# Regional differences in presentation of AIDS in Europe

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## SUMMARY

Data were collected on 6578 patients diagnosed with AIDS at 52 clinical centres in 17 European countries during an 11-year period from 1979 to 1989. The centres were divided into four regions, North, Central, Southeast, and Southwest. Differences in the incidence of most AIDS-defining opportunistic infections and malignancies were found. After adjusting for known possible confounders, statistically significant differences between regions remained. *Pneumocystis carinii* pneumonia (PCP) was more common in Northern Europe, Kaposi's sarcoma and toxoplasmosis in Central Europe, cytomegalovirus retinitis in South-eastern Europe, and extrapulmonary tuberculosis in South-western Europe. These differences we attribute primarily to different degrees of exposure to the respective underlying pathogens. The prevalence of these and other micro-organisms will determine the clinical course of HIV infections in parts of Eastern Europe and elsewhere where the virus now is spreading.

## INTRODUCTION

The damage caused by the human immunodeficiency virus (HIV) gives varied clinical presentations in different individuals. Properties of the virus [1] as well as the immune system response [2] may influence the course of HIV infection. Host factors may be genetic [3] or acquired [4]. As the clinical symptoms of an AIDS-defining event (ADE) are caused by opportunistic infections secondary to the damaged immune system, a necessary prerequisite is that the individual has also been infected with the specific opportunistic pathogen. These pathogens and therefore, also the clinical course of an HIV infection, vary between different geographical localities. For example, *Penicillum marneffei* is a common opportunistic infection in Thailand [5], Cryptococcal meningitis and cryptosporoidosis in parts of Africa [6, 7], and histoplasmosis in parts of America [8]. *Mycobacterium*

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*tuberculosis* is becoming an increasing problem where this micro-organism is widespread in the population [9, 10]. Findings of *Mycobacterium avium* complex (MAC) infections have also been shown to vary between different regions [11].

Besides geographical factors, life style determines the risk for certain infections. For instance, the Human herpes virus 8 (HHV-8), linked to the development of Kaposi's sarcoma (KS) [12], is more commonly found among homosexual men than in other transmission categories. Apart from KS only minor gender differences in the occurrence of opportunistic infections have been described [13].

Following the introduction of highly active anti-retroviral therapy (HAART) in 1996 there has been a rapid fall in disease progression and manifestations of AIDS among Western patients with access to treatment [14, 15]. For the overwhelming majority of patients in the world, and also for a substantial number of patients in economically less developed regions of Europe these drug combinations are not available. The natural history of HIV/AIDS as it presented before HAART could therefore be the clinical reality for many patients and physicians. The aim of this study was, therefore, to investigate regional differences in the clinical consequences of an HIV infection within Europe, using data collected on cases of AIDS during 1979–89. The results can be of particular guidance in health care settings which, today, are also faced with patients with severe immunodeficiency.

## PATIENTS AND METHODS

### Patients

In the 'AIDS in Europe' study [16] information was collected on 6578 patients who had been diagnosed with AIDS at 52 clinical centres in 17 European countries (see Appendix) during an 11-year period from 1 January 1979 to 31 December 1989. Details of the study have been published elsewhere [16]. In short, between May 1991 and August 1992, information was collected from patients charts on demography, serology, CD4 count at date of AIDS diagnosis, zidovudine treatment (the only specific HIV therapy available at the time) as well as diagnoses of opportunistic infections and neoplasms. A standardized data collection form was used. Members of the co-ordinating centre visited the participating centres to ensure that data were correctly transferred from the charts. Of

6655 patients included in the study, 77 patients were subsequently excluded because of not fulfilling inclusion criteria or insufficient available information. The revised Centers for Disease Control definition for AIDS of 1987 was used [17].

The participating centres were divided by two latitudinal lines into regions 'north' (Denmark, Ireland, Finland, northern Germany, The Netherlands, Sweden and United Kingdom), 'central' (Belgium, France, southern Germany, Hungary, Luxembourg, and Switzerland) and 'south'. The southern region has the highest prevalence of HIV infections in Europe [18], and thus there was a sufficient number of cases to allow east–west comparisons. We therefore further divided the Southern region by a longitudinal line into 'Southeast' (Greece, Israel, and Italy) and 'Southwest' (Portugal and Spain). Published data has shown *Mycobacterium tuberculosis* infections to be most common among HIV patients in southwestern Europe (Spain in particular), suggesting not only a possible north–south, but also an east–west difference in the clinical presentation of AIDS [16, 19]. A similar longitudinal division of north and central regions was not possible as there were insufficient data from the eastern parts of these regions in this study.

## Methods

Demographic characteristics within each of the four regions were presented as median and 25th and 75th percentiles (continuous variables), or as frequency of all patients with available data (non-continuous variables). For continuous variables, the Kruskal–Wallis rank sum test was used to test differences, whereas the $\chi^2$ test was applied for differences in frequency. All $P$-values were two-sided, and $P < 0.05$ was considered statistically significant.

Initial AIDS-defining events (ADE) included index diagnosis(es) and the ADE(s) which were diagnosed a month or less after the index diagnosis(es). Percentages of patients with specific ADEs within each region were assessed.

We next calculated the incidence of each subsequent AIDS-defining illness after the initial ADE, using time from the initial ADE to the specific ADE, date of last visit or date of death. Thus, we did not exclude patients if they experienced other ADEs. Furthermore, patients with a specific initial ADE were not included in the assessment of the incidence of this ADE. The AIDS in Europe study has no data on

recurrences of disease. Thus, only the initial episode of each diagnosis was considered, both overall and after stratification for region of Europe. In addition, patients who died within a month of their initial diagnosis were excluded. Confidence intervals (95 % CI) were calculated using a normal approximation, or when appropriate ($< 20$ cases) a Poisson distribution, and differences between regions were assessed by Poisson regression. Regional differences in the incidences of the six most common ADEs (initial as well as subsequent ADEs) were further analysed in a Cox proportional hazards model. The time parameter used was the same as the one used in the incidence assessment. For each of these ADEs, a model was established and included the following baseline parameters: age at diagnosis ($< 29$, 30–39, and $> 40$ years), year of AIDS diagnosis ($< 1987$, 1987, $> 1987$), gender, transmission category (homosexual, intravenous drug use, other, and unknown), zidovudine treatment at baseline (yes/no), initial ADEs (each ADE was classified according to severity [20]). The year 1987 was chosen as the temporal dividing line as this was the year when antiretroviral therapy (principally zidovudine) was first available. For PCP, the analysis was restricted to 5024 patients for whom data on the use of PCP prophylaxis was available. In addition, the Cox models were repeated including the CD4 cell count for the subgroup of 3045 patients for whom the CD4 cell count at diagnosis of AIDS was known.

## RESULTS

Table 1 describes the demographic characteristics of patients from the four regions. Transmission through homosexual contact dominated in Northern Europe whilst intravenous drug use was the most common mode of transmission in Southern Europe. Patients were also older at diagnosis of AIDS in Northern Europe. In the South-east, patients had developed a more pronounced immunodeficiency when diagnosed with AIDS. Treatment with zidovudine was less common at time of AIDS diagnosis in the Southwest.

Table 2 presents data on the frequency of the initial ADEs within each region. Only conditions with a total of 40 or more cases are presented. Significant regional differences were found for all the 15 most common conditions except malignant lymphoma. In the Northern and Central regions Kaposi's sarcoma was more common than in other regions. In the Northern region PCP was the dominant AIDS-

defining condition whilst toxoplasmosis was more common in the Central region. Oesophageal candidiasis was particularly common in the Southeast region whilst extrapulmonary tuberculosis showed exceptionally high figures in the Southwest region. MAC, on the other hand, was more common in the North and Central regions.

Median CD4 cell counts at time of AIDS for the more common ADEs were compared between regions. In the Southwest CD4 counts were not available in sufficient numbers to make estimates reliable. Most conditions were diagnosed at very similar CD4 counts in different regions except AIDS dementia complex which was diagnosed at higher CD4 counts in the Central region, especially compared to the Southeast ($P = 0.003$). KS was diagnosed at somewhat higher CD4 counts in the central region compared especially to the Southeast ($P = 0.05$) whilst malignant lymphoma was diagnosed at higher CD4 counts in the north especially compared to the Central region ($P = 0.04$).

Table 3 presents the incidence of the 15 most common ADEs occurring after an initial diagnosis of AIDS. There were statistically significant differences between regions for most of the ADEs presented and the trends seen in Table 2 are repeated. The Northern region had the highest incidence of PCP, KS, CMV retinitis, MAC, cryptosporidiosis and malignant lymphoma. The Central region instead had the highest incidence of toxoplasmosis whilst the Southwest has the highest incidence of extrapulmonary tuberculosis.

In Table 4, Cox analyses of the effect of region on risk for developing the six overall most common ADEs are presented. When adjusting for differences in baseline characteristics (gender, transmission category, age at AIDS, calendar year of AIDS, and zidovudine treatment) statistically significant differences in the risk of developing a given ADE remained for most diagnoses (oesophageal candidiasis being the exception). In the Central region KS was more commonly seen compared to the other regions. Together with the Southwest toxoplasmosis was also more common in the Central region. In the Southeast CMV retinitis was diagnosed more frequently compared especially to the Southwest. Finally patients in the Southwest had a marked increased risk for developing extrapulmonary tuberculosis. This risk was also higher in the Southeast and Central regions compared to the North.

The results of the Cox models remained unchanged when repeating the analysis including CD4 cell counts

Table 1. *Demographic data for patients included in the AIDS in Europe study*

|  | All centres (n = 6546) | North (n = 2510) | Central (n = 1932) | Southeast (n = 1095) | Southwest (n = 1009) | P-value |
|---|---|---|---|---|---|---|
| Gender (% female) | 8·8 | 2·0 | 14·1 | 16·3 | 7·3 | < 0·001 |
| Transmission category (%) |  |  |  |  |  | < 0·001 |
| Homo-/bisexual | 60·5 | 87·7 | 60·0 | 24·2 | 33·2 |  |
| IVD | 27·1 | 4·4 | 18·5 | 65·7 | 58·3 |  |
| Other | 10·3 | 6·0 | 19·1 | 8·9 | 6·0 |  |
| Not known | 2·1 | 1·9 | 2·4 | 1·3 | 2·6 |  |
| Median age(25–75%) | 34 (28–41) | 37 (31–43) | 34 (29–42) | 29 (26–35) | 30 (26–36) | < 0·001 |
| Available CD4 cell count (%) (n = 3045) | 46·5 | 35·9 | 70·0 | 79·2 | 0 | < 0·001 |
| Median CD4 cell count (cells/mm³, 25–75%) | 84 (31–198) | 90 (30–200) | 90 (33–216) | 78 (32–174) | — | < 0·05 |
| Median year of AIDS diagnosis (25–75%) | 1988 (1987–9) | 1987 (1986–8) | 1988 (1986–9) | 1988 (1987–9) | 1988 (1987–9) | < 0·001 |
| Zidovudine treatment at time of AIDS diagnosis (%) | 7·5 | 6·7 | 9·8 | 10·4 | 1·9 | < 0·001 |

Table 2. *First AIDS-defining event in respective region. Conditions with at least 40 cases presented*

| AIDS defining event* | All centres (n = 6546) | % | North (n = 2510) | % | Central (n = 1932) | % | Southeast (n = 1095) | % | Southwest (n = 1009) | % | P-value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PCP | 2517 | 38·5 | 1250 | 49·8 | 688 | 35·6 | 336 | 30·7 | 243 | 24·1 | < 0·001 |
| Kaposi's sarcoma | 1394 | 21·3 | 680 | 27·1 | 488 | 25·3 | 113 | 10·3 | 113 | 11·2 | < 0·001 |
| Oesophageal candidiasis | 1212 | 18·5 | 395 | 15·7 | 330 | 17·1 | 289 | 26·4 | 198 | 19·6 | < 0·001 |
| Extrapulmonary tuberculosis | 571 | 8·7 | 50 | 2·0 | 115 | 6·0 | 51 | 4·7 | 355 | 35·2 | < 0·001 |
| Toxoplasmosis | 512 | 7·8 | 109 | 4·3 | 216 | 11·2 | 96 | 8·8 | 91 | 9·0 | < 0·001 |
| HIV wasting | 328 | 5·0 | 100 | 4·0 | 62 | 3·2 | 79 | 7·2 | 87 | 8·6 | < 0·001 |
| AIDS dementia complex | 295 | 4·5 |  | 3·2 | 110 | 5·7 | 96 | 8·7 | 9 | 0·9 | < 0·001 |
| Malignant lymphoma | 228 | 3·5 | 89 | 3·6 | 57 | 3·0 | 49 | 4·5 | 33 | 3·3 | 0·17 |
| Cryptosporidosis | 216 | 3·3 | 85 | 3·4 | 79 | 4·1 | 16 | 1·5 | 36 | 3·6 | < 0·001 |
| Herpes simplex ulcer | 199 | 3·0 | 44 | 1·8 | 111 | 5·8 | 26 | 2·4 | 18 | 1·8 | < 0·001 |
| Cryptococcosis | 158 | 4 | 41 | 1·6 | 33 | 1·7 | 54 | 4·9 | 30 | 3·0 | < 0·001 |
| CMV retinitis | 154 | 2·5 | 57 | 2·3 | 28 | 1·5 | 44 | 4·0 | 25 | 2·5 | < 0·001 |
| *Mycobacterium avium* complex | 104 | 1·6 | 47 | 1·9 | 48 | 2·5 | 5 | 0·5 | 4 | 0·4 | < 0·001 |
| Salmonellosis | 70 | 1·1 | 12 | 0·5 | 22 | 1·1 | 13 | 1·2 | 23 | 2·3 | < 0·001 |
| PML | 47 | 0·7 | 14 | 0·6 | 10 | 0·5 | 17 | 1·6 | 6 | 0·6 | 0·005 |

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

among the subset of patients with such data available (data not given).

## DISCUSSION

The study showed a pronounced difference in the occurrence of different ADEs between different regions of Europe, with respect to initial ADEs as well as subsequent ADEs. Most striking was the increased risk for extrapulmonary tuberculosis in South-western Europe whilst toxoplasmosis and KS was more common in Central Europe. Other regional differences were also found.

There could be many reasons for regional dif-

Table 3. *Incidence of new AIDS-defining events after initial diagnosis of AIDS in respective region*

| AIDS defining event* | All centres (*n* = 6546) | North (*n* = 2510) | Central (*n* = 1903) | Southeast (*n* = 1124) | Southwest (*n* = 1009) | *P*-value |
|---|---|---|---|---|---|---|
| PCP | 18·9 (17·6–20·3) | 20·9 (18·5–23·3) | 18·4 (16·2–20·6) | 17·6 (14·0–21·1) | 16·8 (13·6–20·0) | 0·03 |
| Oesophageal candidiasis | 11·6 (10·7–12·4) | 11·5 (10·1–12·8) | 12·2 (10·6–13·7) | 12·7 (9·8–15·6) | 9·1 (6·8–11·4) | 0·36 |
| Kaposi's sarcoma | 10·3 (9·4–11·2) | 14·0 (12·3–15·6) | 11·5 (9·8–13·2) | 4·5 (3·0–6·0) | 3·3 (2·0–4·6) | < 0·0001 |
| CMV retinitis | 9·4 (8·6–10·1) | 11·3 (10·1–12·5) | 8·2 (7·0–9·4) | 10·5 (8·3–12·8) | 4·3 (2·9–5·8) | < 0·0001 |
| Toxoplasmosis | 7·8 (7·1–8·4) | 5·8 (4·9–6·6) | 10·5 (9·1–11·9) | 6·3 (4·5–8·1) | 9·6 (7·4–11·8) | 0·001 |
| AIDS dementia complex | 5·7 (5·2–6·3) | 5·3 (4·5–6·1) | 5·8 (4·8–6·7) | 12·7 (10·1–15·2) | 1·0 (0·3–1·6) | 0·57 |
| *Mycobacterium avium* complex | 4·1 (3·7–4·6) | 7·1 (6·1–8·0) | 2·9 (2·2–3·6) | 0·5 (0·0–0·9) | 0·6 (0·1–1·1) | < 0·0001 |
| Crypto- sporidosis | 3·0 (2·6–3·4) | 3·9 (3·2–4·5) | 2·7 (2·0–3·3) | 1·2 (0·4–1·9) | 3·0 (1·8–4·2) | 0·003 |
| Malignant lymphoma | 2·4 (2·1–2·8) | 3·3 (2·7–4·0) | 1·6 (1·1–2·1) | 1·9 (1·0–2·9) | 1·6 (0·8–2·6) | 0·0004 |
| Herpes simplex ulcer | 2·4 (2·0–2·7) | 1·9 (1·4–2·4) | 4·0 (3·2–4·8) | 1·4 (0·6–2·3) | 0·7 (0·1–1·3) | 0·11 |
| Crypto- coccosis | 2·1 (1·7–2·4) | 2·2 (1·7–2·7) | 1·2 (0·8–1·6) | 2·9 (1·8–4·1) | 3·5 (2·2–4·7) | 0·04 |
| HIV wasting | 1·9 (1·6–2·2) | 2·3 (1·8–2·8) | 0·6 (0·3–0·9) | 4·2 (2·8–5·6) | 1·7 (0·8–2·6) | 0·81 |
| Extra- pulmonary tuberculosis | 1·9 (1·5–2·2) | 0·7 (0·4–1·0) | 2·0 (1·4–2·6) | 2·5 (1·4–3·6) | 7·8 (5·3–10·4) | < 0·0001 |
| PML | 0·8 (0·6–1·0) | 0·7 (0·4–1·0) | 1·0 (0·6–1·4) | 1·1 (0·4–1·7) | 0·2 (0·0–0·6) | 0·63 |
| Salmonellosis | 0·7 (0·5–0·9) | 0·3 (0·1–0·5) | 0·7 (0·3–1·0) | 1·1 (0·4–1·8) | 2·3 (1·3–3·4) | < 0·0001 |

PCP, *Pneumocystis carinii* pneumonia; PML, Progressive multifocal leucoencephalopathy.

ferences in the opportunistic infections seen in HIV infections. For example, in addition to biological factors there may be differences in diagnostic procedures. In the North and Central regions, PCP was the dominating initial ADE. This may be due to diagnostic procedures [21] or a difference in the background prevalence of the micro-organism, as shown in other geographic localities [22]. The fact that the condition in different European regions was diagnosed at very similar CD4 counts makes differences in diagnostic procedures an unlikely explanation. When multivariate analysis was performed (Table 4), this difference between regions remained. Primary prophylaxis against PCP was introduced in the last years of the 1980s and was taken into account in the analysis. As year of diagnosis was included in the analysis any temporal changes up to 1989 should not influence the results [21]. A true regional difference in the general prevalence of *Pneumocystis carinii* was thus probable [22].

The Central region had the highest proportion of toxoplasmosis which also remained after controlling for known possible confounders (Table 4). This corresponds to findings of higher sero-prevalence of antibodies against *Toxoplasma gondii* in the general population in central Europe, with the highest figures found in France [26]. More exposure to raw meat has been one explanation. Reactivation of latent infection naturally becomes a problem when the infection is widespread. Little is known about the natural prevalence of toxoplasma in those parts of Eastern Europe where the prevalence of HIV now is increasing.

In the North and Central regions KS was more common as initial ADEs and accounted for a quarter of the cases (Table 2). This is in contrast to findings in the general non-HIV infected population where KS is more prevalent in Southern Europe [23]. One explanation for the relatively high occurrence of KS among HIV-infected homosexuals is that a transmissible causative agent was also spread within the group [24]. The decline in the epidemic curve for this condition supports the interpretation that men infected through sex with other men were to a larger extent also exposed to HHV-8 [12, 25]. This exposure may also have been more pronounced in the Central region. Taking into account regional demographic

Table 4. *Cox models for regional differences in AIDS-defining events*

| | | Relative risk (95% confidence intervals) | | | | | |
| | | | Unadjusted | | | Adjusted | |
| | Region* | RR | 95% CI | *P*-value | RR | 95% CI | *P*-value |
|---|---|---|---|---|---|---|---|
| *Pneumocystis* | N | 1 | — | | 1 | — | |
| *carinii* | C | 0·89 | 0·75–1·05 | 0·15 | 0·77 | 0·65–0·92 | 0·004 |
| pneumonia† | SE | 0·77 | 0·61–0·97 | 0·03 | 0·81 | 0·62–1·07 | 0·14 |
| | SW | 0·76 | 0·61–0·95 | 0·02 | 0·78 | 0·50–1·21 | 0·26 |
| Kaposi's | N | 1 | — | | 1 | — | |
| sarcoma | C | 0·83 | 0·68–0·99 | 0·04 | 1·28 | 1·06–1·54 | 0·01 |
| | SE | 0·31 | 0·22–0·44 | < 0·0001 | 1·05 | 0·72–1·53 | 0·79 |
| | SW | 0·23 | 0·15–0·35 | < 0·0001 | 0·67 | 0·43–1·04 | 0·07 |
| CMV | N | 1 | — | | 1 | — | |
| retinitis | C | 0·74 | 0·62–0·88 | 0·0008 | 0·84 | 0·69–1·00 | 0·053 |
| | SE | 0·97 | 0·77–1·24 | 0·83 | 1·46 | 1·11–1·91 | 0·007 |
| | SW | 0·39 | 0·27–0·55 | < 0·0001 | 0·58 | 0·40–0·84 | 0·004 |
| Oesophageal | N | 1 | — | | 1 | — | |
| candidiasis | C | 1·07 | 0·90–1·27 | 0·45 | 1·08 | 0·90–1·29 | 0·40 |
| | SE | 1·06 | 0·82–1·37 | 0·64 | 1·12 | 0·84–1·50 | 0·45 |
| | SW | 0·78 | 0·59–1·03 | 0·08 | 0·83 | 0·61–1·14 | 0·24 |
| Extrapulmonary | N | 1 | — | | 1 | — | |
| tuberculosis | C | 2·69 | 1·63–4·45 | < 0·0001 | 8·00 | 1·77–5·11 | < 0·0001 |
| | SE | 3·35 | 1·83–6·12 | < 0·0001 | 3·39 | 1·72–6·69 | 0·0004 |
| | SW | 10·44 | 6·17–17·67 | < 0·0001 | 11·37 | 6·31–20·49 | < 0·0001 |
| Toxoplasmosis | N | 1 | — | | 1 | — | |
| | C | 1·83 | 1·50–2·23 | < 0·0001 | 1·83 | 1·49–2·25 | < 0·0001 |
| | SE | 1·04 | 0·76–1·43 | 0·79 | 1·10 | 0·77–1·56 | 0·60 |
| | SW | 1·61 | 1·22–2·12 | 0·0007 | 1·81 | 1·33–2·46 | < 0·0001 |

* N, North; C, Central; SE, Southeast; SW, Southwest.
† Adjusted analysis restricted to 5024 patients with available data on PCP-prophylaxis.

differences, the higher proportion of HIV transmitted between men in the North and Central regions as well as younger age, and a larger proportion of transmission through needle-sharing in the Southeast and Southwest, a true regional difference in the occurrence of KS in the HIV-positive population remained (Table 4). HHV-8 can thus be expected to have spread to a larger degree in Central Europe.

In the Southeast region, oesophageal candidiasis was particularly important as an initial ADE, second only to PCP. *Candida albicans* is widespread worldwide and if there are no competing opportunistic infections this may become the AIDS-defining condition. This condition is diagnosed without sophisticated laboratory resources. It was however diagnosed at similar levels of immunodeficiency in each region suggesting usage of diagnostic procedures with the same degree of sensitivity. If events after initial ADE are included (Table 4) the regional differences disappear making candida a major problem in all regions for the immunodeficient population.

The Southwest is the only region where PCP was not the most common ADE. Instead extrapulmonary tuberculosis was the leading ADE both as initial diagnosis and as subsequent infections. The obvious explanation for this finding is, of course, that HIV patients in this region, to a higher degree, are, or become, infected with *Mycobacterium tuberculosis*. These regional differences remain strong also in the Cox model (Table 4). The difference can thus not be explained by a large proportion of intravenous drug abusers. Instead a true geographical difference exists. As opposed to extrapulmonary tuberculosis, MAC was less common in the Southwest and instead found

especially in the North and Central regions. Diagnostic routines may vary. Also, little is known about variations in the distribution of mycobacterium of different strains in the environment.

CMV retinitis is uncommon as an initial ADE but more common during the follow-up period. The condition was more common in the Southeast after adjustment for known possible confounders. No obvious explanation for this difference was found. If patients die before developing a severe fall in CD4 counts, this would, of course, lower the incidence.

Lymphomas were diagnosed more often in the Northern region. A possible explanation could be differences in diagnostic procedures [27]. It was diagnosed in the North at higher CD4 counts implying higher awareness or more aggressive investigations for the condition. By contrast, AIDS dementia complex was more common and diagnosed at higher CD4 counts in the Central region. One possible explanation for this discrepancy could be differences in diagnostic procedures and classification, whereby patients in the North were diagnosed as non-Hodgkin's lymphoma and were classified as AIDS dementia complex in Central Europe.

Some general considerations need to be made when interpreting the data. When comparing the distribution of ADEs it is necessary to keep in mind that patients with an AIDS defining illness may be at an increased risk of death or a further AIDS-defining illness [28, 29]. Use of primary prophylaxis, although it was little used in this study, can prevent conditions such as PCP [30] and thus make CMV retinitis and MAC more common as initial ADE among persons who are aware of their HIV infection before developing AIDS.

Differences in transmission patterns in different parts of Europe can also influence age at diagnosis of AIDS. Transmission through needle sharing often takes place at a younger age than sexual transmission. Thus in regions with a high proportion of drug abusers this may explain the lower age at AIDS. KS predominantly affects homosexual men and is therefore more common where this mode of transmission dominates. The Cox models controlled for such factors in order to see what differences in ADEs can be attributed to geographical region, after adjustment for such confounding variables.

Treatment of opportunistic infections has improved during the years. Survival in southern Europe was initially shorter in the epidemic [16], limiting the possibility of ADEs associated with advanced HIV-infection. In spite of this, and possible inadequate diagnostic procedures, MAC, PML, CMV retinitis and non-Hodgkin lymphoma account for 7–11% of initial ADEs. Few patients in the study (7·5%) had zidovudine treatment before initial ADE. However, zidovudine treatment cannot be expected to have had a major impact as zidovudine monotherapy can only be expected to postpone disease progression [31–35].

In summary, differences in populations affected by HIV and transmission categories influence the type of ADEs in different parts of Europe. Adjusting for the known possible confounders, true regional differences remain for developing PCP, toxoplasmosis, CMV retinitis, KS and extrapulmonary tuberculosis. These differences we attribute primarily to variations in degree of exposure to respective pathogens. The prevalence of these and other pathogeneses will determine the clinical course of HIV infections in the parts of eastern Europe and elsewhere where the virus is now spreading.

## APPENDIX

**The Multicentre Study Group on AIDS IN EUROPE** (national coordinators in parentheses). **Belgium** (N. Clumeck), S. DeWit, B. Sommereijns, Saint-Pierre Hospital, Brussels. **Denmark** (J. Nielsen), J. Lundgren, T. Nielsen, C. Pedersen, Hvidovre Hospital; G. Jensen, Frederiksberg Hospital; P. Skinhøj, K. Bentsen, J. Gerstoft, M. Melbye, Rigshospitalet, Copenhagen. **Finland** (A. Ranki), S.-L. Valle, University Central Hospital, Helsinki. **France** (C. Katlama), P. Berlureau, Hospital de la Pitié-Salpétrière, Paris. **Germany** (M. Dietrich), S. Schwander, Bernhard-Nocht-Institut, Hamburg; F.-D. Goebel, Medizinische Poliklinik, Munich. **Greece** (J. Kosmidls) Athens General Hospital; G. Stergiou, T. Gouzia, A. Papadopoulos, 1st IKA Hospital, Athens. **Hungary** (D. Banhegyi) Postgraduate Medical School, Budapest. **Ireland** (F. Mulcahy) St. James's Hospital, Dublin. **Israel** (I. Yust) Ichilov Hospital, Tel Aviv; Z. Ben-Ishal, Rambam Medical Center, Haifa; Z. Bentwich, Kaplan Hospital, Rehovot; T. Sacks, S. Maayan, Hadassah University Hospital, Jerusalem. **Italy** (S. Vella, A. Chiesi) Istituto Superiore di Sanita, Rome: F. Ancarani, G. Scalise, Università di Ancona, Ancona; A. Bertaggia, E. Francavilla, Osp. Civile, Padova; G. Calonghi, Arcispedale S. Maria Nuova, Regio Emilia; A. Cargnel, Osp. Sacco, Milan; M. Arlotti, R. Ciammarughi, Osp. Infermi Rimini, Rimini; A. Colomba, Osp. Casa del Sole, Palermo; F.

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