Malignant tumours in patients with HIV infection

Umberto Tirelli, Silvia Franceschi, Antonino Carbone

This is the seventh in a series of articles examining developments in cancer and updating what we know about the disease

One of the most important though somewhat neglected aspects of research in HIV infection concerns the development, clinicopathological characteristics, and treatment of malignant tumours in infected patients. With the improved survival of patients with AIDS owing to the better prevention and treatment of infectious complications there may well be an increase in AIDS related malignancies. This paper reviews the epidemiology, pathology, and treatment of malignant tumours in patients with HIV.

What are the main types of cancer in AIDS?

At least two malignancies are firmly established as associated with HIV and have long been diagnostic of AIDS—namely, Kaposi's sarcoma and non-Hodgkin's lymphoma (table). When compared with the general

malignancies, such as non-melanomatous skin cancer and cancer of the nose, nasal cavity, and middle ear, based on two or three cases at most, require cautious interpretation as they may represent misclassifications of Kaposi's sarcoma.

Invasive carcinoma of the cervix uteri, often a more aggressive disease than in the general population, has been part of the AIDS case definition since 1993, but data on it are fairly scanty on account of the vast predominance of male cases in North American series.

Characteristics of patients with AIDS and cancer

Kaposi's sarcoma is severalfold more common among patients who acquire HIV by sexual contact rather than parenterally. Among people with newly diagnosed AIDS in the United States the prevalence of Kaposi's sarcoma ranged from 1% in men with haemophilia to 21% in homosexual men⁷ and similar differences were recorded in European countries.⁸ The case for a sexually transmitted aetiology of Kaposi's sarcoma is strong—for example, clustering of cases in Africa,⁷ faecal-oral contact as main route of transmission in homosexual men⁹—whereas the several infectious hypotheses—for example, with cytomegalovirus, mycoplasmas, and retrovirus-like agents—have never been substantiated. The prevalence of Kaposi's sarcoma among heterosexual AIDS patients is lower in white than Caribbean or African born residents of the United States⁷ or heterosexuals in Italy.¹⁰ Lastly, American⁷ but not Italian data¹⁰ suggest that HIV transmission via whole blood carries an increased risk of Kaposi's sarcoma when compared with transmission by clotting concentrates.

The epidemiology of AIDS associated non-Hodgkin's lymphoma is even less well understood. The disease is rarer (accounting for about 3% of AIDS diagnoses worldwide) and substantially underestimated in AIDS surveillance statistics (non-Hodgkin's lymphoma is rarely the presenting disease). In the United States intravenous drug users had around half the probability of presenting with non-Hodgkin's lymphoma when compared with homosexual and bisexual men and patients with haemophilia. In European countries the difference, if any, seemed much smaller, possibly owing to the more homogeneous access to diagnostic procedures across various strata of the population.¹⁰

Other AIDS associated malignancies (cervical cancer, rectal and anal cancer, Hodgkin's disease, and possibly hepatocellular carcinoma) are known or suspected to be caused by infectious agents whose prevalence or aggressiveness is enhanced in most populations at high risk of AIDS.

Geographical differences and temporal trends in AIDS associated Kaposi's sarcoma and non-Hodgkin's lymphoma

The geographical distribution of AIDS related Kaposi's sarcoma closely reflects the prevalence of sexually acquired AIDS worldwide. Thus the proportion of AIDS patients with Kaposi's sarcoma as a presenting disease tends to be much higher in the

Risk of cancer in men with AIDS or at risk of AIDS

Type of cancer	Odds ratios in never married men aged 20-49		Relative incidence ratios in never married men aged 20-49 in 1985-7 v 1973-9 (SEER programme, USA)‡	Standardised incidence ratios among men with AIDS v general population	
	In 1984 v 1973-8, San Francisco City*	In 1985 v 1973-6, Manhattan, New York†		1986-7, Illinois§	1980-7, San Francisco Bay
Kaposi's sarcoma	2479	1850	5060	972	716
Non-Hodgkin's lymphoma	4.2	6.2	10.4	141	71
Hodgkin's disease	1.6	2.5	1.1	—	8.8
Rectal and anal cancer	—	—	2.6	—	3.5

*Biggar *et al* (1987).¹

†Biggar *et al* (1989).¹¹

‡Rabkin *et al* (1991) (surveillance, epidemiology, and end results programme).³

§Côté *et al* (1991).¹

||Reynolds *et al* (1993).²

population in the same area, the risk of Kaposi's sarcoma in men with AIDS was roughly 900-fold greater in the State of Illinois¹ and 700-fold greater in San Francisco Bay.² Data from the same cancer registry linkage studies for non-Hodgkin's lymphoma showed standardised incidence ratios of 141¹ and 71² respectively (table). More detailed analyses by subtype of non-Hodgkin's lymphoma suggested that the standardised incidence ratio in single men aged 20-49 in 1985-7 as compared with 1973-8 was 43 for the extranodal form but only 8 for nodal disease.³ With respect to histological grade, the increased standardised incidence ratio was restricted to intermediate and high grade lymphomas.³

In the largest cancer registry linkage study² solid tumours as a whole did not occur more often than expected among patients with AIDS, but two types of cancer which are not part of the AIDS case definition occurred with significantly increased frequency. These were Hodgkin's disease (standardised incidence ratio 8.8) and cancers of the rectum, anus, and anal canal (standardised incidence ratio 3.5) (table). The increased frequency of rectal and anal cancer was probably explained by the overwhelming prevalence of homosexual males among AIDS cases in San Francisco, anoreceptive intercourse being an important risk factor for the disease. The excess of Hodgkin's disease in a population based cohort of patients with AIDS confirms other reports^{4,6} and suggests that certainly some forms of aggressive Hodgkin's disease with unusual morphology may be part of the malignant presentation of AIDS.⁶

Conversely, significant excesses of a few other rare

Centro Regionale di Riferimento Oncologico, Istituto Nazionale di Ricovero e Cura a Carattere Scientifico, 33081 Aviano, Italy

Umberto Tirelli, *division of medical oncology and AIDS*
Silvia Franceschi, *epidemiology unit*
Antonino Carbone, *division of pathology*

Series editor: G M Mead
(G M Mead is consultant in medical oncology at the Cancer Research Campaign's Wessex Medical Oncology Unit)

Correspondence to: Dr Tirelli.

BMJ 1994;308:1148-53

Kaposi's sarcoma in gingiva

Immunoblastic non-Hodgkin's lymphoma in skin

United States, Canada, and northern Europe (where homosexual cases predominate) than, for instance, in Italy and Spain (where intravenous drug users account for most reported cases of AIDS). The proportion of AIDS patients with non-Hodgkin's lymphoma as the presenting disease is more homogeneous internationally.

The most consistent finding with respect to temporal trends, noted first in the United States⁷ and then in Europe^{11,12} and Australia,¹³ is a steep decline in the proportion of Kaposi's sarcoma in patients with AIDS. It is unlikely that this reduction is totally artefactual (that is, due to changes in the definition of AIDS). More probable explanations include the early predominant involvement of homosexual men (particularly of the most promiscuous cases) in the epidemic and the tendency of Kaposi's sarcoma to be an early manifestation of AIDS, occurring when immunosuppression is still fairly mild. It has also been predicted that the incidence of lymphoma will rise as more patients prolong their pre-AIDS state with prophylaxis.¹⁴

Pathological and biological aspects

KAPOSI'S SARCOMA

Recently we have substantially improved our understanding of the pathogenesis of Kaposi's sarcoma. Exposure to a still unknown sexually transmitted agent other than HIV and subsequent infection of a mesenchymal cell progenitor could predispose to Kaposi's sarcoma.¹⁵ Moreover, the activation of cytokines such as interleukin 1, tumour necrosis factor α , and interleukin 6 in addition to the HIV related immune function abnormalities could result in proliferation of the mesenchymal progenitor cell and affect the rate of growth of Kaposi sarcoma lesions as well.¹⁵ HIV itself, through the expression of the Tat protein, could directly increase the growth of Kaposi sarcoma cells. The role of cytokines in the modulation of Kaposi sarcoma cell growth has important clinical implications, in that several drugs that modulate cytokines could potentially be of benefit to patients with Kaposi's sarcoma. Clinical studies of retinoids, interleukin 4, HIV Tat inhibitors, and oxpentifylline are under way.

There is still uncertainty about the histological nature of Kaposi sarcoma cells. Endothelial cells were first considered the cells of origin¹⁶ because of the presence of factor VIII related antigen in spindle cells. Recently, the identification of smooth muscle specific α actin¹⁷ both in cultures of cells derived from Kaposi sarcoma lesions and in the lesions themselves favour the hypothesis that the cells of origin may be from a smooth muscle cell progenitor.

HIV ASSOCIATED LYMPHOMAS

The range of HIV associated lymphoid neoplasias includes systemic non-Hodgkin's lymphoma, primary lymphoma of the brain, and possibly Hodgkin's disease.¹⁸⁻²¹ HIV associated systemic non-Hodgkin's lymphomas have several pathological features in common. These include a diffuse growth pattern, a high growth rate, and a common B cell derivation, only a minority of non-Hodgkin's lymphomas being of undetermined or T cell phenotype. Moreover, several approaches, including immunophenotypic and immunogenotypic analyses, have defined the clonal nature of most HIV associated non-Hodgkin's lymphomas.¹⁸

From our observations²² and other studies^{20,23-26} it may be concluded that most HIV associated systemic non-Hodgkin's lymphomas have a "blastic" cell morphology. Many consist of small non-cleaved cells of typical Burkitt's lymphoma and their variants with

plasmablastic differentiation,²⁷ or of immunoblasts—usually polymorphic—with plasmacytic features,^{23,26,28} or of centroblasts²⁹ (large non-cleaved cells as defined by the international working formulation for non-Hodgkin's lymphomas) along with their morphological variants.^{23,27} In addition, lymphomas composed of plasmablasts^{18,30} (plasmacytomas) or of blastic cells exhibiting intermediate features between small non-cleaved cells with plasmablastic differentiation²⁷ and immunoblastic plasmacytoid cells²³ (8% in our series²²) may be detected. Finally, anaplastic large cell Ki-1+ lymphomas, a heterogeneous group of high grade lymphomas at the borderline between Hodgkin's disease and non-Hodgkin's lymphoma,³² may occur in HIV infected patients^{18,23,24,28,32,33} (14% in our series²²).

In contrast with the heterogeneity of HIV associated systemic non-Hodgkin's lymphoma, non-Hodgkin's lymphomas arising in the central nervous system represent a more uniform group and in most cases have histological features consistent with immunoblastic plasmacytoid lymphomas.

Conclusive studies on the frequency of Hodgkin's disease in AIDS are lacking and whether Hodgkin's disease should be included among the HIV associated lymphomas is debatable.^{18,20} Recent studies, however, have found a significant difference in the distribution of mixed cellularity and lymphocyte depletion subtypes of Hodgkin's disease in HIV infected patients when compared with Hodgkin's disease in the general population.^{34,35} In particular, several reports have pointed to the high frequency of lymphocyte depletion in series of AIDS associated Hodgkin's disease¹⁸ accompanied by an increase in fibrohistiocytoid stromal cells.⁶

The biological bases and molecular genetics underlying the pathogenesis of these tumours are still largely unclear. A pathogenetic role for Epstein-Barr virus in some HIV associated systemic non-Hodgkin's lymphomas has been proposed.^{28,36-40}

A high prevalence (83-100%) of Epstein-Barr virus has been found in Hodgkin's disease tissue from patients with HIV infection.^{41,42} Applying small non-polyadenylated Epstein-Barr virus RNA (Epstein-Barr virus transcript; EBER) in situ hybridisation to 21 cases of primary central nervous system lymphoma in AIDS patients, MacMahon *et al* found evidence of Epstein-Barr virus infection of the malignant cells in every case.⁴³ Moreover, Epstein-Barr virus genomes associated with Hodgkin's disease and anaplastic large cell Ki-1+ non-Hodgkin's lymphoma arising in HIV-1 positive patients have been shown to be episomal and clonal,⁴⁴ even when detected in metachronous multiple biopsy samples,⁴⁵ indicating that Epstein-Barr virus infected cells have arisen from a single infectious agent.

In a recent study by our group combined in situ hybridisation analyses for viral DNA and EBER (fig 1) and immunohistological detection of Epstein-Barr virus encoded latent membrane protein type 1 showed that there were differences in viral latent gene expression between HIV associated anaplastic large cell Ki-1+ (mostly of B cell phenotype) or immunoblastic lymphomas (latent membrane protein type 1+) (fig 2) and Epstein-Barr virus infected cells of small non-cleaved cell lymphomas (J group; see box) (latent membrane protein type 1-).²²

With respect to additional genetic events contributing to HIV associated non-Hodgkin's lymphoma, activation of the c-myc oncogene has been detected in most small non-cleaved cell lymphomas. By contrast, in immunoblastic plasmacytoid lymphomas c-myc activation is detected in only a minority of tumours.^{36,46,47} Another genetic event recorded in HIV associated non-Hodgkin's lymphoma is p53 inactivation. This is specifically associated with Burkitt's lymphoma (fig 3) and is consistently absent in all other

Right neck mass of Hodgkin's disease

FIG 1—EBER (short non-protein coding Epstein-Barr virus transcripts) in situ hybridisation signal shown as dense grains over nuclei of tumour cells of anaplastic large cell (CD30/Ki-1⁺) lymphoma. (Nuclear fast red counterstain)

FIG 2—Latent membrane protein type 1 staining with variable intensity within cytoplasm of several tumour cells of immunoblastic lymphoma. (Haematoxylin counterstain)

FIG 3—Small non-cleaved cell lymphoma stained with DO7 (which recognises wild and mutant p53 antigen) showing strong nuclear staining (brown) of tumour cells. (Haematoxylin counterstain)

From the pathological and biological data we can formulate a pathological classification of HIV associated systemic lymphomas based on the morphological features of the two main types—that is, blastic and anaplastic cell lymphomas, which include specific cytomorphological subtypes and possibly Hodgkin's disease (box). This classification uses the terminology of the international working formulation and the updated Kiel classification²⁹ and includes morphological variants of the high grade B cell non-Hodgkin's lymphoma described by Hui *et al.*²⁷ It defines precise morphological categories and their association with genetic lesions (box), thus providing a reliable basis for further biologically oriented investigations of the pathogenesis of HIV associated lymphomas.

Clinical manifestations and treatment

KAPOSI'S SARCOMA

At the beginning of the AIDS epidemic Kaposi's sarcoma frequently occurred as an indolent manifestation in patients without any evidence of severe immunosuppression and often as a presenting sign of HIV infection. Now, however, Kaposi's sarcoma is frequently seen as a late manifestation of AIDS and is likely to be associated with an aggressive course.

The lesions usually begin as macular or papular eruptions, sometimes in clusters. These progress to plaque or nodular lesions, which may spontaneously disappear while others appear. Lymphoedema of the legs and face may be severe and heralds the need to start treatment. Kaposi's sarcoma confined to the skin is never a cause of death in AIDS but may cause severe cosmetic problems needing treatment. The outcome of patients with Kaposi's sarcoma is usually determined by the severity of the immunosuppression present and by the related opportunistic infections. Kaposi's sarcoma has been recorded in every site in the body and may be found in gastrointestinal tract, lungs, or lymph nodes without any evidence of cutaneous lesions. Pulmonary Kaposi's sarcoma usually occurs in advanced disease, and when symptomatic an aggressive form of therapy is required. Gastrointestinal Kaposi's sarcoma occurs in almost half of patients with cutaneous lesions but usually does not cause symptoms.

The treatment of Kaposi's sarcoma must be tailored to individual needs. Treatment is not curative and rarely induces complete remission. In patients with Kaposi sarcoma lesions that are not disfiguring and in whom there are no other symptoms no treatment is required. When symptoms occur or cosmetic problems are present various effective (but not curative) treatments are available. Localised cutaneous lesions may effectively be treated with radiotherapy for pain or cosmetic problems with temporary complete remission of lesions in 70% of cases.⁴⁹ Appreciable toxicity, however, occurs with oral radiotherapy.⁵⁰ Intravenous vinblastine, interferon alfa, and laser photocoagulation are reportedly effective in single, especially intraoral, Kaposi sarcoma lesions, with good cosmetic and symptomatic results.⁵¹ These treatments are much better tolerated than radiotherapy. In patients with disseminated and progressive Kaposi sarcoma lesions, or when systemic lesions become symptomatic, chemotherapy or biological response modifiers should be tried. High doses of interferon alfa (10-18 MU daily) have been used, but adverse effects of this drug that are dose dependent and include fever-like symptoms should be weighed carefully against benefit.

Though zidovudine has no antitumour activity, it is often combined with interferon alfa for its anti-HIV effect.⁵² Bone marrow colony stimulating factors have been used successfully to ameliorate neutropenia and allow combination chemotherapy in this setting.⁵³ Combination chemotherapy has been found effective

Classification of systemic lymphomas occurring during HIV-1 induced immunosuppression

Blastic cell lymphomas not associated with Epstein-Barr virus encoded latent membrane protein type 1 expression

- Centroblastic (G (international working formulation))
- Small non-cleaved cell (J (international working formulation); associated with c-myc deregulation + p53 inactivation) with or without plasmablastic differentiation²⁷
- Plasmablastic (plasmacytoma; it is debatable whether extramedullary plasmacytomas should be included among HIV associated lymphomas)
- Blastic cells with intermediate features^{22 23}

Blastic cell lymphomas that may be associated with Epstein-Barr virus encoded latent membrane protein type 1 expression

- Immunoblastic (H (international working formulation); included as separate entity as different in Epstein-Barr viral latent gene expression from other blastic cell systemic lymphomas)

Anaplastic cell lymphomas (associated with monoclonal Epstein-Barr virus infection and latent membrane protein type 1 expression)

- Anaplastic large cell Ki-1⁺³¹
- Hodgkin's lymphoma (mixed cellularity and lymphocyte depletion; it is debatable whether Hodgkin's lymphomas should be included among HIV associated lymphomas)

Kaposi's sarcoma on penis

Kaposi's sarcoma lesions in skin over arms

been used successfully to ameliorate neutropenia and allow combination chemotherapy in this setting.⁵³ Combination chemotherapy has been found effective in patients with disseminated symptomatic and pulmonary Kaposi's sarcoma. The most effective agents are bleomycin, vinblastine, vincristine, cyclophosphamide, etoposide, and doxorubicin.⁵⁴ These agents may be given in various combinations. A randomised study showed that a combination of low dose doxorubicin, bleomycin, and vincristine was more effective than doxorubicin alone.⁵⁵ More intensive therapy is not always associated with increased survival, as the immunosuppressive effects of chemotherapy may increase the number of opportunistic infections in such severely immunocompromised patients. Liposomal doxorubicin⁵⁶ and liposomal daunorubicin⁵⁷ are interesting new approaches in this setting and together with colony stimulating factors are under investigation at present. Angiostatic agents also look hopeful, based on laboratory data.⁵⁸

NON-HODGKIN'S LYMPHOMA

Most patients with AIDS related non-Hodgkin's lymphoma present with fever, loss of weight, and night sweats (B symptoms), widespread disease, and extranodal involvement, the most common sites being the central nervous system, gastrointestinal tract, bone marrow, and liver. Any site of the body, however, may be affected.^{59,60} On account of the unfavourable presentation of non-Hodgkin's lymphoma and the prevalence of high grade subtypes in addition to the underlying HIV infection with associated opportunistic infections, the overall outcome of these malignancies is poor. Nevertheless, some prognostic factors for survival have been identified, and some patients with AIDS related non-Hodgkin's lymphoma can obtain long term survival and even cure with appropriate therapy.

Levine *et al* identified Karnofsky performance score less than 70%, AIDS being diagnosed before non-Hodgkin's lymphoma, bone marrow involvement, and low CD4 counts as associated with a poorer prognosis.⁶¹ Patients who presented with one or more of these features had a significantly shorter survival than those who had none (median survival four months *v* 11 months).⁶¹ Kaplan *et al* identified a CD4 count of fewer than 1000 cells/l as the most important factor in predicting survival, though performance score, development of AIDS before the lymphoma, and presence of advanced disease were also recorded as relevant.⁶² Lastly, Gisselbrecht *et al* identified low performance score, CD4 count less than 1000/l, and AIDS diagnosis before non-Hodgkin's lymphoma as important in predicting survival, half of patients with none of these features being alive two years after the diagnosis of non-Hodgkin's lymphoma.⁶³

Patients with primary central nervous system non-Hodgkin's lymphoma had a significantly shorter median survival than patients with peripheral systemic lymphomas,⁶¹ possibly related to their substantially lower CD4 counts and consequent more severe immunosuppression. It is important to emphasise that leptomeningeal disease is not associated with poorer survival, though it is not unusual to find asymptomatic leptomeningeal lymphomas during the staging procedure. Hence lumbar puncture should be performed routinely in the staging of these patients. On account of the aggressive course of non-Hodgkin's lymphoma, intensive chemotherapy regimens should be used. The risk of severe side effects—particularly bone marrow toxicity—is of special concern in patients with aggressive non-Hodgkin's lymphoma. Gisselbrecht *et al* showed that HIV positive patients in a low risk category—that is, without opportunistic infections and full blown AIDS and with good performance status—

could be treated with intensive chemotherapy such as LNH 84.⁶³ A complete response was obtained in 90 (64%) of 141 patients, a rate not significantly different from that in HIV negative non-Hodgkin's lymphoma (75%). Twenty (14%) patients died during treatment, half due to the toxicity and half due to the progression of the disease.⁶³ For patients with CD4 counts less than 1000/l and performance score less than 80% the probability of survival at two years was 50%.

Levine *et al* have evaluated a low dose methotrexate-bleomycin-doxorubicin-cyclophosphamide-vincristine-dexamethasone (M-BACOD) regimen in patients with and without adverse prognostic factors.⁶⁵ Their findings showed that less intensive regimens of combination chemotherapy with early central nervous system prophylaxis may be comparable to more intensive regimens, which are associated with a high rate of opportunistic infections. Other workers have found that high risk patients respond poorly to low dose chemotherapy with a cyclophosphamide-doxorubicin-vincristine-prednisone (CHOP)-like regimen in association with zidovudine with complicating opportunistic infections and with disappointing overall survival.⁶⁶ Use of bone marrow growth factors, however, might overcome some of these problems. Kaplan *et al* reported benefit with granulocyte-macrophage colony stimulating factor in association with cyclophosphamide-doxorubicin-vincristine-prednisone with a substantial decrease in bone marrow toxicity.⁶⁷ Tirelli *et al* have shown that granulocyte colony stimulating factor in association with chemotherapy greatly decreases bone marrow toxicity and thus the delay between cycles of chemotherapy without any increase in the overall cost of treatment.⁶⁸

The European Organisation for Research and Treatment of Cancer's AIDS and Tumor Study Group has undertaken a multicentre European study of non-Hodgkin's lymphoma in order to compare chemotherapy regimens of different intensity in patients with low, intermediate, and high risk category disease. High risk was defined as the presence of one or more of the following: CD4 count less than 1000/l; performance score $\geq 80\%$; diagnosis of AIDS. Granulocyte colony stimulating factor will be given to all these patients and zidovudine will be given after the induction of chemotherapy.

OTHER TUMOURS

It is now evident that Hodgkin's disease in HIV positive patients presents with special clinicopathological characteristics, including higher frequency of mixed cellularity and lymphocytic depletion subtypes and more widespread disease, and has subsequent poorer outcome than in HIV negative patients.⁶⁹ In the Italian series (the largest published so far) the median CD4 count at diagnosis of Hodgkin's disease was $249 \times 10^6/l$, therefore requiring the use of antiretroviral therapy.⁶⁹ Preliminary data show that the combination of tailored chemotherapy regimens and zidovudine in these patients may result in a substantial decrease in opportunistic infections when compared with patients treated with conventional chemotherapy like mustine-vincristine-procarbazine-prednisone (MOPP) or doxorubicin-bleomycin-vinblastine-dacarbazine (ABVD) without zidovudine.⁶⁸

Women with HIV infection have a high risk of cervical dysplasia and cervical carcinoma. Similarly, there is an increase in anal carcinoma, especially in association with a history of anal intercourse in homosexual or bisexual men. Numerous single case reports and small series have described the development of miscellaneous cancers in HIV infected patients.⁷⁰ The largest group of solid cancers in the series of Monfardini *et al* consisted of germinal testicular cancers in 12 patients without, however, any

Invasive squamous carcinoma in skin rising from posterior region of right axilla in patient with HIV infection

unusual adverse prognostic factors when compared with those observed in the general population.⁴

This work was supported in part by the Istituto Superiore di Sanità, AIDS project 1993, Rome, and by the Associazione Italiana per la Ricerca sul Cancro, Milan.

- Coté TR, Howe HL, Anderson SP, Martin RJ, Evans B, Francis BJ. A systematic consideration of the neoplastic spectrum of AIDS: registry linkage in Illinois. *AIDS* 1991;5:49-53.
- Reynolds P, Saunders LD, Layefsky ME, Lemp GF. The spectrum of acquired immunodeficiency syndrome (AIDS)-associated malignancies in San Francisco, 1980-1987. *Am J Epidemiol* 1993;137:19-30.
- Rabkin CS, Biggar RJ, Horn JW. Increasing incidence of cancers associated with the human immunodeficiency virus epidemic. *Int J Cancer* 1991;47:692-6.
- Monfardini S, Vaccher E, Pizzocaro G, Stellino R, Sinicco A, Sabbatini S, et al. Unusual malignant tumors in 49 patients with HIV infection. *AIDS* 1989;3:449-52.
- Biggar RJ, Horn J, Goedert JJ, Melbye M. Cancer in a group at risk of acquired immunodeficiency syndrome (AIDS) through 1984. *Am J Epidemiol* 1987;126:578-86.
- Ree HJ, Strauchen JA, Khan AA, Gold JE, Crowley JP, Kahn H, et al. Human immunodeficiency virus-associated Hodgkin's disease. *Cancer* 1991;67:1614-21.
- Beral V, Perterman AT, Berkman RL, Jaffe HW. Kaposi's sarcoma among persons with AIDS: a sexually transmitted infection? *Lancet* 1990;335:123-8.
- Serraino D, Salamina G, Franceschi S, Dubois D, La Vecchia C, Brunet JB, et al. The epidemiology of AIDS-associated non-Hodgkin's lymphoma in the World Health Organization European region. *Br J Cancer* 1992;66:912-6.
- Beral V, Bull D, Darby S, Weller I, Carne C, Beecham M, et al. Risk of Kaposi's sarcoma and sexual practices associated with faecal contact in homosexual or bisexual men with AIDS. *Lancet* 1992;339:632-5.
- Serraino D, Zaccarelli M, Franceschi S, Greco D. The epidemiology of AIDS-associated Kaposi's sarcoma in Italy. *AIDS* 1992;6:1015-9.
- Casabona J, Melbye M, Biggar R, AIDS Registry Contributors. Kaposi's sarcoma and non-Hodgkin's lymphoma in European AIDS cases. No excess risk of Kaposi's sarcoma in Mediterranean countries. *Int J Cancer* 1991;47:49-53.
- Serraino D, Franceschi S, Tirelli U, Monfardini S. The epidemiology of acquired immunodeficiency syndrome and associated tumours in Europe. *Annals of Oncology* 1992;3:595-603.
- Elford J, McDonald A, Kaldor J, National HIV Surveillance Committee. Kaposi's sarcoma as a sexually transmissible infection: an analysis of Australian AIDS surveillance data. *AIDS* (in press).
- Gail MH, Pluda JM, Rabkin CS, Biggar RJ, Goedert JJ, Horn JW, et al. Projections of the incidence of non-Hodgkin's lymphoma related to acquired immunodeficiency syndrome. *J Natl Cancer Inst* 1991;83:695-701.
- Miles S. Pathogenesis of human immunodeficiency virus-related Kaposi's sarcoma. *Current Opinion in Oncology* 1992;4:875-82.
- Rutgers JL, Wiczorek R, Bonetti F, Kaplan KL, Posnett DN, Friedman-Kien AE, et al. The expression of endothelial cell surface antigens by AIDS-associated Kaposi's sarcoma: evidence for a vascular endothelial cell origin. *Am J Pathol* 1986;122:493-9.
- Weich HA, Zaki Salahuddin S, Gill P, Nakamura S, Gallo RC, Folkman J. AIDS-associated Kaposi's sarcoma-derived cells in long-term culture express and synthesize smooth muscle alpha-actin. *Am J Pathol* 1991;139:1251-8.
- Carbone A, Tirelli U, Vaccher E, Volpe R, Ghiohni A, Bertola G, et al. A clinicopathologic study of lymphoid neoplasias associated with human immunodeficiency virus infection in Italy. *Cancer* 1991;68:842-52.
- Levine AM. Acquired immunodeficiency syndrome-related lymphoma. *Blood* 1992;80:8-20.
- Lowenthal DA, Straus DJ, Campbell SW, Gold JWM, Clarkson BD, Koziner B. AIDS-related lymphoid neoplasia: the Memorial Hospital experience. *Cancer* 1988;61:2325-37.
- Hessol NA, Katz MH, Liu JY, Buchbinder SP, Rubino CJ, Holmberg SD. Increased incidence of Hodgkin's disease in homosexual men with HIV infection. *Ann Intern Med* 1992;117:309-11.
- Carbone A, Tirelli U, Ghiohni A, Volpe R, Boiocchi M. HIV-associated systemic lymphomas may be subdivided into two main groups according to Epstein-Barr viral latent gene expression. *J Clin Oncol* 1993;11:1674-81.
- Raphael M, Gentilhomme O, Tulliez M, Byron PA, Diebold J, French Study Group of Pathology for Human Immunodeficiency Virus-Assisted Tumors. Histopathologic features of high-grade non-Hodgkin's lymphomas in acquired immunodeficiency syndrome. *Arch Pathol Lab Med* 1991;115:15-20.
- Pedersen C, Gerstoft J, Lundgren JD, Skinhoj P, Bottzauw J, Geisler C, et al. HIV-associated lymphoma: histopathology and association with Epstein-Barr virus genome related to clinical, immunological and prognostic features. *Eur J Cancer* 1991;27:1416-23.
- Joachim HL, Dorsett B, Cronin W, Maya M, Wahl S. Acquired immunodeficiency syndrome-associated lymphomas: clinical, pathologic, immunologic and viral characteristics of 111 cases. *Hum Pathol* 1991;22:659-73.
- Knowles DM, Chamulak GA, Subar M, Burke JS, Dugan M, Wernz J, et al. Lymphoid neoplasia associated with the acquired immunodeficiency syndrome (AIDS): the New York University Medical Center experience with 105 patients (1981-1986). *Ann Intern Med* 1988;108:744-53.
- Hui PK, Feller AC, Lennett K. High-grade non-Hodgkin's lymphoma of B-cell type. I. Histopathology. *Histopathology* 1988;12:127-43.
- Hamilton-Dutoit SJ, Pallesen G, Franzmann MB, Karkov J, Black F, Skinhoj P, et al. AIDS-related lymphoma. Histopathology, immunophenotype, and association with Epstein-Barr virus as demonstrated by in situ nucleic acid hybridization. *Am J Pathol* 1991;138:149-63.
- Stansfeld AG, Diebold J, Kapanci Y, Kelenyi G, Lennett K, Mioduszewska O, et al. Updated Kiel classification for lymphomas. *Lancet* 1988;ii:292-3.
- Voelkerding KV, Sandhaus LM, Kim HC, Wilson J, Chittenden T, Levine AJ, et al. Plasma cell malignancy in the acquired immune deficiency syndrome. Association with Epstein-Barr virus. *Am J Clin Pathol* 1989;92:222-8.
- Stein H, Mason DY, Gerdes J, O'Connor N, Wainscoat J, Pallesen G, et al. The expression of the Hodgkin's disease associated antigen Ki-1 in reactive and neoplastic lymphoid tissue: evidence that Reed-Sternberg cells and histiocytic malignancies are derived from activated lymphoid cells. *Blood* 1985;66:848-58.
- Pallesen G, Hamilton-Dutoit SJ, Rowe M, Lisse I, Ralfkiaer E, Sandvej K, et al. Expression of Epstein-Barr virus replicative proteins in AIDS-related non-Hodgkin's lymphoma cells. *J Pathol* 1991;165:289-99.
- Gonzalez-Clemente JM, Ribera JM, Campo E, Bosch X, Montserrat E, Grau JM. Ki-1+ anaplastic large-cell lymphoma of T-cell origin in an HIV-infected patient. *AIDS* 1991;5:751-5.
- Tirelli U, Serraino D, Carbone A. Hodgkin disease and HIV. *Ann Intern Med* 1993;118:313.
- Serraino D, Carbone A, Franceschi S, Tirelli U, for Italian Cooperative Group on AIDS and Tumours. Increased frequency of lymphocyte depletion and mixed cellularity subtypes of Hodgkin's disease in HIV infected patients. *Eur J Cancer* 1993;29A:1948-50.
- Subar M, Neri A, Inghirami G, Knowles DM, Dalla-Favera R. Frequent c-myc oncogene activation and infrequent presence of Epstein-Barr virus genome in AIDS-associated lymphoma. *Blood* 1988;72:667-71.
- Chappuis BB, Muller H, Stutte J, Hey MM, Hubner K, Muller-Hermelink HK. Identification of EBV-DNA in lymph nodes from patients with lymphadenopathy and lymphomas associated with AIDS. *Virchows Arch [B]* 1990;58:199-205.
- Guarner J, del Rio C, Carr D, Hendrix LE, Eley JW, Unger ER. Non-Hodgkin's lymphomas in patients with human immunodeficiency virus infection. Presence of Epstein-Barr virus by in situ hybridization, clinical presentation, and follow-up. *Cancer* 1991;68:2460-5.
- Shibata D, Weiss LM, Nathwani BN, Brynes RK, Levine AM. Epstein-Barr virus in benign lymph node biopsies from individuals infected with the human immunodeficiency virus is associated with concurrent or subsequent development of non-Hodgkin's lymphoma. *Blood* 1991;77:1527-33.
- Carbone A, Ghiohni A, Zanette I, Canal B, Volpe R. Demonstration of Epstein-Barr viral genomes by in situ hybridization in acquired immune deficiency syndrome-related high-grade and anaplastic large cell CD30+ lymphomas. *Am J Clin Pathol* 1993;99:289-97.
- Uccini S, Monardo F, Ruco LP, Baroni CD, Faggioni A, Agliano AM, et al. High frequency of Epstein-Barr virus genome in HIV-positive patients with Hodgkin's disease. *Lancet* 1989;ii:1458.
- Audouin J, Diebold J, Pallesen G. Frequent expression of Epstein-Barr virus latent membrane protein-1 in tumour cells of Hodgkin's disease in HIV-positive patients. *J Pathol* 1992;167:381-4.
- MacMahon EME, Glass JD, Hayward SD, Mann RB, Becker PS, Charache P, et al. Epstein-Barr virus in AIDS-related primary central nervous system lymphoma. *Lancet* 1991;338:969-73.
- Boiocchi M, De Re V, Ghiohni A, Vaccher E, Dolcetti R, Marzotto A, et al. High incidence of monoclonal EBV episomes in Hodgkin's disease and anaplastic large cell Ki-1-positive lymphomas in HIV-1-positive patients. *Int J Cancer* 1993;54:53-9.
- Boiocchi M, Dolcetti R, De Re V, Ghiohni A, Carbone A. Demonstration of a unique Epstein-Barr virus-positive cellular clone in metachronous multiple localizations of Hodgkin's disease. *Am J Pathol* 1993;142:33-8.
- Ballerini P, Gaidano G, Inghirami G, Gong JZ, Saglio G, Knowles DM, et al. Multiple genetic alterations in AIDS-associated lymphomas. *Blood* 1991;78(suppl 1):327a.
- Ballerini P, Gaidano G, Gong JZ, Tassi V, Saglio G, Knowles DM, et al. Molecular pathogenesis of HIV-associated lymphomas. *AIDS Res Hum Retroviruses* 1992;8:731-5.
- Gaidano G, Ballerini P, Gong JZ, Inghirami G, Neri A, Newcomb EW, et al. P53 mutations in human lymphoid malignancies: associations with Burkitt lymphoma and chronic lymphocytic leukaemia. *Proc Natl Acad Sci USA* 1991;88:5413-7.
- Cooper JS, Steinfeld AD, Lerch I. Intentions and outcomes in the radiotherapeutic management of epidemic Kaposi's sarcoma. *Int J Radiat Oncol Biol Phys* 1991;20:419-22.
- Cooper JS, Fried PR. Oral radiotherapy in patients having AIDS. *Archives of Otolaryngology* 1987;113:327-8.
- Serfling U, Hood AF. Local therapies for cutaneous Kaposi's sarcoma in patients with acquired immunodeficiency syndrome. *Arch Dermatol* 1991;127:1479-81.
- Fischl MA, Uttamchandani RB, Resnick L, Agarwal R, Fletcher MA, Patrone-Reese J, et al. A phase I study of recombinant human interferon-alpha 2a or human lymphoblastoid interferon-alpha n1 and concomitant zidovudine in patients with AIDS-related Kaposi's sarcoma. *Journal of Acquired Immune Deficiency Syndrome* 1991;4:1-10.
- Scadden DT, Bering HA, Levine JD, Bresnahan J, Evans L, Epstein AC, et al. GM-CSF as an alternative to dose modification of the combination zidovudine and interferon-alpha in the treatment of AIDS-associated Kaposi's sarcoma. *Am J Clin Oncol* 1991;14(suppl 1):40-4.
- Buchbinder A, Friedman-Kien AE. Clinical aspects of Kaposi's sarcoma. *Current Opinion in Oncology* 1992;4:867-74.
- Gill PS, Tarick M, McCutchan JA, et al. Systemic treatment of AIDS-related Kaposi's sarcoma: results of a randomized trial. *Am J Med* 1991;90:427-34.
- Northfelt DW, Martin FJ, Kaplan LD, Russell J, Anderson M, Lang J, et al. Pharmacokinetics (PK), tumor localization (TL), and safety of doxil (liposomal doxorubicin) in AIDS patients with Kaposi's sarcoma (AIDS-KS). *Proceedings of the American Society of Clinical Oncology* 1993;51:8.
- Present CA, Scolaro M, Kennedy P, Blayney DW, Wiseman C. Liposomal daunorubicin as tumor-targeted chemotherapy: initial clinical results in Kaposi's sarcoma [abstract]. *Proceedings of the American Society of Clinical Oncology* 1992;11:47.
- Biesert L, Suhartono H, Winker I, Meichsner C, Helsenberg M, Hewlett G, et al. Inhibition of HIV and virus replication by polysulphated polyxylan: HOE/BAY 946, a new antiviral compound. *AIDS* 1989;2:449-57.
- Levine AM, Meyer PR, Begandy MK, Parker JW, Taylor CR, Irwin L, et al. Development of B-cell lymphoma in homosexual men: clinical and immunologic findings. *Ann Intern Med* 1984;100:7.
- Ziegler JL, Beckstead JA, Volberding PA, Abrams DI, Levine AM, Lukes RJ, et al. Non-Hodgkin's lymphoma in 90 homosexual men: relation to generalized lymphadenopathy and the acquired immunodeficiency syndrome. *N Engl J Med* 1984;311:565.
- Levine AM, Sullivan-Halley J, Pike MC, Rarick MV, Loureiro C, Bernstein-Singer M, et al. HIV-related lymphoma: prognostic factors predictive of survival. *Cancer* 1991;68:2466.
- Kaplan LD, Abrams DI, Feigal E, McGrath M, Kahn J, Neville P, et al. AIDS-associated non-Hodgkin's lymphoma in San Francisco. *JAMA* 1989;261:719.
- Gisselbrecht C, Oksenhendler E, Tirelli U, et al. Human immunodeficiency virus-related lymphoma treatment with LNH84 regimen in a "good risk" population. *Am J Med* 1993;95:188-96.

- 64 Coiffier B, Gisselbrecht C, Herbrecht R, Tilly H, Bosly A, Brousse N. LNH84 regimen: a multicenter study of intensive chemotherapy in 737 patients with aggressive malignant lymphoma. *J Clin Oncol* 1989;7:1018-26.
- 65 Levine AM, Wernz JC, Kaplan L, Rodman N, Cohen P, Metroka K, et al. Low dose chemotherapy with CNS prophylaxis and zidovudine maintenance for AIDS-related lymphoma: a prospective multiinstitutional trial. *JAMA* 1991;266:84.
- 66 Tirelli U, Errante D, Oksenhendler E, Spina M, Vaccher E, Serrano D, et al. Prospective study with combined low-dose chemotherapy and zidovudine in 37 patients with poor-prognosis AIDS-related non-Hodgkin's lymphoma. *Annals of Oncology* 1992;3:843-7.
- 67 Kaplan LD, Kahn JO, Crowe S, Northfelt D, Neville P, Grossberg H, et al. Clinical and virologic effects of recombinant human granulocyte-macrophage colony stimulating factor in patients receiving chemotherapy for human immunodeficiency virus associated non-Hodgkin's lymphoma: results of a randomized trial. *J Clin Oncol* 1991;9:929.
- 68 Tirelli U, Errante D, Vaccher E, Tavio M, Accurso V, Bernardi D, et al. Treatment of HIV-related non-Hodgkin's lymphoma (NHL) with chemotherapy (CT) and G-CSF: reduction in the days of hospitalization and toxicity with concomitant overall reduction in the cost. *Proceedings of the American Society of Clinical Oncology* 1993;33:13.
- 69 Tirelli U, Errante D, Vaccher E, Repetto L, Rizzardini G, Spina M, et al. Hodgkin's disease in 92 patients with HIV infection: the Italian experience. *Annals of Oncology* 1992;4:69-72.
- 70 Spina M, Tirelli U. Human immunodeficiency virus as a risk factor in miscellaneous cancers. *Current Opinion in Oncology* 1992;4:907-10.
- 71 Biggar RJ, Burnett W, Miki J, Nasca P. Cancer among New York men at risk of acquired immunodeficiency syndrome. *Int J Cancer* 1989;43:979-85.

Medicine in Europe

Health and social inequality in Europe

Chris Power

This is the seventh in an intermittent series of articles looking at medical issues in Europe

In most European countries health has been shown to be linked to social circumstances—gradients in health status have persisted for decades, despite major changes in the principal causes of death. In central and eastern Europe life expectancy has stagnated since the mid-60s, whereas in the West it has increased; but even in the West it is related to income distribution. Social differences in mortality in men are three times as large in some countries as in others, and are influenced by factors other than conventional risk factors. Substantial declines in mortality and morbidity could result from a narrowing of health inequalities even when differences in health risk between social groups are comparatively small. Policies to reduce health inequalities can be introduced in smaller communities and organisations such as the school and workplace. National policies are variable; factors generating inequalities require action across several policy areas.

The importance of tackling social differences in health to improve national health status is now explicitly recognised in many European countries, such as the Netherlands and Finland, as it is in other developed nations, including Australia and Canada.^{1,4} The World Health Organisation European strategy for Health for All states that "by the year 2000, the actual differences in health status between countries and between groups within countries should be reduced by at least 25%, by improving the level of health of disadvantaged nations and groups."⁵ The commitment to this strategy continues in discussions at the European level, as is apparent from a recent public hearing on the development of public health policy held by the European parliament.⁶

Evidence linking health and social circumstances is available for most European countries,^{7,8} although much of the early evidence came primarily from Britain,⁹ where it continues to generate considerable debate.¹⁰

It is almost universally the case that people in lower social classes have more morbidity and disability and have shorter lives. This is not usually a dichotomy of "privileged" and "unprivileged" but a monotonic decrease in life expectancy and increase in morbidity with declining socioeconomic status. These gradients in health status have persisted for decades, despite major changes in the principal causes of death. Changes in the magnitude of the gradient have occurred over time, however, and there are also variations between countries. My purpose here is to review the current situation in Europe, emphasising

where the most progress in reducing social inequalities in health has been achieved.

There is an additional problem of socially excluded groups, such as immigrant workers and long term unemployed people, who are becoming increasingly isolated from the rest of society in European countries.¹¹ This paper does not address the problems of these groups specifically; it is concerned with the more general aspect of social inequality between European citizens, relating particularly to socioeconomic gradients in health.

Explanations

Explanations for social differences in health tend to be discussed under the general headings shown in box 1. Many studies, particularly in Britain, have investigated these factors and shown that most of them are important.¹² Lifestyles differ between socioeconomic groups, with generally more health damaging behaviour in lower groups,¹³ although patterns vary slightly between European countries.

Explanations for social differences in health

- Lifestyle
- Physical environment
- Socioeconomic environment (including education)
- Access to and response to health care services
- Reverse causality, "selective drift"
- Inherited biological potential

People in lower socioeconomic groups are more likely to live and work in hazardous physical environments.¹⁴

Material and social resources, including educational attainment, also vary across the social scale, with accompanying variations in job control and social networks.¹³⁻¹⁵ The ability of people in lower socioeconomic groups to take advantage of health care services—preventive as well as curative—varies even under universal health care schemes.¹⁶ Selective social drift, whereby the healthiest climb the social hierarchy and the least healthy drift down, may also occur, although it is now regarded as having a weak effect on the distribution of health status in society in comparison with the influences described above.^{15,17}

Finally, there remains a possibility of differences in genetic endowment between social groups, but evidence for this is lacking. The Black report favoured differences in material and social circumstances as the

Epidemiology and Biostatistics, Institute of Child Health, London WC1N 1EH
Chris Power, senior lecturer

BMJ 1994;308:1153-6