Infection related and unrelated malignancies, HIV and the aging population

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Abstract

Objectives

HIV-positive people have increased risk of infection related and infection unrelated malignancies (IRM/IURM). To determine the impact of aging on future IRM and IURM incidence is yet to be determined.

Methods

People enrolled in EuroSIDA followed from the latest of first visit or 01/01/2001 until last visit or death. Poisson regression investigated the impact of aging on the incidence of IRM and IURM adjusting for demographic, clinical and laboratory confounders. Linear exponential smoothing models forecasted future incidence.

Results

15648 people contributed 95033 person years, 610 developed 643 malignancies(IRM:388[60%], IURM:255[40%]). After adjustment, higher IRM incidence was associated with lower CD4 count (CD4 <200:3.77[2.59,5.51]; compared to 500+ cells/mm^3) independent of age, while CD4<200 was associated with IURM in people aged<50 years only (2.51[1.40-4.54]). Smoking was associated with IURM (1.75[1.23,2.49]) compared to never-smokers in people≥ 50 years only, and not with IRM. Both IURM and IRM incidence increased with older age. It is projected that the incidence of IRM will decrease by 29% over a 5-year period from 3.1([1.5-5.9]/1000person-years) in 2011, whereas IURM incidence will increase by 44% from 4.1([2.2-7.2]/1000person-years) over the same period.

Conclusion

Demographic and HIV-related risk factors for IURM (aging and smoking) and IRM (immunodeficiency and ongoing viral replication) differ markedly and the contribution from IURM relative to IRM will continue to increase due to aging of the HIV population , high smoking and lung cancer prevalence and low prevalence of untreated HIV-infection. These

findings suggest the need for targeted preventive measures and to evaluate cost-benefit of screening for IURM in HIV populations.

Introduction

HIV-positive people are at increased risk of many malignancies compared to the general population(1, 2), however the exact mechanisms are poorly understood(3). Increased risk could be due to high prevalence of traditional cancer risk factors such as smoking(4) and alcohol use(5). However, co-infection with other pro-oncogenic viruses(6), immunodeficiency(2),(7), activated inflammation and coagulation(8), potential direct pro-oncogenic effect of HIV and combination antiretroviral therapy (cART) toxicity (3) may also contribute. The introduction of cART in 1996 lead to restored immune function, reduced incidence of AIDS-defining malignancies (ADM)(9-11) and increased survival(12) . As a result, the burden of cancers in the HIV-positive population traditionally associated with older age is becoming increasingly important. There is a growing need to address the changing epidemiology of cancers as the population ages. This has been addressed through several studies from the USA(1, 13), however research in the European population is needed.

The burden of non-AIDS-defining malignancies (NADM) is now surpassing that of ADM in HIV-positive people in the USA and Europe(1, 13). Furthermore, some NADM occur more frequently than ADMs in HIV-positive people, for example, more cases of anal cancer and Hodgkin lymphoma are diagnosed than invasive cervical cancer(1, 14). For these reasons recent research has shifted towards defining malignancies according to infection related (IRM) and infection unrelated (IURM)(8).

The changing epidemiology of malignancies and the impact of aging on cancer incidence needs to be better characterised. The aim of this study was to investigate the impact of aging in HIV-positive people on the incidence of IRM and IURM within EuroSIDA, a large European cohort of HIV-positive people with a long follow-up period and to estimate the likely

impact of IRM and IURM in the HIV-positive population in the next 5 years for future healthcare planning, treatment and prevention.

Patients and methods

EuroSIDA study

EuroSIDA is a prospective observational open cohort of 18,587 HIV-1 positive patients in 108 centres across 33 European countries, Israel and Argentina (details at www.cphiv.dk). Patients were enrolled into 9 cohorts from May 1994 and informed consent was obtained from all patients. All information is prospectively collected via standardised forms which are completed by personnel at the sites at the time of enrolment and every 6 months thereafter. The forms collect basic demographic, clinical and laboratory data, including all CD4 counts and HIV viral-loads (HIV-VL), starting and stopping dates of all antiretroviral drugs, smoking status, and dates and diagnoses of all new AIDS-defining diagnoses (using the 1993 CDC clinical definition(15), includes ADMs) since last follow-up. In 2001, the standardised forms were updated to collect data on all new non-AIDS-defining diagnoses identified by clinical diagnosis or autopsy (including NADM) (16) allowing the sites to report date of diagnosis, method of diagnosis (definitive, presumptive, autopsy), and location (selected from a list of common malignancies or as free text). All reported AIDS and non-AIDS defining malignancies were source verified against case notes at the sites by members of the coordinating office to ensure data accuracy, as well as for all other major clinical events and a random sample of 10% of all other patients. Loss to follow-up in EuroSIDA is <5% per 100 PYFU and consistent over time(17).

Inclusion criteria

All subjects enrolled in EuroSIDA with prospective follow-up after 1 January 2001 were included. Patients were followed from the later of first visit or 1 January 2001 until last visit or

death. Median date of last visit was March 2012 (Interquartile range [IQR] August 2009-June 2012).

All malignancies, both AIDS-defining and non-AIDS, diagnosed during the follow-up period were included and classified using the International Classification of Diseases and Related Health Problems, 10th edition code classification system(18). Multiple malignancies per person were included, however pre-existing cancers, secondary diagnoses, metastasis, and reoccurrence of the same malignancy type, pre-cancers and non-melanoma skin cancers were excluded. IRMs were defined as all malignancies with a probably infectious cause: Kaposi's sarcoma (KS) (caused by human-herpesvirus8 [HHV8]), non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) (Epstein-Barr virus [EBV]), invasive cervical cancers (ICC), selected malignancies of the head and neck (Base of tongue, pharynx, tonsils), anus, penis, vulva and vagina(Human papilloma virus [HPV]), liver (Hepatitis B [HBV] and C[HCV]) and stomach (*H. pylori*]) (19). All remaining malignancies were defined as IURMs.

Statistical methods

Poisson generalised estimating equations assuming auto-regressive (AR1) correlation were used to estimate the association between age and IRM and IURM incidence. Models were adjusted for baseline (ethnicity, region, gender and mode of transmission[Homosexual, male IDU, female IDU, male heterosexual, female heterosexual, missing], BMI) and time-updated (age, calendar year, smoking status [current, previous, never, missing], current HIV-VL plasma levels, CD4 cell count, prior HBV [Prior positive HBsAG surface antigen test or presence of detectable HBV DNA] andHCV [prior positive HCV surface antibody test or presence of detectable HCV RNA] co-infection, prior diagnoses of ADM, NADM, AIDS-defining [excluding ADM], and non-AIDS-defining events [defined as cardiovascular, end-stage renal disease, liver

failure and pancreatitis, excluding NADM](16), cART use [antiretroviral regimen containing ≥3 drugs from any class], and regimen according to intention to treat: PI/NNRTI-based) variables.

It was decided a priori to stratify associations between IRM and IURM with CD4 cell count and smoking status by age (<50 and ≥50 years) due to strong associations with both age and cancer risk. Interactions between age and all other variables were also investigated.

The proportion of excess malignancies within our cohort attributable to each significant modifiable factor and age were calculated using an internally valid version of the population attributable risk in the presence of confounding(20). This is interpreted as the percent of excess malignancies attributable to each factor relative to a reference category, within the cohort.

Future crude IRM and IURM biannual incidence was forecast using linear exponential smoothing models, stratified by baseline age group (<50, ≥50 years), CD4 (<350, ≥350 cells/mm^3), HIV risk group and smoking status. Forecasts were restricted to those enrolled prior to 2001. This ensures a stable population over time (i.e. no new recruitments), however people were allowed to leave the cohort i.e. death or loss to follow-up. No further adjustments for covariates were made.

All statistical tests were two sided and a type I error rate of 5%. All statistical analyses were performed using SAS 9.3 (Statistical Analysis Software, Cary NC, USA).

Results

Characteristics

15,648 persons contributed 95,033 PYFU with a median follow-up of 6.0 (Interquartile range [IQR]:2.5,10.7) years. Baseline characteristics according to malignancy status are shown in Table 1. At baseline 16.0% were aged over 50, 72.6% of the population were male, 88.3% were of white ethnic origin and 38.7% of men were infected with HIV through homosexual exposure. Approximately one third of patients were current smokers and one third had never smoked. The median CD4 at baseline was 410 (IQR:265,588) with 14.8% having CD4$\leq$200 cells/mm^3 and HIV-VL was 123 (IQR: <50,5200) with 54.5% having HIV-VL $\leq$ 400 copies/mL. There were 24.4% and 1.9% of patients who had a prior AIDS and non-AIDS defining event respectively. Co-infection with HCV and was HBV was prevalent in 23.1% and 5.5% of people.

610 people developed 643 malignancies, of which 60.3% were IRM and the remaining 39.7% were IURM (See Table 2**Error! Reference source not found.**). The most common IRMs were NHL(N=116), Anal cancer(85), KS(62) and HL(43). Cancers of the lung(N=55), prostate(28), colorectal(23) and breast(22) were common IURMs. At diagnosis, those who developed IURMs relative to IRM were older (Median age: [IURM] 54 IQR:46,61 vs [IRM] 46 IQR:39,52 years) had a higher CD4 (446 IQR:295,608 vs 342 IQR:182, 546) and lower HIV-VL(<50 IQR:<50,86 vs 61 IQR:<50,20002). A higher proportion had prior HCV co-infection and proportion of prior HBV co-infection was similar. Proportions of ever smokers in IRMs (45%) and IURMS (46%) were similar. The majority of cancers diagnosed in those younger than 50 (N=353 cancers) were IRM (75%), with 31% EBV related and 25% HPV related. In those older (290 cancers), more than half were IURM (57%), accounting for 13% lung cancers and 10% prostate cancers.

Adjusted Incidence of IRM and IURM

In adjusted models, those aged over 50 had 1.62 (95%CI:1.14,2.30) times higher IRM incidence compared to those aged 36-40 years (Table 3), corresponding to a 17% higher incidence per 10 years older age (aRR:1.17; 1.05,1.32). The % of excess IRM attributable to being aged over 50 compared to 36-40 years was 12%. Factors strongly related to high IRM incidence were HIV associated. Specifically, elevated HIV-VL>400 was associated with

higher IRM incidence (1.84; 1.39,2.43, P<0.01) and accounted for 19% of excess malignancies, relative to those with well controlled viraemia (HIV-VL of 400 or less). Lower current CD4 cell count was associated with higher IRM incidence (Table 3), which was similar in those aged ≤ 50 and over 50 years(figure 1C P interaction=0.82). A CD4<200 and 200-349 cells/mm^3 accounted for 21% and 11% of excess IRMs respectively (Table 3) relative to those with a CD4 cell count of 500 or higher. There was no association between IRM incidence and current smoking (Table 3) in younger or older people (figure 1D; P for interaction=0.31). Prior HBV-co-infection was associated with higher IRM incidence (aRR:1.70; 1.24,2.32), but only 5% of IRM were attributable to HBV co-infection within the cohort (Table 3).

IURM incidence was 7.33 (95%CI: 4.07,13.21;P<0.01) and 2.37 (1.31,4.27;P<0.01) fold higher in those aged over 50 and aged 41 – 50 years compared to those aged 36 – 40 years (Table 3), and explained 56% and 17% of excess IURMs within the cohort respectively. This corresponds to a two fold increase in IURM incidence per 10 years older age (aIR:2.07;95%CI:1.84,2.32). Current smoking was associated with elevated IURM incidence and explained 16% of IURMs overall. Stratifying by age, IURM was elevated in current smokers relative to non-smokers in those aged over 50 (aIRR: 1.75; 1.23,4.49;P<0.01; figure 1B), but not in those aged ≤50 (aIRR: 1.12; 0.71,1.77;P=0.51), although the p-value of the interaction term was non-significant (P=0.32). Current smoking was not associated with IURM incidence after exclusion of lung cancers. A low current CD4 count was associated with higher IURM incidence (CD4<200 aRR:1.99; 1.26,3.17;P<0.01, relative to CD4>500 cells/mm^3). Despite this, the overall excess of IURMs attributable to a CD4<200 cells/mm^3 (6%) were small. The association between higher IURM incidence and low CD4 was evident in those aged <50 years (aRR:2.52; 1.40,4.54; P,0.01, figure 1A), but not in those aged>50 (aRR:1.14; 0.62,2.12;P=0.56 figure 1A), although the p-value of the interaction term did not reach statistical significance (P=0.09). Prior HBV-co-infection was also associated with higher IURM incidence (aRR:1.73; 1.17,2.55;P<0.01), but only 5% were attributable to HBV co-infection within the cohort (Table 3).

Future Incidence

There were 6111 people enrolled prior to 1 January 2001 contributing 54030 PYFU (median of 11.1 (IQR: 5.8 – 11.3 PYFU per person) who developed 243 IRM and 161 IURM during follow-up. At baseline 82% were aged under 50, 78% were male and 41% had a CD4 count below 350. There were 47% were homosexual, 25% were heterosexual and 21% were IDUs. 26% were smokers at baseline, 21% were non-smokers at baseline and 52% had unknown smoking status.

Assuming current trends continue, crude IRM incidence for those recruited before 2001 was forecast to decline from an incidence of 3.1(95%CI:1.5,5.9)/1000PYFU in Jul-Dec 2011 to 2.2(95%CI:0.9,4.3) after 5 years (Figure 2A).This was consistent in all strata, with the exception of injecting drug users in which the incidence was stable (

Table 4). Forecasted crude IURM incidence increased from 4.1(95%CI:2.2,7.2) Jul-Dec 2011 to 5.9(95%CI:3.2,10.2) after 5 years Figure 2B, and was consistent in all strata, except never smokers for whom the IURM incidence was forecast to decrease from 1.7 (95%CI:0.0,10.6) in Jul-Dec 2011 to 0.8 (95%CI:0.0,7.0) after 5 years (Table 4). The incidence of IURM surpassed that of IRM from January-June 2009 onwards, and is forcast to continue to increase over the subsequent 5 years.

Discussion

Demographic and HIV-related risk factors for IURM and IRM differ markedly. The incidence of IURM has exceeded that of IRM since January-June 2009 (in those enrolled in EuroSIDA prior to 2001) and the contribution from IURM is forecast to increase over the subsequent 5 years due to aging of the HIV population, high smoking prevalence(4), and low prevalence of untreated and advanced HIV-infection. These findings suggest the need to develop targeted preventive measures and evaluate cost-benefit of screening for IURM in HIV populations. Ours is one of the few large prospective studies in a European population with free access to care. The majority of the research to date has focussed largely on patients within the USA.

IRM incidence was highly associated with traditional HIV factors such as higher HIV-VL and lower CD4 cell count, and to a lesser extent, age. The incidence of IRM steadily increased with lower CD4 cell count category. However the proportion of IRM attributable to older age, higher HIV-VL and lower CD4 were similar to each other in EuroSIDA, due to ongoing aging and low prevalence of uncontrolled HIV-infection in this cohort. Those aged 51 or older may have had longer exposure to oncogenic viruses which could explain the increased IRM incidence.

Older age was the largest contributor to IURM incidence. Our result of a two-fold higher IURM incidence for a 10 year increase in age is similar to findings of the SMART study(21) and to data published online by the European cancer observatory, which showed a 1.9 fold increase in incidence of all malignancies in the general population(22). The effects of aging, including reduced immune function, are thought to be accelerated in HIV-positive populations and may also contribute to an increased IURM incidence(23).

Current smoking status was associated with higher IURM incidence, driven by lung cancer, in people aged over 50, likely reflecting lag time between smoking and the onset of consequences. As the proportion of the cohort aged over 50, 60 and 70 increases, the relative impact of characteristics associated with IURM risk is likely to continue to shift, highlighting the need for ongoing monitoring of the changing epidemiology of malignancies. This is a comparatively new research area in HIV and large, well designed observational studies are crucial to understand both existing and emerging comorbidities in HIV positive people. Higher IURM incidence was associated with a CD4 cell count <200 in people aged under 50 only, which appeared to be due to a relatively high number of lung cancers in this group. However, numbers were small and further investigation was not possible.

The incidence of IRM was forecast to decline over time, likely driven by the low prevalence of advanced and untreated HIV infection, following improvements in treatment efficacy, uptake and adherence. Antiretroviral therapy controls HIV viremia leading to CD4 recovery, and reduces the risk of some IRMs, such as KS and NHL(1, 11, 13, 14, 24), but not all (i.e. HL, ICC and anal cancers)(11, 24, 25) (26). This was consistent in all strata except IDUs, who are less likely to be on treatment and have poorer outcomes. The incidence of IURMs was forecast to gradually increase in the near future, driven by aging of the HIV-positive population. The only exception was in non-smokers, reflecting lower lung cancer rates and further supporting the need for cessation programs. Malignancy incidence in an American study was projected to increase by approximately 45% between 2010 and 2030, driven by malignant diagnoses in older age groups in the general population(27). A similar result was found for the UK population(28).

This study has a number of limitations. EuroSIDA has a relatively large number of prospectively collected source validated malignancies, but despite this, the frequencies of individual malignancies were small and could not be investigated or forecasted individually. Furthermore, this is an observational study and residual confounding cannot be ruled out. The predicted small increase in IURM may be influenced by changes in and uptake of cancer screening practices, such as cervical, breast, colorectal and prostate screening, in clinics. However, no significant changes in the incidence of these cancers occurred in our study, although numbers were small. EuroSIDA does not routinely collect data on screening practices and therefore we cannot investigate the role of screening further. However, recent survey data on HIV management in active EuroSIDA sites found screening rates for cervical and anorectal cancers were low (29). Linear exponential smoothing models are a simple method of forecasting which assume the continuation of previous population trends. A limited amount of historical data was available for forecasting, contributing to uncertainty around forecasts. HIV-specific population projections are not currently available, which prevents the use of more advanced methodologies, such as age-period-cohort models.

As the HIV population ages, the incidence of IURM is expected to increase due to aging of the HIV population and the high prevalence of lung cancer due to smoking, the effects of which generally manifest with longer-term exposure and thus at older ages. Conversely, IRM incidence is expected to decline due to the low prevalence of advanced and untreated HIV infection and severe immunodeficiency. IURM should therefore be a priority in the coming years as higher proportions of HIV positive people live past 50, 60 and 70. Studies evaluating cost-benefit of screening-programmes for HIV-positive people and targeted preventive interventions, such as cessation programs for smoking and alcohol use, and vaccinations for

oncogenic viruses should be considered to reduce the burden of avoidable cancers in the long term.

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Table 1 Baseline Characteristics of persons who have an infection related (IRM) and infection unrelated (IURM) malignancy during follow up

Characteristics		All participants N (%)/ Median(IQR)	IRM	IURM
Overall		15,648 (100.0)	374 (100.0)	247 (100.0)
Categorical N (%)				
Age group				
	< = 35 years	5,419 (34.6)	78 (20.9)	18 (7.3)
	36 - 40 years	3,337 (21.3)	93 (24.9)	40 (16.2)
	41 - 50 years	4,390 (28.1)	133 (35.6)	78 (31.6)
	51 + years	2,502 (16.0)	70 (18.7)	111 (44.9)
Region[3]				
	Argentina	597 (3.8)	13 (3.5)	6 (2.4)
	East	2,733 (17.5)	14 (3.7)	6 (2.4)
	East central	2,041 (13.0)	40 (10.7)	25 (10.1)
	West	3,220 (20.6)	97 (25.9)	71 (28.7)
	North	3,332 (21.3)	86 (23.0)	63 (25.5)
	South	3,725 (23.8)	124 (33.2)	76 (30.8)
White ethnicity		13,821 (88.3)	331 (88.5)	228 (92.3)
Risk group				
	Homosexual (Men only)	6,051 (38.7)	191 (51.1)	123 (49.8)
	IDU (Male)	2,290 (14.6)	49 (13.1)	24 (9.7)
	IDU (Female)	1,091 (7.0)	32 (8.6)	10 (4.0)
	Heterosexual (Male)	2,178 (13.9)	35 (9.4)	32 (13.0)
	Heterosexual (Female)	2,830 (18.1)	43 (11.5)	36 (14.6)
	Other (Male)	910 (5.8)	20 (5.3)	16 (6.5)
	Other (Female)	298 (1.9)	4 (1.1)	6 (2.4)
Smoking status				
	Current	5,393 (34.5)	132 (35.3)	83 (33.6)
	Previous	61 (0.4)	4 (1.1)	1 (0.4)
	Never	5,030 (32.1)	104 (27.8)	66 (26.7)
	Unknown	5,164 (33.0)	134 (35.8)	97 (39.3)

Prior AIDS[1] (excluding ADM)	3,811 (24.4)	122 (32.6)	65 (26.3)
Prior ADM	734 (4.7)	34 (9.1)	17 (6.9)
Prior non-AIDS events[2] (excluding NADM)	297 (1.9)	10 (2.7)	8 (3.2)
Prior NADM	222 (1.4)	5 (1.3)	13 (5.3)
Hepatitis B positive	868 (5.5)	38 (10.2)	23 (9.3)
Hepatitis C positive	3,607 (23.1)	76 (20.3)	35 (14.2)
On cART	11,946 (76.3)	304 (81.3)	215 (87.0)
Numeric Median (IQR)			
CD4 (cells/mm^3)	410 (265,588)	347 (200,523)	390 (259,546)
Nadir CD4 (cells/mm^3)	182 (76,303)	124.5 (47,250)	160 (70,255)
HIV-VL (copies/ml)	123 (<50,5200)	772 (<50,18300)	88 (<50,1501)

Baseline was defined as the latest of first visit or 01 January 2001.

[1] Defined by the1993 CDC clinical definition(15)

[2]Non-AIDS defining events pancreatitis, grade 3 or 4 hepatic encephalopathy or liver-related death, myocardial infarction, stroke, coronary artery bypass graft, coronary angioplasty, carotid endarterectomy (grouped together as serious CV events), and end-stage renal disease (16). NADMs were excluded.

Table 2 Malignancies classified as infection related (IRM) and unrelated (IURM) malignancies

Malignancies	N
Infection related Malignancies (IRM)	***388***
Epstein-Barr virus (EBV)	159
Non-Hodgkin lymphoma (NHL)	116
Hodgkin lymphoma (HL)	43
Hepatitis B and C viruses (HBV and HCV)	
Liver	33
Human herpesvirus-8 (HHV8)	
Kaposi's sarcoma (KS)	62
Human papillomavirus (HPV)	123
Anal	83
Invasive cervical cancer (ICC)	33
Vulva and vagina	3
Penis	3
Base of tongue, pharynx, tonsils	1
H. pylori	
Stomach	11
Infection unrelated cancers (IURM)	***255***

Lung	55
Prostate	28
Colorectal	23
Breast	22
Other	127

Table 3 Adjusted risk ratios (aIRR) and population attributable fractions (PAF%) of Infection related (IRM) and unrelated (IURM) malignancies

Variable	IRM			IURM		
	aIRR (95% CI)	% Attributable	P-value	aIRR (95% CI)	% Attributable	p-value
Age						
<=35 years	1.34(0.90,2.01)		0.15	0.33(0.12,0.96)	-3.1(-11.9,-0.1)	0.04
36 - 40 years	ref	ref	.	ref	ref	.
41 - 50 years	1.34(0.97,1.85)		0.07	2.37(1.31,4.27)	16.5(6.9,21.9)	<.01
51 + years	1.62(1.14,2.30)	12.3(3.9,18.2)	<.01	7.33(4.07,13.21)	55.9(48.8,59.8)	<.01
Calendar year	1.01(0.97,1.05)		0.55	1.00(0.96,1.04)		0.95
HIV-Viral Load >400 copies/mL	1.84(1.39,2.43)	19.3(11.8,24.9)	<.01	0.91(0.62,1.35)		0.66
CD4 cells/mm³						
<200	3.77(2.59,5.51)	20.5(17.1,22.8)	<.01	1.99(1.26,3.17)	6.3(2.6,8.6)	<.01
200 - 349	1.83(1.35,2.48)	10.6(6.1,14.0)	<.01	1.30(0.89,1.88)		0.17
350 - 499	1.24(0.92,1.67)		0.16	1.29(0.95,1.75)		0.11
500 +	ref	ref	-	ref	ref	-
Prior AIDS event (excl ADM)	1.25(1.00,1.57)		0.05	0.85(0.64,1.14)		0.29

Prior ADM	1.41(1.02,1.96)	3.1(0.2,5.2)	0.04	0.92(0.57,1.49)		0.74
Prior non-AIDS event (excl NADM)				1.36(0.88,2.10)		0.17
Prior NADM				2.13(1.42,3.20)		<.01
Hepatitis B [HBV]	1.70(1.24,2.32)	5.3(2.5,7.3)	<.01	1.73(1.17,2.55)	5.0(1.7,7.2)	<.01
Hepatitis C [HCV]	0.77(0.56,1.06)		0.11	0.90(0.60,1.37)		0.62
Transmission group[1]						
Homosexual	ref	ref	-	ref	ref	-
IDU (Male)	0.83(0.57,1.20)		0.32	0.97(0.57,1.64)		0.91
IDU (Female)	1.21(0.79,1.86)		0.39	0.91(0.46,1.80)		0.78
Heterosexual (Male)	0.54(0.38,0.78)		<.01	0.91(0.61,1.36)		0.64
Heterosexual (Female)	0.57(0.40,0.80)		<.01	1.25(0.86,1.83)		0.24
Smoking status[1]						
Never	ref	0.25	-	ref	ref	-
Previous	0.78(0.51,1.19)		0.25	1.24(0.80,1.91)		0.34
Current	1.15(0.91,1.46)		0.24	1.56(1.17,2.08)	16.4(6.8,23.7)	<.01

ADM: AIDS-defining-malignancy NADM: non-AIDS-defining malignancy IDU: Injecting drug user. [1]Missing category not shown.

Models were adjusted for baseline (ethnicity, region, gender and mode of transmission[Homosexual, male IDU, female IDU, male heterosexual, female heterosexual, missing], BMI) and time-updated (age, calendar year, smoking status [current, previous, never, missing], current HIV-VL plasma levels [≤400, >400 copies/mL], CD4 cell count [<200, 200 – 349, 350 – 499, ≥500 cells/mm3], prior HBV/HCV co-infection, prior ADM, prior AIDS-defining diagnoses [excluding ADM], prior NADM, prior non-AIDS-defining events [defined as cardiovascular, end-stage renal disease, liver failure and pancreatitis, excluding NADM]19, exposure to cART [ARV regimen containing at least 3 drugs from any class], and regimen according to intention to treat: PI- or NNRTI-based) variables

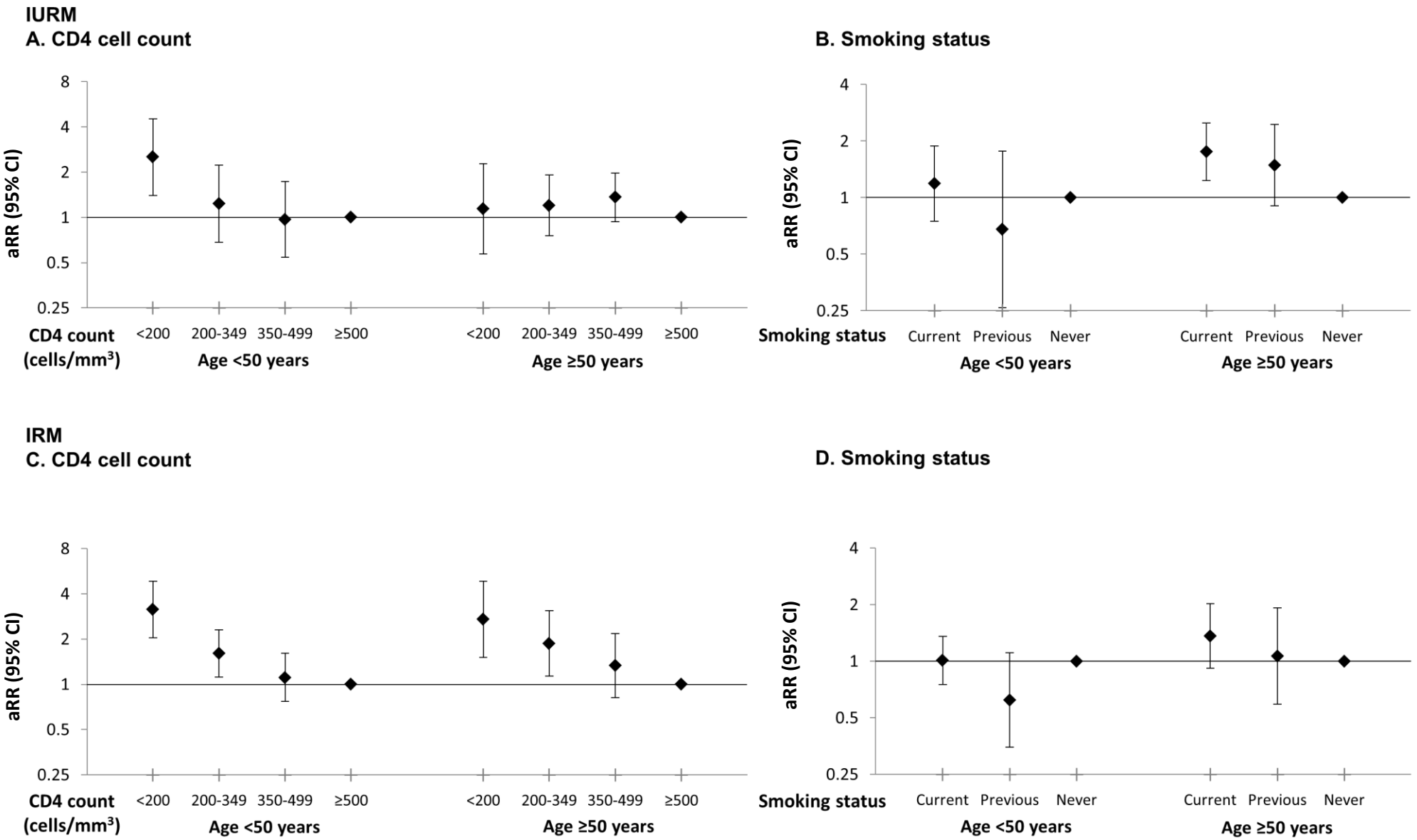
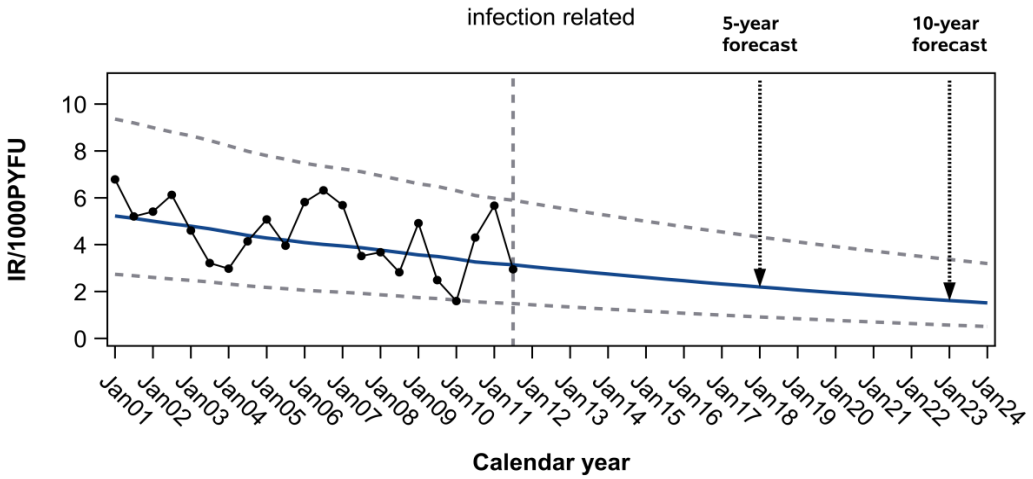

IURM
A. CD4 cell count
aRR (95% CI)
8
4
2
1
0.5
0.25
CD4 count (cells/mm³)
<200
200-349
350-499
≥500
<200
200-349
350-499
≥500
Age <50 years
Age ≥50 years
B. Smoking status
aRR (95% CI)
4
2
1
0.5
0.25
Smoking status
Current
Previous
Never
Current
Previous
Never
Age <50 years
Age ≥50 years
IRM
C. CD4 cell count
aRR (95% CI)
8
4
2
1
0.5
0.25
CD4 count (cells/mm³)
<200
200-349
350-499
≥500
<200
200-349
350-499
≥500
Age <50 years
Age ≥50 years
D. Smoking status
aRR (95% CI)
4
2
1
0.5
0.25
Smoking status
Current
Previous
Never
Current
Previous
Never
Age <50 years
Age ≥50 years

Figure 1 adjusted rate ratios (aRR) of Infection unrelated (IURM) for (A) CD4 count and (B) smoking status and of Infection related related (IRM) for (C) CD4 count and (D) smoking status in those aged <50 and ≥50 years.

Models were adjusted for age, calendar year, gender, ethnicity, region of residence, mode of transmission, current smoking status, baseline hepatitis C and B status, current HIV-VL, cumulative time HIV-VL >400 copies/mL, current CD4, cumulative time CD4<200 cells/mm^3, prior ADM, prior AIDS-defining diagnosis (excluding ADM), prior NADM, prior non-AIDS defining diagnosis (excluding NADM), treatment group, PI use, NNRTI use.

a. Semi-annual crude incidence rate (IR) of IRM/1000 PYFU for those recruited before 2001 with 5 and 10 year forecast.



b. Semi-annual crude incidence rate (IR) of IURM/1000 PYFU for those recruited before 2001 with 5 and 10 year forecast

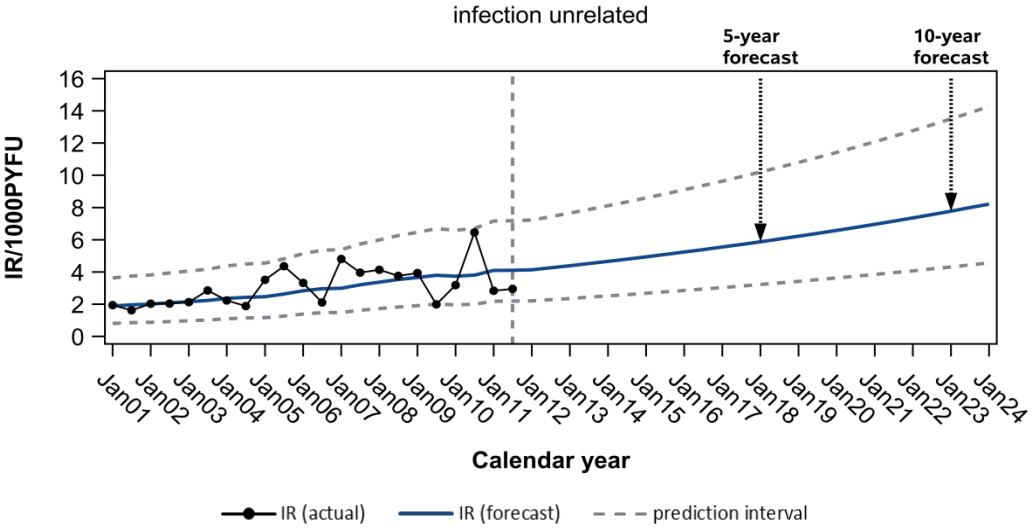


Figure 2 Forecast crude incidence rate (IR) of infection related (IRM) and infection unrelated malignancies (IURM)/1000 PYFU for those recruited before 2001

Table 4 Forecasted incidences of crude infection related and infection unrelated malignancies in people enrolled in EuroSIDA before 1 January 2001 overall and within strata.

Subgroups	Incidence of Infection related malignancies /1000 PYFU			Incidence of Infection unrelated malignancies /1000 PYFU		
	Jul – Dec 2011	Forecast at 5 years	% change	Jul – Dec 2011	Forecast at 5 years	% change
Overall	3.1 (1.5, 5.9)	2.2 (0.9, 4.3)	-29%	4.1 (2.2, 7.2)	5.9 (3.2, 10.2)	44%
baseline age (years)						
< 50	3.3 (1.8, 5.8)	2.4 (1.1, 4.6)	-27%	2.8 (1.0, 6.0)	4.4 (1.9, 9.2)	57%
≥50	1.8 (0, 11.6)	0.7 (0.0, 7.0)	-61%	10.4 (3.4, 28.8)	15.3 (5.1, 42.7)	50%
Baseline CD4 (cells/mm^3)						
<350	4.3 (1.5, 10.2)	2.9 (0.8, 7.4)	-33%	4.1 (0.6, 15.5)	5.6 (1.0, 20.5)	37%
≥ 350	2.7(1.0, 5.7)	2.0 (0.6, 4.6)	-26%	3.6 (1.0, 9.5)	5.2 (1.6, 13.5)	44%
Risk group						
Homosexual	3.1 (1.0, 7.0)	1.6 (0.3, 4.2)	-48%	4.2(1.5, 9.9)	5.0 (1.8, 12.1)	19%
Heterosexual	3.8 (0.6, 13.7)	3.3(0.2, 14.1)	-13%	2.6 (0.0, 11.7)	3.3 (0.2, 14.1)	27%
Injecting drug users	4.9 (1.0, 16.9)	4.9 (0.9, 17.1)	0%	3.4 (0.0, 22.1)	7.0 (0.5, 42.4)	106%
Baseline smoking status						
Smokers	4.2 (0.7, 14.8)	3.3 (0.4, 12.3)	-21%	4.5 (0.3, 21.5)	8.0 (1.1, 36.4)	78%
Non- smokers	3.5 (0.7, 11.4)	2.6 (0.3, 9.2)	-26%	1.7 (0.0, 10.6)	0.8 (0.0, 7.0)	-53%

Conflicts of interest

Dr. Rockstroh reports personal fees from Abbvie, Bionor, BMS, Boehringer, Gilead, Merck, Janssen, Tobira, Tibotec and ViiV, outside the submitted work; all other authors state no commercial or other associations that may pose a conflict of interest.

Ole Kirk has received honorarium, consultancy and/or lecture fees from Abbott, Gilead, GSK, Janssen, Merck, Tibotec and Viiv outside the submitted work.

No other authors declare any conflicts of interest.

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Appendix

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Leah Shepherd developed the project, analysed the data, and was responsible for writing the manuscript. Álvaro H Borges and Ole Kirk contributed with ideas to the study design and analysis, with interpretation of data and with writing the manuscript. Jens Lundgren *p*roposed the project and contributed with study design, ideas for analysis, interpretation of data, writing the manuscript. Bruno Ledergerber, Pere Domingo, Antonella Castagna, Jurgen Rockstroh, Brygida Knysz, Janez Tomazic and Igor Karpov contributed with national coordination, study design, and with writing the manuscript. Amanda Mocroft supervised the project and contributed with ideas to the study design and analysis, with interpretation of data and with writing the manuscript