HAART slows progression to anal cancer in HIV-infected MSM

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Objective: Antiretrovirals do not prevent anal intraepithelial neoplasia. However, the influence of antiretrovirals in the natural history of invasive anal cancer is less clear. The objective is to investigate the impact of antiretrovirals in the time to the development of anal cancer in HIV-positive MSM.

Design: A retrospective analysis of cases of anal cancer in a cohort of HIV-positive MSM receiving antiretrovirals between 1988 and 2008.

Methods: Time from first $CD4^+$ cell count or HIV RNA viral load test to anal cancer diagnosis was analysed using Cox regression and Kaplan–Meier curves. Anal cancer cases treated in the era prior to HAART (<1996) were compared with those treated later (1996–2008).

Results: Anal cancer cases ($n = 37$) were compared with a cohort of 1654 HIV-positive MSM on antiretrovirals. Antiretrovirals were started in the pre-HAART era by 70% of cancer cases, and median $CD4^+$ cell count nadir was 70 cells/μl (10–130). Time to development of anal cancer was shorter for cases treated during the pre-HAART era [AHR 3.04, 95% confidence interval (95% CI) 1.48–6.24, $P = 0.002$], with a $CD4^+$ cell count nadir less than 100 cells/μl (AHR 2.21, 95% CI 1.06–4.62, $P = 0.035$) and longer duration of $CD4^+$ cell count less than 100 cells/μl (AHR 1.33, 95% CI 1.11–1.58, $P = 0.002$).

Conclusion: Results show that severe immunosuppression and starting therapy pre-HAART are associated with an increased risk of anal cancer. HIV-positive MSM initiating antiretrovirals during the HAART era (1996–2008) had a longer time to the development of anal cancer than those treated pre-HAART. Our results suggest that early use of HAART may delay progression to anal cancer.

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Introduction

Invasive anal cancer rates in HIV-infected individuals are significantly higher than the general population, particularly in MSM. Previous cohort studies have shown that risk factors for the development of invasive anal cancer include immunosuppression, prolonged duration of HIV infection and sexual behaviour [1–5].

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The introduction of antiretroviral therapy (ART) has improved the immune status of HIV-infected individuals, thereby reducing infectious complications [6], and substantially extending life expectancy. However, ARTs have not reduced the prevalence of human papillomavirus (HPV) infection, which is the causative agent in more than 90% of invasive anal cancers [7]. In addition, ARTs do not influence the progression of anal intraepithelial neoplasia (AIN) to high-grade lesions, which are the precursors to anal cancer. Some prospective studies suggest that HIV-positive MSM receiving ARTs are as likely to progress to high-grade lesions as those not taking ARTs [8,9]. This has led to the development of screening programmes for AIN, to identify and treat high-grade AIN and prevent progression to invasive disease [10]. In British Columbia, Canada, anal cytology screening is offered to at-risk individuals. If cytology is abnormal, patients are referred to the Anal Dysplasia Clinic (ADC) at St Paul's Hospital, where high-resolution anoscopy is used to diagnose high-grade lesions that are then treated.

Cohort studies have shown that rates of anal cancer have increased in HIV-positive MSM over the past 10–20 years. However, the impact of ARTs on the development of anal cancer is less clear than their role in precursor lesions [2,5,9]. The purpose of this study is to investigate the role of ARTs in the development of invasive anal cancer in a cohort of HIV-positive MSM receiving ARTs. A second purpose was to determine risk factors for high-grade AIN lesions compared with invasive anal cancer in this group.

Materials and methods

A retrospective population-based cohort was created for this study from a linkage of health administrative data from two province-wide health databases: the British Columbia Cancer Registry (BCCR) and the HIV/AIDS Drug Treatment Program (DTP) Registry. As well, data were obtained from the Anal Dysplasia Clinic database at St Paul's Hospital. The BCCR, a province-wide registry of all cancer patients, records information on patient profile, cancer diagnosis, stage and treatment (www.bccancer.bc.ca/HPI/CancerStatistics/default.htm#bccanreg [Accessed 7 January 2013]).

The British Columbia Centre for Excellence in HIV/AIDS established the DTP Registry in 1992 (www.cfenet.ubc.ca/drug-treatment-program [Accessed 6 December 2013]). This registry contains administrative records of antiretroviral prescriptions, patient demographics, clinical and laboratory data, including $CD4^+$ cell count and HIV RNA viral load. Because antiretroviral medications are offered at no cost to all individuals with HIV/AIDS in the province, the number of HIV-positive people receiving antiretrovirals but not included in the registry is expected to be few. Neither the DTP, nor BCCR databases, contain complete information on patient tobacco utilization.

The linked cohort was further linked with the Anal Dysplasia Clinic database, established in 2003, to collect demographic, diagnostic, treatment and outcome data on individuals receiving screening or treatment for AIN at the Anal Dysplasia Clinic at St Paul's Hospital.

The population study cohort was created by the BCCR and then populated by the DTP with ART-related information. The BCCR uses a probabilistic-match procedure on the basis of Personal Health Numbers, names and birth dates contained in the two registries to generate a province-wide listing of HIV-positive individuals in the DTP who were diagnosed with cancer or a precancerous malignancy. This cancer information was then augmented by the DTP with antiretroviral-related treatment information. All individual names and identifying information were stripped in the resulting datasets before being provided to the study data analysts. Analyses were carried out on the aggregate anonymized dataset. A similar secondary data linkage was performed between the Anal Dysplasia Clinic database and the DTP. Ethical approval was obtained from the Research Ethics Boards of the British Columbia Cancer Agency and the University of British Columbia.

Our analysis was limited to men who were known to be MSM identified by means of their reported sexual behaviour, or from the reason they reported for acquiring HIV. The diagnosis of anal cancer was histopathologically confirmed and cancers located in the anus that were not confirmed to be invasive squamous cell carcinoma were excluded ($n = 14$). Statistical analyses included descriptive statistics to compare those with and without anal cancer, and to compare those diagnosed with anal cancer in the pre-HAART (1988–1995) versus HAART (1996–2008) eras. Categorical variables were compared using the Chi-square and Fisher's exact tests, while continuous variables were compared using the Wilcoxon rank-sum test.

The date of first reactive HIV serology is not recorded in the databases; therefore, time from first $CD4^+$ cell count or HIV RNA viral load was used as a surrogate marker for duration of HIV infection. For calculating rates and for time-to-event methods, acquisition of HIV infection was defined as the first $CD4^+$ cell count or viral load (after August 1996), whichever came first. For those individuals diagnosed with invasive anal squamous cell cancer, the event date was the date of cancer diagnosis. For those individuals without a cancer diagnosis, the censoring date was the date of last HIV clinic visit, $CD4^+$ cell count or viral load measurement. Follow-up for this study ended on 28 February 2010.

Anal cancer incidence rates per 100 000 person-years were calculated by treatment era, and the time to anal cancer development was examined using Kaplan–Meier

methods. Cox proportional hazards models were used to model time to anal cancer diagnosis. A backward-selection procedure based on the Akaike Information Criterion was used to select the variables to be included in the final model. Logistic regression models were used to identify risk factors for anal cancer diagnosis when compared with high-grade AIN.

Results

A total of 4937 men have ever received antiretrovirals in the province of British Columbia over the study period. Male participants were excluded from this analysis if they did not identify their transmission risk factor as MSM ($n = 1612$), or if they lacked data on sexual behaviour ($n = 1612$). An additional 22 participants were excluded due to incomplete follow-up. Out of 4937 men, 1691 (34.3%) HIV-positive MSM were identified for the current study.

The link between the Drug Treatment Program and the British Columbia Cancer Registry identified 37 biopsy-proven cases of invasive anal cancer that were diagnosed between 1988 and 2008, occurring in 1691 HIV-positive MSM receiving antiretrovirals.

For cancer cases, the median age at cancer diagnosis was 45 years [interquartile range (IQR) 42–50]. Time from first $CD4^+$ cell count/viral load to cancer diagnosis was 10 years (8–13). On average, cases started ARTs in 1995 (1992–1997) and received them for 7 (5–10) years prior to their cancer diagnosis. Average year of cancer diagnosis was 2004 (2000–2006). Average adherence to antiretrovirals the year prior to cancer diagnosis was optimal (>95%) in 58% of cases, and 49% had a suppressed viral load at the time of cancer diagnosis. However, more than a quarter of cases had developed resistance to nucleoside reverse transcriptase inhibitors (NRTIs) or nonnucleoside reverse transcriptase inhibitors (NNRTIs). Protease inhibitor resistance occurred in 19%, and average $CD4^+$ cell count nadir was 70 cells/μl (IQR 10–130). Most recent $CD4^+$ cell count prior to cancer diagnosis was 420 cells/μl (IQR 190–580). Table 1 compares 37 MSM diagnosed with anal cancer with the rest of the defined cohort with regard to select demographic, clinical and laboratory variables.

Of the 37 cancer cases, 26 initiated antiretrovirals in the pre-HAART era (prior to 1996) compared with 11 cases that started therapy during the HAART era (1996–2008). Incidence rates per 100 000 person-years were 370 in the pre-HAART era versus 93 in the HAART era ($P < 0.001$). The overall incidence rate was 196 per 100 000 person-years.

The Kaplan–Meier plot shows that time from first $CD4^+$ cell count/viral load to anal cancer diagnosis was shorter in the pre-HAART era (log rank $P < 0.001$) (Fig. 1). Cox regression analysis for time to anal cancer also identified $CD4^+$ cell count nadir less than 100 cells/μl [AHR 2.21 (1.06–4.62), $P = 0.035$] and duration of time with $CD4^+$ cell count less than 100 cells/μl [AHR 1.33 (1.11–1.58), $P = 0.002$] as risk factors for shorter duration to development of anal cancer (Table 2). However, less severe immunosuppression, including $CD4^+$ cell count nadir between 100 and 200 cells/μl, and duration of time with a $CD4^+$ cell count between 100 and 200 cells/μl, did not achieve significance. Adherence to antiretrovirals, or resistance to antiretroviral classes, also did not reach significance. HIV viral load testing was not available earlier in the study period, and, therefore, was not used as a variable.

To determine which HIV-positive MSM receiving antiretrovirals would be at the highest risk for development of anal cancer, we compared the 33 anal cancer cases with HIV-positive MSM on antiretrovirals with biopsy-proven high-grade AIN ($n = 144$) identified through our screening programme at the Anal Dysplasia Clinic (four anal cancer cases were excluded because they overlapped with the high-grade AIN group) (Table 3). Logistic regression identified $CD4^+$ cell count nadir less than 100 cells/μl [AOR 3.08 (1.30–7.32), $P = 0.011$] as a risk factor for the development of anal cancer. Receiving antiretrovirals in the pre-HAART era was also a risk factor for the development of anal cancer [AOR 2.67 (1.09–6.55)] (Table 4). High-grade AIN cases were not significantly different from anal cancer cases with respect to time from first $CD4^+$ cell count/viral load to cancer or censor (13 versus 10 years), or duration of immunosuppression with $CD4^+$ cell count less than 200 cells/μl or less than 100 cells/μl.

Table 1. Univariate analysis comparing characteristics of HIV-positive MSM receiving antiretrovirals who developed invasive anal cancer versus those without cancer.

Variable	*n*	Noncancer median (IQR)	*n*	Cancer median (IQR)	*P*
Age current (years)	1654	47 (41–54)	37	48 (46–56)	0.116
$CD4^+$ cell count nadir (cells/μl)	1654	130 (49–210)	37	70 (10–130)	<0.001
Time from first ARV to cancer or censor (years)	1654	9 (4–13)	37	7 (5–10)	0.242
Time from first $CD4^+$ cell count or VL to cancer or censor (years)	1654	11 (6–15)	37	10 (8–13)	0.568
Year of first ARV	1654	1998 (1996–2004)	37	1995 (1992–1997)	<0.001
% of time $CD4^+$ cell count below 200 cells/μl	1648	1 (0–10)	37	8 (0–40)	0.005
% of time $CD4^+$ cell count below 100 cells/μl	1648	0 (0–0)	37	0 (0–7)	0.012

ARV, antiretroviral; IQR, interquartile range; VL, HIV RNA viral load.

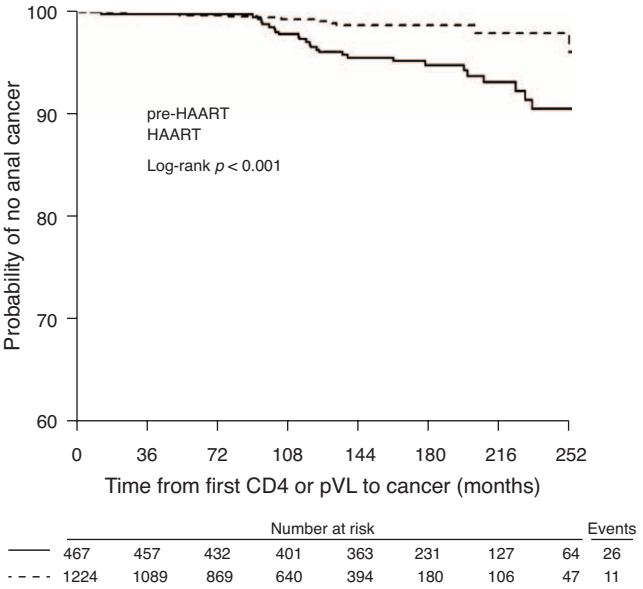

Fig. 1. Kaplan–Meier plot for time from first CD4$^+$ cell count or viral load to anal cancer diagnosis in HIV-positive MSM receiving antiretrovirals. ARV, antiretroviral; VL, HIV RNA viral load.

Discussion

This is the first Canadian study to evaluate a cohort of HIV-positive MSM enrolled in a population-based free ART programme to assess the impact of antiretrovirals on the development of anal cancer. Similar to other cohort studies, we found immunosuppression (CD4$^+$ cell count nadir <100 cells/μl, duration of CD4$^+$ cell count <100 cells/μl) to be an important risk factor for development of anal cancer [2–5]. However, unlike other studies, we found that individuals treated during the HAART era (1996–2008) had a longer time to the development of invasive anal cancer than those treated in the pre-HAART era (before 1996).

Table 2. Cox regression analysis identifying risk factors for the time to development of anal cancer in HIV-positive MSM receiving antiretrovirals ($n = 1691$).

Variable	Unadjusted hazard ratio (95% CI)	*P*	Adjusted hazard ratio (95% CI)	*P*
Injection drug use risk	0.41 (0.14–1.15)	0.091		
First Nations Aboriginal	0.24 (0.03–1.72)	0.155		
AIDS-defining illness at start of ARV	1.97 (0.95–4.06)	0.068		
Overall adherence >95%	0.62 (0.28–1.35)	0.226		
NRTI resistance	1.42 (0.73–2.77)	0.303		
NNRTI resistance	1.42 (0.69–2.93)	0.348		
PI resistance	1.70 (0.75–3.88)	0.206		
CD4$^+$ cell count nadir <200 cells/μl	3.25 (1.15–9.17)	0.026		
CD4$^+$ cell count nadir <100 cells/μl	3.10 (1.56–6.18)	0.001	2.21 (1.06–4.62)	0.035
Age current (per decade)	0.91 (0.62–1.35)	0.653		
First ARV		<0.001		0.002
Before 1995	3.33 (1.63–6.81)		3.04 (1.48–6.24)	
1996+	1.00		1.00	
CD4$^+$ cell count nadir (per 100 cells/μl)	0.49 (0.32–0.75)	<0.001		
Number of VL tests (/year)				
<3	1.62 (0.50–5.27)	0.425		
3–4	0.72 (0.22–2.33)	0.578		
5–6	0.70 (0.23–2.16)	0.541		
>6	1.00			
Year of first ARV	0.82 (0.74–0.90)	<0.001		
% of time CD4$^+$ cell count below 200 cells/μl (per 10%)	1.33 (1.19–1.50)	<0.001		
% of time CD4$^+$ cell count below 100 cells/μl (per 10%)	1.45 (1.25–1.69)	<0.001	1.33 (1.11–1.58)	0.002

ARV, antiretroviral; CI, 95% confidence interval; NNRTI, nonnucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitors, PI, protease inhibitor; VL, HIV RNA viral load.

Table 3. Univariate analysis comparing characteristics of HIV-positive MSM receiving antiretrovirals who developed invasive anal cancer versus those with high-grade anal intraepithelial neoplasia[a].

Variable	*n*	High-grade AIN[a] median (IQR)	*n*	Anal cancer median (IQR)	*P*
Age current (years)	144	47 (40–52)	33	48 (46–56)	0.125
$CD4^+$ cell count nadir (cells/μl)	144	130 (48–200)	33	60 (10–100)	<0.001
VL tests/year	137	5 (4–6)	31	4 (3–5)	<0.001
Time from first ARV to cancer or censor (years)	144	10 (4–14)	33	7 (5–11)	0.208
Time from first $CD4^+$ cell count or VL to cancer or censor (years)	144	13 (6–19)	33	10 (8–15)	0.230
Year of first ARV	144	1997 (1993–2005)	33	1994 (1992–1996)	<0.001
% of time $CD4^+$ cell count below 200 cells/μl	144	1 (0–10)	33	8 (0–48)	0.007
% of time $CD4^+$ cell count below 100 cells/μl	144	0 (0–0)	33	0 (0–14)	0.003

AIN, anal intraepithelial neoplasia; ARV, antiretroviral; IQR, interquartile range; VL, HIV RNA viral load.
[a]High-grade AIN includes AIN II, AIN III, carcinoma-in-situ.

The incidence rate of anal cancer in the pre-HAART era was much higher in our study (370 per 100 000 person-years) than in other studies (10–20 per 100 000 person-years) [1–4,11,12]. The reason for this discrepancy may be due to a difference in cohorts, and our inability to determine whether some men in our registry were MSM. The proportion of anal cancer in our cohort (2.2%) is much larger than any other cohort (<1%). However, the rate of anal cancer in the general population in British Columbia is similar to rates reported elsewhere (men 1.1/100 000 person-years) [13]. Our cohort consists of only HIV-positive MSM receiving antiretrovirals, whereas other cohorts have included non-MSM, and likely had fewer individuals receiving antiretrovirals during the pre-HAART era. Having a cohort with HIV-positive MSM who are at a higher risk for anal cancer than other HIV-positive populations, and receiving antiretrovirals, which may prolong survival, and therefore the exposure period of developing anal cancer, may explain the difference in anal cancer rates when comparing our cohort with others.

Not all studies have reported an increase in the rate of anal cancer during the HAART era. A large French hospital database study observed an increase in anal cancer incidence rates for HIV-positive MSM through 1998, but stabilization in rates after 1999 [2]. A large North American cohort also found that anal cancer rates in HIV-positive MSM exhibited an initial rise during the early HAART era, but have plateaued in recent years [5]. The observation made in the current study that HAART is associated with a longer time to the development of anal cancer would explain why some studies have reported that rates have stabilized in recent years.

Table 4. Logistic regression analysis for risk of anal cancer ($n = 37$) versus high-grade anal intraepithelial neoplasia[a] ($n = 177$).

Variable	Unadjusted odds ratio (95% CI)	*P*	Adjusted odds ratio (95% CI)	*P*
Injection drug use risk	0.76 (0.24–2.39)	0.645		
First Nations Aboriginal	0.44 (0.05–3.58)	0.441		
AIDS-defining illness at the start of ARV	1.76 (0.74–4.30)	0.196		
Overall adherence >95%	0.40 (0.16–1.03)	0.059		
NRTI resistance	1.34 (0.61–2.93)	0.461		
NNRTI resistance	1.88 (0.78–4.53)	0.163		
PI resistance	1.06 (0.40–2.83)	0.911		
$CD4^+$ cell count nadir <200 cells/μl	3.46 (1.00–11.99)	0.051		
$CD4^+$ cell count nadir <100 cells/μl	3.95 (1.71–9.12)	0.001	3.08 (1.30–7.32)	0.011
First ARV		0.004	2.67 (1.09–6.55)	0.032
Before 1995	3.59 (1.52–8.49)			
1996+	1.00			
Age current (per decade)	1.41 (0.91–2.18)	0.126		
$CD4^+$ cell count nadir (per 100 cells/μl)	0.44 (0.26–0.74)	0.002		
Number of VL tests (per year)				
<3	16.71 (3.60–77.54)	<0.001		
3–4	4.33 (1.05–17.95)	0.043		
4–6	2.13 (0.56–8.21)	0.266		
>6	1.00			
Year of first ARV	0.88 (0.81–0.95)	<0.001		
% of time $CD4^+$ cell count below 200 cells/μl (per 10%)	1.35 (1.14–1.60)	<0.001		
% of time $CD4^+$ cell count below 100 cells/μl (per 10%)	1.57 (1.17–2.10)	0.002		

ARV, antiretroviral; CI, 95% confidence interval; NNRTI, nonnucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitors, PI, protease inhibitor; VL, HIV RNA viral load.
[a]High-grade anal intraepithelial neoplasia includes AIN II, AIN III, carcinoma-in-situ.

Most studies have found that HAART does not impact HPV disease in that it does not prevent acquisition of oncogenic types, or progression to high-grade AIN [6,7,14–16]. The increasing rates of anal cancer observed in the HAART era have been attributed to HIV-positive individuals living longer lives, and therefore having time to accumulate genetic mutations that play an important role in anal cancer development. This is supported by studies that have shown that the duration of HIV infection increases the risk of anal cancer development [4,17]. Our study shows that starting antiretrovirals in the pre-HAART era was associated with an increased risk of anal cancer versus high-grade AIN. This raises the question of whether antiretrovirals in the HAART era are somehow protective in preventing progression of dysplasia to cancer.

In our study and others, immunosuppression ($CD4^+$ cell count nadir, or duration of immunosuppression) has also been identified as a risk factor for AIN and/or cancer. Because immunosuppression is inextricably linked to HAART utilization, it is logical that improvements in immune function over time, with the use of HAART, may result in prolonged duration to development of anal cancer. If this is the case, we will likely continue to see a plateauing of the incidence rates of anal cancer.

New treatment guidelines recommend early diagnosis and immediate initiation of antiretrovirals regardless of $CD4^+$ cell counts [18]. Early diagnosis and ART of newly acquired HIV infection may prevent HIV-infected individuals from ever experiencing significant immunosuppression, which further may reduce anal cancer rates.

Prospectively following individuals, who begin treatment during the HAART era with high $CD4^+$ cell count nadirs and well maintained $CD4^+$ cell counts, will be important in determining how anal cancer rates are affected. However, other changing practices, such as utilization of the HPV vaccine [19] and AIN screening programmes, may also impact the rate of anal cancer in this patient population [20]. Our Anal Dysplasia Clinic has been treating high-grade precancer lesions in HIV-positive individuals since 2005, and 17% of the HIV-positive MSM in our cohort have been assessed at the Anal Dysplasia Clinic. Although there has not been a randomized control trial demonstrating that treatment of high-grade AIN prevents the development of invasive cancer, it is a compelling observation that rates of anal cancer decreased during this time period. By treating high-grade AIN in HIV-positive MSM, some cases of invasive anal cancer may be prevented during the HAART era.

This study has several limitations that must be considered. Firstly, we do not have HIV seroconversion data, and instead, the time from first $CD4^+$ cell count or viral load was used as a surrogate marker for the duration of HIV infection. Potentially, some of the individuals with anal cancer were infected with HIV for a long time period prior to their first $CD4^+$ cell count/viral load, which would make our observations less reliable. As well, we have not identified all the men in the DTP database who were MSM. We also excluded individuals not on ARTs, which may have led to a selection bias for sicker individuals, thereby potentially inflating the incidence rate of anal cancer. Finally, we do not have data available for some of the risk factors for anal cancer, such as tobacco use or specific sexual behaviours.

Strengths of this study include limiting the analysis to biopsy-proven HPV-associated squamous cell carcinoma, and excluding carcinoma-in-situ, rectal adenocarcinomas and other cancer types. As well, our cohort has detailed ART information including specific antiretrovirals used, resistance genotypes and adherence data that have been previously validated [21]. These variables were examined but did not impact anal cancer rates. A further strength of our study is our unique patient population; in a Canadian study, data were available for First Nations Aboriginal ancestry. Also, the study population was limited to HIV-positive MSM receiving ART. Lastly, our study was conducted in a province with universal healthcare access, where ARTs, cancer screening and all related care are fully subsidized, thereby removing the potential confounding effects of financial barriers to accessing treatment and care.

Overall, the current study raises the interesting possibility that HAART may prolong time to development of invasive anal cancer in HIV-positive MSM. If externally validated, this would support more widespread testing policies to identify HIV-positive individuals earlier in the course of infection, so that they can be offered early initiation of antiretrovirals, thereby preventing immunosuppression, and potentially decreasing the burden of anal cancer.

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K.C.D., C.G.C., S.M.W., J.S.G.M., R.S.H., N.M.P. gave the study concept and design), A.J.C., R.S.H., A.C. did the data acquisition, K.J.C., A.C., C.G.A.-Y. did the statistical analysis and interpretation of results, K.C.D. and N.M.P. did the drafting of manuscript, and all authors did the revision and review of final manuscript.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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