death [40]. Finally, a systematic review and meta-analysis concluded that 377 to 515 asymptomatic adults will need to undergo guaiac fecal occult blood testing (gFOBT) annually or biannually over 18 years to prevent one colorectal cancer death [41].

In conclusion, our modelling study predicts substantial reductions in anal cancer incidence in MSM in the next 15 years, even in the absence of screening and without further increases in cART coverage. The model also predicts that the introduction of yearly anal Pap screening or anoscopy screening, or CD4 cell count guided anoscopy screening would reduce anal cancer incidence further. It is noteworthy that numbers needed to screen (NNS) to prevent one invasive anal cancer in MSM appear to be lower than the NNS to prevent one invasive cervical cancer in HIV-negative women, where screening is well established [42], and that it may be similar to the NNS in HIV-positive women. Clearly, further research on the cost-effectiveness and acceptability of different strategies for anal cancer screening is warranted. In the meantime, increasing cART coverage further, in MSM and the HIV-positive population in general, remains an important priority in Switzerland and globally.

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Aubert V, Battegay M, Bernasconi E, Böni J, Braun DL, Bucher HC, Calmy A, Cavassini M, Ciuffi A, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H (Chairman of the Clinical and Laboratory Committee), Fux CA, Günthard HF (President of the SHCS), Haerry D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hoffmann M, Hösli I, Kahlert C, Kaiser L, Keiser O, Klimkait T, Kouyos RD, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Marzolini C, Metzner KJ, Müller N, Nicca D, Pantaleo G, Paioni P, Rauch A (Chairman of the Scientific Board), Rudin C (Chairman of the Mother & Child Substudy), Scherrer AU (Head of Data Centre), Schmid P, Speck R, Stöckle M, Tarr P, Trkola A, Vernazza P, Wandeler G, Weber R, Yerly S.

**Conflicts of interest**

There are no conflicts of interest to declare.

## References


1 Machalek DA, Poynten M, Jin F, Fairley CK, Farnsworth A, Garland SM, *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.

2 Schim van der Loeff MF, Mooij SH, Richel O, de Vries HJC, Prins JM. HPV and anal cancer in HIV-infected individuals: a review. *Curr HIV/AIDS Rep* 2014; **11**:250–62.

3 Dalla Pria A, Alfa-Wali M, Fox P, Holmes P, Weir J, Francis N, *et al.* High-resolution anoscopy screening of HIV-positive MSM: longitudinal results from a pilot study. *AIDS* 2014; **28**:861–7.

4 Crum-Cianflone NF, Hullsiek KH, Marconi VC, Ganesan A, Weintrob A, Barthel R V, *et al.* Anal cancers among HIV-infected persons: HAART is not slowing rising incidence. *AIDS* 2010; **24**:535–43.

5 Powles T, Robinson D, Stebbing J, Shamash J, Nelson M, Gazzard B, *et al.* Highly active antiretroviral therapy and the incidence of non-AIDS-defining cancers in people with HIV infection. *J Clin Oncol* 2009; **27**:884–90.

6 Richel O, Van Der Zee RP, Smit C, De Vries HJC, Prins JM. Brief Report: Anal Cancer in the HIV-Positive Population: Slowly Declining Incidence After a Decade of cART. *J Acquir Immune Defic Syndr* 2015; **69**:602–5.

7 Silverberg MJ, Lau B, Justice AC, Engels E, Gill MJ, Goedert JJ, *et al.* Risk of anal cancer in HIV-infected and HIV-uninfected individuals in North America. *Clin Infect Dis* 2012; **54**:1026–1034.

8 de Pokomandy A, Rouleau D, Ghattas G, Trottier H, Vezina S, Cote P, *et al.* HAART and progression to high-grade anal intraepithelial neoplasia in men who have sex with men and are infected with HIV. *Clin Infect Dis* 2011; **52**:1174–1181.

9 Piketty C, Selinger-Leneman H, Grabar S, Duvivier C, Bonmarchand M, Abramowitz L, *et al.* Marked increase in the incidence of invasive anal cancer among HIV-infected patients despite treatment with combination antiretroviral therapy. *AIDS* 2008; **22**:1203–11.

10 Bower M, Powles T, Newsom-Davis T, Thirlwell C, Stebbing J, Mandalia S, *et al.* HIV-associated anal cancer: has highly active antiretroviral therapy reduced the incidence or improved the outcome? *JAcquirImmuneDeficSyndr* 2004; **37**:1563–1565.

11 Guiguet M, Boue F, Cadranel J, Lang J-MM, Rosenthal E, Costagliola D, *et al.* Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. *Lancet Oncol* 2009; **10**:1152–1159.

12 Bertisch B, Franceschi S, Lise M, Vernazza P, Keiser O, Schoni-Affolter F, *et al.* Risk factors for anal cancer in persons infected with HIV: a nested case-control study in the Swiss HIV Cohort Study. *Am J Epidemiol* 2013; **178**:877–84.

13 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**:191–5.

14 Mathews WC, Agmas W, Cachay ER, Cosman BC, Jackson C. Natural history of anal dysplasia in an HIV-infected clinical care cohort: estimates using multi-state Markov modeling. *PLoS One* 2014; **9**:e104116.

15 Nathan M, Singh N, Garrett N, Hickey N, Prevost T, Sheaff M. Performance of anal cytology in a clinical setting when measured against histology and high-resolution anoscopy findings. *AIDS* 2010; **24**:373–379.

16 Berry JM, Palefsky JM, Jay N, Cheng SC, Darragh TM, Chin-Hong P V. Performance characteristics of anal cytology and human papillomavirus testing in patients with high-resolution anoscopy-guided biopsy of high-grade anal intraepithelial neoplasia. *Dis Colon Rectum* 2009; **52**:239–247.

17 Burgos J, Curran A, Landolfi S, Navarro J, Tallada N, Guelar A, *et al.* The effectiveness of electrocautery ablation for the treatment of high-grade anal intraepithelial neoplasia in HIV-infected men who have sex with men. *HIV Med* 2016; **17**:524–31.

18 Richel O, de Vries HJC, van Noesel CJM, Dijkgraaf MGW, Prins JM. Comparison of imiquimod, topical fluorouracil, and electrocautery for the treatment of anal intraepithelial neoplasia in HIV-positive men who have sex with men: an open-label, randomised controlled trial. *Lancet Oncol* 2013; **14**:346–53.

19 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.

20 Sirera G, Videla S, Piñol M, Coll J, García-Cuyás F, Vela S, *et al.* Long-term effectiveness of infrared coagulation for the treatment of anal intraepithelial neoplasia grades 2 and 3 in HIV-infected men and women. *AIDS* 2013; **27**:951–9.

21 Ledergerber B, Egger M, Erard V, Weber R, Hirschel B, Furrer H, *et al.* AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV Cohort Study. *JAMA* 1999; **282**:2220–6.

22 Schoeni-Affolter F, Ledergerber B, Rickenbach M, Rudin C, Günthard HF, Telenti A, *et al.* Cohort profile: the Swiss HIV Cohort study. *Int JEpidemiol* 2010; **39**:1179–1189.

23 Taffé P, May M, Bachmann S, Battegay M, Bernasconi E, Bucher H, *et al.* A joint back calculation model for the imputation of the date of HIV infection in a prevalent cohort. *Stat Med* 2008; **27**:4835–4853.

24 Chiao EY, Giordano TP, Palefsky JM, Tyring S, El Serag H. Screening HIV-infected individuals for anal cancer precursor lesions: a systematic review. *Clin Infect Dis* 2006; **43**:223–233.

25 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**:1284–92.

26 Rembold CM. Number needed to screen: development of a statistic for disease screening. *Br Med J* 1998; **317**:307–312.

27 Goldie SJ, Kuntz KM, Weinstein MC, Freedberg KA, Welton ML, Palefsky JM. The clinical effectiveness and cost-effectiveness of screening for anal squamous intraepithelial lesions in homosexual and bisexual HIV-positive men. *JAMA* 1999; **281**:1822–1829.

28 Lazenby GB, Unal ER, Andrews AL, Simpson K. A Cost-Effectiveness Analysis of Anal Cancer Screening in HIV-Positive Women. *J Low Genit Tract Dis* 2012; **16**:275–280.

29 Ledergerber B, von Overbeck J, Egger M, Luethy R. The Swiss HIV cohort study: rationale, organization and selected baseline characteristics. *Soz und Praeventivmedizin* 1994; **39**:387–394.

30 Kreuter A, Wieland U. Human papillomavirus-associated diseases in HIV-infected men who have sex with men. *Curr Opin Infect Dis* 2009; **22**:109–14.

31 de Pokomandy A, Rouleau D, Ghattas G, Vezina S, Cote P, Macleod J, *et al*. Prevalence, clearance, and incidence of anal human papillomavirus infection in HIV-infected men: the HIPVIRG cohort study. *J Infect Dis* 2009; **199**:965–973.

32 Gervaz P, Hirschel B, Morel P. Molecular biology of squamous cell carcinoma of the anus. Br. J. Surg. 2006; **93**:531–538.

33 Goldie SJ, Kuntz KM, Weinstein MC, Freedberg KA, Welton ML, Palefsky JM. The clinical effectiveness and cost-effectiveness of screening for anal squamous intraepithelial lesions in homosexual and bisexual HIV-positive men. *JAMA* 1999; **281**:1822–1829.

34 Czoski-Murray C, Karnon J, Jones R, Smith K, Kinghorn G. Cost-effectiveness of screening high-risk HIV-positive men who have sex with men (MSM) and HIV-positive women for anal cancer. *Heal Technol Assess* 2010; **14**:iii–iv, ix–x, 1-101.

35 Agency for Healthcare Research and Quality. Guide to Clinical Preventive Services, 2014. Recommendations of the U.S. Preventive Services Task Force. Washington, D.C., 2014. Available from https://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/guide/index.html (accessed 20 Apr2017).

36 Dugué P-A, Lynge E, Rebolj M. Mortality of non-participants in cervical screening: Register-based cohort study. *Int J cancer* 2014; **134**:2674–82.

37 Raffle AE, Alden B, Quinn M, Babb PJ, Brett MT. Outcomes of screening to prevent cancer: analysis of cumulative incidence of cervical abnormality and modelling of cases and deaths prevented. *BMJ* 2003; **326**:901.

38 Sankaranarayanan R, Nene BM, Shastri SS, Jayant K, Muwonge R, Budukh AM, *et al.* HPV screening for cervical cancer in rural India. *N Engl J Med* 2009; **360**:1385–94.

39 Atashili J, Smith JS, Adimora AA, Eron J, Miller WC, Myers E. Potential impact of antiretroviral therapy and screening on cervical cancer mortality in HIV-positive women in sub-Saharan Africa: a simulation. *PLoS One* 2011; **6**:e18527.

40 Marmot MG, Altman DG, Cameron DA, Dewar JA, Thompson SG, Wilcox M, *et al.* The benefits and harms of breast cancer screening: an independent review. *Br J Cancer* 2013; **108**:2205–40.

41 Fitzpatrick-Lewis D, Ali MU, Warren R, Kenny M, Sherifali D, Raina P. Screening for Colorectal Cancer: A Systematic Review and Meta-Analysis. *Clin Colorectal Cancer* 2016; **15**:298–313.

42 Landy R, Castanon A, Hamilton W, Lim AWW, Dudding N, Hollingworth A, *et al*. Evaluating cytology for the detection of invasive cervical cancer. *Cytopathology* 2016; **27**:201–9.

*Table 1: Parameter values progression and regression between precursor states and anal cancer.*

| Progression / regression | | Parameter | Value | Source | Reference |
|---|---|---|---|---|---|
| From | To | | | | |
| AIN 0 | AIN 1 | Rate per person-year with 100-199 CD4 cells/µl | 0.15[a,b] (0.1 - 0.2) | Systematic review and meta-analysis of longitudinal studies in MSM | Machalek *et al* [1] |
| AIN 0 | AIN 1 | Increase in rate per person-year per 100 cells/µl CD4 count decrease | 2.04 (1.44 - 2.88) | Case-control study nested within Swiss HIV Cohort Study, data from MSM | Bertisch *et al* [12] |
| AIN 1 | AIN 2/3 | Weibull shape | 2[b] (1 - 4) | " | Bertisch *et al* [12] |
| AIN 1 | AIN 2/3 | Weibull scale | 7[b] (5 - 10) | " | Bertisch *et al* [12] |
| AIN 2/3 | Anal cancer | Weibull shape | 0.69[b] (0.53 - 0.77) | Cytology-based screening cohort, overall data (78% MSM) | Mathews *et al* [14] |

| | | | | | |
|---|---|---|---|---|---|
| AIN 2/3 | Anal cancer | Weibull scale | 551.13[b] (201.2 - 7395.9) | " | Mathews *et al* [14] |
| AIN 2/3 | AIN 1 | Sensitivity of anal cytology (Pap smears) %) | 81 (69 - 93) | Systematic review of test accuracy studies in MSM and other populations | Chiao *et al* [24] |
| AIN 2/3 | AIN 1 | Treatment efficacy 1 year after treatment (in %) | 48.1[b] (39.7 - 57.8) | Retrospective cohort study of MSM treated in surgical practice | Burgos *et al* [17] |

[a] Identified through model simulations (see text)

[b] Calculated from data presented in cited publication

*Table 2: Characteristics of cohorts of men who have sex with men enrolled in the Swiss HIV Cohort Study, by follow-up period.*

| Follow-up period | No. of men | CD4 cells/µl (median, IQR) | Nadir CD4 cells/µl (median, IQR) | Age (median, IQR) | Current smoking (%) | cART coverage (%) |
|---|---|---|---|---|---|---|
| 1980-1989 | 762 | 340 (140-545) | 228.5 (60.0-440.0) | 36.2 (29.9-43.5) | n.a. | 0% |
| 1990-1999 | 3,018 | 283 (126-469) | 120.0 (20.0-288.8) | 38.5 (32.7-46.4) | n.a. | 45.5% |
| 2000-2009 | 4,087 | 467 (351-613) | 257.0 (165.0-373.5) | 41.7 (36.1-48.4) | 50.4% | 78.2% |
| 2010-2015 | 4,538 | 576 (451-727) | 394.0 (283.0-524.8) | 46.4 (38.9-53.0) | 44.3% | 83.4% |

n.a., not assessed

*Table 3: Comparison of anal cancer screening strategies in a cohort of 10,000 men who have sex with men, followed from 2016 to 2030.*

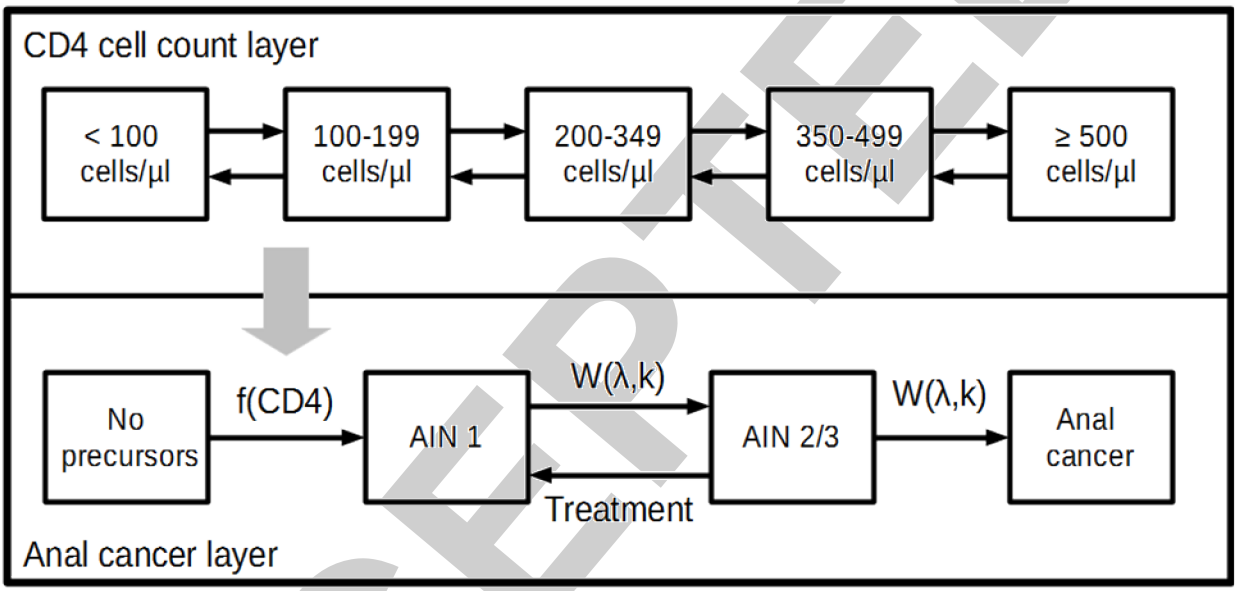
| Strategy | No. of expected invasive cancer cases | No. of screening tests | No. of cancers prevented | No. of men needed to be screened to prevent one cancer | Percent of cases prevented | No. of screening tests to prevent one cancer |
|---|---|---|---|---|---|---|
| No screening | 81.7 (65-100) | 0 | 0.0 | NA | 0% | NA |
| Yearly cytology | 56.5 (42-72) | 118150 | 25.2 (16-35) | 384 (347-422) | 30.9% (30.0-31.8%) | 4684 (4586-4782) |
| Yearly anoscopy | 50.8 (37-65) | 118066 | 30.9 (21-42) | 313 (279-347) | 37.9% (36.9-38.8%) | 3817 (3722-3913) |
| CD4 count dependent anoscopy[a] | 71.1 (55-88) | 2562 | 10.6 (5-17) | 242 (212-272) | 13.0% (12.3-13.6%) | 242 (212-272) |

Results from mathematical modelling study over 15 years (2016-2030). Estimates with 95% confidence intervals are shown.

[a] Men are screened five years after their CD4 cell count fell below 200 cells/μl; 25.6% of men were eligible for CD4 count dependent screening.

*Figure 1: Model structure with CD4 count and anal cancer layers.*

The model is a stochastic, dynamic model. The CD4 count layer of the model is a Markov model and the anal cancer layer a stochastic compartmental model, where transition probabilities are non-Markov.




AIN: Anal Intra-epithelial Neoplasia.

*Figure 2: Simulated anal cancer incidence assuming different intervention scenarios.*