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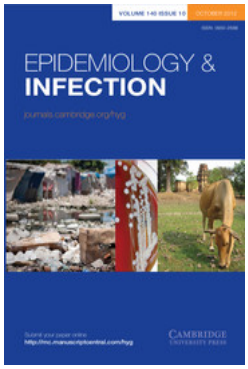

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Regional and temporal changes in AIDS in Europe before HAART

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SUMMARY

In a prospective observational study 4485 patients from 46 clinical centres in 17 European countries were followed between April 1994 and November 1996. Information on AIDS-defining events (ADEs) were collected together with basic demographic data, treatment history and laboratory results. The centres were divided into four geographical regions (north, central, south-west and south-east) so that it was possible to identify any existing regional differences in ADEs. The regional differences that we observed included a higher risk of all forms of *Mycobacterium tuberculosis* infections (Tb) and wasting disease in the south-west and an increased risk of infections with the *Mycobacterium avium* complex (MAC) in the north. In Cox multivariable analyses, where north was used as the reference group, we observed hazard ratios of 6·87, 7·77, 2·29 and 0·16 ($P<0·05$ in all cases) for pulmonary Tb, extrapulmonary Tb, wasting disease and MAC respectively in the south-west. *Pneumocystis carinii pneumonia* (PCP) was less commonly diagnosed in the central region (RH = 0·51, 95% CI 0·32–0·79, $P=0·003$) and most common in the south-east (RH = 1·04, 95% CI 0·71–1·51, $P=0·85$). Comparisons with a similar 'AIDS in Europe' study that concentrated on the early phase of the epidemic reveal that most of the regional differences that were observed in the 1980s still persist in the mid-1990s.

INTRODUCTION

It has previously been shown that there is a regional variation in the clinical course of HIV resulting in different AIDS-defining events (ADEs) in different areas. For example, *Penicillum marneffei* is a common opportunistic infection in Thailand [1], cryptococcal meningitis and cryptosporidiosis are more prevalent in parts of Africa [2, 3] and histoplasmosis is dominant in southern USA [4]. Co-infection with Tb is an increasing problem where the micro-organism *Mycobacterium tuberculosis* and HIV are common [5, 6]. Findings of *Mycobacterium avium* complex

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infections have also been shown to vary between different localities [7].

In the paper 'Regional Differences in Presentation of AIDS in Europe' we presented retrospective data on 6578 patients diagnosed with AIDS at 52 clinical centres in 17 European countries who were followed between 1979 and 1989 [8, 9]. Differences in the presentation of AIDS within Europe has also been described elsewhere [10]. In our earlier study [8] we showed some marked differences: *Pneumocystis carinii pneumonia* (PCP) was more common in northern Europe, Kaposi's sarcoma (KS) and toxoplasmosis in central Europe, cytomegalovirus chorioretinitis (CMV retinitis) in south-eastern Europe and extrapulmonary tuberculosis in the south-west. The regional differences that were previously observed still remained present after adjustments for potential confounders such as demography and CD4 count, therefore we attributed these variations to the different degrees of exposure to the respective underlying pathogens.

In the ongoing, prospective 'EuroSIDA' study that was started in 1994, information is likewise collected on clinical events, treatment and laboratory findings. We were interested in seeing if the regional differences that were observed during the early phase of the epidemic are still present 10 years later. In the 1990s the familiarity of diagnosis and treatment of opportunistic infections is expected to have increased. During this time treatment with single or double nucleoside analogues has also become widespread. We limited our analysis to the period before highly active antiretroviral therapy (HAART), as the introduction of HAART was associated with a rapid fall in the disease progression and manifestation of ADEs among western patients with access to treatment [11–13]. For the overwhelming majority of patients in the world, and also for a substantial number of patients in economically less developed regions of Europe, effective anti-retroviral therapy is still not readily available. The natural history of HIV/AIDS as it presented before HAART is therefore still relevant for many patients and physicians.

METHODS

Patients

EuroSIDA is an ongoing prospective, observational study of 8556 patients with HIV in 63 centres across Europe (including Israel). Details of the study design have been published elsewhere [12, 14]. Only the first two cohorts are included in this study. They consist of 4485 patients from 46 centres in 17 countries who were recruited between April 1994 and June 1996. Eligible patients were those over 16 years of age, who attended a pre-booked visit to the outpatient clinic and had a CD4 count of <500 cells/mm^3 within the 4 months preceding recruitment. Consecutive patients from a specified starting date were included until a predefined number of patients had been enrolled in each centre. Baseline information was collected from patient case notes and by patient interview onto a standardized data collection form. Thereafter information on treatment, clinical condition and laboratory markers was collected every 6 months. The revised CDC definition for AIDS from 1993 was used (with the exception of the criteria <200 CD4 cells/mm^3) [15]. Data were checked for logistical errors by the co-ordinating centre, and all major centres were visited to ensure correct patient inclusion and accurate data recording.

Regional demarcation

In order to make regional comparisons within Europe possible, the continent was, like in the previous study [8], arbitrarily divided into four regions. The centres were initially separated into regions using two latitudinal lines. The north consisted of 14 centres throughout Denmark, Ireland, northern Germany, The Netherlands, Sweden, Norway, and the United Kingdom, central contained 12 centres in Austria, Belgium, France, southern Germany, Luxembourg, and Switzerland and the remaining centres were situated in the south. The southern region was further divided by a longitudinal line into south-east (17 centres in Greece, Israel, and Italy) and south-west (5 centres in Portugal and Spain). Published data has shown that Tb infections, in particular, are most common among HIV patients in south-western Europe, suggesting not only a possible north–south, but also an east–west difference in the clinical presentation of AIDS [9, 16]. A similar longitudinal division of the north and central regions was not possible because there was insufficient data from the eastern parts of these regions within the time period chosen.

Analysis of AIDS-defining events

The analysis was performed on the 4485 patients who were recruited between April 1994 and June 1996. The

Table 1. *Demographic details of HIV-positive study patients by region*

	All centres	North	Central	South-east	South-west	*P* value
Number of patients*	4485	1645	1132	1112	596	
Gender, no. female (%)	918 (21)	234 (14)	248 (22)	302 (27)	134 (23)	<0·001
Age (years) (median, IQR)	35 (31–43)	38 (32–45)	36 (32–44)	33 (30–39)	33 (29–39)	<0·001
Transmission category, no. (%)						
Homo/bisexual	2069 (46)	1062 (65)	542 (48)	274 (25)	191 (32)	<0·001
IDU	1208 (27)	251 (15)	219 (19)	487 (44)	251 (42)	
Haemophiliac/blood transfusion	94 (2)	30 (2)	34 (3)	17 (2)	13 (2)	
Heterosexual	931 (21)	251 (15)	267 (24)	289 (26)	124 (21)	
Other/unknown	183 (4)	51 (3)	70 (6)	45 (4)	17 (3)	
Year of being found HIV+ (median, IQR)	1991 (1987–93)	1990 (1986–92)	1991 (1988–93)	1991 (1987–93)	1992 (1989–93)	<0·001
Haemoglobin level (median, IQR)	13·3 (12·0–14·5)	13·2 (12·0–14·5)	13·4 (12·2–14·5)	13·0 (11·7–14·3)	13·3 (11·9–14·4)	<0·001
CD4 cell count (cells/mm^3) (median, IQR)	170 (50–309)	156 (50–288)	170 (52–315)	180 (51–316)	199 (60–340)	<0·001
Race, no. (%)						
White	4161 (93)	1491 (91)	1038 (92)	1049 (95)	583 (98)	<0·001
Asian	39 (1)	24 (1)	10 (1)	5 (0)	0 (0)	
Black	248 (6)	107 (7)	80 (7)	52 (5)	9 (2)	
Unknown	11 (0)	8 (0)	0 (0)	2 (0)	1 (0)	
Weight (kg) (median, IQR)	67 (60–75)	70 (62–78)	67 (59–74)	65 (58–73)	67 (58–75)	<0·001
ART naive, no. (%)	1193 (27)	531 (32)	278 (25)	225 (20)	159 (27)	<0·001
NRTIs previously used, no. (%)						
0	1197 (27)	533 (32)	280 (25)	225 (20)	159 (27)	<0·001
1	1608 (36)	596 (36)	315 (28)	498 (45)	199 (33)	
2	1338 (30)	412 (25)	380 (34)	345 (31)	201 (34)	
3	286 (6)	86 (5)	124 (11)	41 (4)	35 (6)	
⩾4	56 (1)	18 (1)	33 (3)	3 (0)	2 (0)	
Previous use of PIs						
No. Yes (%)	48 (1)	37 (2)	7 (1)	1 (0)	3 (0)	<0·001
Previous use of MAC prophylactic						
No. Yes (%)	235 (5)	105 (6)	40 (3)	61 (5)	29 (5)	0·01
Previous use of PCP prophylactics						
No. Yes (%)	2349 (52)	897 (55)	572 (51)	532 (48)	348 (58)	<0·001

* ART, anti-retroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; MAC, *Mycobacterium avium* complex; PCP, *Pneumocystis carinii pneumonia*.

baseline demographic data within each region was examined, where baseline was considered to be the time of entry into the study. Kruskal–Wallis tests were used to compare regional differences for continuous variables and, depending on the number of observations, χ^2 or Fisher's exact tests were used to test frequencies.

The distribution of ADEs experienced before enrolment was examined and is presented as a percentage of all the patients in the region. A patient was included in several categories if they experienced more than one ADE before entry. Frequencies were again tested for differences using χ^2 or Fisher's exact tests.

Prospective analysis was performed on all the 4485 subjects included in this study. All follow-up information was censored at 1 November 1996, the date that we assumed HAART had already become widely used. If HAART, defined as usage of at least three anti-retroviral drugs, was introduced earlier than November 1996 then data on these patients was censored at the date of starting HAART. The initial ADE that occurred after inclusion and before November 1996 was investigated using χ^2 or Fisher's exact tests. A patient was only included in more than one category if he or she experienced several ADEs simultaneously. The 16 conditions with $\geqslant 35$ patients suffering from them initially was examined and the number of subjects who experienced each ADE as their first ADE after inclusion is noted and presented as a percentage of all the subjects in that region. For most ADEs EuroSIDA did not collect information on recurring conditions or relapses within the period 1994–6 so only new ADEs were investigated.

We investigated the incidence rates of each ADE after enrolment. Since we had no information on recurring conditions or relapses, all study subjects who had previously experienced an ADE were excluded from the incidence analysis for that specific ADE. The incidence analysis compared rates of new ADEs in subjects with a high CD4 count to subjects with a low CD4 count. The CD4 count is taken as low the first time that it is <200 cells/mm^3 (not excluding times when CD4 returned $\geqslant 200$ cells/mm^3) therefore subjects were included in the high CD4 count risk set up to this point. The follow-up time for patients with a high CD4 count at entry was considered to be time from enrolment until the ADE, death, a drop in the CD4 count to below 200 or 1 November 1996 (date of censoring). Similarly, the follow-up time for patients with a low CD4 count was considered to be the time from enrolment or a drop in the CD4 count until the ADE, death or 1 November 1996. If more than one region had observations in the low and the high CD4 count strata the rate ratios for these regions were compared using a Mantel–Haenszel heterogeneity test. Mantel–Haenszel methods were again used to calculate an overall rate ratio controlling for region to see whether the overall rates of ADEs in subjects with a low CD4 count were significantly different to subjects with a high CD4 count. Incidence rates are presented as 100 person-years of follow up (PYFU).

Regional differences in the incidences of the 16 ADEs with $\geqslant 35$ initial diagnoses after enrolment were analysed using Cox proportional hazard models. The time parameter was considered to be time from enrolment until the ADE, death or 1 November 1996, independent to the CD4 status. The Cox models investigated all subjects who experienced a specific ADE at any time point in the study, not only focusing on the initial ADE. Cox single variable models were performed on region, baseline haemoglobin level, transmission category, gender, age, baseline weight, race, anti-retroviral naivety at baseline, prophylactic drug use against MAC (clarithromycin, ethambutol and rifabutin) and PCP (atovaquone, trimethoprim/sulphamethoxazole, dapsone and pentamidine), cohort, date of being found HIV-infected and baseline CD4 status (high or low) for each of the ADEs. All the variables that were significant/marginally significant ($P<0{\cdot}1$) in the single variable analysis were included in the multivariable models. Variables with an adjusted hazard ratio that was significant at the 5% level ($P<0{\cdot}05$) were retained in the final model. Our aim was to investigate regional variations therefore region was retained in all the multivariable models, irrespective of its significance.

RESULTS

Table 1 shows the demographic characteristics of the HIV-positive patients included in our study for each region. Transmission through homosexual contact was more apparent in northern Europe whilst intravenous drug use was the most common mode of transmission in southern Europe. There was a greater proportion of homosexual men in northern Europe and consequently a higher overall percentage of males. Patients in northern Europe were older at recruitment and

they had been known to be HIV positive for a longer time. They had also developed a more profound immunodeficiency (lower CD4 cell count) at the time of recruitment compared especially to patients in the south-west. The proportion who had had previous treatment with nucleoside analogues varied from 80% in the south-east to 68% in the north. Only 48 patients (1%) had previously been exposed to protease inhibitors. Prophylactic drug use against PCP was common throughout Europe: 52% of the patients had used either dapsone, trimethoprim/sulphamethoxazole, atovaquone or pentamidine before entry whereas prophylactic drug use against MAC was less frequent. Only 5% of the patients had used one or more of rifabutin, clarithromycin or ethambutol before entering the study. Both MAC and PCP prophylaxis showed significant regional variations throughout Europe ($P=0{\cdot}01$ and $P<0{\cdot}001$, respectively).

Table 2 presents data on the frequency of ADEs before entering the study. Only conditions containing a total of 40 or more cases are presented. Significant regional differences were found for 8 of the 17 most common conditions. In the northern and central regions KS was more common than in other regions. In the northern region PCP was the dominating AIDS-defining condition whilst this was relatively uncommon in the south-west. Tb was most common in the south-west region while MAC was more common in the north and central regions. None of the less common ADEs reached any statistically significant differences except candida pneumonia where 10 of 11 registered cases originated from the south-east ($P<0{\cdot}001$).

Table 2 also shows the first ADE presenting after inclusion into the study. Only the 16 conditions with at least 35 events are shown. *Mycobacterium tuberculosis* and wasting disease were most prevalent in the south-west, KS was most commonly found in the central and northern regions whilst PCP was most widespread in the north and south-east. After oesophageal candidiasis, the second most frequently diagnosed disease in the north was MAC whereas in the south-east it was AIDS dementia complex. The north contained 75 initial cases of MAC, corresponding to 13·4% of all the patients in the north who experienced an ADE after inclusion. This is significantly more than in any other region of Europe. In the south-east nearly double the proportion of subjects had AIDS dementia complex as their first ADE compared to those in the north. Among the ADEs with fewer events only cryptococcal meningitis showed a regional tendency. Of 26 cases in total 13 were found in the south-east (P value $=0{\cdot}03$).

Incidence data for the major ADEs in Table 3 show some differences between the regions. Most striking is the high incidence of Tb in the south-west where subjects with a CD4 count <200 cells/mm^3 had an incidence of 3·5 per 100 PYFU and subjects with a CD4 count $\geqslant 200$ had an incidence of 2·4/100 PYFU. There was a noticeably higher incidence of AIDS dementia complex in the south-east compared to other regions where subjects with a CD4 count <200 cells/mm^3 were most at risk. These subjects had an incidence of 4·1/100 PYFU whereas the subjects with higher CD4 counts had an incidence of 0·9/100 PYFU. Subjects from southern Europe were also marginally ($P=0{\cdot}075$) more at risk from wasting than patients from either northern or central Europe. The overall rates of wasting for patients from the south-east and south-west were 3·0 and 3·6 per 100 PYFU, respectively, whereas in the north and central regions these rates were only 2·1 and 1·5 per 100 PYFU, respectively. The combined rate ratios showed significantly different rates of disease between patients with high and low CD4 counts for most of the major ADEs, the main exceptions were recurrent bacterial pneumonia in addition to pulmonary and extrapulmonary Tb.

Cox analysis was performed on the ADEs that occurred during follow up (Table 4). AIDS dementia complex, recurrent bacterial pneumonia, wasting disease, MAC, Tb (both pulmonary and extrapulmonary), PCP and KS were all shown to vary between regions in the single variable analysis. After adjustments were made for confounding factors that were significant at the 5% level most of the regional variations still remained. Region was, however, no longer a significant predictor of the hazard of developing KS.

DISCUSSION

The data that we have presented shows evident differences in ADEs within different regions of Europe in the mid-1990s. Tb continues to be a problem in the south-west and MAC in the north. The epidemiology of these particular pathogens have been described in more detail elsewhere [17].

Before inclusion to the study Pulmonary Tb was diagnosed in 11·9% (32·6% of all patients with an ADE) and extrapulmonary Tb infections in 8·2%

Table 2. *Distributions of diagnosis of ADEs before enrolment and of primary diagnoses of ADEs after enrolment*

AIDS-defining conditions*	Before enrolment						Primary diagnoses after enrolment					
	All centres	North	Central	South-east	South-west	*P* value	All centres	North	Central	South-east	South-west	*P* value
Number of patients	4485	1645	1132	1112	596		4485	1645	1132	1112	596	
AIDS dementia complex	65 (1·4)	29 (1·8)	15 (1·3)	13 (1·2)	8 (1·3)	0·59	102 (2·3)	35 (2·1)	18 (1·6)	44 (4·0)	5 (0·8)	<0·001
Recurrent bacterial pneumonia	53 (1·2)	19 (1·2)	14 (1·2)	12 (1·1)	8 (1·3)	0·97	62 (1·4)	26 (1·6)	16 (1·4)	18 (1·6)	2 (0·3)	0·20
Oesophageal candidiasis	365 (8·1)	148 (9·0)	87 (7·7)	77 (6·9)	53 (8·9)	0·21	210 (4·7)	92 (5·6)	48 (4·2)	53 (4·8)	17 (2·9)	0·37
Cryptococcal meningitis	46 (1·0)	13 (0·8)	13 (1·1)	12 (1·1)	8 (1·3)	0·64	—	—	—	—	—	—
Cryptosporidosis	70 (1·6)	25 (1·5)	16 (1·4)	21 (1·9)	8 (1·3)	0·77	40 (0·9)	16 (1·0)	8 (0·7)	14 (1·3)	2 (0·3)	0·34
CMV retinitis	141 (3·1)	57 (3·5)	27 (2·4)	42 (3·8)	15 (2·5)	0·18	119 (2·7)	45 (2·7)	32 (2·8)	28 (2·5)	14 (2·3)	0·69
CMV in another location	43 (1·0)	24 (1·5)	7 (0·6)	6 (0·5)	6 (1·0)	0·05	84 (1·9)	32 (1·9)	20 (1·8)	22 (2·0)	10 (1·7)	0·96
HSV ulcers	78 (1·7)	41 (2·5)	15 (1·3)	14 (1·3)	8 (1·3)	0·03	64 (1·4)	22 (1·3)	20 (1·8)	17 (1·5)	5 (0·8)	0·28
HIV wasting syndrome	85 (1·9)	28 (1·7)	27 (2·4)	21 (1·9)	9 (1·5)	0·52	106 (2·4)	37 (2·2)	18 (1·6)	28 (2·5)	23 (3·9)	0·005
Microsporidosis with wasting	49 (1·1)	28 (1·7)	18 (1·6)	2 (0·2)	1 (0·2)	<0·001	—	—	—	—	—	—
Mycobact. avium complex	124 (2·8)	72 (4·4)	27 (2·4)	20 (1·8)	5 (0·8)	<0·001	111 (2·5)	75 (4·6)	20 (1·8)	11 (1·0)	5 (0·8)	<0·001
Mycobact. tuberculosis	164 (3·7)	25 (1·5)	33 (2·9)	35 (3·1)	71 (11·9)	<0·001	44 (1·0)	6 (0·4)	8 (0·7)	10 (0·9)	20 (3·4)	<0·001
EPMT	111 (2·5)	16 (1·0)	25 (2·2)	21 (1·9)	49 (8·2)	<0·001	42 (0·9)	9 (0·5)	3 (0·3)	6 (0·5)	24 (4·0)	<0·001
PCP	506 (11·3)	235 (14·3)	108 (9·5)	114 (10·3)	49 (8·2)	<0·001	142 (3·2)	69 (4·2)	19 (1·7)	39 (3·5)	15 (2·5)	0·032
PML	—	—	—	—	—	—	39 (0·9)	13 (0·8)	14 (1·2)	10 (0·9)	2 (0·3)	0·16
Cerebral toxoplasmosis	120 (2·7)	48 (2·9)	35 (3·1)	25 (2·2)	12 (2·0)	0·41	67 (1·5)	24 (1·5)	20 (1·8)	16 (1·4)	7 (1·2)	0·53
Kaposi's sarcoma	334 (7·4)	170 (10·3)	93 (8·2)	45 (4·0)	26 (4·4)	<0·001	114 (2·5)	57 (3·5)	36 (3·2)	13 (1·2)	8 (1·3)	<0·001
Non-Hodgkin lymphoma	40 (0·9)	13 (0·8)	15 (1·3)	5 (0·4)	7 (1·2)	0·13	67 (1·5)	28 (1·7)	17 (1·5)	13 (1·2)	9 (1·5)	0·72
Other ADE	80 (1·8)	20 (1·2)	19 (1·7)	28 (2·5)	13 (2·2)	0·07	75 (1·7)	17 (1·0)	12 (1·1)	32 (2·9)	14 (2·3)	<0·001
No ADE	2970 (66·2)	1039 (63·2)	773 (68·3)	780 (70·1)	378 (63·4)	<0·001	3121 (69·6)	1087 (66·1)	824 (72·8)	772 (69·4)	438 (73·5)	<0·001

Percentage of subjects with each ADE is given in parentheses.

* ADE, AIDS-defining event; CMV, cytomegalovirus chorioretinitis; HSV, herpes simplex virus; EPMT, extrapulmonary *Mycobacterium tuberculosis*; PCP, *Pneumocystis carinii pneumonia*; PML, progressive multifocal leucoencephalopathy.

Table 3. *Incidence rates of specific ADEs in relation to the CD4 count and region*

AIDS-defining conditions	No. patients	All centres	North	Central	South-east	South-west	*P* value (regional differences)
AIDS dementia complex							
⩾200	7	0·9 (0·4–1·8)	0·3 (0·0–2·1)	1·8 (0·6–5·7)	0·9 (0·2–3·7)	1·1 (0·2–8·1)	
<200	150	2·4 (2·0–2·8)	2·6 (2·0–3·3)	1·3 (0·8–1·9)	4·1 (3·2–5·3)	1·0 (0·5–1·9)	
Overall	157	2·2 (1·9–2·6)	2·3 (1·8–3·0)	1·3 (0·9–2·0)	3·7 (2·9–4·7)	1·0 (0·5–1·9)	0·022
Recurrent bacterial pneumonia							
⩾200	8	1·0 (0·5–2·0)	1·2 (0·4–3·1)	0·6 (0·1–4·3)	1·4 (0·4–4·3)	—	
<200	74	1·2 (0·9–1·5)	1·5 (1·1–2·1)	1·0 (0·6–1·5)	1·4 (1·0–2·2)	0·2 (0·1–1·0)	
Overall	82	1·2 (0·9–1·4)	1·5 (1·1–2·0)	0·9 (0·6–1·5)	1·4 (1·0–2·1)	0·2 (0·1–0·9)	0·96
Cryptosporidiosis							
⩾200	1	0·1 (0·0–0·9)	—	—	0·5 (0·1–3·3)	—	
<200	59	0·9 (0·7–1·2)	0·8 (0·5–1·3)	0·8 (0·5–1·4)	1·3 (0·9–2·1)	0·7 (0·3–1·6)	
Overall	60	0·8 (0·7–1·1)	0·7 (0·5–1·2)	0·7 (0·4–1·3)	1·2 (0·8–1·9)	0·6 (0·3–1·4)	0·65
CMV							
⩾200	1	0·1 (0·0–0·9)	0·3 (0·0–2·1)	—	—	—	
<200	239	3·9 (3·4–4·4)	4·6 (3·7–5·5)	3·3 (2·5–4·3)	3·9 (3·0–5·1)	3·3 (2·3–4·8)	
Overall	240	3·4 (3·0–3·9)	4·0 (3·3–4·8)	3·0 (2·3–3·9)	3·4 (2·6–4·4)	3·0 (2·0–4·3)	0·78
CMV in another location							
⩾200	2	0·2 (0·1–1·0)	0·3 (0·0–2·1)	—	0·5 (0·1–3·3)	—	
<200	154	2·4 (2·1–2·8)	2·7 (2·1–3·4)	2·3 (1·7–3·2)	2·5 (1·8–3·4)	1·9 (1·2–3·1)	
Overall	156	2·2 (1·9–2·6)	2·4 (1·8–3·0)	2·1 (1·6–2·9)	2·2 (1·6–3·1)	1·7 (1·1–2·8)	0·81
HIV wasting syndrome							
⩾200	4	0·5 (0·2–1·3)	—	1·2 (0·3–4·8)	0·9 (0·2–3·7)	—	
<200	162	2·6 (2·2–3·0)	2·4 (1·8–3·1)	1·5 (1·0–2·2)	3·3 (2·5–4·4)	4·0 (2·8–5·6)	
Overall	166	2·3 (2·0–2·7)	2·1 (1·6–2·7)	1·5 (1·0–2·2)	3·0 (2·3–3·9)	3·6 (2·6–5·1)	0·075
Mycobact. avium complex							
⩾200	2	0·2 (0·1–1·0)	0·3 (0·0–2·1)	0·6 (0·1–4·3)	—	—	
<200	191	3·1 (2·7–3·5)	5·0 (4·2–6·1)	2·7 (2·1–3·7)	1·8 (1·2–2·6)	1·1 (0·6–2·1)	
Overall	193	2·8 (2·4–3·2)	4·4 (3·6–5·3)	2·5 (1·9–3·4)	1·6 (1·1–2·3)	1·0 (0·5–1·9)	0·65
Mycobacterium tuberculosis							
⩾200	8	1·0 (0·5–2·0)	0·6 (0·1–2·4)	2·4 (0·9–6·3)	—	2·4 (0·6–9·5)	
<200	56	0·9 (0·7–1·2)	0·4 (0·2–0·8)	0·4 (0·2–0·8)	0·9 (0·6–1·6)	3·5 (2·4–5·1)	
Overall	64	0·9 (0·7–1·2)	0·5 (0·3–0·8)	0·5 (0·3–1·0)	0·8 (0·5–1·4)	3·4 (2·3–4·9)	0·006
Extrapulm. *Mycobact. tuberculosis*							
⩾200	5	0·6 (0·3–1·5)	0·3 (0·0–2·1)	—	0·5 (0·1–3·3)	3·5 (1·1–10·8)	
<200	48	0·8 (0·6–1·0)	0·5 (0·3–0·9)	0·2 (0·1–0·6)	0·4 (0·2–0·9)	3·3 (2·3–4·9)	
Overall	53	0·7 (0·6–1·0)	0·5 (0·3–0·9)	0·2 (0·1–0·6)	0·4 (0·2–0·8)	3·4 (2·3–4·8)	0·88
PCP							
⩾200	7	0·9 (0·4–1·9)	0·9 (0·3–2·8)	0·6 (0·1–4·4)	0·9 (0·2–3·8)	1·2 (0·2–8·3)	
<200	181	3·1 (2·7–3·6)	4·1 (3·3–5·1)	1·7 (1·2–2·5)	3·9 (3·0–5·1)	2·4 (1·5–3·8)	
Overall	188	2·9 (2·5–3·3)	3·6 (2·9–4·5)	1·6 (1·1–2·3)	3·5 (2·7–4·5)	2·3 (1·5–3·5)	0·90
PML							
⩾200	0	—	—	—	—	—	
<200	58	0·9 (0·7–1·2)	1·0 (0·7–1·6)	1·0 (0·7–1·6)	0·8 (0·4–1·4)	0·5 (0·2–1·3)	
Overall	58	0·8 (0·6–1·0)	0·9 (0·6–1·4)	0·9 (0·6–1·5)	0·7 (0·4–1·2)	0·4 (0·2–1·1)	—
Cerebral toxoplasmosis							
⩾200	1	0·1 (0·0–0·9)	—	—	0·5 (0·1–3·3)	—	
<200	108	1·7 (1·4–2·1)	1·8 (1·4–2·5)	1·7 (1·2–2·5)	1·7 (1·2–2·5)	1·4 (0·8–2·5)	
Overall	109	1·5 (1·3–1·9)	1·6 (1·2–2·2)	1·6 (1·1–2·3)	1·6 (1·1–2·3)	1·3 (0·7–2·3)	0·44
Kaposi's sarcoma							
⩾200	7	0·9 (0·4–1·8)	1·5 (0·6–3·6)	0·6 (0·1–4·3)	0·5 (0·1–3·3)	—	
<200	140	2·4 (2·0–2·8)	3·5 (2·7–4·4)	3·0 (2·2–4·0)	0·8 (0·5–1·4)	1·4 (0·8–2·5)	
Overall	147	2·2 (1·9–2·6)	3·2 (2·5–4·0)	2·8 (2·1–3·7)	0·8 (0·4–1·3)	1·2 (0·7–2·2)	0·77
Non-Hodgkin lymphoma							
⩾200	5	0·6 (0·3–1·5)	0·3 (0·0–2·1)	0·6 (0·1–4·4)	1·4 (0·4–4·2)	—	
<200	110	1·7 (1·4–2·1)	2·3 (1·8–3·1)	1·3 (0·9–2·0)	1·4 (0·9–2·2)	1·4 (0·8–2·5)	
Overall	115	1·6 (1·3–1·9)	2·1 (1·6–2·7)	1·3 (0·9–1·9)	1·4 (1·0–2·1)	1·3 (0·7–2·3)	0·21

Significantly different incidence rate between patients with a high CD4 count and a low CD4 count were seen. $P<0{\cdot}01$ in all cases except recurrent bacterial pneumonia ($P=0{\cdot}527$), cryptosporidiosis ($P=0{\cdot}017$), *Mycobacterium tuberculosis* ($P=0{\cdot}71$), extrapulmonary *Mycobacterium tuberculosis* ($P=0{\cdot}72$) and non-Hodgkin lymphoma ($P=0{\cdot}015$).

Table 4. *Risk of developing respective condition as first ADE during follow-up in each region*

	Single variable analysis			Multivariable analysis*		
	Hazard ratio	95% confidence interval	*P* value	Hazard ratio	95% confidence interval	*P* value
AIDS dementia complex			<0·001			0·002
North	1·00	—	—	1·00	—	—
Central	0·59	0·37–0·95	0·03	0·69	0·42–1·14	0·15
South-east	1·64	1·15–2·34	0·01	1·44	0·94–2·21	0·10
South-west	0·43	0·21–0·86	0·02	0·37	0·13–1·03	0·06
Recurrent bacterial pneumonia			<0·001			0·01
North	1·00	—	—	1·00	—	—
Central	0·63	0·36–1·12	0·12	0·67	0·36–1·23	0·20
South-east	1·00	0·60–1·65	0·99	0·70	0·38–1·28	0·25
South-west	0·15	0·04–0·61	0·01	0·16	0·04–0·68	0·01
Oesophageal candidiasis			0·12			0·45
North	1·00	—	—	1·00	—	—
Central	0·80	0·59–1·07	0·13	0·81	0·60–1·11	0·20
South-east	0·82	0·61–1·11	0·20	0·82	0·59–1·14	0·24
South-west	0·65	0·43–0·97	0·04	0·79	0·52–1·22	0·29
Cryptosporoidosis			0·29			0·008
North	1·00	—	—	1·00	—	—
Central	1·06	0·53–2·12	0·87	1·34	0·67–2·70	0·41
South-east	1·71	0·92–3·18	0·09	3·20	1·65–6·23	<0·001
South-west	0·89	0·36–2·24	0·81	1·43	0·56–3·62	0·45
CMV chorioretinitis			0·35			0·26
North	1·00	—	—	1·00	—	—
Central	0·77	0·55–1·07	0·12	0·74	0·51–1·07	0·11
South-east	0·87	0·63–1·21	0·41	1·11	0·75–1·63	0·61
South-west	0·75	0·49–1·15	0·19	0·95	0·58–1·54	0·83
CMV in another location			0·71			0·71
North	1·00	—	—	1·00	—	—
Central	0·91	0·61–1·36	0·65	1·16	0·75–1·80	0·50
South-east	0·96	0·64–1·43	0·84	1·33	0·82–2·16	0·24
South-west	0·73	0·42–1·27	0·27	1·14	0·64–2·03	0·65
Herpes simplex virus ulcers			0·05			0·06
North	1·00	—	—	1·00	—	—
Central	1·51	0·91–2·51	0·11	1·63	0·97–2·74	0·06
South-east	0·99	0·55–1·76	0·96	1·07	0·59–1·95	0·82
South-west	0·48	0·18–1·23	0·13	0·56	0·21–1·45	0·23
Wasting disease			<0·001			<0·001
North	1·00	—	—	1·00	—	—
Central	0·74	0·47–1·17	0·20	0·63	0·37–1·08	0·09
South-east	1·48	1·01–2·18	0·04	1·50	0·94–2·39	0·09
South-west	1·76	1·14–2·72	0·01	2·29	1·33–3·95	0·003
Mycobacterium avium complex			<0·001			<0·001
North	1·00	—	—	1·00	—	—
Central	0·59	0·42–0·83	<0·001	0·57	0·39–0·83	<0·001
South-east	0·36	0·24–0·55	<0·001	0·41	0·25–0·68	<0·001
South-west	0·22	0·11–0·44	<0·001	0·16	0·05–0·52	<0·001
Pulmonary tuberculosis			<0·001			<0·001
North	1·00	—	—	1·00	—	—
Central	1·19	0·51–2·76	0·68	0·92	0·38–2·25	0·86
South-east	1·78	0·83–3·86	0·14	1·62	0·74–3·58	0·23
South-west	7·41	3·76–14·56	<0·001	6·87	3·46–13·63	<0·001

Table 4 (*cont.*)

	Single variable analysis			Multivariable analysis*		
	Hazard ratio	95% confidence interval	*P* value	Hazard ratio	95% confidence interval	*P* value
Extrapulmonary tuberculosis			<0·001			<0·001
North	1·00	—	—	1·00	—	—
Central	0·45	0·15–1·38	0·16	0·37	0·10–1·33	0·13
South-east	0·83	0·33–2·08	0·69	0·62	0·22–1·80	0·38
South-west	6·74	3·50–12·96	<0·001	7·77	3·84–15·73	<0·001
PCP			<0·001			0·005
North	1·00	—	—	1·00	—	—
Central	0·45	0·29–0·69	<0·001	0·51	0·32–0·79	0·003
South-east	0·98	0·70–1·38	0·91	1·04	0·71–1·51	0·85
South-west	0·63	0·39–1·03	0·07	0·69	0·41–1·16	0·16
PML			0·36			0·19
North	1·00	—	—	1·00	—	—
Central	1·04	0·56–1·91	0·91	1·28	0·67–2·45	0·45
South-east	0·75	0·37–1·50	0·41	0·80	0·37–1·72	0·57
South-west	0·46	0·16–1·33	0·15	0·41	0·12–1·38	0·15
Cerebral toxoplasmosis			0·94			0·88
North	1·00	—	—	1·00	—	—
Central	1·00	0·62–1·61	1·00	1·02	0·61–1·70	0·94
South-east	0·99	0·61–1·62	0·98	0·91	0·52–1·59	0·74
South-west	0·83	0·43–1·57	0·56	0·77	0·37–1·60	0·48
Kaposi's sarcoma			<0·001			0·12
North	1·00	—	—	1·00	—	—
Central	0·88	0·61–1·27	0·50	1·11	0·75–1·65	0·60
South-east	0·24	0·13–0·44	<0·001	0·55	0·29–1·05	0·07
South-west	0·39	0·20–0·73	<0·001	0·72	0·37–1·42	0·34
Non-Hodgkin lymphoma			0·15			0·68
North	1·00	—	—	1·00	—	—
Central	0·63	0·39–1·01	0·06	0·67	0·39–1·15	0·15
South-east	0·70	0·43–1·11	0·13	0·84	0·47–1·51	0·56
South-west	0·62	0·33–1·16	0·13	0·92	0·48–1·77	0·80

* CMV, cytomegalovirus; PCP, *Pneumocystis carinii pneumonia*; PML, progressive multifocal leucoencephalopathy.

(22·5% of all patients with an ADE) of the patients in the south-west. Furthermore, during follow-up pulmonary and extrapulmonary Tb infections were, together with wasting disease, the dominating ADEs in this region (in the south-west 12·7 and 15·2% of the initial ADEs after inclusion were due to pulmonary Tb and extrapulmonary Tb, respectively). It is possible that among the patients with wasting disease there may also be cases of undiagnosed Tb. In the previous AIDS in Europe study [18] extrapulmonary Tb accounted for over 35% of the AIDS cases in the south-west [8] in addition more pronounced regional differences were seen. Only extrapulmonary Tb was regarded as an ADE at the time, which makes comparisons with the present study difficult. It seems, however that Tb accounted for a larger proportion of ADEs at that time. A fall in Tb has also been noted in other studies [19].

PCP was diagnosed in only 11% of the patients at inclusion to this study. PCP, however, accounts for 33·3% of the 1515 patients who experienced at least one ADE prior to entering the study. More remarkably, among 1364 patients who developed an ADE during follow-up only 10·4% of events are due to PCP. As a comparison PCP accounted for 38·5% of initial diagnosis of AIDS 10 years earlier [8]. This fall can be a consequence of increased use of primary prophylactic antibiotics. There is a regional difference for PCP with fewest cases in the central region. The incidence for PCP here is lower both for patients with

a CD4 count of above and below 200. In the AIDS in Europe study there was also a regional difference in PCP, but in contrast to this present study the north previously had the highest incidence and the south-west had the lowest. Factors behind that finding have been analysed by Lundgren [20]. Further studies are needed to explain this changing pattern.

KS accounted for 21% of AIDS registrations in patients studied in the 1980s. In this study 7·4% of patients had had KS at inclusion (accounting for 22·0% of patients with at least one ADE at inclusion). Only 8·4% of the ADEs that developed during follow up were KS. A fall in PCP and KS during the time period has also been seen among Italian and Australian AIDS patients [21, 22]. KS continues to be more common in northern and central Europe, however in the multivariable analysis other factors than region *per se* are now shown to be of greater importance.

Unlike in the previous study, CMV retinitis, toxoplasmosis and lymphomas did not show any clear regional differences. One explanation could be that diagnostic procedures and therapies have become more uniform within Europe.

When interpreting the data some factors must be kept in mind. The demographic characteristics of the patients studied in the two time periods are different. In the 1980s study the intravenous drug users constituted around 60% of the patients from southern Europe while this percentage has fallen to just over 40% in this study. The selection of patients was also different in the two studies. In the retrospective 'AIDS in Europe' study all the patients had already developed AIDS and some were even deceased at inclusion. In this prospective EuroSIDA study the patients have to present themselves at a pre-booked appointment in order to be recruited. Due to changes in the epidemic the percentage of women in the study has increased from 9 to 21%. Patients in the north continue to be the oldest at time of HIV diagnosis but this difference is less pronounced than 10 years earlier.

Survival in southern Europe was shorter in the patients studied in the 1980s [9], limiting the occurrence of ADEs associated with advanced HIV infection. In this study 83% of the patients had commenced therapy with nucleoside analogues. This treatment can, however only be expected to postpone disease [23–29]. The introduction of HAART changed the distribution of ADEs in Europe [13]. In the present study, however, very few patients had commenced on any protease inhibitor containing therapy due to censoring at initiation of HAART or late 1996.

In summary, major regional differences in the risk of developing important ADEs such as Tb and PCP remain. Minor differences were also seen for AIDS dementia complex and wasting syndrome. These clinically defined conditions were diagnosed at significantly different CD4 levels between regions which may influence the reported incidence. The earlier described regional differences in toxoplasmosis, CMV retinitis, and KS are less evident in this study. The number of events is relatively small which in itself makes it statistically difficult to show differences. If there is a true change this can, for KS, be due to a regionally more similar exposure to underlying co-infections [30–32]. The regional differences reported in this study are likely to reflect true differences in the occurrence of the pathogens, though we cannot definitely exclude the possibility of differences in diagnostic procedures explaining at least part of the regional differences.

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