Impact of screening and antiretroviral therapy on anal cancer incidence in HIV-positive MSM

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Background: The incidence of anal cancer is high in HIV-positive 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 and literature data. We assumed all men to be human papillomavirus 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: no screening, yearly anal cytology (Papanicolaou smears), yearly anoscopy and targeted anoscopy 5 years after CD4$^+$ count dropped below 200 cells/μl.

Results: Median nadir CD4$^+$ cell count of 6411 MSM increased from 229 cells/μl during 1980–1989 to 394 cells/μl during 2010–2015; cART coverage increased from 0 to 83.4%. Modeled anal cancer incidence peaked at 81.7/100 000 in 2009, plateaued 2010–2015 and will decrease 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$^+$ cell count guided anoscopy to 51.3. The numbers needed to screen over 15 years to prevent one anal cancer case were 384 for yearly cytology, 313 for yearly anoscopy and 242 for CD4$^+$ cell count-dependent screening.

Conclusion: Yearly screening of HIV-positive MSM may reduce anal cancer incidence substantially, with a number needed to screen that is comparable with other screening interventions to prevent cancer.

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Introduction

Anal cancer is caused by infection with high-risk types of human papillomavirus (HPV) [1–3]. In HIV-negative MSM, the incidence of anal cancer is around five per 100 000 person-years, which is about five times higher than in the general population [1,2]. In HIV-positive MSM, the incidence ranged between 78 and 168 per 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 HPV which is very frequent in HIV-positive MSM [1–3,8]. Another important risk factor is immunosuppression, characterized by low nadir $CD4^+$ cell counts [4–6,9] or a long duration of exposure to low $CD4^+$ cell 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 intraepithelial neoplasia (AIN) grades 2 or 3, the precursors of anal cancer [2,3,13], are found in 24–50% 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 Papanicolaou (Pap) smears of the anal canal is inexpensive, but with 67–90% 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 (IR) coagulation are the most effective treatments for intraanal AIN 2/3 [2]. Burgos et al. [17] found that 1 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].

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 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 $CD4^+$ cell count layer and an anal cancer layer, which depends on the $CD4^+$ cell count layer (Fig. 1).

The $CD4^+$ cell 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 $CD4^+$ cell count layer, the $CD4^+$ trajectories of MSM are modeled across five $CD4^+$ cell 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 $CD4^+$ cell 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 $CD4^+$ cell count $\left[f(CD4^+) = \beta_0 \times \beta_1^{-CD4^+/100} \right]$. 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 $(k/\lambda)(t/\lambda)^{k-1}$, in which k is the shape parameter and λ 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
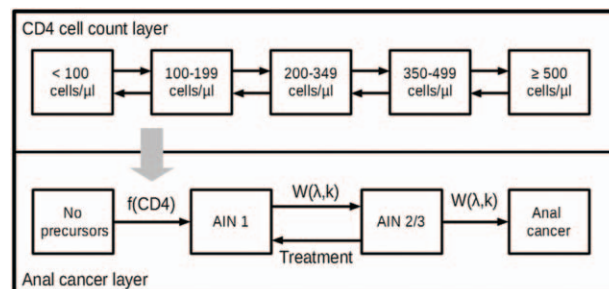

Fig. 1. Model structure with $CD4^+$ cell count and anal cancer layers. The model is a stochastic, dynamic model. The $CD4^+$ cell count layer of the model is a Markov model and the anal cancer layer a stochastic compartmental model, where transition probabilities are non-Markov. AIN, anal intraepithelial neoplasia.

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 SHCS to determine the parameters for the CD4$^+$ cell count layer, including probabilities of transition between CD4$^+$ cell count states and mortality. From 2016 onward, 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 semiannual follow-up visits. We included all MSM who had at least three CD4$^+$ cell 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$^+$ cell 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% confidence interval (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 (λ) 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

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

Progression/regression

From	To	Parameter	Value	Source	Reference
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	[1]
AIN 0	AIN 1	Increase in rate per person-year per 100 cells/μl CD4$^+$ cell count decrease	2.04 (1.44−2.88)	Case-control study nested within Swiss HIV Cohort Study, data from MSM	[12]
AIN 1	AIN 2/3	Weibull shape	2[b] (1−4)	Idem	[12]
AIN 1	AIN 2/3	Weibull scale	7[b] (5−10)	Idem	[12]
AIN 2/3	Anal cancer	Weibull shape	0.69[b] (0.53−0.77)	Cytology-based screening cohort, overall data (78% MSM)	[14]
AIN 2/3	Anal cancer	Weibull scale	551.13[b] (201.2−7395.9)	Idem	[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	[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	[17]

AIN, anal intraepithelial neoplasia; Pap, Papanicolaou.
[a]Identified through model simulations (see text).
[b]Calculated from data presented in cited publication.

Table 2. Characteristics of cohorts of MSM 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	3018	283 (126–469)	120.0 (20.0–288.8)	38.5 (32.7–46.4)	n.a.	45.5
2000–2009	4087	467 (351–613)	257.0 (165.0–373.5)	41.7 (36.1–48.4)	50.4	78.2
2010–2015	4538	576 (451–727)	394.0 (283.0–524.8)	46.4 (38.9–53.0)	44.3	83.4

cART, combination antiretroviral therapy; IQR, interquartile range; n.a., not assessed.

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%: no screening, yearly cytology screening, yearly anoscopy screening and a CD4+ cell count-dependent strategy. In the CD4+ cell count–dependent strategy, we assumed that only those MSM were screened who had had a CD4+ nadir below 200 cells/μl; they underwent anoscopy 5 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% 1 year after treatment initiation for electrocautery or IR 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 with 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% 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 6411 MSM with at least three CD4+ cell counts who were followed in the SHCS between February 1983 and August 2015. Men had between three and 170 CD4+ cell 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+ cell count states (Supplemental Digital Content Table S1, http://links.lww.com/QAD/B109). For example, the rate of transition from CD4+ cell count less than 100 cells/μl to at least 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 onward. 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 (Fig. 2 and, for a version with 95% CIs, Supplemental Digital Content Fig. 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 CIs were wide. The simulated rates matched the observed rates closely from 2003 onward (Supplemental Digital Content Fig. S2, http://links.lww.com/QAD/B109).

Impact of combination antiretroviral therapy coverage and screening

When modeling anal cancer incidence under the assumption of 100% cART coverage from 2016 onward,
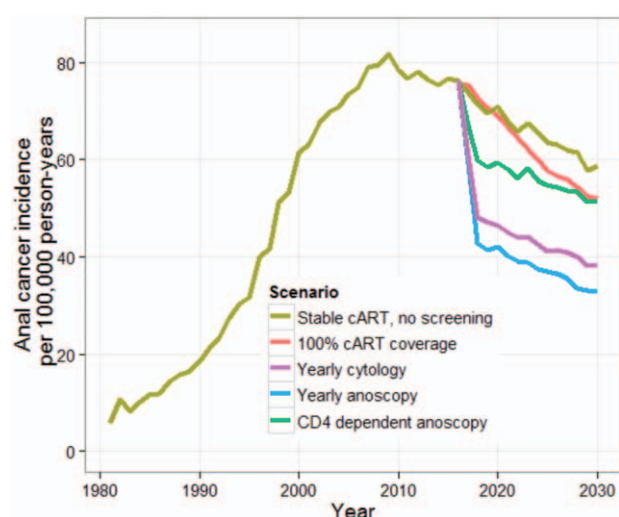
Fig. 2. Simulated anal cancer incidence assuming different intervention scenarios.

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 (Fig. 2), corresponding to a relative reduction of 11.4% compared with 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 with 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, $CD4^+$ cell 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 (Fig. 2).

Table 3 shows the number of expected anal cancer cases, the number of screening tests, the number of cancer cases prevented and the NNS of MSM to prevent one cancer in a hypothetical cohort of 10 000 MSM followed up 2016–2030. 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 $CD4^+$ cell count-dependent screening, 242 MSM would need to be screened once to prevent one anal cancer, but the percentage 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 Figs. S3 and S4, http://links.lww.com/QAD/B109. All strategies were sensitive to the efficacy of electrocautery or IR 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 $CD4^+$ cell 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 three screening strategies ($r = 0.13$, 0.09, 0.09, respectively). Other correlations, including all correlations with transitions between $CD4^+$ cell count states (Supplemental Digital Content Fig. 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 Fig. S5, http://links.lww.com/QAD/B109).

Discussion

This modeling study based on data from the 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

Table 3. Comparison of anal cancer screening strategies in a cohort of 10 000 MSM, 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	Percentage 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)
$CD4^+$ cell 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 modeling study over 15 years (2016–2030). Estimates with 95% confidence intervals are shown.
[a]Men are screened 5 years after their $CD4^+$ cell count fell below 200 cells/μl; 25.6% of men were eligible for $CD4^+$ cell count-dependent screening.

60 per 100 000 by 2030 in the absence of screening. Universal cART coverage from 2016 onward 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 NNS of MSM over 15 years to prevent one case were 384 for yearly cytology, 313 for yearly anoscopy and 242 for CD4$^+$ cell 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 nonconstant 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$^+$ cell 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 United States which reported that during the first 10 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 10 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 aging. 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, in whom 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 reparameterize 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 United States. The authors concluded that with an incremental cost-effectiveness ratio of $13 000 (1997 US dollars, 2-yearly screening in early stage of HIV) per quality-adjusted life year (QALY) gained, such screening offered 'quality-adjusted life expectancy benefits at a cost comparable with other accepted clinical preventive interventions' [27]. Czoski-Murray *et al.* [33] developed decision-analytical models to evaluate the cost-effectiveness of anal Pap screening in HIV-positive and HIV-negative MSM in the United Kingdom. The authors found little evidence that screening 'would generate health improvements at a reasonable cost'. The incremental cost-effectiveness ratio in MSM, regardless of HIV status, was over £44 000 (2007 pounds sterling) per QALY gained. These discrepant findings are probably due to different assumptions regarding the rate of progression from AIN 2/3 to invasive cancer: the British study [33] assumed that the rate of progression was relatively low, and identical in HIV-positive and HIV-negative persons. Although we did not model this explicitly, it becomes clear from our study that the benefit of a screening program would be greatest now and decrease over time as fewer MSM have low nadir CD4$^+$, and more MSM have been vaccinated against HPV.

How does screening for anal cancer in HIV-positive MSM compare with screening for cervical cancer, which is recommended by The United States Preventive Services Task Force [34] 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 [35]. Raffle *et al.* [36] 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 1800 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

1258 for cytology and 684 for HPV testing [37]. Little data are available on the effectiveness of screening in HIV-positive women. A cost–effectiveness analysis based on simulated practice in the United States showed that screening with annual Pap smears was cost-effective [38], 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 377−515 asymptomatic adults will need to undergo guaiac fecal occult blood testing annually or biannually over 18 years to prevent one colorectal cancer death [41].

In conclusion, our modeling 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 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, in whom 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.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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**:250–262.

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**:861–867.

4. Crum-Cianflone NF, Hullsiek KH, Marconi VC, Ganesan A, Weintrob A, Barthel RV, *et al.* **Anal cancers among HIV-infected persons: HAART is not slowing rising incidence.** *AIDS* 2010; **24**:535–543.

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**:884–890.

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**:602–605.

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**:1203–1211.

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?** *J Acquir Immune Defic Syndr* 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**:877–884.

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**:191–195.

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 multistate 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 PV. **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**:524–531.

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**:346–353.

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**:259–265.

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**:951–959.

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**:2220–2226.

22. Schoeni-Affolter F, Ledergerber B, Rickenbach M, Rudin C, Günthard HF, Telenti A, et al. **Cohort profile: the Swiss HIV Cohort study.** *Int J Epidemiol* 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**:1284–1292.

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 Praventivmed* 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**:109–114.

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. 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.** *Health Technol Assess* 2010; **14**:1–101.

34. Agency for Healthcare Research and Quality, Recommendations of the U.S. Preventive Services Task Force. *Guide to clinical preventive services, 2014*. Washington, D.C: Agency for Healthcare Research and Quality; 2014, Available from: https://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/guide/index.html. [Accessed 20 April, 2017].

35. Dugué P-A, Lynge E, Rebolj M. **Mortality of nonparticipants in cervical screening: register-based cohort study.** *Int J cancer* 2014; **134**:2674–2682.

36. 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.

37. 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**:1385–1394.

38. Goldie SJ, Weinstein MC, Kuntz KM, Freedberg KA. **The costs, clinical benefits, and cost-effectiveness of screening for cervical cancer in HIV-infected women.** *Ann Intern Med* 1999; **130**:97–107.

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**:2205–2240.

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**:201–209.