AIDS

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Where is the greatest impact of uncontrolled HIV infection on AIDS and non-AIDS events in HIV?

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Objective

The extent to which controlled and uncontrolled HIV interact with ageing, European region of care and calendar year of follow-up is largely unknown.

Methods

EuroSIDA particpants were followed after 1/1/2001 and grouped according to current HIV progression risk; high risk [CD4 $\leq$350/mm^3, viral load $\geq$10,000 copies/ml], low risk [CD4 $\geq$500/mm^3 , viral load <50 copies/ml], and intermediate [other combinations]. Poisson regression investigated interactions between HIV progression risk, age, European region of care, and year of follow-up and incidence of AIDS or non-AIDS events.

Results

16839 persons were included with 136688 PYFU. In persons aged $\leq$30, those at high risk had a 6-fold increased incidence of non-AIDS compared to those at low risk, compared to a 2-3 fold increase in older persons (p=0.0004, interaction). In Eastern Europe; those at highest risk of non-AIDS had a 12-fold increased incidence compared to a 2-4-fold difference in all other regions (p=0.0029, interaction). Those at high risk of non-AIDS during 2001-2004 had a 2-fold increased incidence compared to those at low risk, increasing to a 5-fold increase $\geq$2013 (p<0.0001, interaction). Differences between high, intermediate and low risk of AIDS were similar across age groups, year of follow-up and Europe (p=0.57, p=0.060, p=0.090 respectively, interaction).

Conclusions

Factors other than optimal control of HIV become increasingly important with ageing for predicting non-AIDS while differences across Europe reflect differences in patient management as well as underlying socioeconomic circumstances. The difference between those at high, intermediate and low risk of non-AIDS ≥2013 likely reflects better quality of care.

Keywords: AIDS; incidence; non-AIDS; risk of HIV disease progression

Introduction

The relative frequency of AIDS, non-AIDS and deaths of persons with HIV has changed significantly since the advent of combination antiretroviral therapy (cART), with the proportion of AIDS and AIDS-related mortality decreasing and the proportion of non-AIDS events increasing [1-3]. The role of immune deficiency and uncontrolled HIV viremia in both AIDS and non-AIDS events is now well established [4-7], with a near normal life expectancy in those with well controlled HIV-infection counts[8-10] and evidence to show that HIV+ persons no longer experience an increased risk of AIDS or death when the CD4 count increases above 500-750/mm^3 [11-13].

As persons with HIV live longer, the role of aging plays an increasingly important role. Older persons have less ability to reconstitute CD4 cells[14], possibly due to a decline in thymus function associated with aging [15, 16]. Long term management of comorbidities in HIV-positive persons, as well as their HIV infection, becomes increasingly important and is now included alongside recommendations for antiretroviral treatment in both US and European HIV treatment and management guidelines [17, 18]. Importantly, there is little known about whether the relative contribution to morbidity and mortality within age groups differs for those with controlled or uncontrolled HIV, which might provide an insight into ageing and HIV pathogenesis.

The underlying incidence of AIDS and non-AIDS events varies considerably across regions of Europe [19], likely due to regional differences in pathogens as well as clinical management and access to care, but whether there are important differences across regions comparing those with controlled or uncontrolled HIV infection is unknown. Equally, the difference in risk of AIDS and non-AIDS for those with controlled or uncontrolled HIV might have widened or narrowed over calendar time, given the significant improvements in cART and management of HIV seen over the past decades.

We hypothesised that there would be differences in AIDS and non-AIDS events between those at low and high risk according to age, region of Europe and calendar year of follow-up. This would address the relative importance of biological aging versus controlled HIV when considering the differences within age groups, and the role of controlled HIV and clinical management when considering differences within regions of Europe or changes over calendar time. To our knowledge, this is a novel way of looking at AIDS and non-AIDS events. The aims of this study were therefore to identify whether risk of HIV disease progression comparing controlled and uncontrolled HIV was different across age groups, year of follow-up or European regions of care between 2001 and 2016.

Patients

EuroSIDA was initiated in 1994 and is a prospective study of 23071 HIV-1-infected persons at 116 centres across Europe, Israel and Argentina; further details are available at http://www.cphiv.dk/Ongoing-Studies/EuroSIDA/About. To date, 10 cohorts of HIV+ individuals have been recruited. Data are collected prospectively at clinical sites and is extracted and sent to the coordinating centre at 12 monthly intervals. For cohorts I–III, eligible persons were those who had had a CD4 count below 500 cells/mm^3 at recruitment or during the previous 4 months. The CD4 count restriction was removed for cohorts IV onwards. Cohort 10 only includes persons coinfected with hepatitis C and HIV. At recruitment, in addition to demographic and clinical information, a complete antiretroviral treatment history is obtained, together with the most recent CD4 count and plasma HIV-RNA measurements. At each follow-up visit, details on all CD4 counts and plasma HIV-RNA values measured since the last follow-up visit are extracted, as are the dates of starting and stopping each antiretroviral drug received and the use of drugs for prophylaxis against opportunistic infections. **AIDS events were diagnosed using the clinical definition from**

the Centers for Disease Control[20]. Cardiovascular events, non-AIDS malignancies, end stage liver disease and end stage renal disease were included as non-AIDS events[21] and fatal events were classified as AIDS or non-AIDS[22]. Participating countries were grouped into Southern Europe [Greece, Israel, Italy, Portugal, Spain, Argentina], Western Europe [Austria, Belgium, France, Germany, Luxembourg, Switzerland] Northern Europe [Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom]; Central Eastern Europe [Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovakia, Slovenia] and Eastern Europe [Belarus, Estonia, Georgia, Latvia, Lithuania, Russian Federation, Ukraine].

Statistical methods

As prospective and quality assured data on non-AIDS events began in 2001, individuals were included from the latest of recruitment to the study or 1 January 2001 (study baseline). Persons were followed to last clinic visit or death (median June 2016 for persons included in these analyses). Individuals without prospective follow-up after baseline were excluded, as were those without a CD4 count or viral load in the 6 months prior to baseline. Each person could experience more than 1 event, but not repeated events of the same type. For example, a person diagnosed with Non-Hodgkin lymphoma on 2 separate occasions would only contribute 1 AIDS defining event to analyses, whilst a person defined with breast cancer and liver cancer would contribute with 2 events.

cART was defined as at least 3 antiretrovirals from any class. Risk of clinical progression was stratified into 3 groups defined a priori; high-risk [viral load $\geq$ 10000 copies/ml and CD4 $\leq$ 350/mm^3], low-risk [viral load < 50 copies/ml and CD4 > 500/mm^3] and intermediate-risk [all other combinations of CD4 counts and viral loads]. Person-years of follow-up (PYFU) and clinical events were allocated to one of these 3 strata and allowed to vary over time; thus

PYFU were allocated according to the most recent CD4 count and viral load measured, using the last value carried forward. The median time between CD4 counts and viral loads among patients included was 3 months (interquartile range 2 – 5 months), with 97% and 96% of CD4 counts and viral loads respectively measured with less than 12 months apart.

The incidence of AIDS and non-AIDS events within these strata were calculated and Poisson regression was used to determine the adjusted incidence rate ratios of those at high-risk compared to those at low-risk, after adjustment for confounding variables. Generalised linear models were adjusted for persons experiencing more than 1 event. *A priori* our primary hypothesis was that there were important differences between those at high, intermediate and low risk of clinical disease progression within different periods of calendar year of follow-up, age, and European region of care; i.e., there was a significant interaction between HIV risk group (high, intermediate and low) and age, calendar periods, or European region of care. In addition to the primary variables of interest (risk of clinical progression, age, European region of care and calendar year of follow-up), models were adjusted for gender, CD4 nadir, HIV exposure group, ethnic origin, prior AIDS and non-AIDS events, and date of enrolment to EuroSIDA as fixed covariates at baseline. Hepatitis B and C status, AIDS events, non-AIDS events, diabetes*, hypertension*, smoking status*, and anaemia* were included as time-updated covariates (*see [21] for definitions). Models were additionally adjusted for non-AIDS events when AIDS was the primary endpoint and AIDS events when non AIDS was the primary endpoint, both as time-updated covariates.

All analyses were performed using SAS version 9.4.

Results

Characteristics and crude incidence rates of clinical progression

16839 persons were included in analyses, summarised in Table 1. At baseline, which was significantly later for those at low risk, 3990 (23.7%) were at low risk of disease progression, 11091 (65.9%) at intermediate risk and 1758 (10.4%) at high risk according to the pre-defined risk strata. Median age at baseline was 40 years (interquartile range [IQR] 34 – 48), and median nadir CD4 was 250/mm^3 (IQR 123 – 403/mm^3). The majority of individuals were male (n=12468; 74.0%), infected with HIV through homosexual exposure (n=6482; 38.5%) and of white ethnic origin (n=14587; 86.6%). Each of the European regions of care was well represented, although the number of persons from Eastern Europe at low risk of disease progression was low.

The median follow-up was 7.9 years (IQR 3.2 – 13.5 years). During 136688 PYFU, there were 1693 AIDS events and 3282 non-AIDS events, giving crude incidence rates of 12.4 (95% confidence interval [CI] 11.8 – 13.0 per 1000 PYFU) and 24.0 (95% CI 23.2 – 24.8 per 1000 PYFU) respectively, as summarised in Table 2. Among the non-AIDS events, deaths from non-AIDS causes was the most frequent event (1323, 40.3%), followed by non-AIDS defining malignancy (840, 25.6%), CVD (814, 24.8%), ESLD (243, 7.4%) and ESRD (62, 1.9%). During 2001-2005, 24.9% of the follow-up was among those at low risk increasing to over 55.8% during 2013 or later. The proportion of follow-up at high risk decreased from 9.4% in 2001-2005 to 2.0% during 2013 or later. As expected, there was a strong gradient of increasing incidence as you moved from low to high risk. The incidence of AIDS increased from 2.9/1000 PYFU in those at low risk to 104.7/10000 PYFU in those at high risk, a 36-fold difference. The incidence of non-AIDS events increased from 16.1/1000 PYFU in those at low risk to 49.5/10000 PYFU in those at high risk, a 3-fold difference.

Table 2 also shows the considerable differences in the incidence of AIDS or non-AIDS events between those at high, intermediate and low risk as well as within age groups, calendar year of follow-up or European region of care.

Differences between those at high and low risk of HIV disease progression across age groups

Table 2 shows the crude incidence rates of AIDS and non-AIDS events, which suggest there may be important differences within age groups when comparing those at high, intermediate and low risk of both AIDS and non-AIDS events. After adjustment, persons aged ≤30 and at high risk at had a 6-fold increased incidence (adjusted incidence rate ratio [aIRR] 6.13; 95% CI 1.87-20.08) of a non-AIDS event compared to those at low risk, while older persons has a 2-3 fold increased incidence (Figure 1a) The difference in risk of a non-AIDS event between those at high, intermediate and low HIV risk significantly decreased as persons aged (Figure 1a, $p<0.0001$, test for interaction), driven largely by the differences in the youngest age group. There were no differences comparing high, intermediate and low risk groups across age groups for AIDS events ($p=0.57$, test for interaction, Figure 1b). For example, after adjustment, persons aged ≤30 and at high risk of AIDS had a 20-fold increased incidence of AIDS events (aIRR 20.51; 95% CI 7.10-59.27) compared to those at low risk, while those aged >50 had a 23-fold increase (aIRR 95% CI 16.87-32.13).

Differences between those at high and low risk of HIV disease progression across European region of care

After adjustment, there were no significant differences between those at high, intermediate and low risk of AIDS events when comparing across European region of care ($p=0.090$, test for interaction), as shown in Table 3. In all regions, compared to those at low risk those at intermediate risk had approximately a 3-fold increased incidence of AIDS after adjustment,

increasing to around a 15-20 fold increase for those at highest risk. Although the difference between those at high, intermediate and low risk of AIDS events appeared slightly different in Eastern Europe, the confidence intervals were wide and the test for interaction was not statistically significant (p=0.090).

In contrast, we found a difference for non-AIDS events (Table 3) between those at high, intermediate and low risk across regions (p=0.0029, test for interaction). This difference was largely driven by Eastern Europe The differences between the HIV risk strata (high, intermediate and low) were 2-4 fold in all regions except Eastern Europe where those at intermediate and highest risk of non-AIDS events had between a 5 and 13-fold increased incidence of non-AIDS events after adjustment, compared to those at low risk.

Differences between those at high and low risk of HIV disease progression and calendar year of follow-up

The differences between those at high, intermediate and low risk in different calendar periods of follow-up are shown in Figures 2a (AIDS) and 2b (non-AIDS). For non-AIDS events, the difference between those at high and low HIV risk of a non-AIDS event increased from a 2-3 fold difference between 2001-2012 to a 5-fold difference in 2013 or larger (p<0.0001, test for interaction). For AIDS events, there was a similar pattern, with the difference between those at low and high risk being 17-fold in 2001-2004 and 25-fold in 2013 or later, although the test for interaction was marginally statistically significant (p=0.060).

when comparing those with uncontrolled and controlled HIV. There are well recognised differences in both HIV and non-HIV associated mortality and morbidity across regions of Europe [19, 29], and these differences are likely to impact on the risk of non-AIDS events in those with uncontrolled and controlled HIV differently. Differences in health policies, quality of care, and patterns of health in those from different socioeconomic groups vary across regions of Europe. For example, in Western Europe (South, West and North combined in these analyses) smoking, lung cancer and cardiovascular disease is decreasing [30] but changes have been slower in Eastern Europe [29]. There is a high proportion of persons from Eastern Europe infected with HIV through IDU [31], with a high prevalence of multidrug resistant tuberculosis[32] which may reflect socioeconomic circumstances or access to care which will also impact on the development of non-AIDS events. Management of HIV-positive persons in Eastern Europe requires a multidisciplinary and coordinated approach to retain individuals in care, and to maintain adherence to antiretrovirals in a setting where HIV+ persons may have less engagement with health care settings [33].

The fact that differences in AIDS events between those at low, intermediate and high risk was similar in different European regions of care highlights again that the development of AIDS is more strongly linked to uncontrolled HIV and that persons with uncontrolled HIV are at a high risk of AIDS events regardless of which region of Europe they are followed up in.

Controlled HIV infection, calendar time and clinical disease

The difference between those with at high, intermediate and low risk of non-AIDS events was greatest in 2013 or later. A similar pattern was seen for AIDS events, but the test for interaction was marginally statistically significant (p=0.060). There has been an increase

over time in durability of cART, both in terms of sustained virologic suppression and in efficacy and tolerability of newer antiretrovirals[34-36]. This likely means that those under follow-up ≥2013 at low risk of non-AIDS, with low viremia and high CD4 count, have a lower viral load and are better monitored for HIV disease and comorbidities, as focus has changed to monitoring for comorbidities and management of HIV as a chronic disease [17, 18]. Those at high risk ≥2013, with high viral loads and lower CD4 counts, likely have quite different characteristics to those at high risk during earlier years. They may be more likely to be individuals with a complex medical history, with adherence problems, and potentially on salvage regimens.

It is important to note some limitations. EuroSIDA has recruited 10 cohorts of HIV-positive individuals and it is likely those recruited later are at lower risk of disease progression, partly shown by the later baseline date of those at low risk. Centres participating in EuroSIDA are not necessarily representative of the European region as a whole, and are centres of excellence, and we may be underestimating the differences between those with uncontrolled and controlled HIV for both AIDS and non-AIDS events. Our analyses are based on studying whether the relationship between controlled and uncontrolled HIV and factors of interest (age, region and calendar year of follow-up) differ, ie, whether there is a significant interaction, rather than how uncontrolled or controlled HIV affects the risk of AIDS or non-AIDS events. Interaction analyses such as these are typically underpowered, which is why a large study such as EuroSIDA is needed for adequately powered analyses, but should also be planned *a priori*, before analyses begin, as in the present analysis.

In conclusion, for the first time, our results highlight that as persons age, factors other than optimal control of HIV become more important for predicting non-AIDS events,

demonstrating the role of biological aging, while the development of AIDS is much more dependent on uncontrolled HIV in all age groups. The differences in non-AIDS events for those at low, intermediate or high risk in different European regions of care likely reflect differences in clinical management as well as underlying socioeconomic circumstances. The lack of differences between those at high, intermediate and low risk of AIDS in different European regions highlights the essential role of controlling HIV infection and starting and maintaining individuals on an effective treatment regimen. The increasing difference in non-AIDS events between those at high, intermediate and low risk over time likely reflects better care, monitoring and management of both HIV and comorbidities for those with well controlled HIV and that continued improvements in management and HIV control are needed for those at highest risk.

Table 1

Characteristics of population, stratified by HIV progression risk at study baseline

		All		Low risk		Intermediate risk		High risk	
		N	%	N	%	N	%	N	%
All		16839	100.0	3990	23.7	11091	65.9	1758	10.4
Gender	Male	12468	74.0	3017	75.6	8195	73.9	1256	71.4
	Female	4371	26.0	973	24.4	2896	26.1	502	28.6
HIV Exposure Group	Homosexual	6482	38.5	1754	44.0	4161	37.5	567	32.3
	IDU	4180	24.8	948	23.8	2749	24.8	483	27.5
	Heterosexual	4908	29.1	1003	25.1	3317	29.9	588	33.4
	Other	1269	7.5	285	7.1	864	7.8	120	6.8
Ethnic Origin	White	14587	86.6	3426	85.9	9651	87.0	1510	85.9
	Other	2252	13.4	564	14.1	1440	13.0	248	14.1

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Prior AIDS		4356	25.9	811	20.3	2982	26.9	563	32.0
Prior non-AIDS		784	4.7	226	5.7	488	4.4	70	4.0
Hepatitis B Status	Negative	13068	77.6	3165	79.3	8572	77.3	1331	75.7
	Positive	753	4.5	145	3.6	521	4.7	87	4.9
	Unknown	3018	17.9	680	17.0	1998	18.0	340	19.3
Hepatitis C Status	Negative	8494	50.4	1929	48.3	5696	51.4	869	49.4
	Positive	5933	35.2	1606	40.3	3738	33.7	589	33.5
	Unknown	2412	14.3	455	11.4	1657	14.9	300	17.1
Region	South	4868	28.9	1089	27.3	3315	29.9	464	26.4
	West	4357	25.9	1309	32.8	2691	24.3	357	20.3
	North	3432	20.4	1021	25.6	2087	18.8	324	18.4
	Central East	2194	13.0	429	10.8	1517	13.7	248	14.1
	East	1988	11.8	142	3.6	1481	13.4	365	20.8

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		Median	IQR	Median	IQR	Median	IQR	Median	IQR
Age	years	40	34 - 48	43	36 - 50	40	34 - 48	38	33 - 44
CD4	/mm^3	430	278 - 623	692	585 - 854	390	272- 496	200	105 - 279
Nadir	/mm^3	250	123 - 403	417	250 - 609	227	112 - 363	145	58 - 241
Baseline	mm/yy	11/05	01/01 - 12/11	07/08	01/01 - 07/14	01/04	01/01 - 04/09	12/03	01/01 - 07/08

Low-risk : CD4 $\geq$500/mm^3 and viral load < 50 copies/ml. High-risk; CD4 $\leq$ 350/mm^3 and viral load > 10000 copies/ml. Intermediate risk; all other CD4/viral load combinations. IDU; intravenous drug user. IQR; interquartile range. Baseline was the later of 1 January 2001 or enrolment in EuroSIDA.

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Table 2

Crude incidence rates (per 1000 PYFU) of AIDS and non-AIDS events within HIV risk strata and age, calendar year of follow-up and European region of care

		All				Low risk				Intermediate risk				High risk			
		Events	PYFU	Rate	95% CI	Events	PYFU	Rate	95% CI	Events	PYFU	Rate	95% CI	Events	PYFU	Rate	95% CI
AIDS		1693	136688	12.4	11.8-13.0	168	58759	2.9	2.4-3.3	861	71587	12.0	11.2-12.8	664	6342	104.7	96.7-112.7
Age	≤30	96	6298	15.2	12.2-18.3	4	1471	2.7	0.7-7.0	38	4187	9.1	6.2-12.0	54	639	84.5	61.9-107.0
	30-40	516	30447	16.9	15.5-18.4	35	10675	3.3	2.2-4.4	231	17524	13.2	11.5-14.9	250	2248	111.2	97.4-125.0
	40-50	578	51196	11.3	10.4-12.2	63	23017	2.7	2.1-3.4	294	25817	11.4	10.1-12.7	221	2362	93.6	81.2-105.9
	>50	503	48747	10.3	9.4-11.2	66	23596	2.8	2.1-3.5	298	24057	12.4	11.0-13.8	139	1094	127.1	106.0-148.2

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Year	2001-4			20.	19.0-							13.0-				108.	
		544	26167	8	22.5	23	6520	3.5	2.1-5.0	255	17191	14.8	16.7	266	2456	3	95.3-121.3
Follow	2005-7			16.	14.6-		1175					12.2-				106.	
		522	32668	0	17.3	52	8	4.4	3.2-5.6	264	18974	13.9	15.6	206	1937	4	91.8-120.9
Up	2008-						1854					9.2-				106.	
	10	380	38537	9.9	8.9-10.9	54	2	2.9	2.1-3.7	201	18822	10.7	12.2	125	1173	6	87.9-125.3
	≥2011						2193										
		247	39315	6.3	5.5-7.1	39	9	1.8	1.2-2.3	141	16599	8.5	7.1-9.9	67	776	86.3	65.6-107.0
Europea	South			12.	11.2-		1712					11.2-					
n		492	40045	3	13.4	52	5	3.0	2.2-3.9	267	20956	12.7	14.3	173	1965	88.1	74.9-101.2
Region	West			10.			1705					10.0-				108.	
		412	37718	9	9.9-12.0	45	2	2.6	1.9-3.4	222	19329	11.5	13.0	145	1337	5	90.8-126.1
Of care	North			10.			1556					9.3-				107.	
		343	32119	7	9.5-11.8	42	3	2.7	1.9-3.5	168	15317	11.0	12.6	133	1240	3	89.0-125.5
	Central			12.	10.4-							8.7-				114.	
	E	211	17555	0	13.6	18	7611	2.4	1.4-3.7	99	9122	10.9	13.0	94	822	4	91.3-137.5

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	East	235	9251	25.4	22.2-28.7	11	1408	7.8	3.9-14.0	105	6863	15.3	12.4-18.2	119	979	121.5	99.7-143.3
Non-AIDS		3282	13668	24.0	23.2-24.8	947	5875	16.1	15.1-17.1	2021	71587	28.2	27.0-29.5	314	6342	49.5	44.0-55.0
Age	≤30	49	6298	7.8	5.6-10.0	4	1471	2.7	0.7-7.0	31	4187	7.4	4.8-10.0	14	639	21.9	12.0-36.7
	30-40	339	30447	11.1	9.9-12.3	55	1067 5	5.2	3.8-6.5	205	17524	11.7	10.1-13.3	79	2248	35.1	27.4-42.9
	40-50	980	51196	19.1	17.9-20.3	266	2301 7	11.6	10.2-12.9	572	25817	22.2	20.3-24.0	142	2362	60.1	50.2-70.0
	>50	1914	48747	39.3	37.5-41.0	622	2359 6	26.4	24.3-28.4	1213	24057	50.4	47.6-53.3	79	1094	72.2	56.3-88.2
Year	2001-4	676	26167	25.8	23.9-27.8	92	6520	14.1	11.2-17.0	464	17191	27.0	24.5-29.4	120	2456	48.9	40.1-57.6
Follow	2005-8	784	32668	24.0	22.3-25.7	205	1175 8	17.4	15.0-19.8	481	18974	25.4	23.1-27.6	98	1937	50.6	40.6-60.6

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Up	2009-12	926	38537	24.0	22.5-25.6	314	1854 2	16.9	15.1-18.8	566	18822	30.1	27.6-32.5	46	1173	39.2	27.9-50.6
	≥2013	896	39315	22.8	21.3-24.3	336	2193 9	15.3	13.7-17.0	510	16599	30.7	28.1-33.4	50	776	64.4	46.6-82.3
European	South	889	40045	22.2	20.7-23.7	241	1712 5	14.1	12.3-15.9	561	20956	26.8	24.6-29.0	87	1965	44.3	35.0-53.6
Region	West	988	37718	26.2	24.6-27.8	296	1705 2	17.4	15.4-19.3	625	19329	32.3	29.8-34.9	67	1337	50.1	38.1-62.1
Of care	North	918	32119	28.6	26.7-30.4	309	1556 3	19.9	17.6-22.1	542	15317	35.4	32.4-38.4	67	1240	54.0	41.1-67.0
	Central E	325	17555	18.5	16.5-20.5	97	7611	12.7	10.2-15.3	181	9122	19.8	17.0-22.7	47	822	57.2	40.8-73.5
	East	162	9251	17.5	14.8-20.2	4	1408	2.8	0.8-7.3	112	6863	16.3	13.3-19.3	46	979	47.0	33.3-60.5

Low-risk : CD4 ≥500/mm^3 and viral load < 50 copies/ml. High-risk; CD4 ≤ 350/mm^3 and viral load > 10000 copies/ml. Intermediate risk; all other CD4/viral load combinations. CI; confidence interval. Central E; Central East.

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Table 3 Adjusted+ incidence rate ratio of AIDS and non-AIDS events, stratified by European region of care

	Low risk			Intermediate risk			High risk		
	aIRR	95% CI	P	aIRR	95% CI	P	aIRR	95% CI	P
AIDS events; p=0.090 test for interaction									
South	1.00			2.92	2.14 – 3.97	<0.0001	14.41	10.24 – 20.72	<0.0001
West	1.00			2.93	2.11 – 4.08	<0.0001	18.90	13.12 – 27.22	<0.0001
North	1.00			2.92	2.07 – 4.14	<0.0001	21.15	14.49 – 30.87	<0.0001
Central East	1.00			3.70	2.21 – 6.18	<0.0001	29.60	17.23 – 50.82	<0.0001
East	1.00			1.51	0.80 – 2.83	0.20	9.45	4.97 – 17.97	<0.0001
Non-AIDS events; p=0.0029 test for interaction									
South	1.00			1.78	1.51 – 2.09	<0.0001	3.20	2.44 – 4.18	<0.0001
West	1.00			1.54	1.33 – 1.78	<0.0001	2.23	1.68 – 3.00	<0.0001

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North	1.00	1.62	1.40 – 1.88	<0.0001	2.34	1.77 – 3.11	<0.0001
Central East	1.00	1.49	1.14 – 1.94	0.003	4.47	3.02 – 6.62	<0.0001
East	1.00	5.64	2.06 – 15.46	0.0008	12.85	4.51 – 36.65	<0.0001

Low-risk : CD4 $\geq$500/mm^3 and viral load < 50 copies/ml. High-risk; CD4 $\leq$ 350/mm^3 and viral load > 10000 copies/ml. Intermediate risk; all other CD4/viral load combinations.

aIRR; adjusted incidence rate ratio. CI; confidence interval. In addition to the primary variables of interest (high, intermediate and low risk of clinical progression, age, European region of care and calendar year of follow-up), models were adjusted for gender, CD4 nadir, HIV exposure group, ethnic origin, prior AIDS and non-AIDS events, and date of enrolment to EuroSIDA as fixed covariates at baseline. Hepatitis B and C status, AIDS events, non-AIDS events, diabetes*, hypertension*, smoking status*, and anaemia* were included as time-updated covariates (*see [21] for definitions). Models were additionally adjusted for non-AIDS events when AIDS was the primary endpoint and AIDS events when non AIDS was the primary endpoint, both as time-updated covariates .

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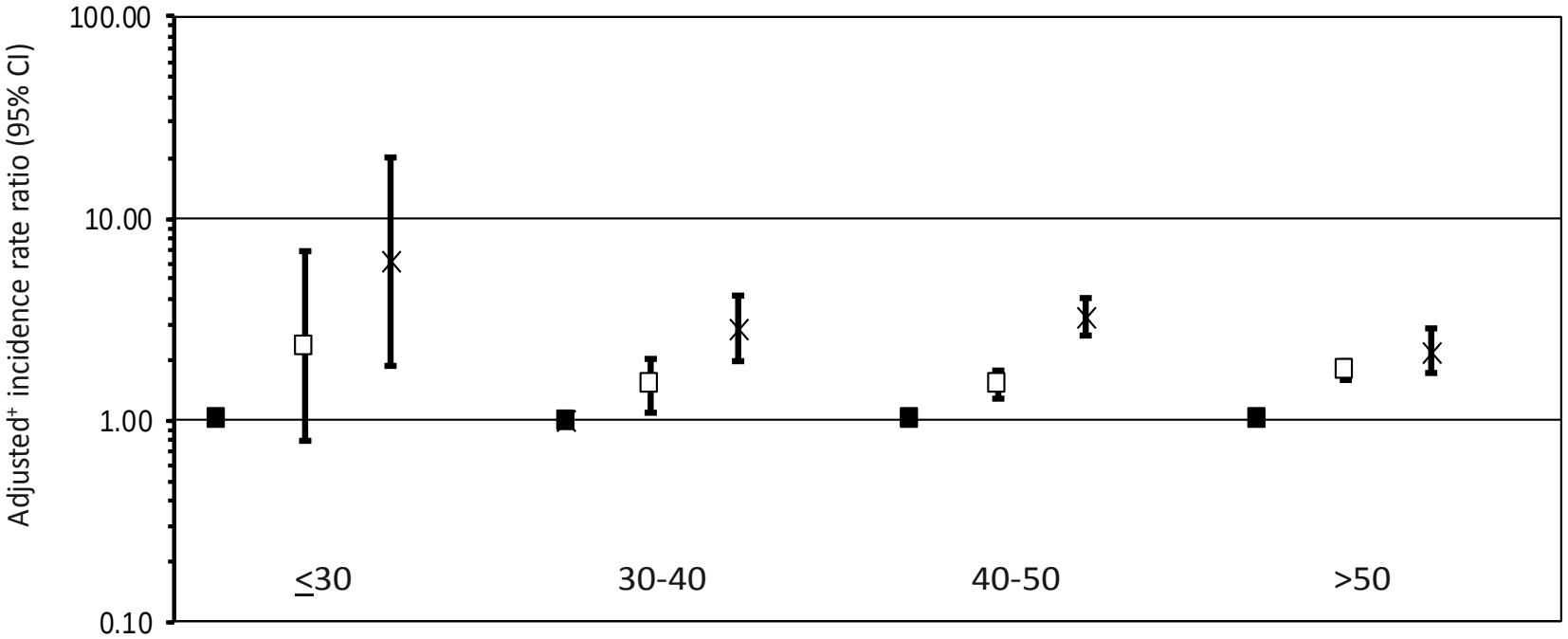
Figure 1a
Relationship between clinical risk strata, age and non-AIDS events



Age group and risk strata : test for interaction *p=0.0004*

In addition to the primary variables of interest (high, intermediate and low risk of clinical progression, age, European region of care and calendar year of follow-up), models were adjusted for gender, CD4 nadir, HIV exposure group, ethnic origin, prior AIDS and non-AIDS events, and date of enrolment to EuroSIDA as fixed covariates at baseline. Hepatitis B and C status, AIDS events, non-AIDS events, diabetes*, hypertension*, smoking status*, and anaemia* were included as time-updated covariates (*see [21] for definitions). Models were additionally adjusted for non-AIDS events when AIDS was the primary endpoint and AIDS events when non AIDS was the primary endpoint, both as time-updated covariates .

Low risk ■	Medium risk □	High risk X
CD4 ≥ 500 and VL < 50	***Any other CD4 / VL***	***CD4 ≤ 350 and VL > 10,000***

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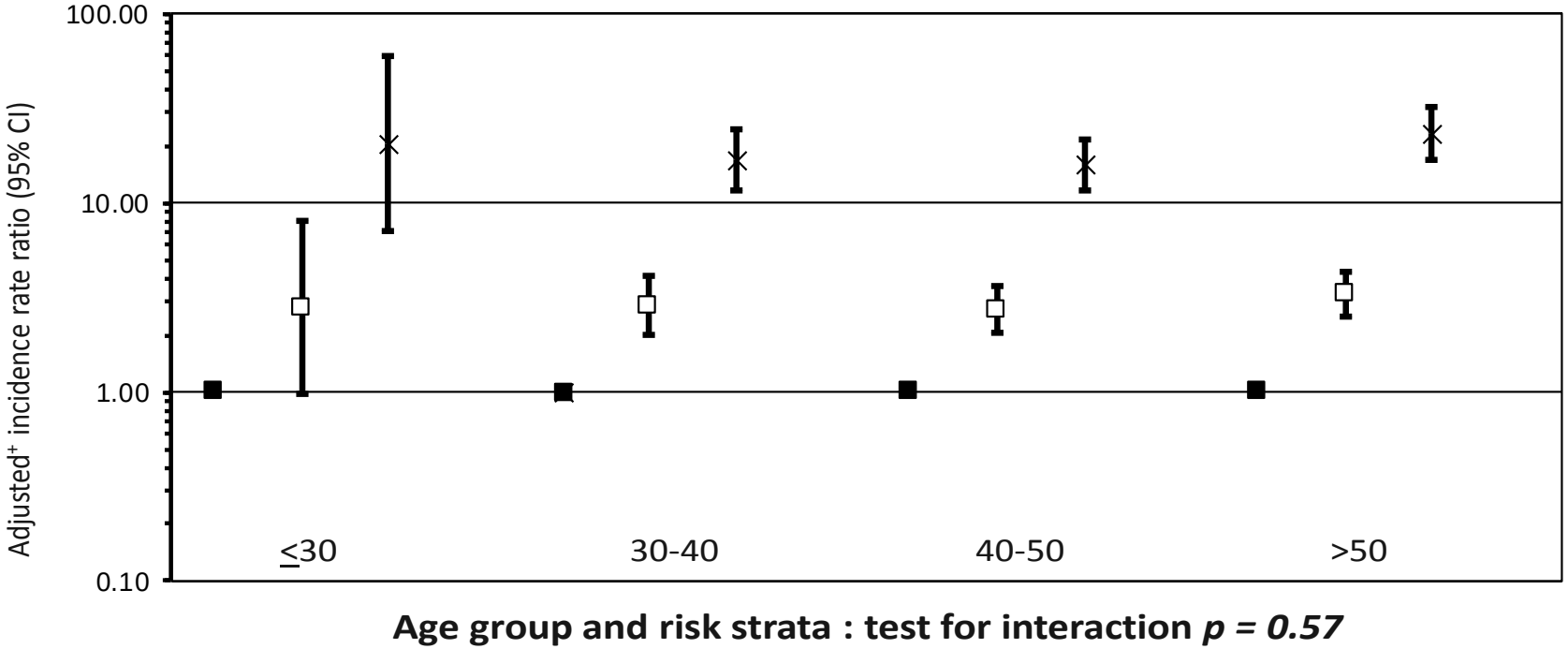
Figure 1b
Relationship between clinical risk strata, age and AIDS events



Age group and risk strata : test for interaction *p = 0.57*

In addition to the primary variables of interest (high, intermediate and low risk of clinical progression, age, European region of care and calendar year of follow-up), models were adjusted for gender, CD4 nadir, HIV exposure group, ethnic origin, prior AIDS and non-AIDS events, and date of enrolment to EuroSIDA as fixed covariates at baseline. Hepatitis B and C status, AIDS events, non-AIDS events, diabetes*, hypertension*, smoking status*, and anaemia* were included as time-updated covariates (*see [21] for definitions). Models were additionally adjusted for non-AIDS events when AIDS was the primary endpoint and AIDS events when non AIDS was the primary endpoint, both as time-updated covariates .

Low risk ■	Medium risk □	High risk X
CD4 ≥ 500 and VL < 50	*Any other CD4 / VL*	*CD4 ≤ 350 and VL > 10,000*

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Figure 2a
Relationship between clinical risk strata, calendar year of follow-up and non-AIDS events

Calendar year of follow-up and risk strata : test for interaction *p=0.0001*

In addition to the primary variables of interest (high, intermediate and low risk of clinical progression, age, European region of care and calendar year of follow-up), models were adjusted for gender, CD4 nadir, HIV exposure group, ethnic origin, prior AIDS and non-AIDS events, and date of enrolment to EuroSIDA as fixed covariates at baseline. Hepatitis B and C status, AIDS events, non-AIDS events, diabetes*, hypertension*, smoking status*, and anaemia* were included as time-updated covariates (*see [21] for definitions). Models were additionally adjusted for non-AIDS events when AIDS was the primary endpoint and AIDS events when non AIDS was the primary endpoint, both as time-updated covariates .

Low risk ■	Medium risk □	High risk X
CD4 ≥ 500 and VL < 50	***Any other CD4 / VL***	***CD4 ≤ 350 and VL > 10,000***

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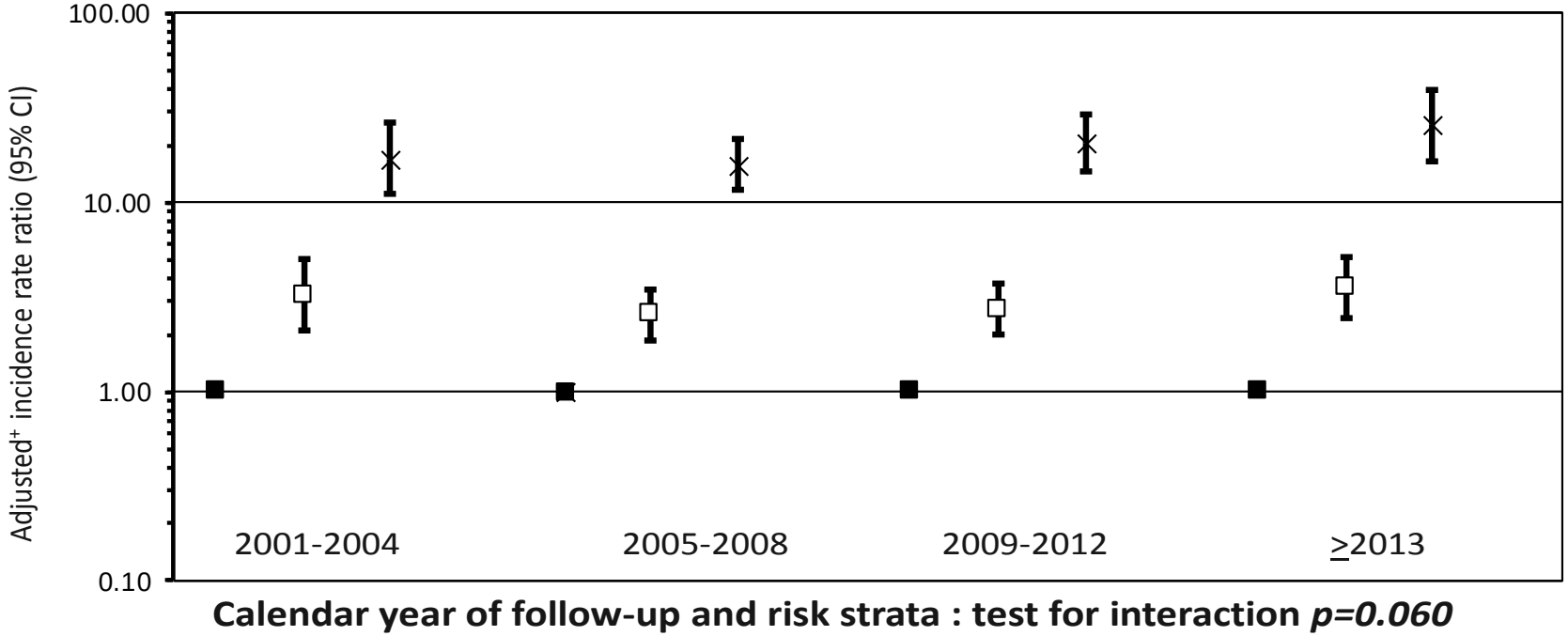
Figure 2b
Relationship between clinical risk strata, calendar year of follow-up and AIDS events



Calendar year of follow-up and risk strata : test for interaction *p=0.060*

In addition to the primary variables of interest (high, intermediate and low risk of clinical progression, age, European region of care and calendar year of follow-up), models were adjusted for gender, CD4 nadir, HIV exposure group, ethnic origin, prior AIDS and non-AIDS events, and date of enrolment to EuroSIDA as fixed covariates at baseline. Hepatitis B and C status, AIDS events, non-AIDS events, diabetes*, hypertension*, smoking status*, and anaemia* were included as time-updated covariates (*see [21] for definitions). Models were additionally adjusted for non-AIDS events when AIDS was the primary endpoint and AIDS events when non AIDS was the primary endpoint, both as time-updated covariates .

Low risk ■	Medium risk □	High risk X
CD4 ≥ 500 and VL < 50	*Any other CD4 / VL*	*CD4 ≤ 350 and VL > 10,000*

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