Anal intraepithelial neoplasia in HIV+ men

Epidemiology, cancer risk stratification and prevention of recurrences

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CHAPTER 3

Anal Cancer in the HIV-Positive Population: Slowly Declining Incidence After a Decade of cART

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ABSTRACT

We surveyed trends in incidence (1995–2012) and risk factors for anal cancer in the Dutch HIV-positive population. After an initial increase with a peak incidence in 2005–2006 of 114 [95% confidence interval (CI): 74 to 169] in all HIV+ patients and 168 (95% CI: 103 to 259) in HIV+ men who have sex with men (MSM), a decline to 72 (95% CI: 43 to 113) and 100 (95% CI: 56 to 164), respectively, was seen in 2011–2012. Low nadir CD4, alcohol use, and smoking were significantly associated with anal cancer in MSM. In conclusion, anal cancer remains a serious problem in predominantly HIV+ MSM. However, it seems that incidence rates are levelling off.

INTRODUCTION

Since the introduction of combination antiretroviral therapy (cART), anal cancer is a highly prevalent problem in the HIV-positive population, especially in men who have sex with men (MSM).[1, 2] Given the similarities between anal and cervical cancer, screening for and treatment of premalignant lesions to prevent anal cancer is now subject of discussion. Premalignant anal lesions [anal intraepithelial neoplasia (AIN)] are highly prevalent in HIV+ MSM.[1] Unfortunately, the gold standard for screening, high-resolution anoscopy, is time consuming and cumbersome for the patient. Identification of risk factors could be a way to focus screening programmes. So far, risk factors for (HG)AIN in HIV+ MSM do not seem to be reliable to guide a screening programme.[3] Since we assume that only a minority of AIN will undergo malignant transformation and the goal of screening is to prevent anal cancer, identification of risk factors for anal cancer might be an alternative to identify those who most need screening.

In this study, we explored the incidence of anal cancer in the Dutch HIV+ population in the cART era, and we analysed a range of potential risk factors in relation to anal cancer in HIV+ MSM.

METHODS

Data were selected from the ongoing *AIDS Therapy Evaluation in the Netherlands (ATHENA)* national observational HIV cohort, a nationwide data set, which includes anonymised data from all HIV-1–infected patients under care in the 26 HIV treatment centres in the Netherlands. Epidemiological, clinical, virological, and immunological data are collected retrospectively at entry in the cohort and prospectively thereafter.[4]

For this study, cases of anal cancer were identified for the period 1995–2012 and incidence rates of anal cancer were calculated per 100,000 person-years of follow-up. Follow-up time was from the date of HIV diagnosis till the date of diagnosis of anal cancer, death, last clinical visit, lost to follow-up, or closure of the database (February 1, 2013). Incidence rates were calculated for the whole cohort and for MSM, heterosexual men, men infected otherwise, and women separately. Trends in time were calculated per blocks of 2 years for the whole cohort and MSM separately. Each treatment centre was visited to verify the source documents and confirm pathological diagnoses.

To determine risk factors for anal cancer, we included all HIV-infected MSM in the *ATHENA* cohort. We estimated hazard ratios (HRs) for progression to anal cancer using univariable and multivariable Cox proportional hazard modelling including the following parameters: follow-up period (<2004, ≥2004), age at HIV diagnosis (<36, ≥36 years), time between HIV diagnosis and start cART (<14, ≥14 months), cumulative time on cART (per 6 months increase), nadir CD4 count (<110, 110–230, 230–338, ≥338 cells), cumulative time spent below 200 CD4 cells (<4, 4–19, ≥19 months), cumulative time spent with plasma HIV-RNA over 1000 copies per millilitre (<18, ≥18 months, no time spent above 1000 copies/mL), alcohol abuse (>28 glasses per week), and ever smoking (yes, no, unknown).

Categorical variables were classified based on the median, tertiles, or quartiles of the total MSM population. A multivariable model was used to adjust for potential confounders. Factors with a *p* value <0.05 were considered significant.

RESULTS

Between 1995 and 2012, 20,765 HIV+ patients were under surveillance in the 26 Dutch HIV centres, with 164,101 person-years of follow-up (**Table 1**). One hundred thirty-seven cases of anal cancer were identified. The anal cancer incidence in the whole HIV-positive population was 83 [95% confidence interval (CI): 70 to 99] per 100,000 person-years. Of note, 109/137 cases of anal cancer were found among HIV+ MSM, leading to an incidence rate of 116 (95% CI: 95 to 140) per 100,000 person-years. The incidence rate among heterosexual men was 44 (95% CI: 21 to 83), among women 12 (95% CI: 3 to 30), and in men infected otherwise or with unknown cause 97 (95% CI: 53 to 164) per 100,000 person-years.

TABLE 1 | Baseline characteristics of the 20,765 patients in the *ATHENA* Cohort who were in follow-up from 1995 to 2012.

	Total no. patients	Cases with anal cancer
Total	20,765	137
Age at HIV diagnosis (yrs; median, IQR)	36 (29–44)	38 (32–45)
HIV transmission route, *n* (%)		
MSM	11,796 (57)	109 (80)
Heterosexual	6799 (33)	13 (9)
IDU	733 (4)	5 (4)
other	1437 (7)	10 (7)
Gender, *n* (%)		
Male	16,572 (80)	133 (97)
Female	4193 (20)	4 (3)
Region of origin, *n* (%)		
The Netherlands	11,415 (55)	107 (78)
Sub-Saharan Africa	3063 (15)	2 (1)
Western Europe	1340 (6)	9 (7)
Other	4947 (24)	19 (14)
Nadir CD4 (x10^6/L; median, IQR)	200 (80–314)	70 (20–164)
cART	17,712 (85)	135 (99)
Ever smoking, *n* (%)		
No	2937 (14)	15 (11)
Yes	8902 (43)	89 (65)
Unknown	8906 (43)	33 (24)
Alcohol abuse, *n* (%)		
No	4508 (22)	16 (12)
Yes	10,365 (50)	75 (55)
Unknown	5892 (28)	46 (34)
Died	2172 (10)	52 (38)

The cumulative loss to follow-up rates were 1180 (6%) after 5 years, 1723 (11%) after 10 years, and 3091 (17%) after 15 years (loss to follow-up was defined as no clinical visits without date of death). Numbers are *n* (%) unless otherwise stated. Alcohol abuse is defined as more than 28 (men) or 21 (women) glasses per week. IDUs, intravenous drug users; IQR, interquartile range.

Analysis of trends in time showed an anal cancer incidence in the overall HIV-infected population of 14 (95% CI: 0 to 77) per 100,000 person-years in 1995/1996 and 72 (95% CI: 43 to 113) in 2011/2012, with a peak incidence in 2005–2006: 114 (95% CI: 74 to 169) per 100,000 person-years (**Figure 1**). In HIV+ MSM, these incidence rates were 22 (95% CI: 1 to 127) for 1995/1996 and 100 (95% CI: 56 to 164) for 2011/2012, with a peak of 168 (95% CI: 103 to 259) per 100,000 person-years in 2005/2006 (**Figure 1**).

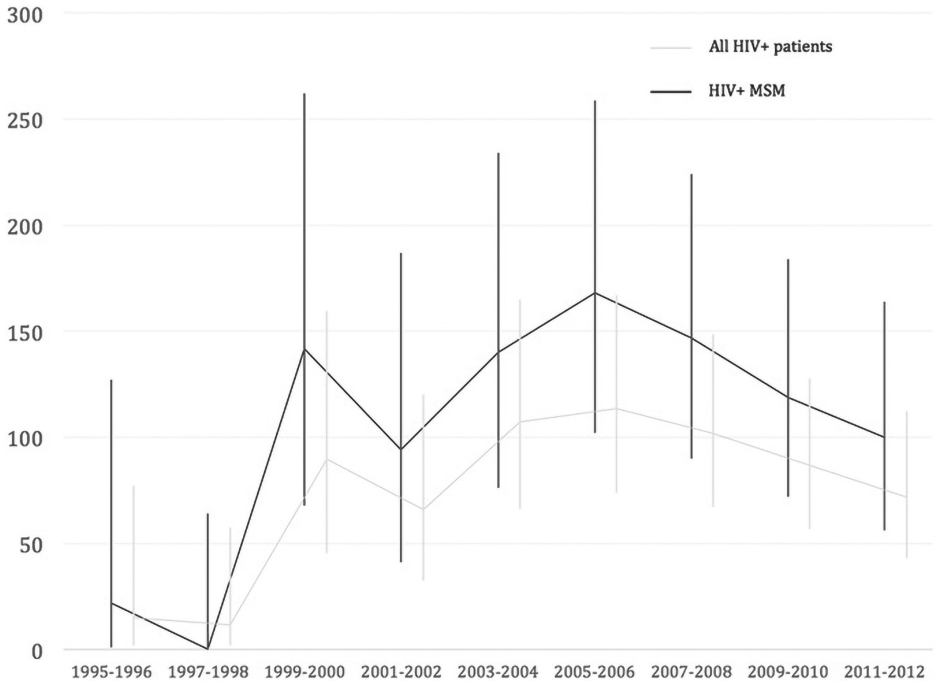

FIGURE 1 | Anal cancer incidence per 100,000 person-years (with 95% CIs) for 9 consecutive 2-year blocks in all HIV+ patients and HIV+ MSM separately in the Netherlands (1995–2012).

Univariable analysis showed a significant correlation of a low nadir CD4 cell count with anal cancer [HR = 2.38 (95% CI: 1.59 to 3.56) for nadir CD4 <110 cells/mm3], alcohol abuse (HR = 1.96; 95% CI: 1.13 to 3.39), and smoking (HR = 1.64; 95% CI: 1.10 to 2.45). Multivariable analysis showed the same significant parameters with hazard ratios of 2.41 (95% CI: 1.5 to 3.89), 2.23 (95% CI: 1.28 to 3.89), and 1.60 (95% CI: 1.07 to 2.41), respectively.

DISCUSSION

In this study, we found a remarkable increase in the incidence of anal cancer among HIV+ patients since the introduction of cART, predominantly among HIV+ MSM, followed by a slight decrease since 2006. CIs of the anal cancer incidence in MSM and heterosexual men and women did not overlap. This means that the incidence of anal cancer among MSM is significantly higher. Furthermore, a low nadir CD4 cell count, smoking, and alcohol abuse are associated with an increased risk of anal cancer.

In the past decade, several studies showed an increase in anal cancer incidence, predominantly among HIV+ MSM, despite the widespread use of cART.[1, 2] This seems conflicting with the finding that long-term use of cART is negatively associated with the risk of the anal cancer precursor AIN[3, 5] and the finding that a high current CD4 cell count decreases the risk of anal cancer.[6] Possibly, the increased anal cancer risk caused by a longer lifespan in the cART era outweighs the presumed protective effect of immune restoration. Our study showed for MSM a peak incidence of 168 per 100,000 person-years in 2006. This is one of the highest incidence rates reported to date in this risk group. A review from 2012 reported incidences between 65 and 109 per 100,000 person-years in the cART era (evaluation periods ending in 2003– 2007).[1] So, widespread use of cART is not slowing the rising incidence.[2]

Our findings regarding risk factors are in line with previous studies. A very low nadir CD4 cell count increases the risk of AIN 2/3.[5] A study among HIV+ men showed a significant correlation between low nadir CD4 cell counts and anal cancer. Taking a nadir CD4 cell count <200 as reference, a nadir CD4 cell count between 200 and 350 cells per cubic millimetre showed a hazard ratio of 0.42 (p <0.0001) for anal cancer and a nadir CD4 cell count of >350 a hazard ratio of 0.34.[7] Another recent study showed a hazard ratio of 0.87 for anal cancer risk per log2 increase in nadir CD4 cell count.[8] We found a hazard ratio for anal cancer of 2.42 in patients with a nadir CD4 cell count <110.

What is new in our study is that we found a decrease in anal cancer incidence after 2006. Although statistical significance could not be demonstrated (CIs overlap), it does show a steady trend. One previous study also suggested a plateau in the anal cancer incidence. The peak incidence in this study of 159 in 2000–2003 in HIV+ MSM was followed by a decrease to 131 in 2003–2007.[9] Our study shows a continuing decreasing trend, to an incidence in HIV+ MSM of 100 in 2011/2012. The gradual small-scale introduction of AIN screening programmes in the Netherlands cannot explain this. A more likely explanation might be that the long-term use of cART is negatively associated with the risk of the anal cancer precursor AIN,[3, 5] which in time might gradually affect anal cancer incidence, and furthermore, given the tendency to start cART with higher CD4 counts, the HIV+ MSM population less and less suffers from low nadir CD4 cell counts. For cervical cancer, no decrease in incidence has been observed yet in the cART era.[10]

We found a hazard ratio of 1.60 for anal cancer in current or previous smokers. Smoking has previously been associated with an increased risk of anal cancer.[11] Smoking is much more common in the HIV-positive population, and HIV-infected smokers lose more life-years to smoking than to HIV.[12] To our knowledge, no previous studies showed a link between alcohol (ab)use and anal cancer. We found a hazard ratio of 2.23 for HIV+ MSM drinking more than 28 glasses of alcohol per week. Because alcohol use has a disinhibiting effect, it possibly leads to increased sexual risk behaviour, which in turn is a risk factor for anal cancer.

Strong points of our study are the use of a nationwide database including all patients under HIV care in the Netherlands, confirmation of all histological diagnoses, and careful documentation of risk factors. We have possibly missed cases if the diagnosis anal cancer was not reported by the treating physician, but this means that the incidence of anal caner we found is likely an underestimation. A limitation of our study is that the low absolute number of anal cancers made it difficult to demonstrate statistical significance of the observed trends in time.

In conclusion, this study confirms the high incidence of anal cancer among HIV+ patients, predominantly among HIV + MSM. Furthermore, our data suggest that continued use of cART, and starting cART at higher CD4 counts, might in time lead to a decrease in anal cancer incidence. In the meantime, although there is still uncertainty on the effectiveness of anal cancer screening programmes, the very high anal cancer incidence justifies screening programmes for AIN among HIV+ MSM.

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CONTRIBUTION OF AUTHORS

JMP and HJCdV are principal investigators of the study. OR, RPvdZ, and JMP were involved in data collection. OR, RPvdZ, and CS managed the database. OR and CS performed the statistical analyses. OR and JMP drafted the first version of the manuscript. All authors critically reviewed the manuscript and approved the final version.

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