For Health Professionals.

Prescribing and Adverse Event reporting information

Dovato
dolutegravir/lamivudine

POWER REIMAGINED

AN INNOVATIVE, GUIDELINE-RECOMMENDED REGIMEN FOR YOUR PATIENTS LIVING WITH HIV

- **POWERFUL, DURABLE EFFICACY**[1,2]
- **HIGH BARRIER TO RESISTANCE**[1,2]
- **TDF, TAF AND ABC FREE**

DOVATO is indicated for the treatment of HIV-1 in adults and adolescents above 12 years weighing at least 40 kg, with no known or suspected resistance to the integrase inhibitor class, or lamivudine.

GOING BEYOND SUPPRESSION

gemini 1 gemini 2

METABOLIC PARAMETERS AND BIOMARKER CHANGES AT 144 WEEKS

DOVATO vs DTG + TDF/FTC in treatment-naïve patients[1]

	Changes in bone turnover biomarkers significantly favour DOVATO vs DTG + TDF/FTC[1] The GEMINI studies did not determine whether these changes translate to clinical differences.
	Changes in renal function biomarkers significantly favour DOVATO vs DTG + TDF/FTC[1] The GEMINI studies did not determine whether these changes translate to clinical differences. Renal-related AEs leading to withdrawal were comparable across both arms.[1]
	Improvements in TC/HDL ratio occurred in both arms, with a statistically greater reduction in the DTG + TDF/FTC arm[1]
	Overall mean weight change from baseline was +3.7 kg in the DOVATO arm and +2.4 kg in the DTG + TDF/FTC arm[1]

TANGO

CHANGES IN METABOLIC PARAMETERS AT 48 WEEKS AFTER SWITCHING FROM TAF-CONTAINING REGIMENS

DOVATO vs TAF-containing regimens in virologically suppressed patients[2-4]

	INSULIN RESISTANCE SIGNIFICANTLY FEWER patients with insulin resistance* after switching to DOVATO from a TAF-containing regimen[2]
	LIPIDS SIGNIFICANT IMPROVEMENTS in most lipid parameters in the DOVATO arm vs the TAF-containing regimens arm, including TC/HDL ratio[2]
	BONE AND RENAL BIOMARKERS MINIMAL CHANGES in bone turnover and renal function biomarkers across both arms[2,3†]
	WEIGHT GAIN AND METABOLIC SYNDROME OBSERVED SIMILAR[4‡]: • Small increases in mean weight (≈0.8 kg) in both arms • Increases in metabolic syndrome‡ • Median changes in fasting glucose and HbA_{1c}

DTG 50 mg + 3TC 300 mg used in the GEMINI studies.
*Defined as homeostatic model assessment of insulin resistance (HOMA-IR) ≥2.[2]
†Longer-term data required to determine clinical impact of switching to DOVATO from TAF-containing regimens.
‡Defined by the International Diabetes Federation as a combination of risk factors for cardiovascular disease.[5]

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ORIGINAL RESEARCH

Infection-related and -unrelated malignancies, HIV and the aging population

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Objectives

HIV-positive people have increased risk of infection-related malignancies (IRMs) and infection-unrelated malignancies (IURMs). The aim of the study was to determine the impact of aging on future IRM and IURM incidence.

Methods

People enrolled in EuroSIDA and followed from the latest of the first visit or 1 January 2001 until the last visit or death were included in the study. Poisson regression was used to investigate the impact of aging on the incidence of IRMs and IURMs, adjusting for demographic, clinical and laboratory confounders. Linear exponential smoothing models forecasted future incidence.

Results

A total of 15 648 people contributed 95 033 person-years of follow-up, of whom 610 developed 643 malignancies [IRMs: 388 (60%); IURMs: 255 (40%)]. After adjustment, a higher IRM incidence was associated with a lower CD4 count [adjusted incidence rate ratio (aIRR) CD4 count < 200 cells/μL: 3.77; 95% confidence interval (CI) 2.59, 5.51; compared with ≥ 500 cells/μL], independent of age, while a CD4 count < 200 cells/μL was associated with IURMs in people aged < 50 years only (aIRR: 2.51; 95% CI 1.40–4.54). Smoking was associated with IURMs (aIRR: 1.75; 95% CI 1.23, 2.49) compared with never smokers in people aged ≥ 50 years only, and not with IRMs. The incidences of both IURMs and IRMs increased with older age. It was projected that the incidence of IRMs would decrease by 29% over a 5-year period from 3.1 (95% CI 1.5–5.9) per 1000 person-years in 2011, whereas the IURM incidence would increase by 44% from 4.1 (95% CI 2.2–7.2) per 1000 person-years over the same period.

Conclusions

Demographic and HIV-related risk factors for IURMs (aging and smoking) and IRMs (immunodeficiency and ongoing viral replication) differ markedly and the contribution from IURMs relative to IRMs will continue to increase as a result of aging of the HIV-infected population, high smoking and lung cancer prevalence and a low prevalence of untreated HIV infection. These findings suggest the need for targeted preventive measures and evaluation of the cost–benefit of screening for IURMs in HIV-infected populations.

Keywords: aging, HIV, malignancies, virus-associated malignancies

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*See Appendix for members of the EuroSIDA Study Group.

Introduction

HIV-positive people are at increased risk of many malignancies compared with the general population [1,2]; however, the exact mechanisms are poorly understood [3]. The increased risk could be attributable to a high prevalence of

traditional cancer risk factors such as smoking [4] and alcohol use [5]. However, coinfection with other pro-oncogenic viruses [6], immunodeficiency [2,7], activated inflammation and coagulation [8], a potential direct pro-oncogenic effect of HIV and combination antiretroviral therapy (cART) toxicity [3] may also contribute to the increased risk. The introduction of cART in 1996 led to restored immune function, a reduced incidence of AIDS-defining malignancies (ADMs) [9–11] and increased survival [12]. As a result, the burden of cancers traditionally associated with older age is becoming increasingly important in the HIV-positive population. There is a growing need to address the changing epidemiology of cancers as the population ages. This has been done in several studies in the USA [1,13]; however, research in the European population is needed.

The burden of non-AIDS-defining malignancies (NADMs) is now surpassing that of ADMs in HIV-positive people in the USA and Europe [1,13]. Furthermore, some NADMs 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 as infection-related malignancies (IRMs) and infection-unrelated malignancies (IURMs) [8].

The changing epidemiology of malignancies and the impact of aging on cancer incidence need to be better characterized. The aim of this study was to investigate the impact of aging in HIV-positive people on the incidence of IRMs and IURMs within EuroSIDA, a large European cohort of HIV-positive people with a long follow-up period, and to estimate the likely impact of IRMs and IURMs in the HIV-positive population in the next 5 years for future health care planning, treatment and prevention.

Patients and methods

The 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 nine cohorts from May 1994 and informed consent was obtained from all patients. All information is prospectively collected via standardized 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-VLs), starting and stopping dates of all antiretroviral drugs, smoking status, and dates and diagnoses of all new AIDS-defining diagnoses [using the 1993 Centers for Disease Control and Prevention (CDC) clinical definition [15], which includes ADMs] since last follow-up. In 2001, the standardized forms were updated to collect data on all new non-AIDS-defining diagnoses identified by clinical diagnosis or autopsy (including NADMs) [16], allowing the sites to report date of diagnosis, method of diagnosis (definitive, presumptive or autopsy), and location (selected from a list of common malignancies or as free text). All reported AIDS-defining 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 person-years of follow-up (PYFU) and is consistent over time [17].

Inclusion criteria

All subjects enrolled in EuroSIDA with prospective follow-up after 1 January 2001 were included in the study. Patients were followed from the later of the first visit or 1 January 2001 until the last visit or death. The median date of the last visit was March 2012 [interquartile range (IQR) August 2009 to June 2012].

All malignancies, both AIDS-defining and non-AIDS-defining, 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, reoccurrence of the same malignancy type, pre-cancers and nonmelanoma skin cancers were excluded. IRMs were defined as all malignancies with a probably infectious cause: Kaposi's sarcoma (KS) [caused by human herpesvirus-8 (HHV8)], non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) (caused by Epstein–Barr virus (EBV)], invasive cervical cancers (ICCs), and selected malignancies of the head and neck (base of tongue, pharynx and tonsils), anus, penis, vulva and vagina [caused by human papilloma virus (HPV)], liver [caused by hepatitis B virus (HBV) and hepatitis C virus (HCV)] and stomach (caused by Helicobacter pylori [H.Pylori] [19]. All remaining malignancies were defined as IURMs.

Statistical methods

Poisson generalized estimating equations assuming autoregressive (AR1) correlation were used to estimate the association between age and IRM and IURM incidence. Models were adjusted for the following baseline

variables: ethnicity, region, gender, mode of transmission [homosexual, male injecting drug user (IDU), female IDU, male heterosexual, female heterosexual or missing] and body mass index (BMI); they were also adjusted for the following time-updated variables: age, calendar year, smoking status (current, previous, never or missing), current HIV-VL plasma level, CD4 cell count, prior HBV [prior positive HBV surface antigen (HBsAg) test or presence of detectable HBV DNA] and HCV (prior positive HCV surface antibody test or presence of detectable HCV RNA) coinfection, prior diagnoses of ADMs, NADMs, AIDS-defining events (excluding ADMs) and non-AIDS-defining events (defined as cardiovascular, end-stage renal disease, liver failure and pancreatitis, excluding NADMs) [16], cART use (antiretroviral regimen containing at least three drugs from any class), and regimen according to intention to treat [protease inhibitor (PI)- or non-nucleoside reverse transcriptase inhibitor (NNRTI)-based].

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

The proportions 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 percentage 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 and ≥ 50 years), CD4 count (< 350 and ≥ 350 cells/μL), 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 (because of death or loss to follow-up). No further adjustments for covariates were made.

All statistical tests were two-sided and the type I error rate was 5%. All statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC, USA).

Results

Characteristics

A total of 15 648 persons contributed 95 033 PYFU with a median follow-up time 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% of patients were aged ≥ 50 years, 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 count at baseline was 410 (IQR 265, 588) cells/μL, with 14.8% having a CD4 count ≤ 200 cells/μL, and HIV-VL was 123 (IQR < 50, 5200) HIV-1 RNA copies/mL, with 54.5% having HIV-VL ≤ 400 copies/mL. Prior AIDS-defining and non-AIDS-defining events were present in 24.4% and 1.9% of patients, respectively. Coinfection with HCV and HBV was prevalent in 23.1% and 5.5% of people, respectively.

A total of 610 people developed 643 malignancies, of which 60.3% were IRMs and the remaining 39.7% were IURMs (Table 2). The most common IRMs were NHL (n = 116), anal cancer (85), KS (62) and HL (43). Lung (n = 55), prostate (28), colorectal (23) and breast (22) cancers were common IURMs. At diagnosis, those who developed IURMs relative to those who developed IRMs were older [median age 54 (IQR 46, 61) years for IURMs *vs*. 46 (IQR 39, 52) years for IRMs] and had a higher CD4 count [median 446 (IQR 295, 608) cells/μL *vs*. 342 (IQR 182, 546) years, respectively] and a lower HIV-VL [median < 50 (IQR < 50, 86) copies/mL *vs*. 61 (IQR < 50, 20 002) copies/mL, respectively]. A lower proportion of those with IURMs had prior HCV coinfection and the proportions of those with prior HBV coinfection were similar. Proportions of ever smokers with IRMs (45%) and IURMS (46%) were similar. The majority of cancers diagnosed in those younger than 50 years (n = 353 cancers) were IRMs (75%), with EBV related malignancies accounting for 31% of IRMs and HPV related malignancies accounting for 25%. In those aged ≥ 50 years (290 cancers), more than half had IURMs (57%), with lung cancer accounting for 13% of IURMs and prostate cancer accounting for 10%.

Adjusted incidence of IRM and IURM

In adjusted models, those aged ≥ 50 years had a 1.62 (95% CI 1.14, 2.30) times higher IRM incidence compared with those aged 36–40 years (Table 3), corresponding to a 17% higher incidence per 10 years older age (adjusted rate ratio (aRR) 1.17; 95% CI 1.05, 1.32). The percentage of excess IRMs attributable to being aged ≥ 51 years compared with 36–40 years was 12%. Factors strongly related to a high IRM incidence were HIV associated. Specifically, HIV-VL > 400 copies/mL was associated with a higher IRM incidence (aRR 1.84; 95% CI 1.39, 2.43; P < 0.01) and accounted for 19% of excess malig-

Table 1 Baseline characteristics of persons who had infection-related malignancies (IRMs) and infection-unrelated malignancies (IURMs) during follow-up

Characteristic	*n* (%) or median (IQR) All participants	IRMs	IURMs
Overall	15 648 (100.0)	374 (100.0)	247 (100.0)
Categorical [*n* (%)]			
Age group			
≤ 35 years	5419 (34.6)	78 (20.9)	18 (7.3)
36–40 years	3337 (21.3)	93 (24.9)	40 (16.2)
41–50 years	4390 (28.1)	133 (35.6)	78 (31.6)
≥ 51 years	2502 (16.0)	70 (18.7)	111 (44.9)
Region‡			
Argentina	597 (3.8)	13 (3.5)	6 (2.4)
East	2733 (17.5)	14 (3.7)	6 (2.4)
East central	2041 (13.0)	40 (10.7)	25 (10.1)
North	3220 (20.6)	97 (25.9)	71 (28.7)
West	3332 (21.3)	86 (23.0)	63 (25.5)
South	3725 (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)	6051 (38.7)	191 (51.1)	123 (49.8)
IDU (male)	2290 (14.6)	49 (13.1)	24 (9.7)
IDU (female)	1091 (7.0)	32 (8.6)	10 (4.0)
Heterosexual (male)	2178 (13.9)	35 (9.4)	32 (13.0)
Heterosexual (female)	2830 (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	5393 (34.5)	132 (35.3)	83 (33.6)
Previous	61 (0.4)	4 (1.1)	1 (0.4)
Never	5030 (32.1)	104 (27.8)	66 (26.7)
Unknown	5164 (33.0)	134 (35.8)	97 (39.3)
Prior AIDS* (excluding ADMs)	3811 (24.4)	122 (32.6)	65 (26.3)
Prior ADMs	734 (4.7)	34 (9.1)	17 (6.9)
Prior non-AIDS-defining events† (excluding NADMs)	297 (1.9)	10 (2.7)	8 (3.2)
Prior NADMs	222 (1.4)	5 (1.3)	13 (5.3)
HBV positive	868 (5.5)	38 (10.2)	23 (9.3)
HCV positive	3607 (23.1)	76 (20.3)	35 (14.2)
On cART	11 946 (76.3)	304 (81.3)	215 (87.0)
Numeric [median (IQR)]			
CD4 count (cells/μL)	410 (265, 588)	347 (200, 523)	390 (259, 546)
Nadir CD4 count (cells/μL)	182 (76, 303)	124.5 (47, 250)	160 (70, 255)
HIV-VL (copies/ml)	123 (< 50, 5200)	772 (< 50, 18300)	88 (< 50, 1501)

ADM, AIDS-defining malignancy; cART, combination antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; IDU, injecting drug user; IQR, interquartile range; NADM, non-AIDS-defining malignancy; VL, viral load.
Baseline was defined as the latest of the first visit or 1 January 2001.
*Defined by the 1993 Centers for Disease Control and Prevention (CDC) clinical definition [15].
†Non-AIDS-defining events were 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 cardiovascular events) and end-stage renal disease [16]. NADMs were excluded.

nancies, relative to those with well-controlled viraemia (HIV-VL ≤ 400 copies/mL). A lower current CD4 cell count was associated with a higher IRM incidence (Table 3), which was similar in those aged < 50 years and ≥ 50 years (Fig. 1c; P interaction = 0.82). CD4 counts < 200 and 200–349 cells/μL accounted for 21% and 11% of excess IRMs, respectively (Table 3), relative to those with a CD4 count of ≥ 500 cells/μL. There was no association between IRM incidence and current smoking (Table 3) in younger or older people (Fig. 1d; P for interaction = 0.31). Prior HBV coinfection was associated with a higher IRM incidence (aRR 1.70; 95% CI 1.24, 2.32), but only 5% of IRMs were attributable to HBV coinfection within the cohort (Table 3).

The IURM incidence was 7.33-fold (95% CI 4.07, 13.21; $P < 0.01$) and 2.37-fold (95% CI 1.31, 4.27; $P < 0.01$) higher in those aged ≥ 51 years and aged 41–50 years compared with those aged 36–40 years (Table 3), and explained 56% and 17% of excess IURMs within the cohort, respectively. This corresponds to a twofold increase in IURM incidence per 10 years older age (aRR 2.07; 95% CI 1.84, 2.32). Current smoking was

Table 2 Malignancies classified as infection-related malignancies (IRMs) and infection-unrelated malignancies (IURMs)

Malignancies	*n*
IRMs	388
Epstein–Barr virus	159
Non-Hodgkin lymphoma	116
Hodgkin lymphoma	43
Hepatitis B and C viruses	
Liver cancer	33
Human herpesvirus-8	
Kaposi's sarcoma	62
Human papillomavirus	123
Anal cancer	83
Invasive cervical cancer	33
Cancer of the vulva and vagina	3
Cancer of the penis	3
Cancer of the base of the tongue, pharynx and tonsils	1
H. pylori	
Stomach cancer	11
IURMs	255
Lung cancer	55
Prostate cancer	28
Colorectal cancer	23
Breast cancer	22
Other	127

associated with elevated IURM incidence and explained 16% of IURMs overall. Stratifying by age, IURMs were elevated in current smokers relative to nonsmokers in those aged ≥ 50 years (aRR 1.75; 95% CI 1.23, 4.49; $P < 0.01$; Fig. 1b), but not in those aged < 50 years (aRR 1.12; 95% CI 0.71, 1.77; $P = 0.51$), although the *P*-value of the interaction term was nonsignificant ($P = 0.32$). Current smoking was not associated with IURM incidence after the exclusion of lung cancers. A low current CD4 count was associated with a higher IURM incidence (CD4 count < 200 cells/μL: aRR 1.99; 95% CI 1.26, 3.17; $P < 0.01$, relative to CD4 count > 500 cells/μL). Despite this, the overall excess of IURMs attributable to a CD4 count < 200 cells/μL (6%) was small. The association between higher IURM incidence and low CD4 count was evident in those aged < 50 years (aRR 2.52; 95% CI 1.40, 4.54; $P = 0.01$; Fig. 1a), but not in those aged ≥ 50 years (aRR 1.14; 95% CI 0.62, 2.12; $P = 0.56$; Fig. 1a), although the *P*-value of the interaction term did not reach statistical significance ($P = 0.09$). Prior HBV coinfection was also associated with higher IURM incidence (aRR 1.73; 95% CI 1.17, 2.55; $P < 0.01$), but only 5% were attributable to HBV coinfection within the cohort (Table 3).

Future incidence

There were 6111 people enrolled prior to 1 January 2001, contributing 54 030 PYFU [median of 11.1 (IQR 5.8–11.3) PYFU per person] who developed 243 IRMs and 161 IURMs during follow-up. At baseline, 82% of patients were aged < 50 years, 78% were male and 41% had a CD4 count < 350 cells/μL. Forty-seven per cent were homosexual, 25% were heterosexual and 21% were IDUs. Twenty-six per cent were smokers at baseline, 21% were nonsmokers at baseline and 52% had unknown smoking status.

Assuming current trends continue, the crude IRM incidence for those recruited before 2001 was forecast to decline from an incidence of 3.1 (95% CI 1.5, 5.9)/1000 PYFU in July to December 2011 to 2.2 (95% CI 0.9, 4.3)/1000 PYFU after 5 years (Fig. 2a). This was consistent in all strata, with the exception of IDUs, in whom the incidence was stable (Table 4). The forecasted crude IURM incidence increased from 4.1 (95% CI 2.2, 7.2)/1000 PYFU in July to December 2011 to 5.9 (95% CI 3.2, 10.2)/1000 PYFU after 5 years (Fig. 2b), and was consistent in all strata, except in never smokers for whom the IURM incidence was forecast to decrease from 1.7 (95% CI 0.0, 10.6)/1000 PYFU in July to December 2011 to 0.8 (95% CI 0.0, 7.0)/1000 PYFU after 5 years (Table 4). The incidence of IURMs surpassed that of IRMs from January to June 2009 onwards, and was forcast to continue to increase over the subsequent 5 years.

Discussion

Demographic and HIV-related risk factors for IURMs and IRMs differ markedly. The incidence of IURMs has exceeded that of IRMs since January–June 2009 (in those enrolled in EuroSIDA prior to 2001) and the contribution from IURMs is forecast to increase over the subsequent 5 years as a result of aging of the HIV-positive population, a high smoking prevalence [4], and a low prevalence of untreated and advanced HIV infection. These findings suggest the need to develop targeted preventive measures and evaluate the cost–benefit of screening for IURMs in HIV-positive 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.

A higher IRM incidence was strongly associated with traditional HIV factors such as a higher HIV-VL and a lower CD4 cell count and, to a lesser extent, older age. The incidence of IRMs steadily increased with lower CD4 count category. However, the proportions of IRMs attributable to older age, higher HIV-VL and lower CD4 count were similar to each other in EuroSIDA, as a result of ongoing aging and a low prevalence of uncontrolled HIV infection in this cohort. Those aged ≥ 51 years may have

Table 3 Adjusted rate ratios (aRRs) and population attributable fractions of infection-related malignancies (IRMs) and infection-unrelated malignancies (IURMs)

	IRMs			IURMs		
Variable	**aRR (95% CI)**	**% attributable**	***P*-value**	**aRR (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)	< 0.01
≥ 51 years	1.62 (1.14, 2.30)	12.3 (3.9, 18.2)	< 0.01	7.33 (4.07, 13.21)	55.9 (48.8, 59.8)	< 0.01
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)	< 0.01	0.91 (0.62, 1.35)		0.66
CD4 count						
< 200 cells/μL	3.77 (2.59, 5.51)	20.5 (17.1, 22.8)	< 0.01	1.99 (1.26, 3.17)	6.3 (2.6, 8.6)	< 0.01
200–349 cells/μL	1.83 (1.35, 2.48)	10.6 (6.1, 14.0)	< 0.01	1.30 (0.89, 1.88)		0.17
350–499 cells/μL	1.24 (0.92, 1.67)		0.16	1.29 (0.95, 1.75)		0.11
≥ 500 cells/μL	Ref	Ref	–	Ref	Ref	–
Prior AIDS event (excluding ADMs)	1.25 (1.00, 1.57)		0.05	0.85 (0.64, 1.14)		0.29
Prior ADMs	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–defining event (exclusing NADMs)				1.36 (0.88, 2.10)		0.17
Prior NADMs				2.13 (1.42, 3.20)		< 0.01
HBV	1.70 (1.24, 2.32)	5.3 (2.5, 7.3)	< 0.01	1.73 (1.17, 2.55)	5.0 (1.7, 7.2)	< 0.01
HCV	0.77 (0.56, 1.06)		0.11	0.90 (0.60, 1.37)		0.62
Transmission group*						
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)		< 0.01	0.91 (0.61, 1.36)		0.64
Heterosexual (female)	0.57 (0.40, 0.80)		< 0.01	1.25 (0.86, 1.83)		0.24
Smoking status*						
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)	< 0.01

ADM, AIDS-defining-malignancy; CI, confidence interval; NADM, non-AIDS-defining malignancy; HBV, hepatitis B virus; HCV, hepatitis C virus; IDU, injecting drug user.
Models were adjusted for the following baseline variables: ethnicity, region, gender, mode of transmission (homosexual, male IDU, female IDU, male heterosexual, female heterosexual and missing) and body mass index; and for the following time-updated variables: age, calendar year, smoking status (current, previous, never and missing), current HIV viral load plasma levels (≤ 400 and > 400 copies/mL), CD4 cell count (< 200, 200–349, 350–499 and ≥ 500 cells/μL), prior HBV/HCV coinfection, prior ADMs, prior AIDS-defining diagnoses (excluding ADMs), prior NADMs, prior non-AIDS-defining events (defined as cardiovascular, end-stage renal disease, liver failure and pancreatitis, excluding NADMs), exposure to combination antiretroviral therapy (antiretroviral regimen containing at least three drugs from any class) and regimen according to intention to treat (protease inhibitor- or nonnucleoside reverse transcriptase inhibitor-based).
*Missing category not shown.

had longer exposure to oncogenic viruses, which could explain the increased IRM incidence.

Older age was the largest contributor to IURM incidence. Our finding of a twofold higher IURM incidence for a 10-year increase in age is similar to findings of the The Strategies for Management of Antiretroviral Therapy (SMART) study [24] and to data published online by the European Cancer Observatory, which showed a 1.9-fold increase in the incidence of all malignancies in the general population [23]. 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 [22].

Current smoking status was associated with a higher IURM incidence, driven by lung cancer, in people aged ≥ 50 years, probably reflecting the lag time between smoking and the onset of consequences. As the proportion of the cohort aged over 50, 60 and 70 years 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 infection and large, well-designed observational studies are crucial to understand both existing and emerging comorbidities in HIV-positive people. A higher IURM incidence was associated with a CD4 cell count < 200 cells/μL in people aged < 50 years only, which appeared to be attributable to a relatively high number of lung cancers in this group. However, numbers were small and further investigation was not possible.

The incidence of IRMs was forecast to decline over time, probably driven by the low prevalence of advanced

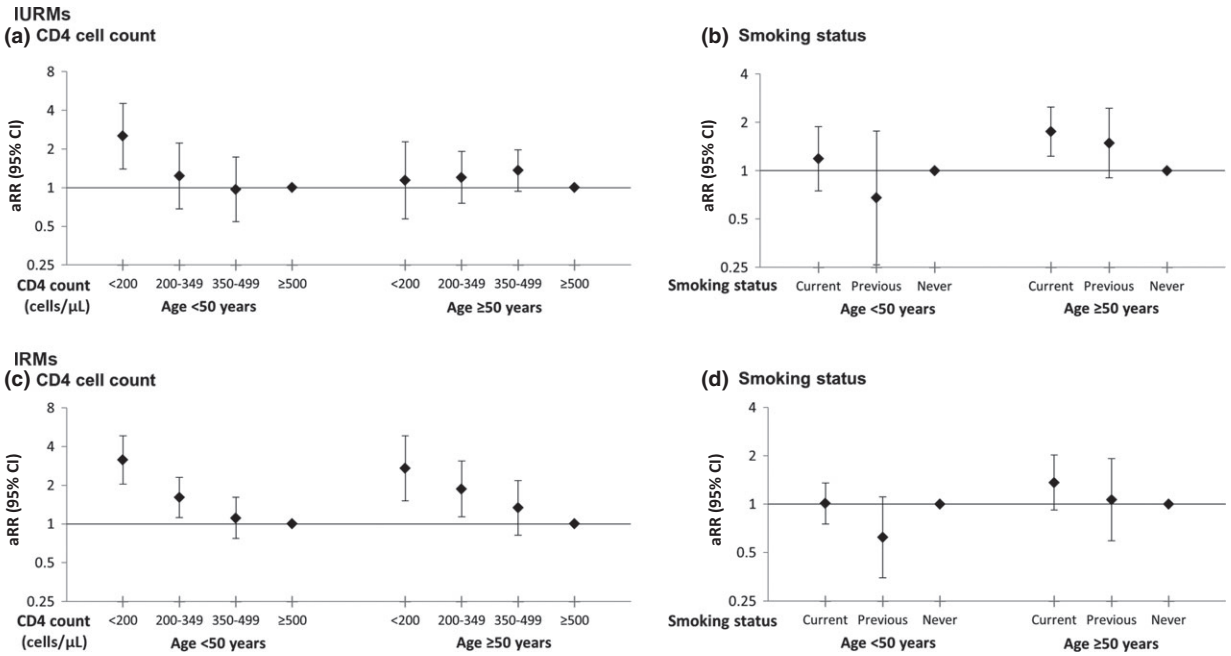

Fig. 1 Adjusted rate ratios (aRRs) of infection-unrelated malignancies (IURMs) for (a) CD4 count and (b) smoking status and of infection-related malignancies (IRMs) for (c) CD4 count and (d) smoking status in those aged < 50 and ≥ 50 years. Models were adjusted for age, calendar year, gender, ethnicity, region of residence, mode of transmission, current smoking status, baseline hepatitis C and B status, current HIV viral load, cumulative time of HIV viral load > 400 copies/mL, current CD4 count, cumulative time of CD4 count < 200 cells/μL, prior AIDS-defining malignancies (ADMs), prior AIDS-defining diagnosis (excluding ADMs), prior non-AIDS-defining malignancies (NADMs), prior non-AIDS-defining diagnosis (excluding NADMs), treatment group, protease inhibitor use and nonnucleoside reverse transcriptase inhibitor use. CI, confidence interval.

and untreated HIV infection, following improvements in treatment efficacy, uptake and adherence. Antiretroviral therapy controls HIV viraemia, leading to CD4 recovery, and reduces the risk of some IRMs, such as KS and NHL [1,11,13,14,25], but not all (e.g. HL, ICC and anal cancers) [11,25–27]. 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 programmes. The 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 [28]. A similar result was found for the UK population [21].

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 IURMs 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 that screening rates for cervical and anorectal cancers were low [29]. Linear exponential smoothing models are a simple method of forecasting which assumes 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-infected population ages, the incidence of IURMs is expected to increase as a result of aging of the HIV-infected population and the high prevalence of lung cancer caused by smoking, the effects of which generally

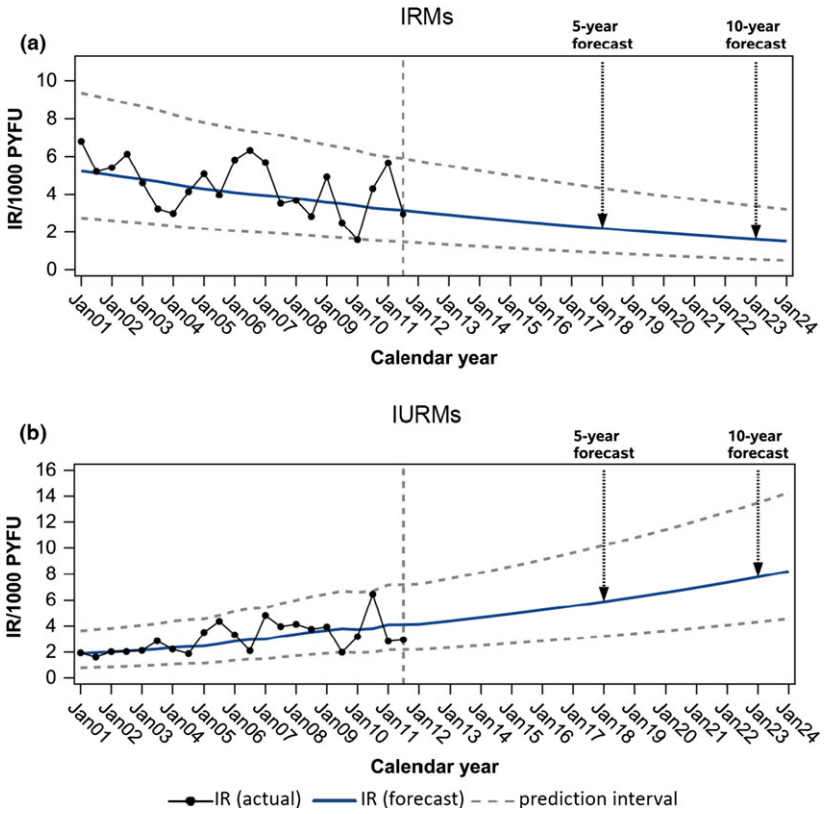

Fig. 2 Forecast crude incidence rate (IR) of infection-related malignancies (IRMs) and infection-unrelated malignancies (IURMs)/1000 person-years of follow-up (PYFU) for those recruited before 2001. (a) Semi-annual crude IR of IRMs/1000 PYFU for those recruited before 2001 with 5- and 10-year forecast. (b) Semi-annual crude IR of IURMs/1000 PYFU for those recruited before 2001 with 5- and 10-year forecast.

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

	Incidence of infection-related malignancies /1000 PYFU			Incidence of infection-unrelated malignancies /1000 PYFU		
Subgroups	July–December 2011	Forecast at 5 years	% change	July–December 2011	Forecast at 5 years	% change
Overall baseline age	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
< 50 years	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 years	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 count						
< 350 cells/μL	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 cells/μL	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 user	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
Nonsmokers	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

PYFU, person-years of follow-up.

manifest with longer term exposure and thus at older ages. Conversely, IRM incidence is expected to decline as a result of the low prevalence of advanced and untreated HIV infection and severe immunodeficiency. IURMs should therefore be a priority in the coming years as higher proportions of HIV-positive people live past 50, 60

and 70 years. Studies evaluating the cost–benefit of screening programmes for HIV-positive people and targeted preventive interventions, such as cessation programmes 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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Author contributions: LS developed the project, analysed the data, and was responsible for writing the manuscript. ÁHB and OK contributed to the study design and analysis, interpretation of the data and writing of the manuscript. JL proposed the project and contributed to the study design, ideas for analysis, interpretation of the data and writing of the manuscript. BL, PD, AC, JR, BK, JT and IK contributed to national coordination, study design and writing of the manuscript. AM supervised the project and contributed to the study design and analysis, interpretation of the data and writing of the manuscript.

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