STUDIES ON THE PROGNOSIS

OF PATIENTS WITH THE

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

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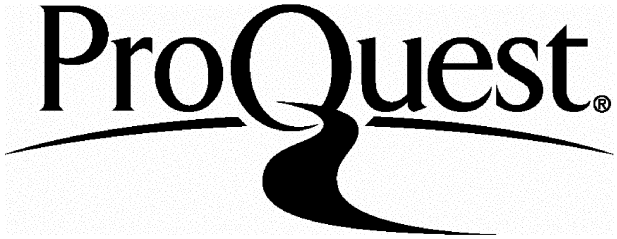

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ABSTRACT

This thesis presents the epidemiological results of the follow-up of almost nine thousand patients with AIDS diagnosed between 1979 and July 1995 from three groups; the AIDS in Europe Study Group, the Royal Free Hospital cohort and the Chelsea and Westminster Hospital cohort. There is known to be considerable heterogeneity in survival after an AIDS defining diagnosis, such differences may be caused by a variety of factors and it is these factors which are explored in this thesis.

AIDS defining events have been ranked in terms of survival. Median survival ranged from 2 to 19 months depending on the diagnosis but the ranking of diseases was consistent after stratification for year of diagnosis, whether the event was an initial or subsequent diagnosis, and whether zidovudine treatment had been initiated. Median survival after an initial AIDS diagnosis in a large group of UK AIDS patients was 20 months, somewhat longer than previously estimated. Patients diagnosed with AIDS after 1987 were significantly more likely to survive their initial AIDS defining event than patients diagnosed before this date. The CD4 lymphocyte count, which drops throughout infection with HIV, and age were found to be strongly related to survival. The median CD4 lymphocyte count at which AIDS defining events occur varied quite widely, similarly, the incidence of AIDS defining events was highly dependent on the CD4 count. Each successive diagnosis of an AIDS defining illness was found to increase the risk of death significantly independently of the latest CD4 lymphocyte count; categorising the events as mild, severe and very severe led to a staging system which also utilised the CD4 lymphocyte count. This staging system was validated on two further cohorts of patients with remarkable agreement. Following the recent identification of a herpes virus thought to play a role in the development of Kaposi's sarcoma, patients who were treated with foscamet and ganciclovir were found to be at a reduced risk of Kaposi's sarcoma during subsequent follow-up.

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I am indebted to my family and friends for their continued support during the many years I have been studying for different qualifications; my father and brothers may now be convinced that the years of studying are drawing to a close. In particular, thanks go to Jonathan Downing for the many hours spent encouraging me to finish this thesis. I count myself as extremely lucky to have had the support of two families, and my 'outlaws' must be thanked for their help, sympathy and hospitality over the years.

This thesis is dedicated to Evelyn Ruth Mocroft, a very special mother, who would have been bursting with pride in the finished product.

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CHAPTER 1 - INTRODUCTION

1.1 HIV and AIDS

1.1.1 The AIDS Epidemic

In 1981, cases of previously rare diseases, such as *Pneumocystis carinii* pneumonia and Kaposi's sarcoma, were observed in a few homosexual patients in the United States[1-4]. A retrospective investigation by the Centers for Disease Control (CDC) in America suggested that the earliest case of the syndrome appeared in 1978[5]. Later that year the disorder was being described in other patient groups, including intravenous drug users (IDU's) whose sexual orientation was reported as either heterosexual or unknown[6], blood transfusion recipients[7], men with haemophilia[8], those whose only apparent exposure was heterosexual sex[9] and children born to infected mothers[10]. This syndrome was named the Acquired Immune Deficiency Syndrome (AIDS).

Following an investigation into these reports, the CDC adopted a definition for AIDS[11]. The original definition specified AIDS to be:

> *'a person who has had a reliably diagnosed disease that is at least moderately indicative of an underlying cellular immune deficiency (such as an opportunistic infection, or Kaposi's sarcoma in a person aged less than 60 years), but who, at the same time, has had no known underlying cause of cellular immune deficiency, nor any other cause of reduced resistance reported to be associated with that disease'*

The first case of AIDS in the United Kingdom was reported in December 1981[12], which was followed by the Public Health Laboratory Services (PHLS) Communicable Disease Surveillance Centre (CDSC) setting up a voluntary reporting scheme to monitor the incidence of Kaposi's sarcoma and opportunistic infections in Britain.

Several revisions have been made to the definition of AIDS, in 1985, 1987, and 1992[13-15], and include changes to those diseases that make up the surveillance definition of the disease, and to take account of the discovery of the Human Immunodeficiency Virus (HIV) in 1983, a ribonucleic acid (RNA) retrovirus, which is the causative agent of AIDS[16-18]. In 1986, a second HIV virus, now called HIV-2, was isolated[19]. The most recent amendment to the AIDS definition was made in 1992[15] with the inclusion of three new AIDS defining conditions; recurrent pneumonia within a twelve month period, pulmonary

tuberculosis and invasive cervical carcinoma. In addition, a diagnosis of profound immunodeficiency in the absence of clinical symptoms was adopted as an AIDS defining diagnosis in the United States. Each of the clinical conditions currently used as an AIDS indicator diagnosis is shown in Table 1.1. It should be remembered however that AIDS is a surveillance definition for a disease, and the choice of the diseases that define AIDS is somewhat arbitrary and mainly reflects the diseases that are common in the United States. To date, notification of an AIDS diagnosis remains voluntary in most countries.

1.1.2 The Growth of the Epidemic

Figure 1.1

Cumulative AIDS cases from 1978 to 31.12.95[20]

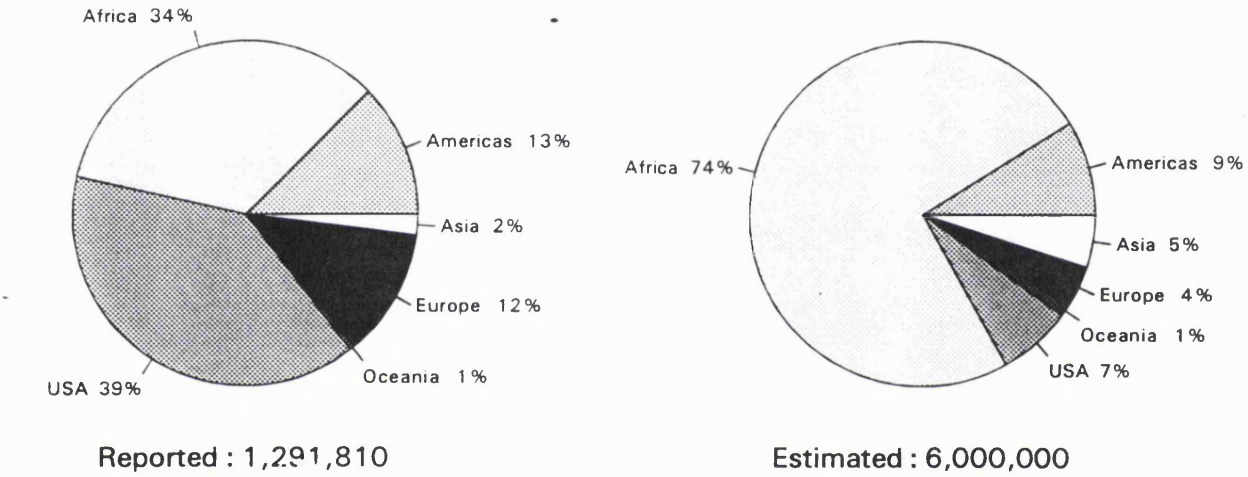


Figure 1.1 shows the breakdown by continent of the 1,291,810 AIDS cases which had been reported to the World Health Organisation (WHO) by the end of 1995. Also shown, based on revised estimates of HIV seroprevalence, is the estimated 6 million cases of AIDS which have occurred in adults and children worldwide[20]. The number of AIDS cases actually reported worldwide is an underestimate of the actual number of cases due to underreporting, underdiagnosis, and delays in reporting. However, AIDS is usually the end manifestation of infection with HIV, and it is estimated that around 17 million people were infected with HIV by the end of 1995[20]. Geographically, sub-Saharan Africa accounted for the majority of these infections, with over 11 million people thought to be infected, either through heterosexual exposure or mother to child transmission. Following the first cases reported in America and Europe, the epidemic has spread equally through both sexes particularly rapidly in Thailand and India (4 million infections in Asia)

Table 1.1

Current AIDS defining illnesses[15]

Candidiasis: trachea, bronchi or lungs
Candidiasis: oesophageal
*Cervical carcinoma, invasive
Coccidioidomycosis: extrapulmonary
Cryptococcosis: extrapulmonary
Cryptosporidiosis: with diarrhoea for over 1 month
Cytomegalovirus retinitis
CMV disease not in liver, spleen or nodes
Encephalopathy (dementia) due to HIV
Herpes simplex: ulcer(s) for over 1 month or bronchitis, pneumonitis, oesophagitis
Histoplasmosis: disseminated or extrapulmonary
Isosporiasis: with diarrhoea for over 1 month
Kaposi's sarcoma
Lymphoma, Burkitt's, or equiv. term
Lymphoma, immunoblastic or equiv.
Lymphoma, primary in brain
Mycobacterium avium: extrapulmonary
**M. Tuberculosis:* pulmonary
M. Tuberculosis: extrapulmonary
Mycobacterium of other species, disseminated
Pneumocystis carinii pneumonia
*Pneumonia: recurrent within a twelve month period
Prog. multifocal leukoencephalopathy
Salmonella septicaemia, recurrent
Toxoplasmosis of brain
Wasting syndrome due to HIV

* Diagnoses added in 1993 CDC revision of the surveillance definition

AIDS INDICATOR DISEASE*	Definitive or Presumptive	Definitive diagnostic method **or** presumptive diagnositic criteria.
Bacterial infections, multiple or recurrent in a child aged less than 13 years	Definitive	culture, antigen detection, CSF microscopy.
Candidiasis, trachea, bronchi or lungs	Definitive	gross inspection at endoscopy/post-mortem or by microscopy (histology or cytology).
Candidiasis of oesophagus	Definitive	gross inspection at endoscopy/post-mortem or by microscopy (histology or cytology).
	Presumptive	recent onset retrosternal pain on swallowing or radiological evidence and confirmed oral or pharyngeal candidiasis.
Cervical carcinoma, invasive	Definitive	histology.
Coccidioidomycosis, disseminated or extrapulmonary	Definitive	microscopy, culture of, or antigen detection in, affected tissue.
Cryptococcosis, extrapulmonary	Definitive	microscopy, culture of, or antigen detection in, affected tissue.
Cryptosporidiosis, with diarrhoea for over 1 month	Definitive	stool microscopy.
Cytomegalovirus retinitis	**Presumptive**	loss of vision and characteristic appearance on serial ophthalmoscopy, progressing over several months.
Cytomegalovirus disease (onset after age 1 month) not in liver, spleen or nodes	Definitive	culture lung tissue, microscopy (histology or cytology), antigen or nucleic acid detection
Encephalopathy (dementia) due to HIV	Definitive	HIV infection and disabling cognitive and/or motor dysfunction, or milestone loss in a child, with no other causes by CSF examination, brain imaging or post-mortem.
Herpes simplex: ulcers for 1 month or bronchitis, pneumonitis, oesophagitis (onset after age 1 month)	Definitive	culture, microscopy of, or antigen detection in, affected tissue.
Histoplasmosis, disseminated or extrapulmonary	Definitive	microscopy, culture of, or antigen detection in, affected tissue.
Isosporiasis, with diarrhoea for over 1 month	Definitive	microscopy (histology or cytology).
Kaposi's sarcoma	Definitive	microscopy (histology or cytology).
	Presumptive	characteristic erythematous/violaceous plaque-like lesion on skin or mucous membrane.
Lymphoid interstitial pneumonia and/or pulmonary lymphoid hyperplasia in a child aged less than 13 years	Definitive	microscopy (histology or cytology).
	Presumptive	diffuse bilateral reticulonodular pulmonary interstitial infiltrates for over 2 months and no pathogen identified and no antibiotic response.
Lymphoma: Burkitt's or immunoblastic or primary in brain*	Definitive	microscopy (histology or cytology).
Mycobacteriosis disseminated* (including extrapulmonary TB)	Definitive	culture.
	Presumptive	AFB (species not identified by culture) on microscopy of stool specimen or normally sterile body fluid/tissue, not lungs, skin, cervical or hilar nodes.
Mycobacteriosis pulmonary tuberculosis*	Definitive	culture or other definitive demonstration of *M.tuberculosis* infection.
	Presumptive	clinical diagnosis, with or without AFB on microscopy, resulting in initiation of anti-TB therapy.
Pneumocystis carinii pneumonia	Definitive	microscopy (histology or cytology).
	Presumptive	recent onset dyspnoea on exertion or dry cough, and diffuse bilateral interstitial infiltrates on CXR and pO2 <70mm Hg (9.3kPa) and no evidence of bacterial pneumonia.
Pneumonia recurrent within a 12 mth period	Definitive	two episodes proven microbiologically.
	Presumptive	CXR or clinical diagnosis.
Progressive multifocal leukoencephalopathy	Definitive	electron microscopy, antigen detection in brain or urine, antibody in serum or CSF.
Salmonella (non-typhoid) septicaemia, recurrent	Definitive	culture.
Toxoplasmosis of brain onset after age 1 month	Definitive	microscopy (histology or cytology), mouse inoculation, tissue culture.
	Presumptive	recent onset focal neurological abnormality or reduced level of consciousness, and mass effect lesion on scan, and serological evidence or specific therapy response.
Wasting syndrome due to HIV	Definitive	weight loss (over 10% baseline) with no other cause, and 30 days or more of either diarrhoea or weakness with fever.

*Full case definition and notes on AIDS indicator diseases for neoplasms, mycobacteriosis and indicator diseases in children are available from CDSC.

1993 CLASSIFICATION SYSTEM

Category A: Acute (primary) HIV infection or Asymptomatic HIV infection or Persistent Generalized Lymphadenopathy.

Category B: Symptomatic with conditions other than those included in categories A or C attributed to HIV infection or which are indicative of a defect in cell mediated immunity.

For example:-

Bacillary angiomatosis œ Candidiasis, oropharyngeal (thrush) œ Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy œ Cervical dysplasia (moderate or severe)/cervical carcinoma in situ œ Constitutional symptoms, such as fever (38.5 C) or diarrhoea lasting > 1 month œ Hairy leukoplakia, oral œ Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome œ Idiopathic thrombocytopenic purpura œ Listeriosis œ Pelvic inflammatory disease œ Peripheral neuropathy.

Category C: Clinical conditions listed in the AIDS surveillance case definition presumptively or definitively diagnosed(see above).

and Latin America (2 million infections). In the United States and Europe the main groups affected by the epidemic continue to be homosexual men and IDU's[21].

1.1.3 The AIDS Epidemic in the United Kingdom

A total of 13,394 AIDS cases, of whom 12,092 (90.3%) were male, have been reported in the United Kingdom from 1982 (when reporting began) to the end of September 1995. By this date, 9,447 (71%) were known to have died[22]. A total of 7,132 cases (53%) were from the North Thames region alone. At the end of September, 1995, 27,845 patients have been reported as infected with HIV.

1.1.4 Transmission of HIV

The initial impression was that only individuals from high risk groups, such as homosexual men, IDU's and patients receiving blood products were at risk of HIV infection, but it soon became clear that this was not the case and that heterosexual transmission could take place[23]. HIV has been isolated from semen, cervical secretions, tears, saliva and breast milk. The concentration varies in each type of fluid, and it is possible that the stage or duration of infection and the biological properties of the virus or host may determine the transmission of HIV to uninfected sexual contacts[24]. Infection may also occur through the donation of organs, through needlestick accidents in health care workers, and from mother to child during pregnancy, at birth, or through breast feeding. Reported rates of transmission from mother to child range from 7 - 39%[25-28]. The treatment of HIV infected pregnant women with zidovudine, and the treatment of the new born child has been shown to substantially reduce the risk of transmission[29].

1.2 The Natural History of Infection with HIV

1.2.1 Seroconversion

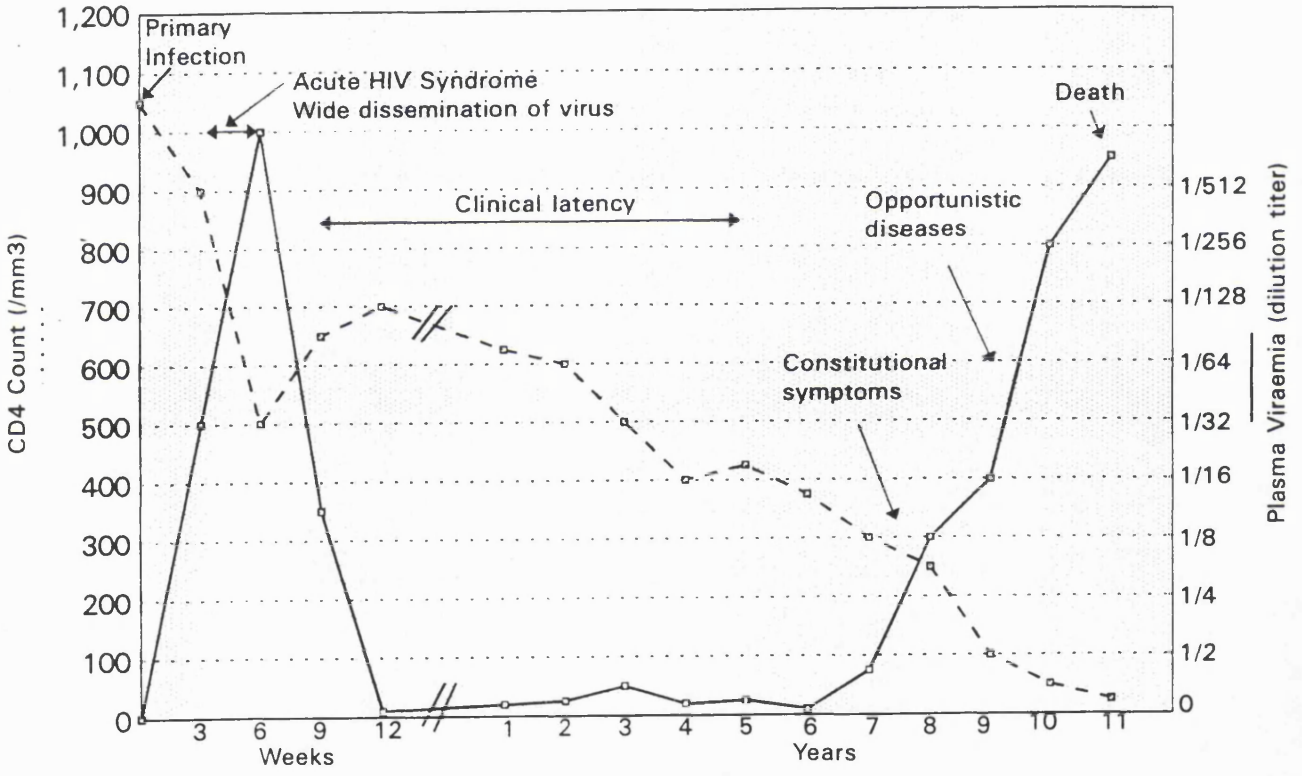
Infection with HIV can produce a varied clinical picture. Acute infection with HIV (or seroconversion illness) has been described as a 'mononucleosis-like syndrome' similar to glandular fever. Clinical symptoms may include fever, sweats, headache, diarrhoea, anorexia, lethargy, sore throats and a rash[30]. Responses to infection with the virus include the development of HIV p24 antigen, increased production of neopterin and beta-2-microglobulin, and lymphopenia[31]. Studies of persons with a documented HIV seroconversion that have specifically investigated the prevalence and features of primary HIV infection have estimated that symptomatic seroconversion occurs in between 40-80% of patients[31-35].

1.2.2 The Pathogenesis of infection with HIV

The pathogenesis of HIV infection as it is understood this far is depicted in Figure 1.2[36]. During the first few weeks of primary infection with HIV, there is a rapid replication of HIV producing a very high viral load, similar to that seen in advanced HIV infection. At this stage, CD4 cell counts often decline transiently. This intense viral production is associated with a wide dissemination of the virus to various organs, including the brain and lymphoid tissues[36]. After the first few weeks of infection, the viral load falls to lower levels. However, viral replication continues and the CD4 count continues to fall gradually. The level at which the viral replication plateaus may be related to clinical outcome[37].

Figure 1.2

The pathogenesis of HIV infection[36]



1.2.3 Symptomatic Disease

Some time after seroconversion, usually measured in years, clinical symptoms begin to appear, which include seborrhoeic eczema, herpes simplex, herpes zoster, oral hairy leucoplakia, oral candidiasis, thrombocytopenia, lymphadenopathy, anorexia, skin complaints and night sweats[23].

To briefly describe these pre-AIDS but presumably HIV-related symptoms, seborrhoeic eczema is one of the more common skin complaints, and presents as a scaly red rash on the face and scalp. Oral candidiasis (thrush), is characterised by the presence of white patches on the mucous membranes which can be easily removed. Oral hairy leucoplakia appears to be unique to HIV infected patients, and consists of white hairy lesions on the tongue and cheeks[38]. Herpes zoster, or shingles, is an acute skin eruption caused by the varicella zoster virus. Thrombocytopenia, defined as a low platelet count, can have more serious consequences; spontaneous bleeding may occur in severe cases. Treatment is available, such as platelet transfusion, removal of the spleen or antiretroviral therapy[23]. The lymphadenopathy seen in HIV patients has been called persistent generalised lymphadenopathy syndrome (or PGL), and is characterised by enlarged, often tender, lymph nodes that persist for at least three months[38]. All the conditions described here are rarely severe, but are often recurrent and resistant to normal treatment[39].

1.3 Project Aims and Objectives

The period of survival from an initial or subsequent AIDS diagnosis and the clinical events that occur are important subject areas when studying the syndrome called AIDS. Monitoring of the particular AIDS defining events and their outcome and interrelationship with each other and to survival can increase the understanding of the disease process. Such monitoring can also provide valuable information on the resources needed for health care planning and for assessment of various treatments and drugs available. AIDS and HIV results in a considerable cost, not only in human suffering, but also to health services. Studies of HIV and AIDS patients in the early 1990's in the UK estimated that the cost of caring for each AIDS patient was between fourteen and sixteen thousand pounds[40-41], taking account of only hospital and drug costs. Other, more hidden costs, include time off work and the effect of the death of the younger population on productivity and services. A clear understanding of the prognosis of AIDS patients forms the basis of developing a strategy for both health education and research.

Therefore the main aims of this thesis are to describe the prognosis of patients with AIDS, in terms of immunological, virological and clinical events that occur during follow-up, with special emphasis on the ranking of AIDS defining diseases which occur. More specific aims include:

i) to develop a ranking of AIDS defining diseases in terms of severity and to

determine the median survival after each of the diagnoses (Chapter 3)

ii) to investigate the relationship between cofactors such as age, exposure category, year of diagnosis and gender on disease progression and survival, together with the role of prognostic variables known at baseline, such as CD4 lymphocyte count and AIDS defining diagnosis (Chapter 4)

iii) to determine the median CD4 lymphocyte count at which each AIDS defining disease occurs, and to investigate the incidence of each AIDS defining disease across a wide range of CD4 lymphocyte counts (Chapter 5)

iv) to develop a grading system for AIDS patients using clinical and immunological data, and to validate this grading system on other groups of patients (Chapter 6)

v) to investigate the association between the use of antiherpes virus drugs (ganciclovir, foscarnet and acyclovir) and the development of Kaposi's sarcoma, following the identification of a new human herpes virus thought to play a role in the development of Kaposi's sarcoma (Chapter 7)

1.4 Layout of the Thesis

Chapter 2 describes the patients on which this thesis is based, the data which is available for analysis, and a description of the statistical methods that have been used. Also included is a description of the centres, procedures for clinical follow-up and information about treatment policies and research at each site. Following this, the Chapters follow the order described above. Each Chapter follows the same format, a literature review of the subject for each chapter, results and discussion. Each chapter has its own conclusions, but a final discussion to draw together the different threads of this thesis appears in Chapter 8.

CHAPTER 2 - PATIENTS AND METHODS

2.1 Introduction

The data analysed in this thesis are from three different sources; from the Royal Free Hospital and from the Chelsea and Westminster Hospital in London, and from a large European retrospective cohort study of patients with AIDS, the AIDS in Europe Study. In this chapter, the care at each of the hospitals and treatment policies are described, together with some details of the history of the AIDS in Europe Study, how the patients were selected and methods of data collection and analysis.

2.2 HIV/AIDS care at the Royal Free Hospital

The Royal Free Hospital HIV/AIDS unit appointed Dr Margaret Johnson, the first HIV/AIDS consultant in the United Kingdom, in 1989, which placed the unit into a General Medicine speciality rather than being part of a Genito-Urinary Medicine department. As activity in the Unit increased, a second consultant post was created in 1992. The Ian Charleson Day Centre was first used for treatment in 1991, and was officially opened by Sir Ian McKellan in October 1992. It is a purpose built facility, with six day beds which can be used for a variety of treatments and investigations such as pentamidine nebulisers, transfusion or endoscopy. There is also an outpatient area and all clinics are held in the centre. A walk-in service is available for patients who are feeling unwell, or who need repeat prescriptions. For patients requiring admission to the hospital, there are 14 specialist beds allocated to AIDS patients as part of a 20 bed general ward.

At a patient's first visit, a full clinical and social history is taken, which is recorded on a report form (Appendix 1.1) and computerised on the HIV/AIDS unit database. Subsequently, patients are seen every three to six months, or more regularly if clinically indicated. At each visit, the patient has a full clinical examination, and blood is taken for routine investigations, such as CD4 lymphocyte count. From August 1994, in addition to the initial form collecting patient history, a clinical report form (Appendix 1.2) has been completed during each patient consultation, which is also computerised. Prior to this date, data for specific analyses was collected retrospectively from patient notes. Non-routine data for specific research projects is collected on an ad-hoc basis.

In a large hospital setting such as this, there is a large scope for data collection and analyses, and while work has been done on many different aspects of HIV progression,

this thesis concentrates on the data items collected up to August 31 1994, shown in Table 2.1.

Table 2.1

Data included in analyses from the Royal Free hospital

Demographic	Sex
	Date of Birth
	Exposure Category
Clinical	Date of first clinic visit
	Date of last HIV negative test (if available)
	Date of first HIV positive test
	Date and diagnosis of all AIDS defining diagnoses[+•]
	Date of last patient follow-up
	Date of death
Laboratory Markers	Date and result of all CD4 lymphocyte counts
Treatment Information	Date of starting[•]:
	zidovudine
	ddI
	ddC
	nebulised pentamidine[!]
	cotrimoxazole[!]
	dapsone[!]
	clindamycin[!]
	acyclovir

[+] Only the first occurrence of each AIDS defining illness was collected
[•] Data items were collected by a retrospective search through patient notes
[!] Primary or secondary prophylaxis for *Pneumocystis carinii* pneumonia

2.2.1 Treatment Policies at the Royal Free Hospital

As this thesis uses data from patients collected before 31 August 1994, the treatment policies reflect those in use prior to August 1994.

Primary prophylaxis for *Pneumocystis carinii* pneumonia began in 1988 with nebulised pentamidine (300mg, monthly). Since 1991 cotrimoxazole has been used for primary prophylaxis (960 mg per day), except for those patients who were intolerant of this

treatment, who remained on nebulised pentamidine. Secondary prophylaxis follows the same protocol as described above, except that nebulised pentamidine is administered fortnightly.

Treatment for HIV infection itself began in 1987 with zidovudine, a nucleoside analogue, and tended to be at high doses (1000 mg per day). In 1994, patients were treated with much lower doses (500-600 mg per day), and often in combination with other antiretrovirals such as didanosine (ddI) and zalcitabine (ddC). For those patients who are not participating in trials, treatment with both antiretroviral therapy and primary *Pneumocystis carinii* pneumonia prophylaxis begins when a patient becomes symptomatic, or when the CD4 cell count has dropped below 200/mm^3. In addition to in-house studies on particular groups of patients, such as the seroconverter study, there are a wide range of clinical trials undertaken in the unit covering Phase I to Phase III studies. On average, 15 such studies will be ongoing at any one time, with approximately 250 patients participating.

2.3 HIV/AIDS care at the Kobler Centre, Chelsea and Westminster Hospital

The epicentre of the HIV epidemic in London was in the catchment area of the old St Stephen's Hospital on Fulham Road, Chelsea. Patients first began attending in 1981 and a small unit developed around the John Hunter Clinic in the Genito-urinary (GU) Medicine Department. The unit expanded under the auspices of Dr Adam Lawrence, GU Physician, and Dr Brian Gazzard, Consultant Gastroenterologist, using National Health Service (NHS) monies. In 1989 the St Stephen's Centre was opened adjacent to the hospital. This is a multi-disciplinary, five floor unit comprising a GU medicine facility and an HIV outpatient and day ward facility with six beds and an endoscopy suite. A wide range of treatment and investigations are offered and walk-in services are available for a patient to be seen for emergencies.

In 1990, the inpatient facilities relocated to Westminster Hospital, since St Stephen's main site was demolished, and the new Chelsea and Westminster, the flagship hospital of the NHS in London, was built on the site and reopened in 1993. HIV facilities include two wards, each with 21 beds, under the supervision of Dr Mark Nelson. As outpatients, patients are seen at three to six monthly intervals, or more often when clinically required. Should they require admission they are first seen as an outpatient or via casualty and then admitted to the ward. Physicians work between the outpatient and inpatient facilities

and there is a comprehensive, interactive computer system covering all HIV and AIDS information. Members of the Royal Free and Chelsea and Westminster Collaborative Group are shown in Appendix 2.1. At each visit, patients are examined and bloods taken for a wide range of investigations, including immunological tests. Clinical events are reported during patient consultation and this data is added to the computer database. Non routine data for specific research projects is collected on an ad hoc basis.

Data from the Chelsea and Westminster Hospital that has been analysed in this thesis is shown in Table 2.2. This thesis used data collected up to July 31 1995.

Table 2.2
Data from the Chelsea and Westminster hospital

Demographic	Sex
	Date of Birth
	Exposure Category
Clinical	Date of first clinic visit
	Date of first HIV positive test
	Date and diagnosis of all AIDS defining diagnoses
	Date of last patient follow-up
	Date of death
Laboratory Markers	Date and result of all CD4 lymphocyte counts
Treatment Information	Date of starting:
	zidovudine
	ddI
	ddC
	3TC
	PCP prophylaxis*
	acyclovir
	ganciclovir
	foscarnet

* Specific type of PCP prophylaxis used is not available

2.3.1 Treatment Policies at the Chelsea and Westminster Hospital

The treatment polices given below were those in use at July 1995, the cut-off date for data from the Chelsea and Westminster Hospital analysed in this thesis.

Primary prophylaxis for *Pneumocystis carinii* pneumonia began in 1986 with cotrimoxazole (960 mg daily). Desensitisation is attempted in patients who are intolerant of treatment with cotrimoxazole. A further alternative is treatment with 300mg nebulised pentamidine at fortnightly intervals, or 100 mg dapsone daily, in combination with pyremethamine, 25 mg twice weekly.

Treatment with zidovudine began in 1987 when the drug was licensed, there is no strict policy for the commencement of treatment. Currently, treatment with antiretrovirals may be with zidovudine, didanosine (ddI), zalcitabine (ddC), lamivudine (3TC), stavudine (D4T), or loviride, a non-nucleoside reverse transcriptase inhibitor. As at the Royal Free Hospital, there are a wide range of trials undertaken in the unit covering Phase I to Phase III studies. On average, 25 will be ongoing at any one time, with approximately 300 patients participating.

Both the Royal Free and the Chelsea and Westminster Hospitals are committed to research and participation in clinical trials involving patients with HIV. The patients attending the centres are aware of this policy and this may affect the patient population seen at these sites, in particular, this policy may encourage groups of patients who are willing to try experimental therapies and who wish their HIV disease to be extensively monitored.

2.4 The AIDS in Europe Study

The AIDS in Europe Study, coordinated in Copenhagen by the project leader Dr Jens Lundgren, attending physician, was a large European project which retrospectively gathered data on AIDS patients from 52 centres in 17 countries across Europe. Members of the study group are given in Appendix 2.2. Participating centres provided data on all patients diagnosed with AIDS between 1979 and 31 December 1989. The 23 Italian centres that participated each enrolled only a predefined proportion of their patients, based on month of birth, as individual centres could not complete forms for all AIDS patients seen in each centre. This procedure was supervised by the Istituto Superiore di Sanita in Rome.

Information was collected from patients' notes on standardised data collection forms, shown in Appendix 1.3. Information collected included demographic data, serology (results of tests for HIV antibodies), CD4 cell count within three months of diagnosis, time of initiation and permanent discontinuation of zidovudine, and time of diagnosis of opportunistic infections and malignancies and how these diagnoses were established. All time variables were recorded as month and year.

The collection of data was performed by retrospective review of case notes between May 1991 and August 1992. Members of the coordinating centre visited all major centres to ensure that data was correctly transferred from the patient charts to the data collection form. All forms received by the coordinating centre were checked by scientific staff for logical errors. In total, 6655 patients were enrolled. Seventy seven patients were excluded because the time of AIDS diagnosis or time of last follow-up was not known, because clinical information was missing, or because the subject was under 16 years of age at the time of diagnosis. A total of 13764 AIDS defining diseases were observed in the remaining patients.

2.5 Summary of Inclusion and Exclusion Criteria

Each of the chapters in this thesis includes a variety of patients from different sources, with a range of inclusion and exclusion criteria. This information is summarised in Table 2.3. The surveillance definition of AIDS has changed considerably over the thirteen years of data collection included in this thesis. Patients in the AIDS in Europe Study were diagnosed with AIDS according to the 1987 criteria from the CDC[14]. Patients from the Royal Free and Chelsea and Westminster Hospitals were diagnosed with AIDS according to the surveillance definition in use at the time. Patients have not been retrospectively diagnosed with AIDS. For example, a patient with recurrent pneumonia in 1990 and no further AIDS defining illnesses would not be notified as an AIDS patient in 1993 until they prospectively developed an AIDS defining illness included in the revised surveillance definition of 1993[15]. After 1993, patients with no clinical diagnosis and a CD4 lymphocyte count of below 200/mm^3 were not included as AIDS patients.

2.6 Statistical Methods

The statistical methods used in this thesis allow for right censoring of the survival data. This occurs when patients followed up during the study are lost to follow-up, or have not

Table 2.3

Summary of patients : inclusion and exclusion criterion

Chapter	Subject	Number of Patients	Source	Period of Study		Inclusion Criteria	Exclusion Criteria
				From	To		
3	Survival after each AIDS defining illness	6548	AIDS in Europe Study Group	1979	31/12/89	AIDS diagnosis	Incomplete Information
4	Survival after an AIDS diagnosis	2625	385 RFH 2240 CWH	1986 1982	31/8/94 31/7/95	AIDS diagnosis	No follow-up visit
5	Incidence of AIDS defining Illnesses	4883	907 RFH 3976 CWH	1986 1982	31/8/94 31/7/95	HIV +ve	No follow-up visit, no CD4 counts
6	Staging AIDS patients	385	RFH	1986	31/8/94	AIDS diagnosis	No follow-up visit
7	Kaposi's sarcoma, anti herpesvirus treatment	3688	CWH	1982	31/7/95	HIV +ve	KS at/within month of first visit, no CD4 counts

RFH; Royal Free Hospital Cohort
CWH; :Chelsea and Westminster Hospital Cohort

died by the cut-off date for the analysis. For these patients all that is known is that they were alive on the date they were last seen. In these circumstances the period of observation was cut off before the event of interest occurred, and is described as right-censored.

Kaplan-Meier and lifetable analyses provide a visual display of the cumulative rates of progression to clinical/immunological endpoints[42]. The median survival can be read directly from these curves as the time at which 50% of the patients in the group are expected to remain disease free. The log-rank test is used to compare the survival of independent groups[43]. This is a non-parametric test for testing the null hypothesis that the groups are from the same population as regards survival experience. The Cox proportional hazards model is used to assess the independent effects of covariates on patient survival/progression time [43]. All proportional hazards models used in this thesis were fitted using PROC PHREG in SAS software[44].

A person-years analysis was used to determine the rates of events, such as death rates, or the rate of developing opportunistic infections. This methodology was developed by Case and Lea[45], and has often been used to analyse mortality in occupational health research. Consider the following example; the death rate of patients with HIV will vary according to CD4 lymphocyte count. It would be sensible to determine the death rate over a range of CD4 count strata. Each patient passes through such strata during the period of follow-up, and experiences a risk of the event in each strata according to the length of time in the strata and the death rate. This risk is accumulated as long as the person remains in the strata, and ends either with the death of the patient or a decline in CD4 counts such that the patient moves to a lower strata. Patients are not allowed to move back through the strata. The observed number of deaths in each strata is assumed to follow a Poisson distribution. The death rate in each strata is calculated as the number of deaths divided by the person-years of follow-up within that strata, and has variance

$$\text{Variance (death rate)} = \text{observed number of deaths}/(\text{person-years follow-up})^2$$

2.6.1 Endpoints and Censoring Data

As data from the Royal Free Hospital and Chelsea and Westminster Hospital is regularly updated, a convenient date must be chosen as the end-date of the analysis, after which time the patient follow-up is censored if they were known to be alive at this date. The end date of the study is chosen such that follow-up to this date is essentially complete

for the majority of patients. For the Royal Free Hospital dataset, this date is 31 August 1994, for the Chelsea and Westminster Hospital, patient follow-up is censored at 31 July 1995. For patients from the AIDS in Europe Study, patients who did not die were censored on the date they last attended clinic.

In analyses such as these, bias can arise if the likelihood of the person being included in the analysis depends on how rapidly the individual has progressed. For example, consider a patient who was diagnosed with AIDS at a hospital in 1990 and then transferred to the Royal Free Hospital in 1992. Such a patient cannot be used to tell us anything about the probability of surviving for the first two years, as if the person had died within two years they would not be able to transfer their care to another hospital. Such a patient can only be included in the 'risk set', that is, the group of people at risk of death, after 1992, when their survival is two years. This phenomenon is referred to as left-truncation. It is not known whether this bias arises in the AIDS in Europe study, the inclusion criteria was all patients who had been diagnosed with AIDS. No information was available on the date of first visit to a centre. However, analysis of survival after AIDS using data from either the Royal Free Hospital or the Chelsea and Westminster hospital may be biased in this way, and in these analyses, left-truncation should be used. Graphs representing the probability of survival may be used when patient follow-up is left and right truncated to estimate median survival, and are based on a lifetable analysis[46]. The probability of survival after a given time is calculated as the probability of surviving to that date, multiplied by the probability of surviving a further day.

There are two main types of analyses included in this thesis. The first considers the progression of disease until death, where patient follow up is from the diagnosis of HIV or AIDS until death or last patient visit. The second follows patients until the diagnosis of a particular disease, and in patients in whom this disease is not diagnosed, patients are censored at death or last patient visit, whichever occurs first.

2.6.2 The Cox Proportional Hazards Model

This method (described in detail in Appendix 3) provides estimates of the relative hazard of progressing to each endpoint for each covariate of interest. The hazard function used in the Cox proportional hazards model is closely related to the Kaplan-Meier survival curve, and represents the probability that an individual progresses to an endpoint in a short time interval after a given time, assuming no events thus far[47]. The proportional hazards model makes no assumption about the shape of the hazard function, only that

it is proportional across different values of the covariate.

Where time dependent covariates are used, patients enter the risk set as their first measurement becomes available, i.e., they are left-truncated. In a similar way, when patients are left-truncated, patients enter the risk set on the date of the first visit to the Royal Free or Chelsea and Westminster Hospitals.

2.6.3 Assumptions of the Proportional Hazards Model

Two assumptions are made when this model is used. The first is that of proportional hazards, where for example, the relative hazard of death of a person aged 60 compared to a person aged 40 is assumed to remain the same, regardless of the time that has elapsed since baseline. Tests for non-proportionality are performed by the inclusion of an interaction term between the logarithm of the time since baseline (i.e. survival time) and the covariate of interest. If, after including this term, the model fits significantly better, there is evidence of non-proportional hazards.

If the assumption of proportional hazards does not hold, the estimates of the relative hazard of death (or any given endpoint) may be inaccurate. There are several ways in which this problem can be overcome. The simplest method in to include the interaction between survival time and the covariate of interest. However, the relative hazards from this model are difficult to interpret. An alternative is to split the follow-up time into distinct epochs, and the relative hazard of death within each time period calculated. For example, the relative hazard of death in the first two years of follow-up could be compared to the relative hazard of death after two years. For the estimates of the relative hazard of death within two years, patients who survive for longer than two years are censored at two years. Patients who die or are lost to follow-up within two years are not included in the estimates of the relative hazard after two year follow-up. For the second epoch, patients remaining in the risk set have survival times calculated from two years until their death or loss to follow-up. The tests of proportional hazards can then be retested within each epoch, and if there is still evidence that the proportional hazards assumption does not apply, the time periods can be broken down further.

The second assumption is that there is a log-linear relationship between the hazard and exposure; that is, the hazard rate is multiplied by a constant factor for each unit increase in the exposure. This assumption is more difficult to test, but could be tested by the transformation of the covariate of interest, for example, by taking the logarithm or square

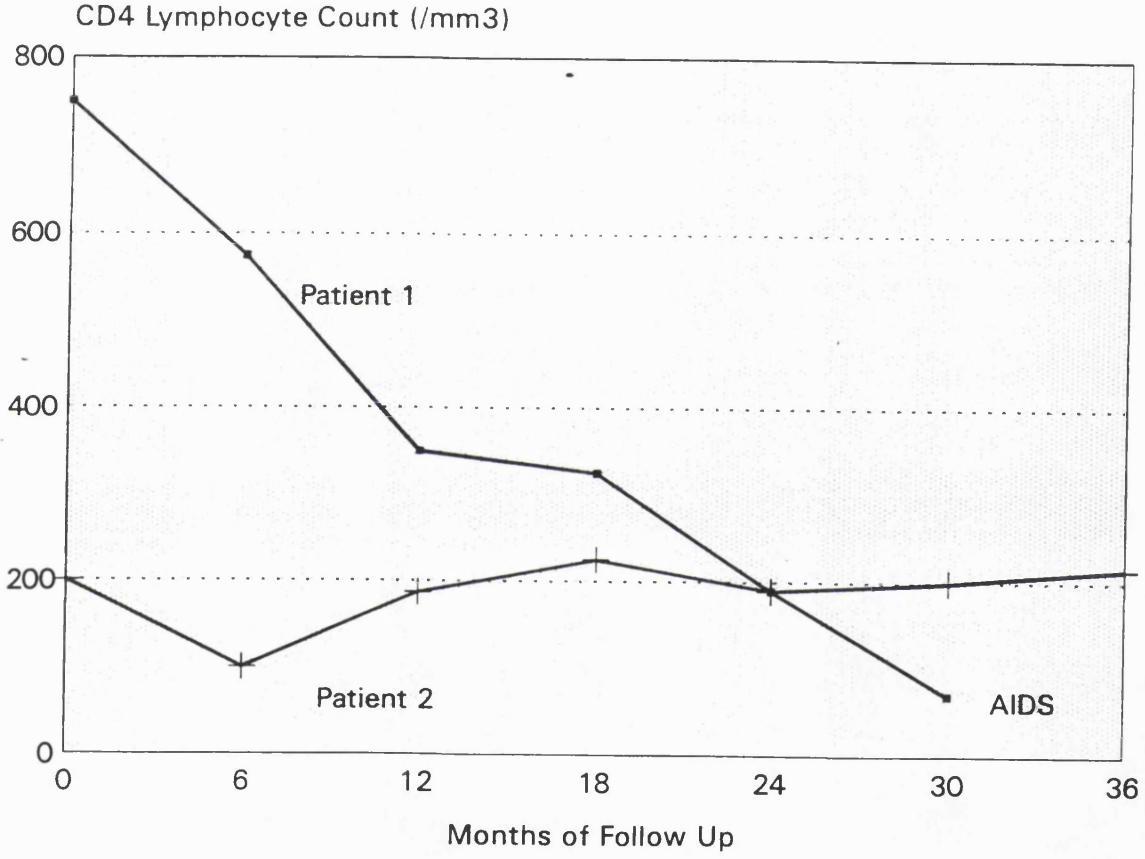
root of the variable. Again if this transformed measurement provides a better fitting model, there is evidence that the assumption does not hold.

2.6.4 Interpretation of the Model

The relationship between a laboratory marker, such as CD4 lymphocyte count, and disease progression is commonly analysed in two different ways, each of which is interpreted differently. This is illustrated in Figure 2.1 and discussed below.

Figure 2.1

Interpretation of the Cox proportional hazards model



2.6.4.1 Fixed Covariates at Baseline

This analysis attempts to answer the question of whether a single measurement of the marker can predict disease progression over the entire follow-up period, even though this may be several years. In the world of limited resources, this method of analysis can identify the most powerful predictor of clinical events based on a single measurement. This method is the most commonly used approach in the literature, and several issues

are raised in this thesis concerning this method of analysis. For example, in Figure 2.1 patient 2 has a low CD4 lymphocyte count but does not develop AIDS, while patient 1 has an initially high CD4 lymphocyte count but develops AIDS during follow-up. This is inconsistent with the suggestion that a lower CD4 count is strongly associated with risk of developing AIDS.

2.6.4.2 Time Updated Covariates

Here the model used takes account of the changes over time of the prognostic marker. The degree to which the latest value of the marker predicts disease development is then measured over a short time period, when all values of the marker recorded during follow-up are used. This method has important clinical applications, when the clinician has just remeasured the prognostic marker, and wishes to determine if the patient is at risk of disease progression before the next visit. In this situation the short term prediction is more useful. In Figure 2.1, the CD4 lymphocyte counts of patient 2 remained stable throughout follow-up, while those of patient 1 declined dramatically. This is consistent with an association between a low CD4 lymphocyte count and the development of AIDS.

CHAPTER 3 - DISEASE PROGRESSION AND RANKING OF DISEASES

3.1 Introduction

The analyses presented in this chapter are from the AIDS in Europe Study. Survival from each of the AIDS defining diseases is considered and used to develop a ranking of diseases. The extent to which the ranking of diseases holds after stratification for potentially important confounding factors, such as the use of zidovudine, year of diagnosis and CD4 lymphocyte count is considered.

3.2 Literature Review

In clinical trials of treatment for HIV infection, the major outcome is often based on clinical endpoints such as death, or development of a further AIDS defining illness[48-56]. However, the events which constitute an endpoint may not be equally weighted, and thus vary considerably in terms of the risk of death[57]. For example, a patient with a series of opportunistic events such as cryptosporidiosis followed by toxoplasmosis within a few months, may be considered to have a more favourable outcome than a patient experiencing a single, comparatively mild disease, such as oesophageal candidiasis, if this event occurred earlier during follow up.

A summary measure, utilising the natural rankings of the diseases may be appropriate and useful in clinical trials. To date, however, few studies have specifically addressed the ranking of AIDS defining diseases[58-59]. Crowe *et al*[59] defined the order of commonly encountered HIV-related opportunistic infections and malignancies according to the median CD4 lymphocyte count at which they occur. More recently, Luo *et al*[58] divided diseases into two classes; 'mild' and 'severe', and showed that the prognosis in each class was quite distinct. In addition, it was formally confirmed that survival in AIDS patients with more than one AIDS defining illness at initial diagnosis of AIDS was reduced compared to patients with a single diagnosis, as suggested by a number of earlier studies[58,60-63].

Some rankings of disease may be implied from observational studies of the natural history of patients with AIDS. There is considerable evidence that patients diagnosed with Kaposi's sarcoma, considered to be an early AIDS diagnosis[64], have a better survival than those diagnosed with most other AIDS defining illness[58,60-63,65-76] possibly because Kaposi's sarcoma tends to develop at higher CD4 lymphocyte counts than other

diagnoses[59,77]. Diseases such as lymphoma have a particularly poor prognosis[58,62,71,75-76,78], as does cytomegalovirus disease[58,67,71,75,79] and infection with *Mycobacterium avium* complex[79-80], the latter two of which tend to occur during the latter stages of AIDS when the CD4 lymphocyte count has fallen to 50/mm^3 or less[59,77,81].

Mortality after a second episode of *Pneumocystis carinii* pneumonia was initially reported to be higher compared to a first episode, which may have been due to the lack of effective treatment[82-83]. More recent evidence has shown similar survival rates for first and subsequent episodes[84]. In addition to Kaposi's sarcoma, diagnoses such as oesophageal candidiasis and extrapulmonary tuberculosis have longer median survival times[74,79,85,86], while the severity of disease resulting from an infection such as cryptosporidiosis is highly variable. Such variation may be related to the degree of immunosuppression at diagnosis[87].

3.3 Survival and Ranking of Diseases

3.3.1 Survival Following a Given Diagnosis

The median survival after a given diagnosis of each of nineteen AIDS indicator illnesses, regardless of whether this occurred as a first AIDS defining condition or during subsequent follow-up, is shown in Table 3.1, together with the 25th and 75th percentiles. Survival after a diagnosis of either histoplasmosis or isosporiasis could not be calculated, as only 17 patients were diagnosed with each of these diseases. Diseases have been assigned a rank according to their median survival. Where diseases share a similar prognosis, they have been ranked according to the number of diagnoses made; the higher number is assigned the lowest rank.

A diagnosis of progressive multifocal leukoencephalopathy was associated with the worst median survival of just two months, extrapulmonary tuberculosis had the most favourable prognosis of 19 months. More than half of the AIDS defining illnesses had a median survival of six months or under; only three diagnoses (*Pneumocystis carinii* pneumonia, Kaposi's sarcoma and extrapulmonary tuberculosis) had a median survival of over twelve months. The most commonly diagnosed AIDS defining diseases were *Pneumocystis carinii* pneumonia (3293 patients), Kaposi's sarcoma (1919 patients) and oesophageal candidiasis (1869 patients).

Table 3.1

Median survival time (months) for each AIDS defining event

Disease*	**N**	**Median Survival (25-75 percentile)**	**Rank+**
Progressive multifocal leukoencephalopathy	104	2 (1 - 5)	1
Malignant lymphoma	401	3 (1 - 8)	2
AIDS dementia complex	697	4 (1 - 12)	3
Cytomegalovirus (exc. retinitis)	641	4 (0 - 12)	4
Mycobacterium avium, extrapulmonary	401	4 (2 - 12)	5
Other *mycobacterium*, extrapulmonary	107	5 (1 - 11)	6
Candidiasis, pulmonary	78	5 (1 - 11)	7
Cytomegalovirus retinitis	804	6 (3 - 13)	8
Cryptosporidiosis	432	6 (2 - 16)	9
Cryptococcosis	308	6 (1 - 15)	10
Toxoplasmosis	1028	8 (3 - 17)	11
HIV wasting syndrome	463	8 (2 - 20)	12
Salmonella septicaemia	123	10 (4 - 20)	13
Herpes simplex, not skin	59	10 (2 - 21)	14
Oesophageal candidiasis	1869	12 (5 - 23)	15
Herpes simplex ulceration	367	12 (5 - 23)	16
Pneumocystis carinii pneumonia	3293	14 (5 - 25)	17
Kaposi's sarcoma	1919	15 (7 - 26)	18
Tuberculosis, extrapulmonary	695	19 (7 - 37)	19

* Diseases are ranked according to median survival. In the case of similar median survival times, diseases are ranked according to number of patients

\+ Survival for each disease is calculated regardless of whether it was the first or subsequent AIDS event.

3.3.2 Survival After an Initial Diagnosis Compared to Subsequent Diagnoses

The overall ranking of diseases, as assigned in Table 3.1, were also found to be consistent when events were stratified according to whether the diagnosis occurred as an initial AIDS defining event or during subsequent follow-up, as shown in Table 3.2.

Table 3.2

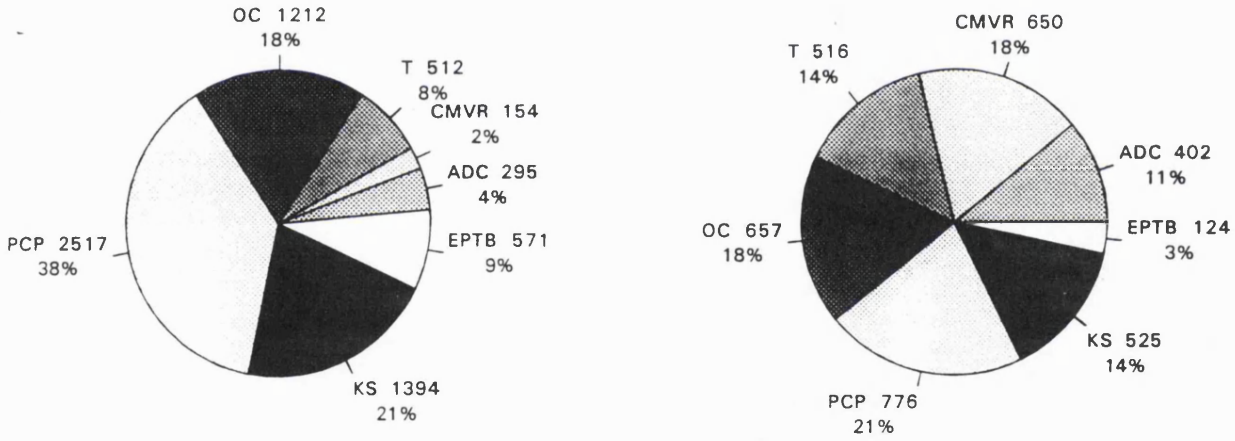
Median survival time (months) - stratification for time of AIDS event

Disease	Initial event		During follow-up	
	N	Median Survival	N	Median Survival
Progressive multifocal leukoencephalopathy	47	2	57	2
Malignant lymphoma	228	5	173	1
AIDS dementia complex	295	8	402	3
Cytomegalovirus (exc. retinitis)	240	7	401	3
Mycobacterium avium, extrapulmonary	104	8	297	4
Other *mycobacterium*, extrapulmonary	40	8	67	4
Candidiasis, pulmonary	48	6	30	5
Cytomegalovirus retinitis	154	8	650	6
Cryptosporidiosis	216	8	216	5
Cryptococcosis	158	9	150	4
Toxoplasmosis	512	11	516	6
HIV wasting syndrome	328	12	135	3
Salmonella septicaemia	70	15	53	7
Herpes simplex, not skin	30	17	29	5
Oesophageal candidiasis	1212	14	657	8
Herpes simplex ulceration	199	15	168	9
Pneumocystis carinii pneumonia	2517	17	776	7
Kaposi's sarcoma	1394	17	525	8
Tuberculosis, extrapulmonary	571	22	124	8

Diseases are ranked in the same order as found in Table 3.1. Diseases diagnosed during follow-up have a much shorter median survival time; none have a median survival of longer than 9 months. In general, when a disease was diagnosed as an initial AIDS defining event, median survival was twice as long as when the diagnosis was made during subsequent follow-up.

Figure 3.1 illustrates the frequency with which diseases were diagnosed as an initial AIDS defining event or as a subsequent event, for the seven most common diagnoses in this patient group. Those diseases with the highest ranks and the longest median survival from Table 3.1, such as *Pneumocystis carinii* pneumonia and Kaposi's sarcoma, were all diagnosed much more commonly as an initial AIDS defining event ($p < 0.0001$, chi-squared test). In contrast, diseases with the lowest ranks, such as cytomegalovirus retinitis and AIDS dementia complex, were all diagnosed more commonly during follow-up ($p < 0.0001$, chi-squared test).

Figure 3.1
Initial and subsequent AIDS defining illnesses



Initial AIDS Defining Event

Subsequent AIDS Diagnosis

PCP; *Pneumocystis carinii* pneumonia, OC; oesophageal candidiasis, T; toxoplasmosis, CMVR; cytomegalovirus retinitis, ADC; AIDS dementia complex, EPTB; extrapulmonary tuberculosis, KS; Kaposi's sarcoma

3.3.3 The Role of CD4 Lymphocyte Count at Initial AIDS Diagnosis

CD4 lymphocyte counts at the time of initial AIDS diagnosis (or within three months of this date) were available for 3053 patients (46.4%), and may be an important confounder when considering the association between type of AIDS diagnosis and survival. Table 3.3 shows survival after an initial AIDS diagnosis, stratified by CD4 lymphocyte count

Table 3.3

Median survival (months) following an initial AIDS defining event, stratified by CD4 lymphocyte count

CD4 Lymphocyte Count (/mm^3)	less than 50		50 - 99		Over 100	
	N	Survival	N	Survival	N	Survival
Malignant lymphoma	69	2	36	1	82	4
AIDS dementia complex	178	3	81	4	140	7
Cytomegalovirus (exc. retinitis)	156	2	75	2	106	3
Mycobacterium avium, extrapulmonary	84	4	53	5	62	5
Cytomegalovirus retinitis	180	6	100	7	123	5
Cryptosporidiosis	61	5	37	4	73	11
Toxoplasmosis	225	10	124	9	209	8
HIV wasting syndrome	95	5	54	6	68	6
Oesophageal candidiasis	358	9	202	12	403	14
Herpes simplex ulceration	79	9	48	13	94	16
Pneumocystis carinii pneumonia	621	13	329	15	644	15
Kaposi's sarcoma	286	10	154	13	448	18
Tuberculosis, extrapulmonary	44	12	33	14	118	23

(less than 50/mm^3, 50/mm^3 - 99 /mm^3 and 100/mm^3 or more). The number of patients in some strata were quite small, thus Table 3.3 shows median survival for only those diseases in which there were more than 30 patients in each strata, listed according to the ranks assigned in Table 3.1.

The ranking of diseases was broadly consistent within each CD4 lymphocyte count strata, although the CD4 lymphocyte count at which some diseases were diagnosed did not seem to greatly influence survival. For example, patients diagnosed with HIV wasting syndrome had a median survival of 5 months in those patients in whom the CD4 count at diagnosis was below 50/mm^3, while in patients with higher CD4 lymphocyte counts survival was only six months. This is in contrast to Kaposi's sarcoma, the prognosis of which was much more dependent on CD4 lymphocyte count, from a median survival of 10 months in patients with a CD4 lymphocyte count of less than 50/mm^3, to 18 months in patients with CD4 lymphocyte counts of 100/mm^3 or more. However, the most consistent finding was that median survival increased as the CD4 lymphocyte count at diagnosis increased.

3.3.4 The Impact of Treatment with Zidovudine

When stratification was based on whether or not zidovudine had already been initiated at the time of diagnosis, as shown in Table 3.4, the ranking of diseases was well maintained for patients not treated with zidovudine. Median survival in this group of patients also tended to be longer (by one or two months) than for patients in whom zidovudine treatment had begun, although the same ordering of diseases was observed. However, AIDS free survival time has been reported to be extended by the use of zidovudine[49,51,88], thus in patients who had started zidovudine, the initial AIDS defining event may have been delayed by a few months and may therefore occur at lower CD4 lymphocyte counts. In addition, patients who have already been diagnosed with AIDS and then develop a further AIDS defining condition will be more likely to have begun treatment with zidovudine than patients who develop that particular disease at the time of initial AIDS diagnosis. To investigate this bias further patients were further stratified into those with and without a previous AIDS defining condition, as shown in Table 3.5. Again, the diseases are ranked in the same order as Table 3.1, and only those diseases with more than 30 patients in each strata are shown. Patients who had not begun treatment with zidovudine at the time of their initial AIDS defining illness survived an average of between one and four months longer after their initial AIDS defining

Table 3.4

Median survival (months) - stratification for use of zidovudine at time of diagnosis

Disease	Zidovudine at time of diagnosis			
	Yes		No	
	N	Median Survival	N	Median Survival
Progressive multifocal leukoencephalopathy	33	2	71	2
Malignant lymphoma	108	2	293	4
AIDS dementia complex	211	3	486	4
Cytomegalovirus (exc. retinitis)	196	3	445	4
Mycobacterium avium, extrapulmonary	142	5	259	4
Other *mycobacterium*, extrapulmonary	34	5	73	3
Candidiasis, pulmonary	13	3	65	6
Cytomegalovirus retinitis	383	7	421	5
Cryptosporidiosis	111	5	321	7
Cryptococcosis	71	5	237	7
Toxoplasmosis	300	8	728	9
HIV wasting syndrome	106	6	357	9
Salmonella septicaemia	21	9	102	10
Herpes simplex, not skin	8	14	51	10
Oesophageal candidiasis	380	9	1489	13
Herpes simplex ulceration	98	10	269	13
Pneumocystis carinii pneumonia	474	12	2819	15
Kaposi's sarcoma	327	9	1592	16
Tuberculosis, extrapulmonary	71	12	624	20

Table 3.5

Median survival (months) - stratification for use of zidovudine at time of diagnosis and the occurrence of a previous AIDS defining condition

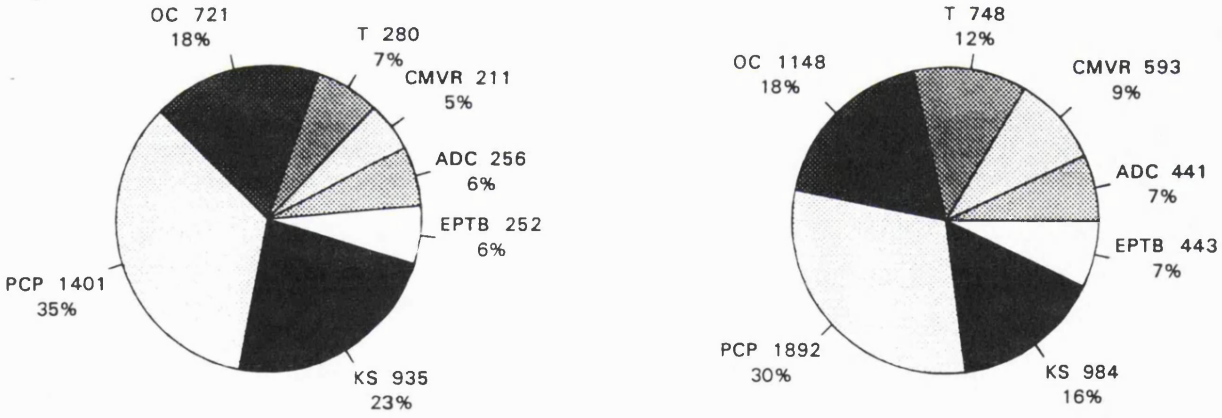
Disease	Zidovudine Initiated				Zidovudine Naive			
	First Event		Subsequent Event		First Event		Subsequent Event	
	N	Median Survival	N	Median Survival	N	Median survival	N	Median Survival
Toxoplasmosis	44	10	256	8	469	11	260	5
HIV wasting syndrome	41	11	65	4	287	12	70	3
Oesophageal candidiasis	96	11	284	8	1117	15	373	5
Pneumocystis carinii pneumonia	184	16	290	8	2333	17	486	7
Kaposi's sarcoma	78	14	249	8	1316	17	277	8

diagnosis compared to patients who had started treatment. The opposite was seen when considering survival after a subsequent AIDS defining event; patients who had started zidovudine at the time of diagnosis of a subsequent event survived an average of between one and three months longer than those who had not been treated with zidovudine before the diagnosis of a subsequent event. The ranking of diseases assigned in Table 3.1 was generally maintained across all strata.

3.3.5 Temporal Changes in Survival

Patients diagnosed later in the epidemic, after 1987, also tended to have slightly longer median survival times when compared to those patients who were diagnosed before 1987, as shown in Table 3.6. However, the severity of the diseases, as assigned by the ranks in Table 3.1, remained consistent within time periods. The frequency of diagnoses of the seven most commonly diagnosed diseases remained fairly constant before and after 1987, as illustrated in Figure 3.2.

Figure 3.2
AIDS diagnoses made before and after 1988



Diagnosis made in 1987 or earlier

Diagnosis made 1988 or later

PCP; *Pneumocystis carinii* pneumonia, OC; oesophageal candidiasis, T; toxoplasmosis, CMVR; cytomegalovirus retinitis, ADC; AIDS dementia complex, EPTB; extrapulmonary tuberculosis, KS; Kaposi's sarcoma

The proportion of patients diagnosed with *Pneumocystis carinii* pneumonia or Kaposi's sarcoma fell after 1988, and there was a corresponding increase in the proportion of

Table 3.6

Median survival (months) - stratification for year of diagnosis

Disease	1987 or earlier		1988 or later	
	N	Median Survival	N	Median Survival
Progressive multifocal leukoencephalopathy	29	1	75	2
Malignant lymphoma	134	3	267	3
AIDS dementia complex	256	4	441	4
Cytomegalovirus (exc. retinitis)	240	3	401	4
Mycobacterium avium, extrapulmonary	130	3	271	5
Other *mycobacterium*, extrapulmonary	106	5	1	-
Candidiasis, pulmonary	41	6	37	5
Cytomegalovirus retinitis	211	6	593	6
Cryptosporidiosis	172	6	260	6
Cryptococcosis	114	7	194	6
Toxoplasmosis	280	7	748	9
HIV wasting syndrome	127	8	336	8
Salmonella septicaemia	47	10	76	10
Herpes simplex, not skin	28	7	31	17
Oesophageal candidiasis	721	10	1148	13
Herpes simplex ulceration	162	10	205	13
Pneumocystis carinii pneumonia	1401	12	1892	16
Kaposi's sarcoma	935	14	984	15
Tuberculosis, extrapulmonary	252	19	443	20

patients diagnosed with cytomegalovirus retinitis and toxoplasmosis.

3.3.6 Survival Among Patients with Lymphoma: Site of Lymphoma

The median survival after a diagnosis of lymphoma was particularly poor (3 months), as shown in Table 3.7. Table 3.7 further considers the prognosis associated with the diagnosis of a lymphoma, stratified by the site of lymphoma. Nine patients were recorded as having both types of lymphoma. Patients diagnosed with a primary brain lymphoma had a shorter median survival of just one month, which was found to be consistent across all the strata investigated. In patients where the diagnosis was of a peripheral lymphoma, survival was between one and five months. The longest median survival after a lymphoma was diagnosed was in those patients in whom the diagnosis was their initial AIDS defining event.

3.3.7 Site of Organ Involvement of Kaposi's Sarcoma and Survival

In order to study whether different types of organ involvement in Kaposi's sarcoma was associated with a different prognosis, a sub-group analysis was performed on the AIDS in Europe data set. In this analysis, those centres who had not provided information on which organs were involved when Kaposi's sarcoma was diagnosed were excluded. A total of 809 diagnoses were recorded in the remaining 2674 patients

When the site of Kaposi's sarcoma was stratified according to whether or not the diagnosis was an initial AIDS defining event, as shown in Figure 3.3, it was clear that the majority of the initial AIDS defining diagnoses of Kaposi's sarcoma were cutaneous, while subsequent diagnoses were much more commonly systemic Kaposi's sarcoma (pulmonary, glandular and gastrointestinal tract).

Figure 3.3

Site of diagnosis of Kaposi's sarcoma

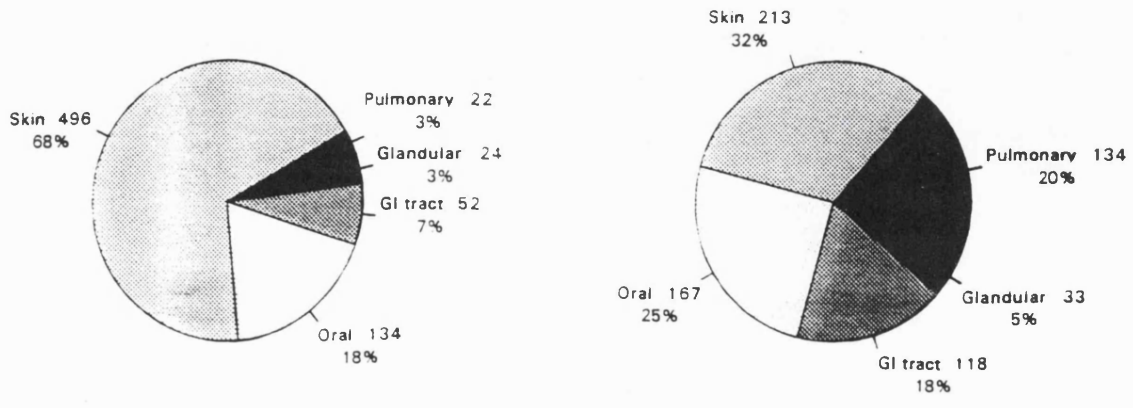


Table 3.7

Median survival (months, number of patients) after a diagnosis of malignant lymphoma

Type	Overall	At AIDS	After AIDS	+ Zid.	- Zid.	1987 or earlier	1988 or later
All	2 (401)	5 (228)	1 (173)	2 (108)	4 (293)	3 (134)	3 (267)
Peripheral	4 (322)	5 (208)	2 (114)	3 (71)	4(251)	4 (116)	4 (206)
Primary in brain	1 (88)	1 (21)	1 (67)	1 (43)	1 (45)	1 (21)	1 (67)

Table 3.8

Median survival (months, number of patients*) after a diagnosis of Kaposi's sarcoma

Site of Kaposi's sarcoma	Overall	At AIDS	After AIDS	+ Zid.	- Zid.	1987 or earlier	1988 or later
1 site+	13 (809)	16 (574)	7 (235)	9 (173)	14 (636)	13 (417)	13 (392)
Skin	13 (709)	15 (496)	8 (213)	10 (163)	14 (546)	13 (363)	12 (346)
Oral	10 (301)	14 (134)	7 (167)	8 (84)	12 (217)	10 (154)	11 (147)
GI tract	5 (170)	9 (52)	2 (118)	2 (63)	5 (107)	5 (89)	5 (81)
Glandular	4 (57)	9 (24)	0 (33)	1 (16)	4 (41)	4 (36)	4 (21)
Pulmonary	3 (156)	7 (22)	2 (134)	3 (27)	2 (129)	2 (62)	3 (94)

* Survival from a first diagnosis of KS, irrespective of location

\+ Only patients from centres who completed information on site of KS were included (2764 patients)

Table 3.8 shows the results of this sub-group analysis. The median survival after a diagnosis of Kaposi's sarcoma varies quite widely, according to the site of involvement. By far the most common site of Kaposi's sarcoma was skin, or cutaneous Kaposi's sarcoma, which also had the most favourable prognosis of 13 months. Median survival after a diagnosis of pulmonary Kaposi's sarcoma was particularly poor, with an overall median survival time of three months. This median survival dropped to two months when the diagnosis was made during follow-up, and did not differ according to the use of zidovudine at the time of diagnosis. In general median survival for patients diagnosed with cutaneous Kaposi's sarcoma (skin or oral lesions) was between two and four times longer than patients with systemic involvement (Gastrointestinal tract, pulmonary, glandular), across the various strata investigated.

3.4 Discussion

The AIDS in Europe Study is one of the largest studies worldwide of unselected AIDS patients in whom AIDS events during follow-up has been recorded. As such it is an outstanding resource for the study of survival after an AIDS diagnosis. Survival after a specific AIDS defining event has been ranked from worst to best prognosis according to median survival.

The median survival after an initial AIDS diagnosis, as shown in Table 3.2, agrees well with other studies in which patients with an initial AIDS defining diagnosis of *Pneumocystis carinii* pneumonia or Kaposi's sarcoma had a median survival of approximately 17 months[58,63,69,71-72,75,86,89-90]. Similarly, the median survival of 22 months observed in patients diagnosed with extrapulmonary tuberculosis agreed well with other studies[78-79]. There was a shorter median survival time amongst patients diagnosed with oesophageal candidiasis than previously reported[58,71,75,79,86]. This analysis also provides estimates of survival after diagnosis of the less common AIDS defining illnesses, such as progressive multifocal leukoencephalopathy, recurrent salmonella and pulmonary candidiasis.

3.4.1 The Impact of a Second Opportunistic Infection on Patient Prognosis

Table 3.2 illustrated that when a disease occurred after the time of the initial AIDS event, it was associated with a shorter survival time, although the ranking of the diseases was generally maintained. Those studies that have considered survival after the diagnosis of a second AIDS defining illness subsequent to the first have reported that the diagnosis

of a second AIDS defining illness during follow-up increased the risk of death considerably[92-93]. The treatment of a second AIDS defining illness may be more complicated; this may be due to drug intolerance[94-95], the effects of drugs on concomitant disease[96], problems with patient compliance[97], or simply a more aggressive disease pattern.

Stratifying initial AIDS defining diagnosis according to CD4 lymphocyte count within three months of this diagnosis did not substantially alter the rankings of disease, although this information was not available for all patients. Results from the AIDS in Europe Study published in 1994[74] suggested that patients for whom CD4 lymphocyte count at AIDS diagnosis was unknown have a similar median survival to the whole patient group (17 months). It is unlikely therefore that the ranking of diseases after stratification by the CD4 lymphocyte count would alter substantial if this extra information was available.

3.4.2 Treatment with Zidovudine

Patients treated with zidovudine had shorter median survival times in this study compared to patients who were not treated, as shown in Table 3.4, although again, the overall ranking of diseases was maintained. Patients who begin treatment prior to an AIDS diagnosis tend to have lower CD4 lymphocyte counts when AIDS develops[98], consistent with a delay in the development of AIDS, as reported in clinical trials of the efficacy of zidovudine[49,55,94]. This may explain the shorter survival times seen in those patients who were treated with zidovudine prior to an AIDS diagnosis. In addition, there is some concern that the efficacy of zidovudine may be short lived[99-101], and after a variable period of time most patients resume the immunological and clinical decline seen before therapy was started. Studies have shown that drug resistance may be a factor in further disease progression[102], or that the drug may have serious adverse effects when used for long periods of time[99-100].

In patients diagnosed with a subsequent AIDS defining disease, patients treated with zidovudine survived for between one and three months longer than those had not started treatment at the time of diagnosis of a subsequent AIDS defining event. Patients who had not begun treatment by this point may have been too sick to begin treatment, or there may be problems with patient compliance[97]. In addition, zidovudine has serious side effects such as anaemia, neutropenia, nausea and vomiting[103-104], which may discourage its use in patients who have already reached an advanced stage of disease, where the quality of life is of paramount importance[105].

3.4.3 Temporal Changes in Survival

The results of Table 3.6, which document a small increase in survival after 1987, agree with the results of many other studies which have demonstrated a temporal increase in survival[63,70-71,73,75,86,89-90,106-108]. The improvement in survival has been attributed to several factors, including increased awareness and support for AIDS patients over time[73,109], the change of the surveillance definition in 1987 and 1993[14-15], improvements in diagnosis and earlier detection of disease[71-72], treatment with zidovudine[48,89,110] and prophylaxis against *Pneumocystis carinii* pneumonia[111-113].

However, as discussed above, prophylaxis against *pneumocystis carinii* pneumonia and treatment with zidovudine has been shown to delay the initial AIDS defining illness[49,55,94,98,106], and for this reason you may expect survival after AIDS to have decreased in more recent years. This phenomenon will be investigated further in Chapter 4.

3.4.4 Differential Survival According to Site of Lymphoma

The development of a lymphoma primary to the central nervous system was originally considered to be one of the initial criteria for a diagnosis of AIDS[11]. It was not until 1985 that sufficient epidemiological data was available to prove that the incidence of systemic lymphoma of high grade, B cell type was also increased in patients with HIV[114], and was subsequently added to the revised definition in 1985[13]. Primary central nervous system lymphomas occur in approximately 3% of patients with AIDS[115-116], although it is possible that some lymphomas remain undetected until autopsy[117].

The prognosis of patients with a lymphoma was very poor, but is comparable with estimates of survival from other studies[114,118-119]. The differences in survival observed according to site of lymphoma were not surprising given the published literature[120]. The particularly poor prognosis observed in patients with a primary brain lymphoma may be due to a more advanced stage of HIV infection, or may reflect the lack of specific therapy[121]. In common with other studies, patients diagnosed with a lymphoma of any site after an initial AIDS defining event have a very poor prognosis[119,122-123].

3.4.5 Visceral and Systemic Kaposi's Sarcoma

The differences in survival according to the location of Kaposi's sarcoma in such a large group of patients has not been previously documented, and may be due to several factors; that systemic Kaposi's sarcoma tends to develop later than cutaneous Kaposi's

sarcoma at lower CD4 lymphocyte counts[124] or that systemic Kaposi's sarcoma may be more life threatening with only palliative treatment available. Such treatment often takes the form of chemotherapy, resulting in further immunosuppression, perhaps leading to an increased risk of a further disease. In the AIDS in Europe study population 13% of patients had systemic Kaposi's sarcoma at initial AIDS diagnosis, somewhat lower than a previous estimates[125]. However, greater patient and physician awareness may mean that diagnoses of Kaposi's sarcoma are now made before the onset of systemic symptoms[109].

3.5 Biases in this Study

Possible biases of this study include differences in how the patients were diagnosed within various centres, and changing ability to diagnose disease over time. It should also be noted that, with the exception of Kaposi's sarcoma and lymphoma when stratifying by site of involvement, only the first occurrence of each disease was used in this analysis. The determination of precisely when a disease recurs can be very subjective, and will depend on how aggressively a disease was treated in the first instance, and subsequent maintenance therapy.

This study used AIDS diagnoses in line with the 1987 criteria from the CDC[14]. In 1993 these criteria were revised to incorporate additional AIDS-defining events of pulmonary tuberculosis, recurrent bacterial pneumonia and invasive cervical carcinoma[15]. Only as time progresses will information on the severity of these diseases become available. Clinical experience in the management of bacterial pneumonia suggests that this event is easily manageable, but the risk of developing bacterial pneumonia is inversely related to CD4 lymphocyte count[126]. However, with the present knowledge, both pulmonary tuberculosis and bacterial pneumonia should be classified as having a relatively good prognosis. The epidemiological knowledge of cervical carcinoma in AIDS patients is poor at present, and so this disease is difficult to place in the current rankings.

3.6 Summary

The results of this analysis identify a clear ranking of disease, which was generally maintained after stratification for each of the factors discussed above. These results may be of use in the design of clinical trials, where there is a need for classifying events on the basis of firm criteria, such as survival[57]. The diseases could be grouped into three

on the basis of survival exceeding 12 months, between 6 and 12 months, and less than 6 months, as set out below

Mild (Rank 15-19)	Oesophageal candidiasis, recurrent herpes simplex (skin), *pneumocystis carinii* pneumonia, Kaposi's sarcoma, extrapulmonary tuberculosis
Severe (Rank 8-14)	Cytomegalovirus retinitis, cryptosporidiosis, cryptococcosis, toxoplasmosis, HIV wasting syndrome, salmonella septicaemia, recurrent herpes simplex (not skin)
Very severe (rank 1-7)	Progressive multifocal leukoencephalopathy, lymphoma, HIV encephalopathy, cytomegalovirus (exc. retinitis), *mycobacterium* avium, other *mycobacterium*, pulmonary candidiasis

In a clinical trials setting, patients could be classified as reaching an endpoint when they progress to a group of diseases more severe than the one in which they started. Similarly, progression to a more severe disease, as measured by a lower rank, could be a possible endpoint. Such approaches could shorten the duration of clinical trials and allow more trials involving patients at an advanced stage of AIDS. This study design has already been adopted in at least one clinical trial; the CAESAR trial recruited 1892 patients with CD4 lymphocyte counts between 50 and 250/mm^3 and added lamivudine therapy to the current antiretroviral regime. This trial has already been completed and the results presented[127]; lamivudine was shown to reduce the risk of disease progression or death.

CHAPTER 4 - BASELINE FACTORS, COFACTORS AND DISEASE PROGRESSION

4.1 Introduction

A cofactor can be defined as a factor, demographic, clinical or behavioral, which may influence disease progression in some way and which is external to infection with HIV, such as age or gender. Other factors present at diagnosis of AIDS may help identify the long term risk of death. Such 'baseline factors' include CD4 lymphocyte count and initial AIDS defining diagnosis. There is a great deal of variability in the incubation period of HIV, that is, the period between infection with HIV, and the development of AIDS which may suggest the existence of cofactors which interact with HIV to accelerate disease progression. In this chapter, six potential cofactors and baseline factors and their relationship with survival after an AIDS diagnosis are investigated, using data from the combined cohorts from the Chelsea and Westminster and Royal Free Hospitals. The relationship between age, gender, exposure category, initial AIDS defining illness, year of diagnosis and CD4 count at initial AIDS diagnosis are discussed.

The role of AIDS defining disease in subsequent survival was reviewed and analysed in Chapter 3 using data from the AIDS in Europe study. The role of initial AIDS defining illness is further investigated in this Chapter, together with the relationship with baseline CD4 lymphocyte count and other factors associated with disease progression.

4.2 Literature Review

4.2.1 Demographic Cofactors

Demographic factors, such as age, gender, ethnic origin, exposure category and socioeconomic status may play a role in survival after an AIDS diagnosis. Whilst it is not generally possible to alter such factors, their relationship with survival may help explain HIV pathogenesis. In addition, identification of the relationships between demographic factors and survival is important for predicting an individual patient's prognosis and for the development of treatment strategies for such patients.

While some reports have questioned whether age is an important cofactor[71,94,128], most agree that older people are more likely to experience shortened survival following a diagnosis of AIDS[58,61-63,65-66,69-70,73-75,78,91,129-130]. The underlying reason for this association, which is also found when considering the time from HIV infection to AIDS[131-134], is not known but may relate to a poorer capacity for lymphocyte production in older persons[135],

or may be a marker for a characteristic which makes it more difficult for older people to resist the pathological effect of HIV[136-137].

Thinking has been divided on whether ethnicity affects survival after an AIDS diagnosis and this may be due to the under representation of minority ethnic groups in some studies, or to the changing distribution of ethnic groups in cohorts of HIV infected patients. Historically, early studies from the United States which were of sufficient size to consider survival differences between racial groups showed that African American and Hispanic patients had poorer survival than caucasians after an AIDS diagnosis[61,68-69,90,130,138], although this may simply have reflected poorer access to care[138]. Minority ethnic groups may reside in an area where there is less medical care and treatment, or simply may not be able to afford care. Their disease may go unnoticed for longer, making it more life threatening and serious when it is finally diagnosed. In contrast, the majority of more recent studies show no survival differences according to race[70-72,94,139]. Studies of African patients who live in London have suggested that African patients present with more advanced disease[140-141], but there are no marked differences in survival, compared to HIV infected patients born in developed countries[140,142]. In common with the studies from Brazil and Thailand[85,143-144], survival in patients with AIDS in Africa is generally thought to be poor when compared to developed countries[145-146], probably reflecting access to care and the high incidence and poor control of other infectious diseases, such as tuberculosis and diarrhoeal disease[147-148].

The majority of early studies suggested poorer survival after AIDS diagnosis in women than in men[61-62,66,69,90,129]. However, more recent studies suggest there is no difference in survival between the sexes[70,74,94,149-154]. The findings of the earlier studies may have reflected poorer access to health care in women, lack of time and other family pressures[155-156], or the lack of recognition of women as a risk group[157]. The literature regarding the prognostic role of pregnancy in the course of HIV is contradictory[158]; some studies have suggested a faster progression of HIV following pregnancy[159], while others have concluded that pregnancy does not accelerate progression to AIDS[160-161]. Those studies which do consider the role of pregnancy in progression are more often directly concerned with disease progression to AIDS rather than death[159,162], and studies to date have been limited by small sample sizes or insufficient follow-up.

Comparison of survival in different exposure groups is often complicated by confounding with other factors, such as the AIDS defining diseases which may be preferentially

diagnosed in some exposure groups. For example, Kaposi's sarcoma has been shown to occur more commonly in homosexual men[163], to develop at higher CD4 counts[59,77], and as discussed in Chapter 3, have a more favourable prognosis than other AIDS defining illnesses. Any group of patients that is more likely to develop Kaposi's sarcoma may be expected to have longer survival after the initial AIDS defining diagnosis than patients who develop other AIDS indicator illnesses. Equally, any differences in survival between men and women may also be attributable to the AIDS defining diseases which are commonly diagnosed. Consequently, differences in survival after an AIDS diagnosis in different exposure categories have been suggested, although the results are rarely consistent[58,62-63,67,70,74,85,128-129,139,164].

The relationship between survival after AIDS and several other factors has also been investigated. Such factors include knowledge of HIV status prior to the diagnosis of AIDS, which provides conflicting results[165-166], and the realistic acceptance of a terminal disease which has been proposed to significantly decrease survival in patients with late stage disease[167]. Regular follow-up care following diagnosis has been shown to increase survival[168], and this is probably attributable to antiretroviral treatment and disease specific prophylaxis. Survival in those patients cared for by more experienced clinicians in the management and care of patients with AIDS has been reported to be increased[109,169]. Patients infected with HIV from lower socioeconomic groups may have poorer survival, independently of access to care[154,170-171]. Further factors investigated, but found to have no relationship with survival include the number of sexual partners after diagnosis of AIDS[172-173], depression[174-175], continued smoking, drug use, and alcohol intake[173].

4.2.2 Clinical Factors

The relationship between initial AIDS defining condition and subsequent survival was reviewed and investigated in Chapter 3. The relationship between survival and coinfection with other viruses, such as cytomegalovirus and hepatitis is unclear. Several reports have suggested that there is no clear evidence for poorer survival in patients coinfected with either hepatitis B or hepatitis C[176-178]. However, a recent study of haemophiliac patients reported a poorer survival among patients coinfected with hepatitis C[179]. Studies of children suggest a poorer survival amongst children coinfected with hepatitis[180], in particular hepatitis B[181]. Studies of the role of coinfection of HIV with cytomegalovirus are difficult to perform as up to 90% of homosexual men are infected[182], and among homosexual men infected with HIV, seropositivity for cytomegalovirus infection approaches 100%[183]. In a group of haemophiliacs with HIV, seropositivity for

cytomegalovirus was associated with a poorer survival[184], while a study among patients without haemophilia found that seropositivity for cytomegalovirus was not related to patient survival[185].

Patients who experience a symptomatic seroconversion have been reported to have a faster disease progression compared to those that do not[35,186-187], although only one study has specifically discussed shorter survival in patients who were symptomatic at seroconversion[186]. Studies of seroconverters are difficult to construct; the number of people with known dates of seroconversion in cohort studies is often small, follow-up is limited to several years and progression may be defined in terms of markers rather than clinical disease. In addition, patients are often asked to recall their symptoms after diagnosis of HIV, a method which could easily be biased[186].

4.2.3 The CD4 Lymphocyte Count

Lymphocytes play an important role in the body's immune system. CD4 lymphocytes help in antibody production and coordinate immune responses, and appear to be one of the main targets of HIV. The loss of CD4 lymphocytes results in immunosuppression and hence the AIDS defining illnesses commonly seen in patients with AIDS[188-189]. The CD4 lymphocyte count has been shown to decline throughout infection with HIV[190-192]. Patients with AIDS tend to die when the CD4 lymphocyte count is close to zero[188,193-194]. In uninfected children a natural decline in CD4 counts to the age of 14 has been observed[195]. The normal range of CD4 lymphocytes in uninfected adults is approximately 500/mm^3 to 1000/mm^3 [195-196], although these levels may vary according to gender[195-197]. These levels may drop rapidly in the months following infection with HIV[198-199]. Thereafter CD4 counts return to near-normal levels before dropping at a rate of 50-80/mm^3 per year[192,200-205].

The CD4 count at initial AIDS diagnosis may be related to a patient's CD4 lymphocyte count prior to seroconversion to HIV, whereby persons with higher CD4 lymphocyte counts at seroconversion later develop AIDS at a higher count[206]. AIDS normally occurs when the CD4 count has dropped to below 200/mm^3 [75,77,98,206-207], but susceptibility to AIDS defining diagnosis appears to occur at lower CD4 lymphocyte count for some diseases than others. For example, Kaposi's sarcoma, lymphomas and cryptosporidiosis occur on average at CD4 counts between 150 - 200/mm^3, while cytomegalovirus retinitis is rarely diagnosed at CD4 counts of above 50/mm^3 [59,77,81]. Approximately 50% of patients have been shown to have a CD4 count of below 50/mm^3 at their initial AIDS defining

diagnosis[77]. Many of the observational studies of survival after an initial AIDS defining diagnosis show that patients with a higher CD4 count at diagnosis have a more favourable prognosis[58,71,74-75,89,92,106,128,154-155,208-211].

The average CD4 lymphocyte count at initial AIDS defining diagnosis has declined quite markedly over time, from counts in the region of 100/mm^3 early in the epidemic to the much lower level observed in recent studies[74,106,212-213]. This has been attributed to the widespread use of antiretroviral therapy and prophylaxis against *Pneumocystis carinii* pneumonia[71,98], which have been shown to delay the initial AIDS defining condition[50,100,110,214-215]. If the onset of AIDS has been delayed substantially, further improvements in survival time in patients with AIDS may only occur as more efficient treatments for the opportunistic infections and underlying immunodeficiency are developed.

4.3 Survival in the Royal Free and Chelsea and Westminster Patient Cohorts

Two thousand, six hundred and twenty five patients from the Royal Free Hospital (n=385, 14.7%) and the Chelsea and Westminster Hospital (n=2240, 85.3%) were diagnosed with AIDS during the study period. The median duration of follow-up was 15.4 months (range 0 - 128 months), during which time 1613 patients (61.5%) have died. The first diagnosis of AIDS was made at the Chelsea and Westminster Hospital in 1982 and in 1986 at the Royal Free Hospital.

For the purpose of this chapter, five age groups were created based on ten year intervals (age 25 years or less, age 26 - 35 etc.). Similarly, CD4 lymphocyte count at initial AIDS diagnosis was divided into three categories using commonly used cut-off points (100/mm^3 or more, 50 - 99/mm^3, and less than 50/mm^3). Those patients who did not have a CD4 lymphocyte count within three months of their initial AIDS diagnosis (1002 patients, 38.2%) were grouped together to form a fourth category. Clinical events were also grouped together; the three most commonly reported AIDS defining illnesses (*Pneumocystis carinii* pneumonia, Kaposi's sarcoma and oesophageal candidiasis) formed single categories, while all other patients who were diagnosed with a single condition at AIDS were grouped together. Patients who were diagnosed with two or more diseases at initial presentation were grouped separately (there was not sufficient data within this category to group pairs of diseases together for further comparison). As treatment for patients with AIDS was introduced during 1987, patients who developed

AIDS before 1988 were placed in one group, while those diagnosed with AIDS after that date were grouped in two-year intervals. Estimates of median survival in the groups after 1987 were sufficiently similar to combine these groups and simply compare the prognosis of patients diagnosed with AIDS before 1988 and 1988 or later.

4.3.1 A Description of the Patients

Table 4.1 describes the patients included in the analyses presented in this chapter, together with the number of deaths in each patient group.

Table 4.1 (i)

Patients from the Royal Free (RFH) and Chelsea and Westminster Hospitals (CW); ***Gender, centre and exposure category***

		Patients		Deaths	
		N	%	N	%
All patients		2625	100	1613	61.5
Centre	RFH	385	14.7	204	53.0
	CW	2240	85.3	1409	62.9
Gender	Male	2497	95.2	1552	62.2
	Female	125	4.8	58	46.4
Exposure Category	Unknown	49	1.9	34	69.4
	Homosexual/bisexual	2206	84.0	1356	61.5
	Heterosexual	92	3.5	64	69.6
	Intravenous drug users	94	3.6	45	47.9
	Other	184	7.0	114	62.0

The population was, on average, quite young; the median age at AIDS diagnosis was 35.7 years (range 2.1 - 72.2 years). Male patients (median age 35.9 years) were significantly older than female patients (median age 30.2 years; $p < 0.0001$; Wilcoxon). Patients from the homosexual/bisexual exposure category were, on average, the oldest patient group (median age 36.2 years), while intravenous drug users were the youngest (median age 31.7 years). Compared to the Chelsea and Westminster Hospital, there was a significantly higher proportion of females in the Royal Free Hospital Cohort (3.6% and 11.6% respectively, $p < 0.0001$; chi-squared), and a significantly lower proportion of patients belonged to the homosexual/bisexual exposure category (87.2% and 65.5%

respectively, $p < 0.0001$; chi-squared). The proportion of females with AIDS increased over time, from 1.3% (5 patients) prior to 1988 to 7% (31 patients) in 1994 and 1995 ($p < 0.0001$, chi-squared). Similarly, the proportion of diagnoses from the Royal Free Hospital has also increased, from 1.5% (5 patients) before 1988 to 21.1% (231 patients) during 1991-1993 ($p < 0.0001$, chi-squared).

Table 4.1 (ii)

Patients from the Royal Free and Chelsea and Westminster Hospitals;

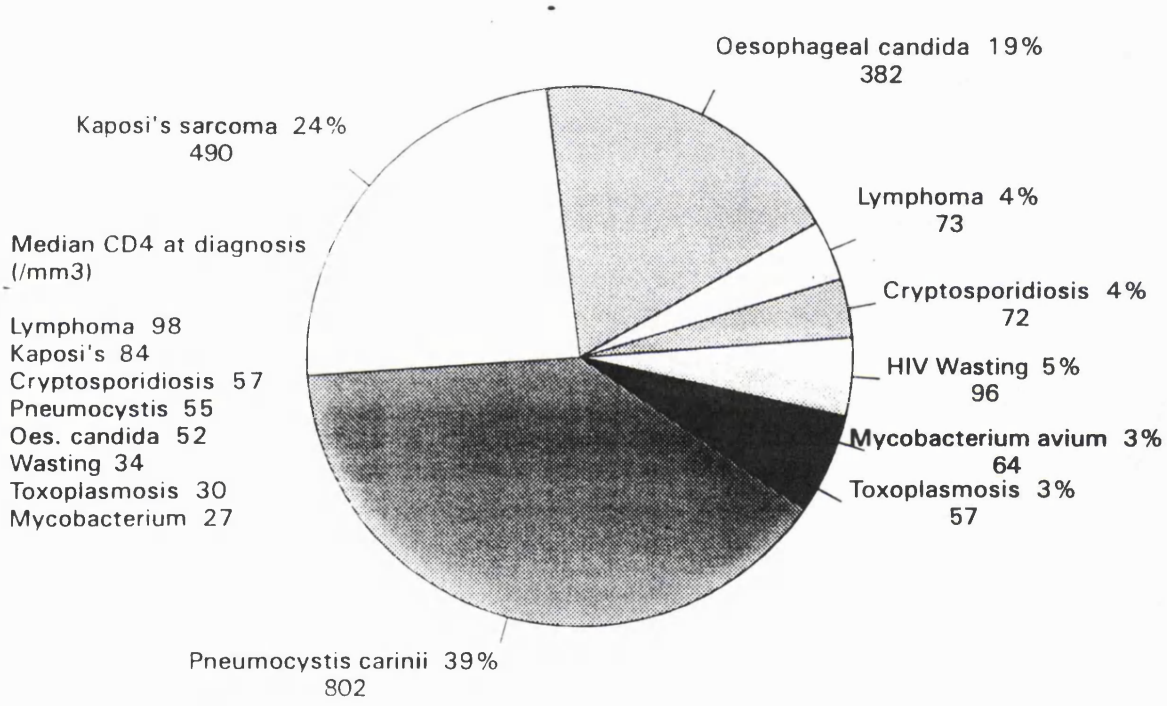
Age, year of AIDS diagnosis, CD4 lymphocyte count and initial AIDS diagnosis

		Patients		Deaths	
		N	**%**	**N**	**%**
Age Group	25 years or less	118	4.5	64	54.2
	26 - 35 years	1105	42.1	638	57.7
	36 - 45 years	917	34.9	582	63.5
	46 - 55 years	377	14.4	245	65.0
	over 55 years	108	4.1	84	77.8
Year of AIDS diagnosis	1987 or earlier	339	12.9	285	84.1
	1988 - 1990	747	28.5	597	79.9
	1991 - 1993	1093	41.6	630	57.6
	1994 - 1995	446	17.0	101	22.7
CD4 count	unknown	1002	38.2	633	63.2
	less than 50/mm^3	753	28.7	504	66.9
	50 - 99 /mm^3	311	11.8	200	64.3
	100/mm^3 or more	359	21.3	279	49.4
AIDS diagnosis	Oesophageal candida	382	14.6	206	53.9
	Kaposi's sarcoma	490	18.7	288	58.8
	Pneumocystis carinii pneumonia	802	30.6	509	63.5
	Other single diagnosis	708	27.0	417	58.9
	2 or more diseases	243	9.3	193	79.4

Figure 4.1 shows the eight most common initial AIDS defining diagnoses that were made, together with the median CD4 lymphocyte count at the time of diagnosis. The single most common AIDS defining diagnosis was *Pneumocystis carinii* pneumonia (n=802, 30.6%), followed by Kaposi's sarcoma (n=490, 18.7%) and oesophageal candidiasis (n=382, 14.6%). No other single diagnosis was made in over 100 patients. Kaposi's sarcoma was significantly more likely to be diagnosed in men than women (19.1% and 9.6% respectively, $p < 0.0001$; chi-squared), as was oesophageal candidiasis (14.8% and 9.6% respectively, $p < 0.0001$; chi-squared). There were no other differences in frequency of AIDS defining illnesses between men and women.

Figure 4.1

Initial AIDS defining illnesses and CD4 lymphocyte count



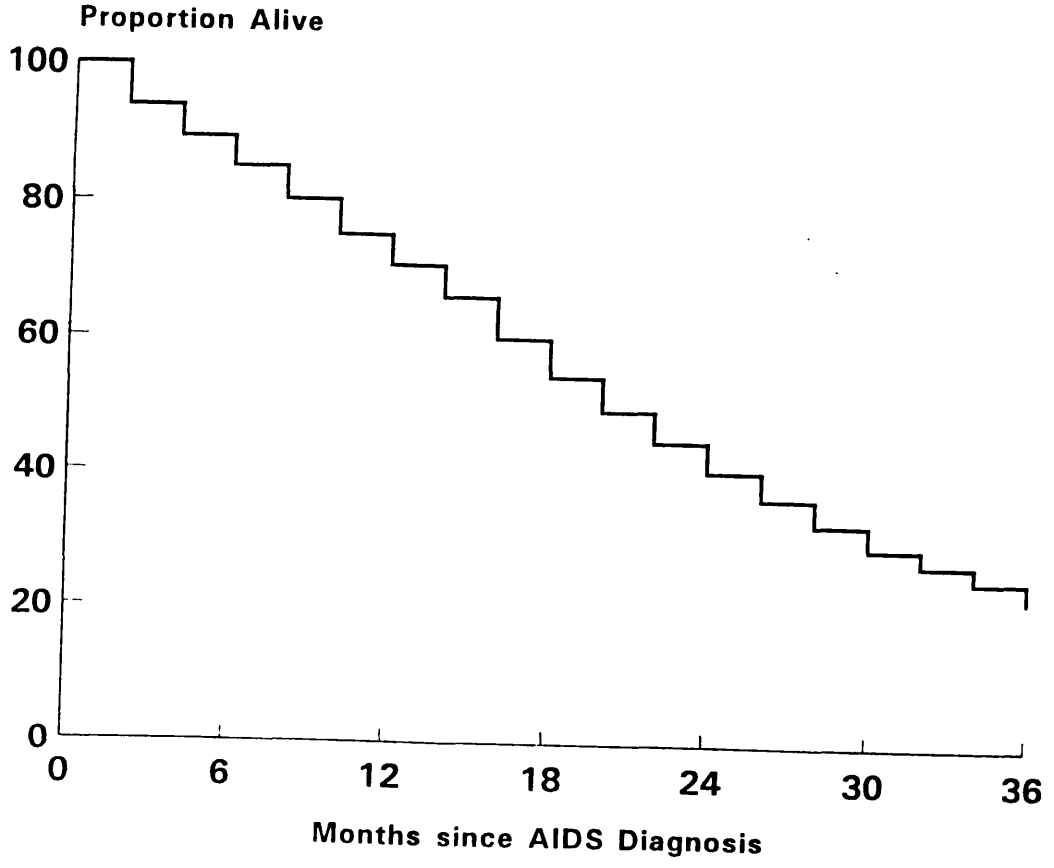
The median CD4 lymphocyte count within 3 months of the initial AIDS defining diagnosis, available for 1623 patients (61.8%) was 56/mm^3 (90% range 6 - 416/mm^3), and was found to be significantly higher among patients from the Royal Free Hospital (median 62/mm^3 and 54/mm^3 respectively, $p = 0.0169$; Wilcoxon). The CD4 lymphocyte count at initial AIDS diagnosis decreased significantly over time, from 90/mm^3 in patients diagnosed with AIDS before 1988, to 61/mm^3 during 1988 to 1990, 55/mm^3 during 1991 to 1993 and to 40/mm^3 in those diagnosed with AIDS during 1994 and 1995 ($p < 0.0001$, Wilcoxon test). Patients diagnosed with a lymphoma had the highest median CD4 count at diagnosis

(98/mm^3) while patients in whom *Mycobacterium avium* complex was the initial diagnosis had the lowest CD4 lymphocyte count at diagnosis (27/mm^3; $p < 0.0001$, Wilcoxon test).

4.3.2 Estimates of Median Survival After an AIDS Diagnosis

The median survival after an initial AIDS diagnosis for all patients, shown in Figure 4.2, was 20 months; 70.8% of patients were alive twelve months following an AIDS diagnosis, at 24 months this proportion had dropped to 40.5%. Five patients from the Chelsea and Westminster cohort were known to be alive ten years after their AIDS defining diagnosis. All five diagnoses were definitive, and included three of Kaposi's sarcoma, one of oesophageal candida and one of *Pneumocystis carinii* pneumonia.

Figure 4.2
Lifetable progression rates; all patients



Estimates of the median survival and the proportion of patients alive one and two years after diagnosis are shown in Table 4.2. It was interesting to note that there were only minor differences in median survival between men and women (two months) and centres (one month).

Table 4.2

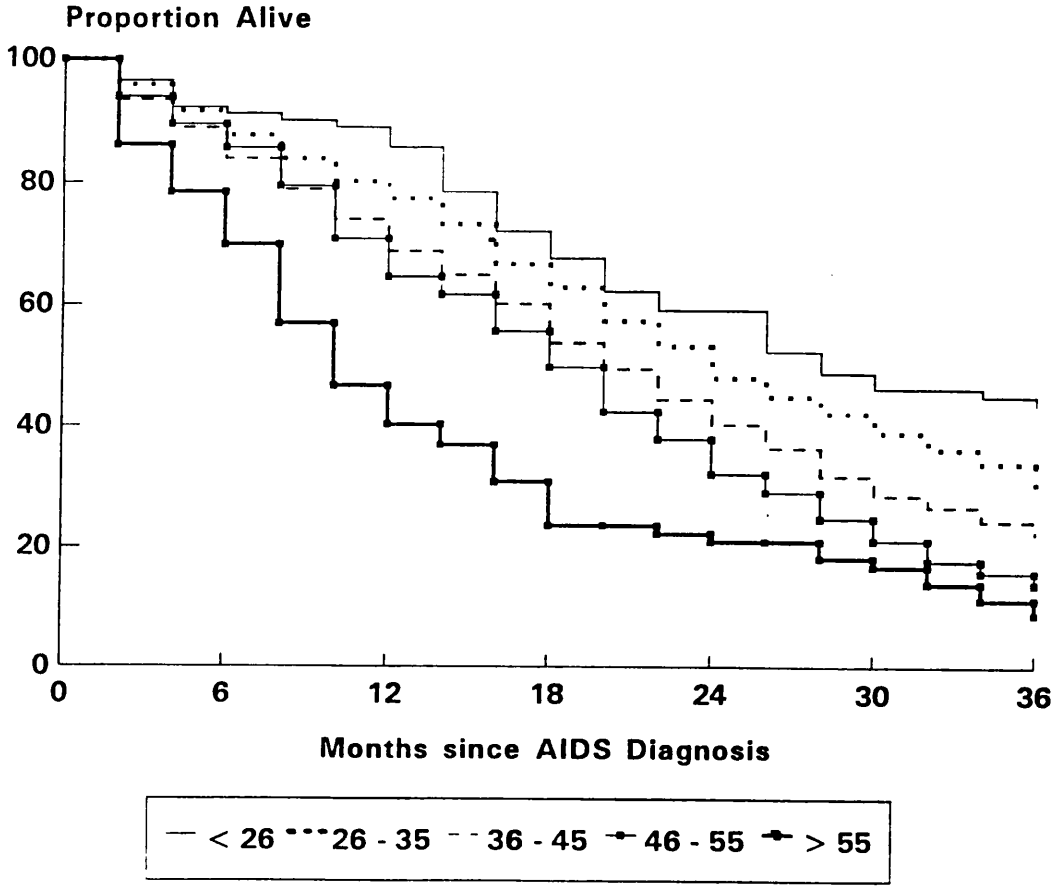
A description of survival (months) after an AIDS diagnosis

		Median Survival	% Alive At 1 year	2 years	p value
Centre	Royal Free	21	73.3	45.5	0.92
	Chelsea and Westminster	20	70.6	41.0	
Gender	Male	19	69.0	36.2	0.80
	Female	21	69.4	48.1	
Exposure Category	Unknown	7	34.7	17.7	0.0001
	Homosexual/bisexual	21	72.0	42.8	
	Heterosexual	13	50.7	31.1	
	Intravenous drug users	23	80.9	45.0	
	Other	20	72.7	39.0	
Age group	25 years or less	28	86.0	59.3	0.0001
	26 - 35 years	24	77.5	48.2	
	36 - 45 years	20	68.9	40.4	
	46 - 55 years	17	64.7	30.8	
	over 55 years	10	40.3	21.0	
Year of AIDS diagnosis	1987 or earlier	19	65.9	40.8	0.73
	1988 or later	21	71.8	42.0	
CD4 count	unknown	20	69.2	40.9	0.0001
	less than 50/mm^3	18	64.0	35.7	
	50 - 99/mm^3	21	73.4	44.1	
	100/mm^3 or more	32	86.1	62.2	
AIDS diagnosis	Oesophageal candida	24	79.8	49.3	0.0001
	Kaposi's sarcoma	22	76.3	45.8	
	Pneumocystis carinii pneumonia	22	76.7	44.2	
	Other single diagnosis	17	60.0	35.8	
	2 or more disease	16	61.1	29.7	

There was a strong relationship between age at initial AIDS defining illness and survival after an AIDS diagnosis, as illustrated in Figure 4.3; median survival decreased quite dramatically as age increased. For example, median survival in patients aged 25 or less at initial AIDS diagnosis was 28 months compared to 10 months in patients aged over 55 at diagnosis of AIDS.

Figure 4.3

Lifetable progression rates; age at initial AIDS defining diagnosis



Survival also varied considerably in different exposure categories; intravenous drug users, homosexual or bisexual men and the 'other' exposure category all had similar median survival times of between 20 - 23 months. Heterosexuals had a considerably shorter median survival time of 13 months, while those patients for whom an exposure category could not be (or was not) established had a median survival of just 7 months. Similar estimates of median survival were observed for patients diagnosed with oesophageal candidiasis, Kaposi's sarcoma and *Pneumocystis carinii* pneumonia (between 22 and 24 months), while patients diagnosed with any other single diagnosis or with 2 or more diseases simultaneously had poorer survival (17 and 16 months respectively).

The relationship between CD4 lymphocyte count at AIDS diagnosis and subsequent survival is shown in Figure 4.4. Those patients with a CD4 count of 100/mm^3 or more at AIDS had a median survival almost twice that of patients with a CD4 count of below 50/mm^3 at diagnosis (33 months and 18 months respectively).

Figure 4.4

Lifetable progression rates; CD4 lymphocyte count at initial AIDS defining diagnosis

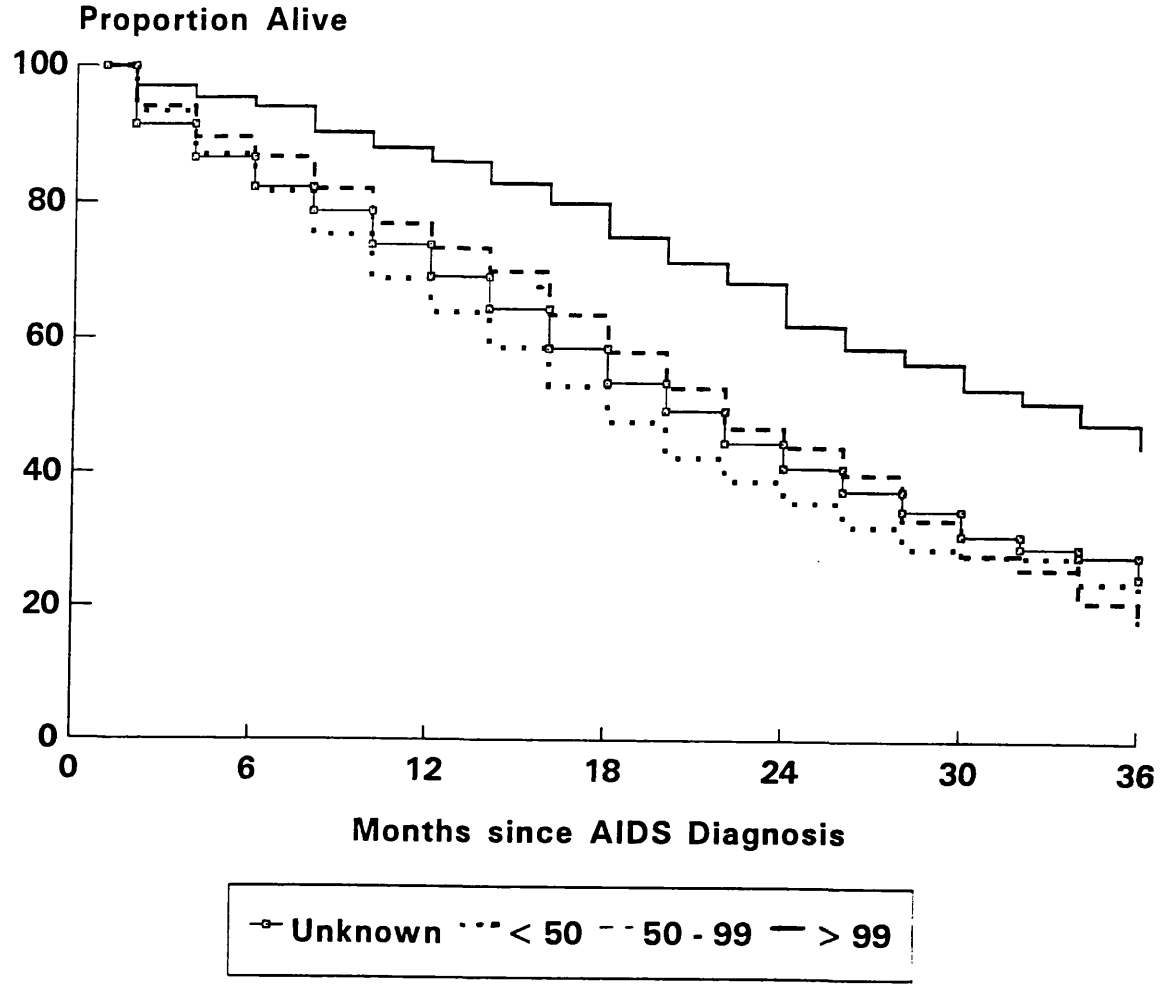
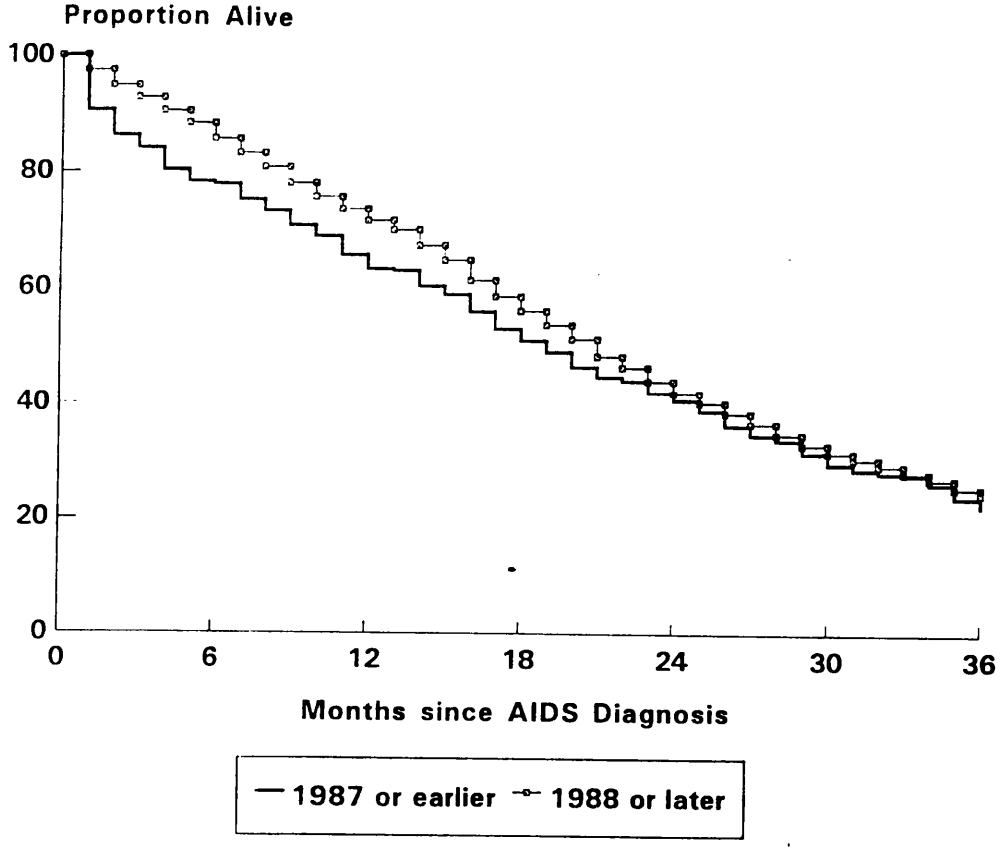


Figure 4.5 illustrates the relationship between year of diagnosis and survival. The probability of survival diverges rapidly; within three months patients diagnosed after 1987 are at a much lower risk of death than patients diagnosed before this date. The survival curves converge as survival time increases, and by two years, there is little difference in survival between patients diagnosed before and after 1987. As the survival curves converge, patients diagnosed with AIDS after 1987 must be at a slightly higher risk of death after three months than patients diagnosed with AIDS before this time. Figure 4.5 suggested that the formal test of the proportional hazards assumption would not hold.

Figure 4.5

Lifetable progression rates; year of initial AIDS defining diagnosis



4.3.3 The Relative Hazard of Death : Univariate Models

Both age and CD4 lymphocyte count are continuous variables which may be related to the risk of death, and may be modelled in Cox proportional hazards models as either categorical or continuous variables. The results of modelling them in both ways are shown in Table 4.3. Clearly modelling either age or CD4 lymphocyte count as categorical variables results in considerable loss of information and a poorer fit of the model, as measured by the change in the log-likelihood after the addition of the covariate of interest. A higher value of this test statistic suggests a better fit of the model.

Various transformations of age, such as square root or logarithm, do not improve the fit of the model, and while fitting age as a categorical variable overcame the problem of non-proportional hazards, a lot of information was lost, as reflected by the poorer fit of the model. Therefore all subsequent models included age as a continuous, untransformed variable. A logarithmic transformation of the CD4 lymphocyte count provided the best fitting model. By using logarithms (base 2) the relative hazard of death associated with a decreasing CD4 lymphocyte count is easily interpreted as the increased relative risk of death associated with a 50% difference in the CD4 lymphocyte

Table 4.3

Age and CD4 lymphocyte count - transformations and alternative models

		RH	95% CI	Model fit* (df)	p+
Difference in age	per 10 yr	1.30	1.23 - 1.37	86.25 (1)	0.019
	per log	2.68	2.17 - 3.32	85.16 (1)	0.020
	per sqrt	1.39	1.30 - 1.48	86.48 (1)	0.017
Age group	25 years or less	1.00	-		-
	26 - 35 years	1.38	1.07 - 1.77		0.58
	36 - 45 years	1.74	1.35 - 2.24	84.05 (4)	1.00
	46 - 55 years	2.12	1.61 - 2.79		0.60
	Over 55 years	3.16	2.28 - 4.37		0.35
Difference in CD4 count	per 100/mm^3	1.65	1.54 - 1.77	178.94 (1)	0.45
	per 50%	1.35	1.30 - 1.40	268.38 (1)	0.43
	per log	1.54	1.46 - 1.62	268.38 (1)	0.43
	per 1 square root	1.12	1.10 - 1.14	248.81 (1)	0.83
CD4 lymphocyte group	100/mm^3 or more	1.00	-		-
	50 - 99/mm^3	1.96	1.63 - 2.36		0.78
	less than 50/mm^3	2.80	2.41 - 3.26	191.34 (3)	0.55
	Unknown	1.78	1.55 - 2.05		0.002

RH; relative hazard, CI; confidence interval, df; degrees of freedom, p; p-value

* This is the change in the log-likelihood test statistic after addition of the covariate, age or CD4 lymphocyte count to the Cox proportional hazards model

\+ p-value from a test of the proportional hazards assumption for each covariate

count. Thus for each 50% lower CD4 lymphocyte count at initial AIDS defining diagnosis the relative risk of death increased by 35% (Relative hazard (RH) 1.35; 95% confidence interval (CI) : 1.30 - 1.40, $p < 0.0001$). The results of Table 4.3 show that older age is associated with an increased relative risk of death. The relative hazard of death

associated with a 10 year difference in age may be interpreted as the average increased risk of death in a patient with AIDS relative to a person who was 10 years younger at initial AIDS diagnosis. Thus each 10 year difference in age was associated with a 30% higher relative risk of death (RH 1.30, 95% CI 1.23 - 1.37; $p < 0.0001$).

Table 4.4 shows the univariate relative hazard of death and the tests of the proportional hazards assumption for the other baseline factors.

Table 4.4

Univariate relative hazard of death and tests of the proportional hazards assumption

		RH	95% CI	p	p+
Centre	RFH	1.00	-	-	-
	CWH	1.01	0.87 - 1.17	0.92	0.73
Gender	Male	1.00	-	-	-
	Female	0.97	0.75 - 1.26	0.80	0.12
Exposure Category	Homosexual/bisexual	1.00	-	-	-
	Unknown	3.11	2.21 - 4.38	0.0001	0.29
	Heterosexual	1.57	1.22 - 2.01	0.0004	0.36
	Intravenous drug users	0.73	0.51 - 1.02	0.068	0.87
	Other	1.20	1.00 - 1.44	0.054	0.14
Year of AIDS	1987 or earlier	1.00	-	-	-
	1988 or later	1.02	0.90 - 1.17	0.73	0.0001
AIDS Diagnosis	*Pneumocystis carinii* pneumonia	1.00	-	-	-
	Oesophageal candida	0.80	0.68 - 0.94	0.0074	0.08
	Kaposi's sarcoma	0.85	0.73 - 0.98	0.023	0.67
	Other single diagnosis	1.18	1.03 - 1.34	0.014	0.0001
	2 or more diseases	1.39	1.18 - 1.65	0.0001	0.17

RH; relative hazard, CI; confidence interval, p; p-value, RFH; Royal Free Hospital, CWH; Chelsea and Westminster Hospital

+ p-value from a test of the proportional hazards assumption for each covariate

These results mirror those of Table 4.2, the lifetable estimates of median survival. Interactions between the variables were also examined in Cox proportional hazards models with the main and interaction terms as explanatory variables. After adjustment for the baseline CD4 lymphocyte count, there were no significant interactions between the main variables. In particular, there was no interaction between year of diagnosis and specific AIDS defining illnesses.

4.3.4 The Proportional Hazards Assumption

One of the important assumptions made when using Cox proportional hazard models is that of proportional hazards, as discussed in section 2.4.5. This assumption was tested and the results were shown in Tables 4.3 and 4.4. Age, year of diagnosis, and initial AIDS defining illness did not satisfy the assumption. For example, in the case of age, the increased hazard of death in older patients relative to younger patients decreased as survival from AIDS increased. In contrast, when looking at year of diagnosis, the lower relative hazard of death in AIDS patients diagnosed after 1987 increased as survival from AIDS increased.

To overcome this problem of non-proportional hazards, follow-up time was divided into distinct periods. Initially, follow-up time was divided into one year periods, but the proportional hazards assumption was still violated in the first year for year of diagnosis. The first year was then split into separate time periods and the best fitting model was obtained when survival in the first three months, fourth to sixth month, and sixth to twelfth month were considered. The results of this model when year of diagnosis was the covariate of interest are shown in Table 4.5.

Table 4.5

Relative hazard of death in distinct time periods and year of diagnosis

Time period	RH*	95% CI	p	p+
3 mths or less	0.45	0.31 - 0.66	0.0001	0.11
4 - 6 mths	1.02	0.60 - 1.74	0.96	0.11
7 - 12 mths	0.96	0.68 - 1.35	0.80	0.94
13 - 24 mths	1.18	0.84 - 1.65	0.35	0.75
Over 24 mths	1.10	0.76 - 1.49	0.62	0.62

* RH; relative hazard, CI; confidence interval, p; p-value

\+ p-value from a test of the proportional hazards assumption for each covariate

In each case, the relative hazard describes the risk of death for a patient diagnosed after 1988 relative to a patient diagnosed in 1987 or earlier. As described in section 2.5.4, follow-up time has been divided into distinct periods. The univariate risk of death within each time period has been calculated. For example, patients with longer than three months follow-up are censored at three months when the risk of death within the first three months is calculated. In the second period, follow-up commences at three months after initial AIDS diagnosis and is censored at six months unless death occurs during this period.

It was clear that the relationship between survival and year of diagnosis after the first three months was sufficiently similar to combine the later time periods and estimate the relative hazard of death in the first three months and the relative hazard of death after this time, given that patients have survived the first three months. Similar results were found for age and AIDS defining illness (data not shown).

4.3.5 Adjusted Relative Hazards of Death

The lifetable diagrams give a visual interpretation of the survival in different subgroups, however, it is not possible to adjust for several factors at the same time. For example, the observed differences in survival between exposure categories may be attributable to differences in the CD4 lymphocyte count at initial AIDS diagnosis rather than to a true difference in prognosis. The results of a multivariate analysis, where all cofactors are included in the model in the same time are shown in Table 4.6. As the proportional hazards assumption was violated for several covariates the relative hazard of death is shown separately for the first three months and after this time period.

There were no significant differences in relative risk of death in either time period according to the hospital of diagnosis or gender. Compared to homosexuals or bisexuals, only patients for whom exposure category could not be determined were at a significantly raised risk of death, consistent in both time periods and possibly corresponding to a later presentation in this group of patients (RH period 1 : 3.75, 95% CI 1.20 - 11.75; p = 0.024. RH period 2 : 2.60, 95% CI 1.41 - 4.79; p = 0.0021). As in the univariate analyses there was a strong age effect within both time periods, but the relative hazard of death within each time period was, broadly speaking, consistent. Similarly, the strong relationship observed in the univariate analysis between CD4 lymphocyte count and relative risk of death remained. The narrow confidence intervals around the estimates in both time periods indicates the precision of the estimates.

Table 4.6 (i)

A multivariate analysis examining all cofactors using continuous variables

Centre, gender and exposure category

		Within 3 months of AIDS			After 3 months		
		Relative Risk of Death	**95% Confidence Interval**	**p - value**	**Relative Risk of Death**	**95% Confidence Interval**	**p - value**
Centre	Royal Free	1.00	-	-	1.00	-	-
	Chelsea and Westminster	1.17	0.67 - 2.01	0.58	1.02	0.84 - 1.24	0.82
Gender	Male	1.00	-	-	1.00	-	-
	Female	1.49	0.63 - 3.51	0.36	0.81	0.52 - 1.25	0.34
Exposure Category	Homosexual/bisexual	1.00	-	-	1.00	-	-
	Heterosexual	2.39	0.96 - 5.62	0.082	1.01	0.64 - 1.59	0.96
	Intravenous drug users	0.97	0.23 - 4.14	0.96	1.22	0.73 - 2.01	0.45
	Other	0.82	0.39 - 1.74	0.60	1.35	0.74 - 1.74	0.53
	Unknown	3.75	1.20 - 11.75	0.024	2.60	1.41 - 4.79	0.0021

Table 4.6 (ii)

A multivariate analysis examining all cofactors using continuous variables

Age, CD4 lymphocyte count, initial AIDS defining diagnosis and year of initial AIDS defining diagnosis

		Within 3 months of AIDS			After 3 months		
		Relative Risk of Death	**95% Confidence Interval**	**p - value**	**Relative Risk of Death**	**95% Confidence Interval**	**p - value**
Age (per 10 yr increase)		1.58	1.30 - 1.92	0.0001	1.41	1.30 - 1.52	0.0001
CD4 Count (per 50% decrease)		1.41	1.22 - 1.64	0.0001	1.59	1.50 - 1.68	0.0001
AIDS Diagnosis	*Pneumocystis carinii* pneumonia	1.00	-	-	1.00	-	-
	Oesophageal candida	0.21	0.07 - 0.59	0.0030	0.91	0.74 - 1.12	0.37
	Kaposi's sarcoma	0.37	0.16 - 0.83	0.020	1.09	0.88 - 1.34	0.43
	Other single diagnosis	1.43	0.92 - 2.22	0.11	1.30	1.08 - 1.57	0.0050
	2 or more diseases	1.16	0.60 - 2.24	0.65	1.25	0.98 - 1.59	0.070
Year of diagnosis	1987 or earlier	1.00	-	-	1.00	-	-
	1988 or later	0.44	0.22 - 0.86	0.017	1.02	0.79 - 1.31	0.91

In the three months immediately following diagnosis of AIDS, patients diagnosed with Kaposi's sarcoma or oesophageal candidiasis as an initial AIDS defining illness were at a significantly reduced risk of death, relative to patients diagnosed with *Pneumocystis carinii* pneumonia as an initial AIDS defining illness (RH 0.21 and 0.37; 95% CI 0.07 - 0.59 and 0.16 - 0.83, p = 0.0030 and 0.016 respectively). After this time, patients with either of these diagnoses as an initial AIDS defining illness were at a similar relative risk of death as patients diagnosed with *Pneumocystis carinii* pneumonia.

In the three months following diagnosis of AIDS, patients diagnosed after 1987 were at a significantly reduced risk of death compared to patients diagnosed before this date (RH 0.44; 95% CI 0.22 - 0.86). However, after three months patients diagnosed after 1987 had a similar risk of death compared to those patients diagnosed before this date.

4.4 Discussion

This large cohort of patients with AIDS helps to identify and confirm cofactors of disease progression. There have been many studies published about the survival of patients with AIDS, which have been summarised in Table 4.7. This table is ranked by the number of patients in the study. The larger studies tend to be based on surveillance data, which is limited to basic data collection and follow-up. This results of this analysis are included in Table 4.7 and are highlighted for comparison. This study is among the largest and has one of the most favourable estimates of median survival, 20 months.

4.4.1 The Relationship Between Gender and Survival

In the developed world, the proportion of women infected with HIV is fast increasing; AIDS is now the leading cause of death among black women aged 25-44 in New York and New Jersey[227]. It was therefore reassuring to find women survived equally long as men, confirming the majority of recent studies which addressed this question[70,74,152,154]. In the early years of the epidemic, HIV in women was often diagnosed concurrently with opportunistic infections[61]. The improved survival now observed in women may be due to community educational efforts about risk behaviour[228] and knowledge and recognition of infection or the necessity of treatment during asymptomatic infection[49]. An alternative explanation for the poorer survival observed in women in early years may be that, even when HIV was diagnosed in women, they may have had limited access to approved[229] and experimental therapy[230]. Such issues may be more specific to the United States than the United Kingdom, due to our more universal health care system. Access to

therapy and participation in clinical trials in women across Europe and in the UK has been investigated more recently, with differing results[231-232]. The most likely explanation for the early reports of differences in mortality are differences in ethnic and socioeconomic circumstances and access to therapy, rather than gender specific differences in mortality.

Table 4.7 (i)

Median survival (months) in published studies of AIDS patients

Studies of greater than 1,000 patients

Study (Year)	Ref	Country of Origin	N	Median Survival	% alive at 1 year	% alive at 2 years
Piette (92)	216	US	43795	12.7	49.1	18.4
Blum (94)	90	US	23324	13.7	54.7	31.9
Piette (91)	69	US	23271	11.5	n/a	n/a
Lundgren (94)	74	Europe	6578	17.0	n/a	n/a
Rothenberg (87)	61	US	5833	11.4	48.8	28.2
Lemp (90)	63	US	4233	12.5	51.6	20.2
Whitmore (93)	73	UK	3984	16.7	n/a	n/a
Chang (93)	70	US	3699	11.5	48.8	29.0
Luo (95)	58	Australia	3204	14.3	57.2	26.4
This Study		**UK**	**2625**	**20.0**	**70.8**	**40.5**
Chequer (92)	85	Brazil	2135	5.1	32.0	21.0
Seage (93)	72	US	1931	13.5	54.0	23.0
Holman (92)	217	US	1394	13.1	52.7	n/a
Payne (90)	218	US	1015	17.0	65.4	35.1

n/a not available

Table 4.7 (ii)

Median survival (months) in published studies of AIDS patients

Studies of less than 1,000 patients

Study (Year)	Ref	Country of Origin	N	Median Survival	% alive at 1 year	% alive at 2 years
Zangerle (95)	219	Austria	901	18.0	61.0	39.0
Jacobson (93)	71	US	891	16.4	62.3	33.4
Osmond (94)	106	US	761	15.9	n/a	n/a
Stehr Green (89)	91	US	716	11.7	49.2	28.9
Reeves (88)	66	UK	663	12.4	n/a	n/a
Buira (92)	129	Spain	629	26.0	n/a	n/a
Whyte (90)	62	Aus	554	10.4	n/a	n/a
Monforte (92)	220	Italy	547	12.0	n/a	n/a
Friedland (91)	67	US	526	9.5	39.0	8.0
Bachetti (88)	65	US	505	11.0	44.0	18.0
Bindels (91)	78	Neth	409	16.0	56.1	33.0
Kitayaporn (96)	143	Thailand	329	7.0	39.2	19.9
Durant (91)	221	France	281	14.0	53.9	32.4
Pederson (90)	128	Denmark	231	13.0	53.0	29.0
Schinaia (93)	222	Italy	226	9.2	n/a	n/a
Santos (94)	144	Brazil	224	5.0	n/a	n/a
Greco (86)	164	Italy	222	n/a	35.7	22.7
Swanson (94)	94	Aus	185	11.8	n/a	n/a
Carlson (91)	223	NZ	179	13.4	54.0	23.0
Ghirardini (95)	224	Italy	176	17.0	n/a	n/a
Marasca (86)	60	UK	168	13.5	n/a	n/a
Eskild (92)	165	Norway	166	11.0	n/a	n/a
Bindels (95)	76	Neth	160	18.0	62.0	37.0
Eskild (90)	225	Norway	100	9.3	n/a	n/a
Low (96)	140	UK	96	20.0	n/a	n/a
Dickson (93)	226	NZ	69	9.5	48.0	20.0

n/a not available

4.4.2 Similar Estimates of Survival at Two Main Sites of HIV Care in London

As described earlier, the two hospitals at which patients studied in this chapter are seen are two of the larger centres of HIV and AIDS care in London. Both hospitals have similar policies for treatment and recruitment of patients to clinical trials, and collaborate on a wide range of projects. There were no differences in survival between the two sites, suggesting a certain uniformity of care. The patients seen at each hospital varied, the Royal Free Hospital saw a greater proportion of women, heterosexuals and intravenous drug users than the Chelsea and Westminster Hospital, and its caseload seems to have increased more rapidly in recent years.

4.4.3 Mode of Exposure and Survival

There has been a suggestion of higher mortality in intravenous drug users with AIDS, from drug overdose and violence, including murder and suicide[233], and because they have been reported to experience a faster rate of CD4 lymphocyte decline than other exposure groups[234]. This study agreed with other reports which found no increased risk of death among intravenous drug users in comparison to other exposure groups[70,74,139]. The lack of differences in survival may be indicative of equal access to care and treatment. An alternative explanation is that early reports of a poorer survival in a given exposure category[62,85,129,155] may have failed to take account of confounding cofactors, such as the AIDS diagnosis, age, or the CD4 lymphocyte count at which AIDS was diagnosed.

There was an increased risk of death for those patients for whom exposure category was not known, even after adjustment for confounding variables. These patients may form a unique group who were too ill to be questioned about likely risk behaviour. Such patients may present with a wide variety of serious medical problems, or may not be well enough to be offered standard therapy with its associated toxicities and side effects[103-104].

4.4.4 The Relationship Between Age and Survival

This study agrees with many others which have shown that older patients with AIDS have a worse prognosis[58,61,63,65,70,73-75,91,130,134,173]. One study has shown that older age is associated with the development of neoplasms but not opportunistic infections[235], and if this is the case, older people may be expected to experience different diseases throughout follow-up with AIDS. The effect of further AIDS defining illnesses and the relationship with age and survival is further discussed in Chapter 6. One further explanation for the poorer prognosis observed in older patients may be differences in the rate of CD4 lymphocyte decline, which may be more rapid in older people[205,236].

In the univariate analysis, there was some evidence that the proportional hazards assumption did not hold for age, that is, the increased relative hazard of death in older patients diminished with time. This may be a selection effect whereby the oldest patients die most rapidly and lower the age of the surviving population, the age effect then no longer appears as large. Such an effect in AIDS patients has not been described in detail in other studies. Mariotti *et al*[237] found a greater effect of age on progression from seroconversion to severe symptoms and disease than for symptomatic disease to AIDS, while a study of haemophiliacs showed a diminishing effect of age over time when AIDS was the endpoint[238].

4.4.5 CD4 Lymphocyte Counts : An Important Factor in Survival

This study has confirmed the strong relationship between CD4 lymphocyte count at AIDS diagnosis and subsequent survival[58,71,74-75,92,106,128,154-155,208-210]. The median survival of 18 months among patients with a CD4 lymphocyte count below 50/mm^3 at diagnosis was similar to that found by others[74-75,239]. However, the estimate of median survival among patients with a CD4 lymphocyte count above 100/mm^3 at diagnosis was 33 months, considerably longer than the 20.2 months estimated by Saah *et al*[75]. The median survival in patients with a CD4 lymphocyte count of 100/mm^3 will depend on the exact distribution of CD4 lymphocyte counts above this cut-off level, and may also depend on year[240]. The median CD4 lymphocyte count at AIDS, 56/mm^3, was consistent with that of US surveillance data[77,241], with surveillance data from Germany[98] and a further large US observational study[242]. The median CD4 lymphocyte count at initial AIDS defining illness in this patient group was somewhat lower than found in earlier studies[198,243], probably due in part to the widespread use of prophylaxis for *Pneumocystis carinii* pneumonia and treatment with zidovudine[98].

In this patient population, the average CD4 lymphocyte count at initial AIDS defining illness has declined quite markedly over time, consistent with the results from other studies[74,98,106,212-213] and suggesting that the diagnosis of AIDS has been delayed and is now diagnosed in patients who are more immunocompromised. In addition, the pattern of AIDS defining illnesses has been changing; Kaposi's sarcoma and *Pneumocystis carinii* pneumonia have become less common as initial AIDS defining illnesses, whereas diseases associated with more advanced immunosuppression, such as cytomegalovirus and *Mycobacterium avium* complex have become more common[98,244]. If the onset of AIDS has been delayed substantially then you may expect survival after an AIDS

diagnosis to decrease. The results of this Chapter show no such decrease in survival, and this may indicate that the time between seroconversion and death is increasing. The CD4 lymphocyte count has been shown to decline throughout infection with HIV[208], and the risk of death following an AIDS diagnosis may change in relation to the decreasing CD4 lymphocyte count. The role of the CD4 lymphocyte count and all AIDS indicator diseases that occur throughout follow-up are considered further in Chapters 5 and 6.

4.4.6 The Role of Initial AIDS Defining Diagnosis

Kaposi's sarcoma and lymphoma had the highest CD4 lymphocyte counts on average at initial AIDS diagnosis (medians of 84/mm^3 and 98/mm^3 respectively), although this was lower than has previously been previously suggested[59,77]. Patients diagnosed with *Mycobacterium avium* complex, wasting syndrome or toxoplasmosis had the lowest CD4 lymphocyte counts at diagnosis, consistent with these diseases being late stage diagnoses[58,79].

In the three months following AIDS diagnosis, patients diagnosed with Kaposi's sarcoma and oesophageal candidiasis were at a significantly reduced risk of death relative to patients diagnosed with *Pneumocystis carinii* pneumonia, which may suggest that these are milder diseases which can initially be treated and are less likely to be terminal when first diagnosed. This is consistent with results from other studies, where these diagnoses have the longest median survival[58,71,74-75,79,86], and with the results of Chapter 3, where these diseases had a more favourable prognosis. After three months, patients diagnosed with other single diseases as an initial AIDS defining illness were at a significantly increased risk of death compared to patients diagnosed with *Pneumocystis carinii* pneumonia. Diagnoses in this category include lymphomas, toxoplasmosis, cytomegalovirus disease and infection with mycobacteria, all of which have a poor prognosis[58,71,74,79,85] and, with the exception of lymphomas, tend to be diagnosed at lower CD4 lymphocyte counts.

4.4.8 Relationship between Year of Diagnosis and Survival

Many studies have indicated that survival in AIDS patients has improved over time[63,70-71,73-75,86,89-90,106-108,211,219,221] and possible contributory factors were discussed in Chapter 3. It was disappointing to find the results of this analysis do not directly show an increase in survival in later years. Once again, it should be remembered that the diagnosis of AIDS is now being made at later stages of immunodeficiency, and the fact that median survival has not decreased may suggest that the time between seroconversion and death is

increasing. In addition, the patients included in this thesis generally would not have had access to new powerful drugs, such as ritonavir, lamivudine and indinavir, and the implications of recent advances in treatment are discussed further in Chapter 8.

In the first three months following diagnosis, patients diagnosed in later years were at a significantly reduced relative risk of death, and this may be due to improvements in treating the initial AIDS defining illness[245]. Before 1988, patients often died of their initial AIDS defining illness and a significant proportion of patients would die within three months. In 1987 Rothenberg *et al*[61] stated that almost 12% of patients died within a month of their initial AIDS diagnosis. A later study showed that before 1987, almost one quarter of patients died within three months of their initial AIDS defining illness, while during 1987 - 1990 this proportion had dropped to 14%[73]. Furthermore, a report of survival based on the UK surveillance data showed that the relationship between year of diagnosis and survival was strongest in the first year following an AIDS diagnosis[246]. In this study, three months after diagnosis there was no difference in the risk of death according to year of diagnosis.

4.5 Summary

Previous reports of survival among patients with AIDS have suggested that there may be differences in survival according to gender or exposure category. This study finds no evidence of such differences, using data from 2625 patients with AIDS from two large London hospitals. Survival was found to be considerably longer than in the majority of previously published studies. Survival in the first three months following an AIDS diagnosis has improved since 1988, but survival after three months has not improved. This is consistent with reports that, although short term survival may be improving, the long term prognosis of patients with AIDS remains poor[74]. Only one in fifteen patients remained alive five years after their initial AIDS defining illness. The decreasing CD4 lymphocyte count at initial AIDS defining diagnosis indicates that patients are being diagnosed with AIDS at ever more advanced stages of immunodeficiency. The strongest predictors of death were age and CD4 lymphocyte count at diagnosis. Survival also differed according to the initial AIDS defining disease.

CHAPTER 5 - AIDS DEFINING ILLNESSES AND THE CD4 LYMPHOCYTE COUNT

5.1 Introduction

Chapter 4 considered the role of fixed factors in progression from AIDS to death; for example, the CD4 lymphocyte count at initial AIDS diagnosis was described as fixed because only this first value of the CD4 lymphocyte count was used to determine the relative hazard of death in Cox proportional hazard models. No information about CD4 lymphocyte counts or further AIDS defining illnesses recorded during follow-up was included in the analysis. Using data from both the Royal Free and Chelsea and Westminster Cohorts, this chapter reviews the relationship between a specific laboratory marker, the CD4 lymphocyte count, and the AIDS defining illnesses which occur. In contrast to Chapters 3 and 4 which only included patients with AIDS, this Chapter includes all HIV positive patients with at least one CD4 lymphocyte count measured during follow-up, as shown in Table 2.3.

In this Chapter, I will present results which show the median CD4 lymphocyte count at which each AIDS defining illness occurs and the median survival after each AIDS defining illness. There is in excess of ten thousand person years of follow-up in this patient group and regular CD4 lymphocyte count measurements. This allowed the range in incidence of each of the AIDS defining illnesses across a wide spectrum of CD4 lymphocyte counts to be determined.

5.2 Literature Review

A natural order of AIDS defining diseases, defined by the CD4 lymphocyte count, has been suggested[59,77,248]. Knowledge of the risk of a specific disease according to the level of CD4 counts allows clinicians to focus on screening and prophylaxis, and enables individuals at the highest risk of disease to be advised appropriately about treatment. It is also important to establish if the incidence of a particular disease varies according to basic demographic variables, such as age or sex, or if the incidence of the disease continues to increase as the CD4 lymphocyte count decreases. Again, such information can be used to target those patients at greatest risk of disease.

There are few datasets of sufficient size to consider the incidence of each AIDS defining incidence, or to consider how the incidence changes as the CD4 lymphocyte count

declines. Surveillance data can be used to look at the incidence and prevalence of initial AIDS defining illnesses[63,73], but such data rarely collects information about all the AIDS defining illnesses that were diagnosed throughout follow-up. One study, in 1994, reported the incidence of opportunistic infections in patients with CD4 lymphocyte counts below 100/mm^3, but did not look at the incidence at more finely divided categories of CD4 lymphocyte count[249]. To date, no one has discussed the incidence of each of the AIDS defining illnesses over the full range of CD4 counts.

By looking at the incidence of each AIDS defining illness according to CD4 lymphocyte count, clinicians can determine which patients are at highest risk of an opportunistic infection, and who may need more intensive clinical monitoring. In some cases this may include prophylaxis. Trials of new agents for prophylaxis of opportunistic infections are increasingly being undertaken. Determining the optimal time to initiate prophylaxis is of great importance, as is estimating the cost and benefit from such new interventions[250].

It should be remembered that individual measurements of the CD4 lymphocyte count can be highly variable; Hoover *et al* showed that a patient with a measured CD4 lymphocyte count of 500/mm^3 may have a true count of between 297 and 841/mm^3 [251]. This variability is due to measurement error, the high variability in total lymphocyte counts and natural biological variation, such as the presence of other illnesses, pharmacological agents and diurnal variations[252-254]. Further, measurement of the CD4 lymphocyte count is affected by seasonal variation[254], storage methods[254] and exercise[255].

5.3 Details of the Patient Population

As discussed above, patients without AIDS were also included in this analysis. In total, 4883 HIV positive patients from the Royal Free (907 patients, 18.6%) and Chelsea and Westminster Hospitals (3976, 81.4%) have had at least one CD4 lymphocyte count measured over a median follow-up period of 27.6 months (90% range 1 - 107.6 months), measured from the date of the first hospital visit. Measurement of the CD4 lymphocyte count began in March 1983 at the Chelsea and Westminster site and in February 1982 at the Royal Free. The median number of CD4 lymphocyte count determinations during follow-up was 7 (90% range 1 - 33). During follow-up, CD4 lymphocyte counts were measured more regularly at the Royal Free Hospital; the median number of CD4 counts measured per year of follow-up was 7.8 at the Royal Free and 3.4 at the Chelsea and Westminster Hospital ($p < 0.0001$, Wilcoxon).

Table 5.1 describes the patients included in this chapter and the distribution of CD4 lymphocyte counts at the date of their inclusion in this analysis. Differences between groups were tested using the Wilcoxon or Kruskall-Wallis test, and the results are also show in Table 5.1.

Table 5.1

A description of patients and CD4 lymphocyte counts at first visit

		N	%	Median	Mean	p-value*
All patients		4883	100	270	307	-
Centre	RFH	907	18.6	340	362	0.0001
	CW	3976	81.4	253	289	
Gender	Male	4513	92.5	266	304	0.13
	Female	364	7.5	290	333	
Age Group	25 yrs or less	713	14.6	402	421	
	26 - 35 yrs	2385	48.8	299	330	
	36 - 45 yrs	1263	25.9	200	251	0.0001
	46 - 55 yrs	419	8.6	140	229	
	over 55 years	103	2.1	153	198	
Exposure Category	Homo/bisexual	3959	81.1	266	305	
	Heterosexual	147	3.0	203	257	
	Intravenous drug users	300	6.1	336	358	0.0001
	Other	399	8.2	286	323	
	Unknown	78	1.6	82	197	
Year of HIV Diagnosis	1987 or earlier	978	20.0	241	286	
	1988-1989	976	20.0	260	293	
	1990-1991	1129	23.1	278	315	0.0080
	1992-1993	1163	23.8	285	322	
	1994-1995	637	13.0	230	291	

RFH; Royal Free Hospital, CW; Chelsea and Westminster Hospital

* Differences between groups were tested using the Wilcoxon test, or the kruskall-Wallis test

Some patients may have transferred from another hospital, and in these cases, the CD4 lymphocyte count at presentation was not the first ever CD4 count measured in these patients, but a measurement at their first visit to the Royal Free or the Chelsea and Westminster hospitals. The median CD4 count within six months of the initial visit was 270/mm^3 (90% range 10 - 760/mm^3), and this information was available for 3517 patients (72.0%). Patients from the Chelsea and Westminster had significantly lower CD4 counts at first visit compared to patients from the Royal Free Hospital (253/mm^3 versus 340/mm^3, $p < 0.0001$, Wilcoxon), while males and females tended to present at a similar level of immunodeficiency. There was a clear trend for older patients to present at lower CD4 lymphocyte counts ($p < 0.0001$, Kruskall-Wallis test). Patients for whom exposure category could not be determined presented at a much later disease stage compared to other exposure groups ($p < 0.0001$, Kruskall-Wallis test), while intravenous drug users had the highest CD4 counts at presentation. There was no clear relationship between CD4 lymphocyte count at first visit and year of diagnosis with HIV. The median CD4 lymphocyte count at a patient's first visit appeared to increase in the years up to 1994, but after this time the median CD4 lymphocyte count dropped considerably.

5.4 Distribution of CD4 Lymphocyte Counts at AIDS Defining Illnesses

During the follow-up period, 3780 AIDS defining illnesses were diagnosed in 1713 patients. An additional 556 patients gave a history of a previous AIDS defining illness at their first visit, and information from these illnesses was excluded from this analysis. For example, a patient who reported a previous diagnosis of oesophageal candidiasis as an initial AIDS defining illness at their first visit to the Royal Free Hospital would not contribute any information to the analysis of the average CD4 lymphocyte count at diagnosis of oesophageal candidiasis, even if it was still present at their first visit or recurred 12 months later. If this patient was then diagnosed with cryptosporidiosis after 6 months follow-up, this data would be included in the estimate of the median CD4 lymphocyte counts at which cryptosporidiosis occurs. As in the analyses presented in earlier Chapters, only the first occurrence of each AIDS defining illness has been noted.

Table 5.2 describes the AIDS defining illnesses diagnosed in this group, together with the number of patient deaths. This table is ordered according to the number of patients with each diagnosis.

Table 5.2

Frequency of diagnosis of AIDS defining illnesses

Diagnosis	Diagnoses		Deaths	
	N	%	N	%
Pneumocystis carinii pneumonia	649	17.4	452	69.6
Oesophageal candidiasis	589	15.7	388	65.9
Kaposi's sarcoma	510	13.6	341	66.9
Mycobacterium avium complex	372	9.9	291	78.2
Cytomegalovirus retinitis	367	9.8	304	82.8
Other Cytomegalovirus disease	327	8.7	262	80.1
Cryptosporidiosis	162	4.3	110	67.9
Lymphomas	145	3.9	119	82.1
Wasting syndrome	139	3.7	104	74.8
Toxoplasmosis	133	3.6	105	78.9
HIV encephalopathy	113	3.0	93	82.3
Cryptococcosis	78	2.1	55	70.5
Other AIDS defining diagnoses[!]	64	1.7	55	85.9
Herpes simplex virus	48	2.3	32	66.7
Extrapulmonary tuberculosis	44	1.2	24	54.5
Recurrent pneumonia[*]	33	0.9	26	78.8
Pulmonary tuberculosis[*]	7	0.2	2	28.6

[*] AIDS defining illnesses added to the CDC surveillance definition in 1992[15]. Only diagnoses made after this date are included.

[!] Includes histoplasmosis, isosporiasis, progressive multifocal leukoencephalopathy and salmonella septicaemia

The five most common AIDS defining illnesses were, in decreasing order, *Pneumocystis carinii* pneumonia (649 patients, 17.4%), oesophageal candidiasis (589 patients, 15.7%), Kaposi's sarcoma (510 patients, 13.6%), *Mycobacterium avium* complex (372 patients, 9.9%) and cytomegalovirus retinitis (367 patients, 9.8%). Between 48% and 80% of patients who ever developed a disease died during follow-up. The highest proportion of deaths was found in those diagnoses which occurred at lower CD4 lymphocyte counts, such as cytomegalovirus and *Mycobacterium avium* complex.

Table 5.3

Distribution of CD4 lymphocyte counts for AIDS defining illnesses

Diagnosis			**CD4 Count Percentiles**				
	N[1]	**%**	**Median**	**5**	**25**	**75**	**95**
Cytomegalovirus retinitis	235	63.5	11	2	5	24	84
Mycobacterium avium complex	226	60.8	12	2	6	31	156
Other Cytomegalovirus disease	226	69.1	20	3	8	45	180
Cryptosporidiosis	119	73.5	27	4	10	66	300
Cryptococcosis	57	73.1	28	4	10	60	207
Toxoplasmosis	98	73.7	29	1	9	78	198
Wasting syndrome	112	80.6	32	3	14	83	283
Oesophageal candidiasis	468	79.5	42	4	15	112	351
Herpes simplex virus	39	81.3	43	5	10	120	285
Pneumocystis carinii pneumonia	509	78.4	44	5	16	104	276
Other AIDS defining diagnoses[!]	40	62.5	48	3	20	87	197
Kaposi's sarcoma	410	80.4	48	5	18	135	450
HIV encephalopathy	66	58.4	51	4	16	121	252
Lymphomas	89	61.4	62	5	12	140	494
Recurrent pneumonia[*]	26	78.8	64	4	14	251	634
Pulmonary tuberculosis[*]	5	71.4	89	20	38	300	480
Extrapulmonary tuberculosis	31	70.5	102	4	40	192	430

[1] Number of patients with a CD4 lymphocyte count measured within four weeks of diagnosis

[*] AIDS defining illnesses added to the CDC surveillance definition in 1992[15]. Only diagnoses made after this date are included.

[!] Includes histoplasmosis, isosporiasis, progressive multifocal leukoencephalopathy and salmonella septicaemia

Table 5.3 presents the distribution of CD4 lymphocyte counts within four weeks of diagnosis. The median CD4 lymphocyte count at diagnosis ranged from 11/mm^3 in patients diagnosed with cytomegalovirus retinitis to 102/mm^3 in patients diagnosed with extrapulmonary tuberculosis. There were no differences in the median CD4 lymphocyte count at diagnosis of any AIDS defining illnesses, according to age, year of HIV diagnosis or exposure categories. In addition, when age and year of HIV diagnosis were considered as continuous variables, there was no correlation between CD4 lymphocyte count at diagnosis, age and year of HIV diagnosis for any of the AIDS defining illnesses. It was interesting to note that both cytomegalovirus retinitis and lymphomas occurred at significantly higher median CD4 lymphocyte counts in men compared to women (p=0.047 and 0.012 respectively, Wilcoxon), as shown in Table 5.4. It should be remembered however that the number of women diagnosed with either disease and with a CD4 lymphocyte count measured within four weeks of diagnosis was small. In women, the median CD4 lymphocyte count at a diagnosis of cytomegalovirus retinitis or lymphoma was 5/mm^3 and 10/mm^3 respectively, in men the CD4 lymphocyte count at diagnosis were 11/mm^3 and 68/mm^3.

Table 5.4

Gender differences in CD4 lymphocyte count at diagnosis

Diagnosis	Gender	N[1]	%	Median	90% range	Mean	SD
Cytomegalovirus retinitis	Male	226	92.9	11	2 - 84	32	174
	Female	7	7.1	5	1 - 15	7	5
Lymphoma	Male	82	91.7	68	5 - 494	128	157
	Female	7	8.3	10	21 - 175	32	63

SD; standard deviation

1 Number of patients with a CD4 lymphocyte count measured within four weeks of diagnosis

5.5 Survival after an AIDS Defining Illness

Table 5.5 describes the survival after each AIDS defining illness, together with the proportion of patients who remained alive at 12 and 24 months following diagnosis, and

is ordered from the least to longest survival. This analysis was similar to that of Chapter 3, based on the patients from the AIDS in Europe study, and was repeated to compare survival after specific AIDS defining illnesses in the two London cohorts to that of the European study. The survival is calculated from the date of first diagnosis of the disease, regardless of whether this diagnosis occurred as an initial AIDS defining illness or during subsequent follow-up.

Table 5.5

Median survival (months) after an AIDS defining illness

	Median Survival (95% CI)	**% Alive (SE) at 1 year**	**2 years**
Other AIDS defining diagnoses[!]	3.4 (1.9 -7.6)	28.6 (6.2)	8.2 (4.1)
Lymphoma	3.5 (2.3 - 5.1)	22.5 (3.7)	11.4 (3.1)
HIV encephalopathy	5.9 (3.8 - 7.5)	30.2 (4.6)	7.2 (3.2)
Cytomegalovirus	7.1 (5.8 - 8.6)	30.5 (2.8)	13.1 (2.1)
Mycobacterium avium complex	7.4 (6.4 - 8.2)	29.3 (2.6)	8.9 (1.9)
Cytomegalovirus retinitis	7.8 (6.7 - 8.7)	31.6 (2.2)	9.6 (1.5)
Toxoplasmosis	8.4 (4.5 - 10.5)	38.9 (4.5)	13.1 (3.7)
Cryptosporidiosis	10.2 (8.9 - 12.0)	39.8 (4.4)	20.5 (4.0)
Cryptococcosis	11.1 (7.9 - 14.2)	48.7 (6.2)	13.7 (4.9)
Wasting syndrome	12.3 (9.3 - 13.5)	50.0 (4.5)	19.7 (3.8)
Recurrent pneumonia[•]	14.2 (10.6 - 47.8)	56.3 (5.8)	42.2 (6.1)
Oesophageal candidiasis	15.3 (14.7 - 17.1)	61.3 (2.2)	31.3 (2.3)
Pneumocystis carinii pneumonia	15.7 (14.3 - 16.8)	58.7 (2.1)	30.5 (2.1)
Herpes simplex	15.9 (10.0 - 25.3)	61.2 (7.4)	37.8 (7.7)
Kaposi's sarcoma	16.4 (14.9 - 18.4)	64.6 (2.3)	32.3 (2.4)
Extrapulmonary tuberculosis	19.2 (11.5 - 35.0)	62.1 (7.8)	41.8 (9.1)
Pulmonary tuberculosis[•]	25.1 (11.2 - 25.3)	66.2 (8.5)	52.2 (9.9)

SE; standard error, CI; confidence interval

• AIDS defining illnesses added to the CDC surveillance definition in 1992[15]. Only diagnoses made after this date are included.

! Includes histoplasmosis, isosporiasis, progressive multifocal leukoencephalopathy and salmonella septicaemia

The diagnosis with the most favourable prognosis was tuberculosis; patients diagnosed with pulmonary tuberculosis had a median survival in excess of two years, while patients diagnosed with extrapulmonary tuberculosis had a median survival of 19.2 months. Patients diagnosed with a lymphoma had a particularly poor median survival of under 4 months. Diagnoses of progressive multifocal leukoencephalopathy (39 patients), histoplasmosis (6 patients), isosporiasis (9 patients) and recurrent salmonella septicaemia (10 patients) were very rare, and these four diagnoses were grouped together as an 'other' category. No patients were diagnosed with coccidioidomycosis. The median survival of 3.4 months for this group of diagnoses was also particularly poor.

Of 145 patients diagnosed with a lymphoma, 36 (24.7%) patients were diagnosed with a primary brain lymphoma. The median survival in these patients was just 0.8 months (95% CI 0.5 - 1.1 months). The median survival in patients diagnosed with a lymphoma of any other site was significantly longer, 5.7 months (95% CI 4.3 - 7.1 months, $p < 0.0001$, Log-rank test).

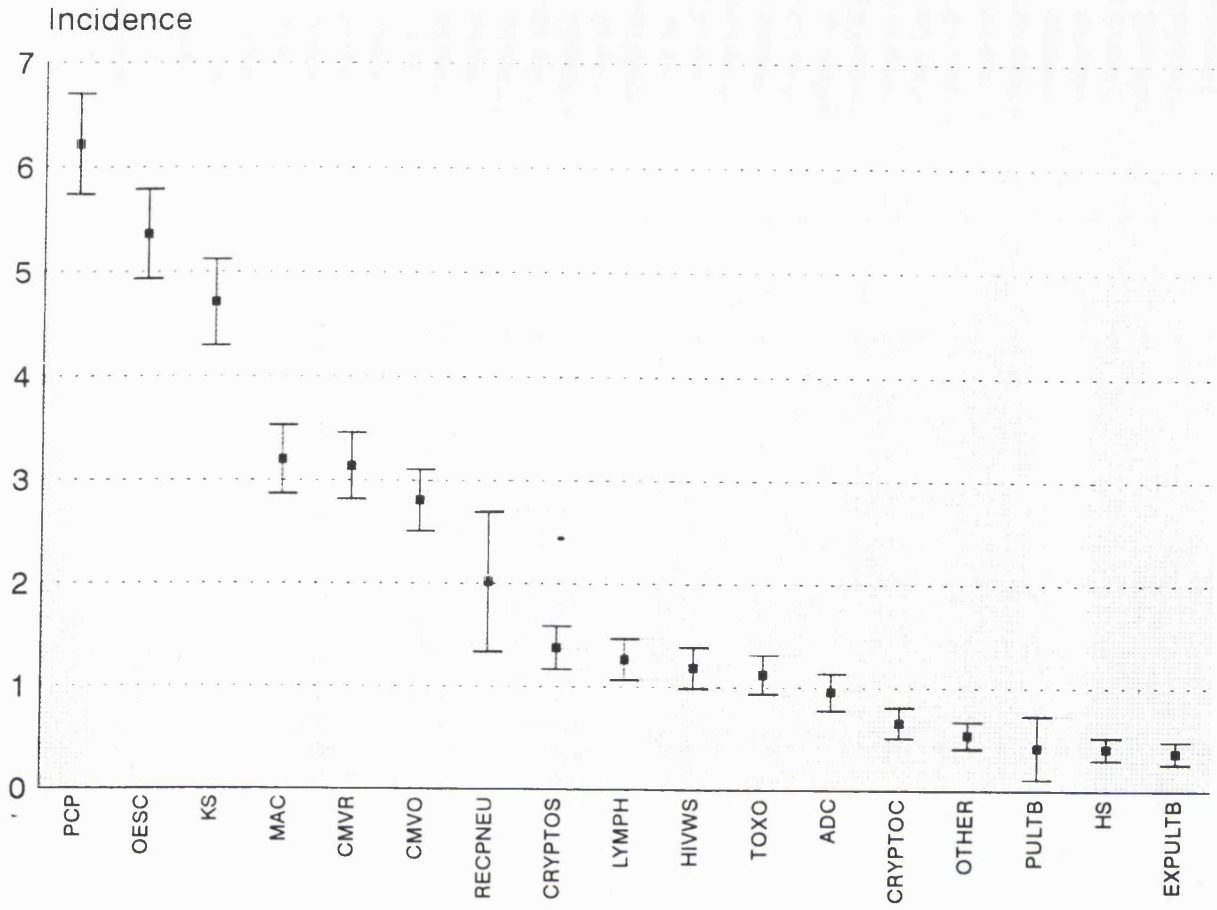
With the exception of lymphoma, it was interesting to note that the median survival generally reflected the CD4 lymphocyte counts at which the diagnoses occur. Those diseases diagnosed at higher CD4 lymphocyte counts, such as Kaposi's sarcoma and tuberculosis, had the most favourable prognosis, while diagnoses such as cytomegalovirus and *Mycobacterium avium* complex had a much poorer survival and tended to be diagnosed at lower CD4 lymphocyte counts. As survival after an AIDS diagnosis is related to CD4 lymphocyte count as well as AIDS defining diagnoses, it would be essential to adjust for the CD4 lymphocyte count in a Cox proportional hazards model which considered the relative hazard of death among patients diagnosed with cytomegalovirus and *Mycobacterium avium* complex, for example.

5.6 The Incidence of AIDS Defining Illnesses

Figure 5.1 summarises the overall incidence of each of the AIDS defining illnesses, together with 95% confidence intervals, ordered from the most common diagnosis to the least. The incidence is expressed per 100 years of patient follow-up (PY). Patients were followed up from the date of their first CD4 lymphocyte count. Patients who died were censored at date of death, all other patients were censored at their last clinic visit; the implications of this are discussed further in Chapter 5.7.

Figure 5.1

The incidence of AIDS defining illnesses



With the exception of pulmonary tuberculosis and recurrent pneumonia which were added to the surveillance definition for AIDS in 1992, for each disease the total duration of follow-up exceeds ten thousand patient years of follow-up. Diagnoses made in patients prior to their first visit to either the Royal Free or Chelsea and Westminster Hospitals were excluded from this analysis, in the same way as described earlier. Similarly, only the first occurrence of each AIDS defining illness was included in this analysis. The overall incidence ranges from 6.22 per 100 PY (95% CI: 5.74 - 6.70) for *Pneumocystis carinii* pneumonia to 0.37 per 100 PY for extrapulmonary tuberculosis (95% CI: 0.26 - 0.48).

As expected, the incidence of Kaposi's sarcoma was much higher in males compared to females (incidence 4.96 and 0.91 respectively; 95% CI 4.53 - 5.39 and 0.18 - 1.64 respectively) and in homosexual men compared to all other exposure categories combined (incidence 5.13 and 2.23; 95% CI 4.67 - 5.59 and 1.49 - 2.97 respectively). The incidence of oesophageal candidiasis was also considerable higher among male

patients compared to females (incidence 5.53 and 2.64; 95% CI 5.08 - 5.98 and 1.39 - 3.89 respectively). Also of note was the dramatic increase of *Mycobacterium avium* complex in patients diagnosed with HIV in later years. The incidence of *Mycobacterium avium* complex increased from 2.92 per 100 person-years follow-up in patients diagnosed with HIV before 1988 (95% CI 2.38 - 3.46) to 14.8 per 100 person-years follow-up in patients diagnosed with HIV after 1992 (95% CI 11.7 - 17.9).

Table 5.6

Incidence of AIDS defining illnesses and CD4 lymphocyte count

CD4 lymphocyte count	**>200**	**200-101**	**100-51**	**50-26**	**25-0**
Pneumocystis carinii pneumonia	1.35	4.94	13.22	22.11	26.05
Oesophageal candidiasis	1.03	4.24	10.66	15.49	20.06
Kaposi's sarcoma	1.49	3.26	10.05	13.24	14.93
Mycobacterium avium complex	0.16	0.90	2.71	7.28	17.48
Cytomegalovirus retinitis	0.05	0.35	1.68	6.63	19.18
Other cytomegalovirus disease	0.25	1.11	2.73	6.95	13.77
Recurrent pneumonia *	0.18	0.00	3.20	12.15	6.28
Cryptosporidiosis	0.19	0.76	2.38	3.50	5.31
Lymphoma	0.31	0.55	2.91	3.02	3.70
HIV wasting syndrome	0.19	0.71	2.31	3.52	4.03
Toxoplasmosis	0.12	0.61	1.89	3.18	4.28
HIV Encephalopathy	0.12	0.66	2.00	2.49	3.19
Cryptococcosis	0.05	0.45	1.09	2.89	2.03
Other AIDS defining diagnoses[!]	0.00	0.40	1.18	1.36	1.99
Pulmonary tuberculosis[*]	0.18	1.27	1.07	1.31	0.64
Recurrent herpes simplex	0.08	0.30	0.20	1.24	1.54
Extrapulmonary tuberculosis	0.12	0.50	0.89	0.68	0.71

* AIDS defining illnesses added to the CDC surveillance definition in 1992[15]. Only diagnoses made after this date are included.

! Includes histoplasmosis, isosporiasis, progressive multifocal leukoencephalopathy and salmonella septicaemia

Table 5.6 presents the incidence of each AIDS defining illness according to CD4 lymphocyte count categories. Note that as patients were not allowed to move in the reverse direction through the CD4 lymphocyte count categories, the data presented is the incidence according to the minimum CD4 count measured. Generally, the incidence of each AIDS defining illness continued to increase as the CD4 lymphocyte count decreased. Diseases which were less common as the initial AIDS defining illness, such as cytomegalovirus and *Mycobacterium avium* complex, had a very low incidence until the CD4 lymphocyte count had declined to below 50/mm^3, while diseases such as Kaposi's sarcoma and *Pneumocystis carinii* pneumonia had a higher incidence at higher CD4 lymphocyte counts.

5.7 Discussion

Once again, this Chapter has included data from a large number of patients which enables results for most of the AIDS defining illnesses to be presented. In particular, this Chapter has described the median CD4 lymphocyte count at which each AIDS defining illness occurs and highlighted several potential differences between the sexes in term of the median CD4 lymphocyte count at diagnosis. I have also shown survival after each AIDS defining diagnosis in the Royal Free and Chelsea and Westminster Hospital cohorts, and compared this survival to that of the AIDS in Europe study in Chapter 3. Further results from this Chapter include the incidence of each diagnosis across a wide range of CD4 lymphocyte counts, information that could be used in the development of prophylaxis, or in individual patient management strategies.

5.7.1 CD4 Lymphocyte Count and AIDS Defining Diseases

It is clear that there are considerable differences in the CD4 lymphocyte count at which different AIDS defining illnesses occur. Previous studies have described the distribution of CD4 lymphocyte counts according to AIDS defining illnesses[58-59,92,248], but these studies tended to be on much smaller numbers of patients, which meant that the average CD4 lymphocyte count at which some of the less common diseases occur could not be estimated. The order of disease in this study was consistent with those of other studies. This order ranges from diseases such as lymphomas and tuberculosis, which typically occur at higher CD4 lymphocyte counts[59,92,256-257], to diseases such as *Mycobacterium avium* complex and cytomegalovirus disease which are infrequently observed in patients with CD4 lymphocyte counts above 50/mm^3 [59,92,258-263].

Cytomegalovirus retinitis and lymphomas were diagnosed at significantly higher median CD4 lymphocyte counts in men compared to women. These results have not been previously reported by other workers, and the exact reasons for these findings are unclear. The number of women with a CD4 lymphocyte count measured within four weeks of diagnosis was quite small, and with a larger sample size the results may alter. In addition, if women were truly diagnosed with cytomegalovirus syndromes at higher CD4 lymphocyte counts, you would also expect to see a difference in CD4 lymphocyte count at diagnosis of other cytomegalovirus disease, rather than retinitis alone, which was not the case.

5.7.2 Survival after an AIDS Defining Diagnosis

Survival after each of the AIDS defining illnesses in this Chapter was consistent with results of Chapter 3, survival in the AIDS in Europe study. If the results of Table 5.5 were ranked they would follow almost exactly the rankings seen in Table 3.1. The median survival after each diagnosis in the Royal Free and Chelsea and Westminster cohorts was between one and four months longer than the survival found using the AIDS in Europe data. This is consistent with the results of Chapter 4, where the estimate of median survival in the combined cohorts following an initial AIDS defining illness was 20 months, compared to the median of 17 months from the AIDS in Europe study group[74].

The longer survival seen in this patient group may be attributable to several factors. The AIDS in Europe study recruited patients with AIDS diagnosed prior to 1990 while the majority of patients in this chapter were diagnosed with AIDS after 1990, thus the increase in survival may represent an improvement in the prognosis of patients with AIDS. At the Royal Free and Chelsea and Westminster Hospitals, both didanosine (ddI) and zalcitabine (ddC) began to be used in combination with zidovudine after 1990. ddI was the second drug to be licensed to treat patients with HIV, the approval was based on small phase I trials in which there was an improvement in weight, CD4 lymphocyte count and other laboratory markers[264-266]. ddC became available shortly afterwards, again, based on results from small scale trials[267-268]. There is now strong evidence of a benefit to survival, over and above that provided by zidovudine alone, when patients with CD4 lymphocyte counts above 200/mm^3 are treated with either ddI or ddC in addition to zidovudine[269-271]. The survival benefit of the addition of ddI or ddC to zidovudine in patients with AIDS or lower CD4 lymphocyte counts is less clear[272-273]. Other possible reasons for an improvement in survival were discussed in Chapter 3 and include differences in diagnosis or increased access to different antiretroviral treatments and

prophylaxis against *Pneumocystis carinii* pneumonia.

Also consistent with the results of Chapter 3 was the finding that patients with a primary brain lymphoma had a much poorer median survival than patients diagnosed with any other type of lymphoma. With the exception of invasive cervical carcinoma, which was not diagnosed in either cohort, diagnoses added to the surveillance definition of AIDS in 1993[15] generally had a longer median survival than most other diagnoses. This Chapter provides one of the first estimates of survival associated with the new diagnoses added to the surveillance definition of AIDS in 1993.

Diagnoses included in the 'other' category were those rarely diagnosed, and include progressive multifocal leukoencephalopathy, recurrent salmonella septicaemia, isosporiasis and histoplasmosis. Coccidioidomycosis and histoplasmosis are both extremely uncommon outside the Southern United States[274-275]. Isosporiasis has been documented to occur in just 0.2% of patients with AIDS in the United States[276], while an analysis of patients diagnosed with AIDS between 1981 and 1990 documented that 0.7% of patients were diagnosed with progressive multifocal leukoencephalopathy[277]. As this group of diseases are rarely diagnosed, little is known about their median survival. The results of Table 5.3 suggest a poor prognosis for this combined group, which was not unexpected given that the majority of patients in this category were diagnosed with progressive multifocal leukoencephalopathy, which has been shown to be universally fatal within 6 months of diagnosis[278]. In addition, this diagnosis was shown in Chapter 3 to have a median survival of 1 month. A further explanatory factor may be that as the diseases are rarely encountered, recognition and identification may be delayed in comparison to those diseases which more commonly occur.

5.7.3 The Incidence of AIDS Defining Illnesses

The observed incidence of disease per 100 person-years of follow-up of disease will be highly dependent on the distribution of the CD4 lymphocyte count of the patients studied. For example, a study of AIDS patients would find a higher overall incidence of disease than reported here. In contrast, a study of seroconverters would report a much lower incidence of AIDS defining illnesses than reported here. This makes comparisons with other studies difficult, as few studies have reported the incidence of AIDS defining diseases across a range of CD4 lymphocyte strata. In other studies, the incidence of disease has often been quoted as a proportion of patients who develop disease within one or two years of the CD4 lymphocyte count dropping below some arbitrary level[212,279-

[280]. Given the pathogenesis of infection with HIV, the CD4 lymphocyte count will continue to fall during the follow-up of such studies[36], and hence the results of this Chapter provide more reliable evidence of the likelihood of developing an AIDS defining illness, given the latest CD4 lymphocyte count.

Those studies which have addressed the incidence of illnesses as the CD4 lymphocyte count decreased report similar findings to this study, that is, that the incidence increased as CD4 lymphocyte count decreased[281-282], although the categories of CD4 lymphocyte count used in these studies were much wider than those used here. This study is unique in the number of patients included and its use of follow-up CD4 lymphocyte counts, which enable the occurrence of a disease to be related to the CD4 lymphocyte count at which it occurs much more closely.

The incidence of all AIDS defining illnesses was highly dependent on the CD4 lymphocyte count. This information may prove to be extremely useful in the development of prophylaxis and screening tests. For example, the incidence of cytomegalovirus retinitis in patients with a CD4 lymphocyte count above 25/mm^3 was extremely low, hence prophylaxis may only be appropriate in patients with very low CD4 lymphocyte counts. Similarly, if a patient presented with symptoms suggestive of cytomegalovirus retinitis, measurement of the CD4 lymphocyte count may provide some indication of how likely the diagnosis is. For the majority of the diseases, the incidence increased as the CD4 lymphocyte declined. Late stage diseases, such as cytomegalovirus retinitis and *Mycobacterium avium* complex, had a relatively low incidence before the CD4 lymphocyte count dropped below 25/mm^3. However, it should be noted that at CD4 lymphocyte counts between 25/mm^3 and 50/mm^3, the incidence of, for example, cytomegalovirus, was higher than the incidence of *Pneumocystis carinii* pneumonia at CD4 lymphocyte counts of between 100/mm^3 and 200/mm^3. Diseases such as *Pneumocystis carinii* pneumonia, Kaposi's sarcoma and oesophageal candidiasis had a relatively high incidence through all CD4 categories.

The incidence of oesophageal candidiasis was significantly lower in females compared to males. This contrasts with previous reports, where oesophageal candidiasis has been reported more commonly in females[156,228,283-284]. The higher frequency reported in females previously has been attributed to the frequency of vaginal candidiasis observed in women infected with HIV[283]. There was also a reduced incidence of Kaposi's sarcoma in females and in all exposure groups compared to homosexual men, although the incidence in the

combined exposure group was higher than expected. It is possible that this category contained a high proportion of patients included in the 'unknown' exposure category who were actually homosexual or bisexual men. Kaposi's sarcoma has been reported to be up to 10 times more common in homosexual men[115,285], and has been reported in most other exposure groups to a certain extent[286]. A woman's risk of developing Kaposi's sarcoma may be closely associated to her partner's exposure category[286]. Various studies have now provided evidence that a new human herpes virus may be the cause of Kaposi's sarcoma[287-289], and this may help to explain the high risk of Kaposi's sarcoma in homosexual men.

There were no other differences between the sexes in terms of the incidence of AIDS defining illnesses, in contrast to previous reports which have suggested that, in addition to oesophageal candidiasis, toxoplasmosis, recurrent herpes simplex infections, HIV wasting syndrome and cytomegalovirus all occur more commonly in women[152,156,228,290]. As the incidence of disease has been shown to be strongly related to CD4 lymphocyte count, some of these studies may have failed to adjust for gender-related differences in CD4 lymphocyte count.

This study confirmed an increased incidence of *Mycobacterium avium* complex in patients diagnosed with HIV in more recent years, but found no evidence of an increase in cytomegalovirus infections[245,279,291-292]. By preventing or delaying death from opportunistic infections such as *Pneumocystis carinii* pneumonia without stopping the decline in immune function, clinical manifestations more common with advanced immunosuppression become more common[249,293].

Details of the ethnic origin of patients in this study were not available, although the majority of the patients were of Caucasian origin. There is some evidence to suggest differences in the incidence of AIDS defining illnesses according to race[141,156,284-285,294-295].

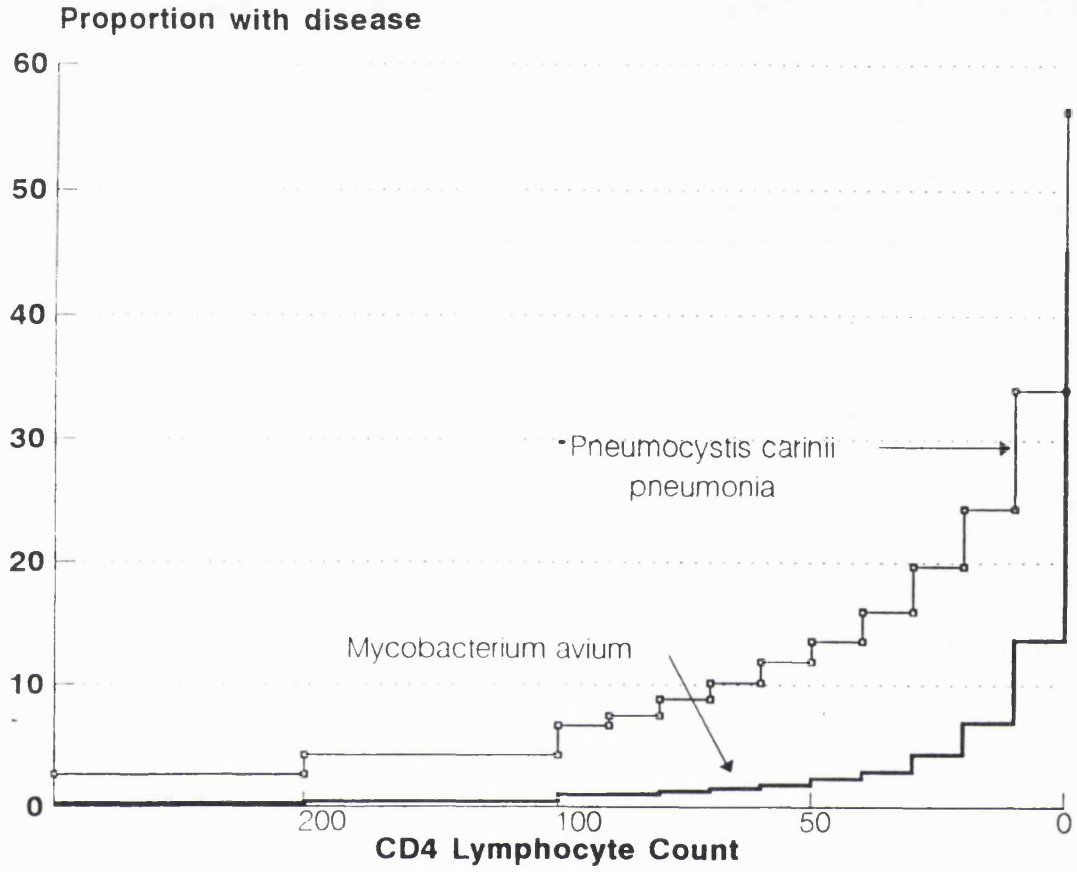
5.7.3.1 Kaplan-Meier estimates of disease progression

An alternative method of looking at the risk of disease would be to use Kaplan-Meier progression curves to estimate the proportion of patients who were disease free as the CD4 lymphocyte count dropped, using the lowest CD4 lymphocyte count recorded. For example, Figure 5.2 illustrates the Kaplan-Meier progression curves of the probability of developing *Pneumocystis carinii* pneumonia or *Mycobacterium avium* complex, according to the lowest CD4 lymphocyte count. There may be problems with the interpretation of

this type of analysis and this is discussed further in Chapter 5.7.4.

Figure 5.2

Kaplan-Meier estimates of disease progression; CD4 lymphocyte count



At CD4 lymphocyte counts of 100/mm^3, the cumulative proportion of patients who were estimated to develop either *Pneumocystis carinii* pneumonia or *Mycobacterium avium* complex was 6.7% and 1% respectively, if there were no deaths from *Pneumocystis carinii* pneumonia or *Mycobacterium avium* complex respectively. At CD4 lymphocyte counts of 50/mm^3, this proportion had increased to 13.6% and 2.3%, while at a zero CD4 lymphocyte count, these proportions were estimated to be 56.3% and 45.2%. These results are consistent with those presented earlier. Diagnoses of *Pneumocystis carinii* pneumonia are extremely common and occur across a wide range of CD4 lymphocyte counts, but the incidence continues to increase as the CD4 lymphocyte count decreases. In contrast, diagnoses of *Mycobacterium avium* complex are comparatively rare at higher CD4 lymphocyte counts, but become increasingly common as the CD4 lymphocyte count falls to very low levels.

5.7.4 Potential Biases in these Analyses

An important potential bias which may affect the results of this Chapter is discussed by Hoover *et al*[296-297]. Suppose for example, that at 3 years after diagnosis of AIDS, Kaplan-Meier curves suggested that 50% of patients would have cytomegalovirus. This figure is difficult to interpret. Common interpretations of this figure are that it estimates that 50% of patients will have developed cytomegalovirus after three years[262,279], or that, given a patient is alive in three years, there is a 50% chance that they will have developed cytomegalovirus[298-299]. If there are a lot of deaths in the cohort during follow-up then these interpretations are both inaccurate. The more accurate interpretation of the figure is that it is the cumulative proportion of patients who would develop cytomegalovirus if there were no deaths from causes other than cytomegalovirus by a given point of time. This interpretation is only valid if all patients are equally likely to be censored. If this assumption cannot be made then the Kaplan-Meier estimates have no meaning.

It is clear that in some circumstances this assumption may not be appropriate, and alternative models to overcome this problem are discussed in detail by Hoover *et al*[296-297]. Such models assume that patients are not lost to follow-up, which may not be the case with a mobile clinic population. In this Chapter, it is difficult to assess the extent of this bias, but several attempts to overcome it have been made. For example, in the person-years analysis, patients were stratified by CD4 lymphocyte count. Most patients with a CD4 lymphocyte count of 25/mm^3 or below will be at an equally high risk of death as cytomegalovirus, that is, the probability of death and cytomegalovirus will be independent. Equally, patients with a CD4 lymphocyte count of above 200/mm^3 will have a low risk of death from cytomegalovirus or any other cause. In the same way, a Kaplan Meier plot of the proportion of patients with disease according to the lowest CD4 lymphocyte count should not be seriously biased. This is because you assume that, for a given minimum CD4 lymphocyte count, the probability of a patient dying from anything other than cytomegalovirus is independent of the probability that a patient dies from cytomegalovirus disease.

A further potential bias is that patients may not report their previous history of AIDS defining illnesses accurately. According to data collected from patients at their first visit, almost 65% were diagnosed with HIV less than three months prior to their first visit, therefore up to one third of patients may have been treated for HIV and experienced clinical events before attending the Royal Free or Chelsea and Westminster Hospitals. If a patient had been diagnosed with Kaposi's sarcoma but not reported this at their first

visit to the Royal Free Hospital, they could be incorrectly included in an analysis of the average CD4 lymphocyte count at Kaposi's sarcoma at their first recurrence of this disease. If this bias was present, it would have the effect of lowering the CD4 lymphocyte counts at which each disease occurs, inflate the incidence of disease at lower CD4 lymphocyte counts, and decrease survival after a specific diagnosis. It is difficult to ascertain the extent to which patients self reporting agrees with medical history. Previous studies in unrelated medical conditions have suggested that recall of medical histories depends on the diagnosis, the length of the recall period and a potential reluctance to answer sensitive questions[300-302]. However, the results of this Chapter (in terms of survival and the median CD4 lymphocyte count at which AIDS defining illnesses occurred) agreed with other studies in the area. If such a bias acts here, its effect should be small; patients in the Royal Free and Chelsea and Westminster Cohorts have favourable survival times when compared to other patient groups.

5.9 Summary

The data in this chapter provide potentially important information about the risk of AIDS defining illnesses at lower CD4 lymphocyte counts, enabling disease specific prophylaxis to be targeted at an appropriate population. As the repertoire of drugs available for prophylaxis and treatment of patients with HIV grows, patients may take ever increasing quantities of medication, which raises questions about compliance and the interaction of drugs[303-304]. Determining the optimum time to start prophylaxis is therefore of paramount importance, both in terms of cost and benefit. As more prophylactic agents are developed in the future, this data may prove to be useful as historical controls for the incidence of diseases before the specific prophylaxis was introduced. These results would also be of value to clinicians interested in estimating the costs of caring for patients with opportunistic infections, as this will vary greatly in different CD4 lymphocyte count strata[250].

CHAPTER 6 - DEVELOPMENT OF A STAGING SYSTEM FOR PATIENTS WITH AIDS

6.1 Introduction

Chapters 3, 4 and 5 have illustrated the wide difference in the prognosis of patients with AIDS. The considerable heterogeneity between AIDS patients in terms of survival means that it is not helpful to think of AIDS as a discrete homogeneous state, but that a finer distinction would be of use in many circumstances, including clinical trial design and resource planning. In this chapter, a staging system is developed from the Royal Free Hospital dataset, which classifies the condition of AIDS patients into three grades, each with a distinct prognosis. This staging system is then validated on the Chelsea and Westminster cohort and on the Royal Free Hospital Haemophilia cohort, which has been described previously in detail[305]. The use of the score in the design of clinical trials and patient management is also discussed.

6.2 Derivation and Publication of A Staging System for AIDS Patients

A staging system for AIDS patients was originally derived using data from the Royal Free Hospital Cohort, with a study end date of February 1994. This was published in July 1995 and a copy of the paper is included in Appendix 4[306]. For consistency with the rest of the thesis, I will derive and validate the staging system once more on the latest data set available, which includes data from the Royal Free up to August 1994 and data from the Chelsea and Westminster up to July 1995. The score derived on the latest dataset differs slightly from that originally published, as expected with a slightly different dataset and more endpoints. In a practical situation, where clinicians may be trying to calculate a score or stage a patient with AIDS, the original published score should be used.

6.3 Literature Review

Although several attempts to define the severity of AIDS have been made, this idea is still being developed[307]. General measures of severity of illness, such as MedisGroups or Apache II, were developed to define the severity of illness of patients admitted to intensive therapy units and would not readily adapt to patients with AIDS, as they fail to use information about AIDS specific events[307-309]. Several classification systems have been proposed which stage patients with HIV[310-314], and have used a range of clinical and laboratory criteria for staging. The disadvantages of some of these staging systems, as reviewed by Rabeneck *et al* in 1991[315], is that they are not necessarily based on severity

of illness, and a large number of people cannot be classified. Clearly there are major differences in the prognosis of patients with AIDS; researchers have reported that most opportunistic diseases increase the risk of death[316-318], and I have demonstrated that some of the heterogeneity in terms of survival can be explained in terms of the different prognosis associated with each diagnosis.

There have been several attempts to subdivide patients with AIDS according to prognosis. Justice *et al* proposed a staging system based on physiological deficits, such as nutritional deficit, haemocrit levels and white blood cell count, rather than demographic or diagnostic features[319]. This system has been shown to predict mortality at 30 days[320]. Turner *et al* proposed a survival based severity index called the 'severity index for adults with AIDS' (SIAA)[79]. This index was developed from current expert opinion, and created three AIDS defining diagnosis groups and then determined the risk of subsequent complications and risk of death. The SIAA has been shown to offer greater prognostic discrimination than the CD4 lymphocyte counts at diagnosis of AIDS[321].

A more recent staging system developed by Justice *et al* proposed a global measure, assessed in the course of inpatient nursing, which specified four levels of functional ability ranging from mostly able to care for self during activities of daily life to total dependency on nurses or other care providers[322]. This staging system had the ability to discriminate inpatient mortality, but further validation or applications to out-patients has yet to be described. This staging system also used no information from CD4 lymphocyte counts, which has been shown to decline throughout infection with HIV[190-191], and which has been shown to tend to be close to zero when patients die[188,193,323].

To derive a staging system, the impact of disease on a given patient should be assessed in terms of predefined clinical and laboratory parameters. Patients should be easily dividable into strata within which each patient has the same or similar susceptibility to the outcome[324]. A staging system that is based on severity of disease has the following characteristics that distinguish it from a non-prognostic scale[315];

i) the purpose of the system is prognostic (the purpose of a classification system is solely descriptive)
ii) the outcome event should be clearly stated in advance
iii) the stages of illness should be hierarchically arranged
iv) the stages of disease should be mutually exclusive and should encompass

all individuals with that disease.

Practically, staging systems for patients with HIV and AIDS could be of use in many situations. They may help a clinician in advising their patient over planning for the future, for example, to determine if this patient is well enough to go on a trip for six months, or to determine if the patient is eligible for a hospice place, given that the hospice will only accept a patient with a life expectancy of under three months. Staging systems are also potentially of use to guide diagnostic and therapeutic decisions and allow appropriate prognostic stratification in clinical trials.

6.4 Defining the Severity of AIDS Defining Illnesses

Before analyzing the data, the severity of AIDS defining illnesses was graded using previously published results. The AIDS in Europe study published a report of survival in 1994[74], and reported more favourable survival times after an initial AIDS defining diagnosis for patients with *Pneumocystis carinii* pneumonia (20 months), Kaposi's sarcoma (21 months), oesophageal candidiasis (19 months) and extrapulmonary tuberculosis (28 months). This study reported a particularly poor survival for patients with a lymphoma (6 months), and intermediate survival times were reported for all other diagnoses combined (13 months). There was no information about the prognosis of patients diagnosed with recurrent pneumonia or pulmonary tuberculosis from the AIDS in Europe study, but based on the results of Chapter 5 these diagnoses have been included as mild (median survival 14 and 25 months respectively). On the basis of the prognosis attached, three groups of AIDS defining illnesses were defined;

Mild	oesophageal candidiasis, Kaposi's sarcoma, pulmonary and extrapulmonary tuberculosis, recurrent pneumonia and *Pneumocystis carinii* pneumonia
Severe	all other AIDS defining illnesses excluding lymphoma
Very Severe	lymphomas

6.5 Patients from the Royal Free Hospital Cohort

In total, 385 patients with AIDS have been followed up for a median duration of 14.0 months (90% range 1.5 - 43.0 months). A total of 734 AIDS defining illnesses were diagnosed and 204 patients died (53.0%). The patients included in this Chapter are

described briefly in Table 6.1.

Table 6.1

Description of patients with AIDS at the Royal Free Hospital

		N	%
All patients		385	100
Vital status	Alive	181	47.0
	Dead	204	53.0
Gender	Male	341	88.6
	Female	44	11.4
Exposure Category	Homo/Bisexual	271	70.4
	Heterosexual	59	15.3
	IDU	26	6.8
	Other	29	7.5
CD4 count at initial AIDS diagnosis ($/mm^3$)	Unknown	74	19.2
	50 or less	133	34.5
	51 - 200	99	25.7
	Above 200	79	20.5
Year of initial AIDS diagnosis	1990 or earlier	120	31.2
	1991 - 1992	139	36.1
	After 1992	126	32.7

In common with data presented in earlier chapters, the majority of the AIDS patients were male (341 patients, 88.6%), and homosexual or bisexual (271 patients, 70.4%). A considerable number of patients reported their exposure category as heterosexual (59 patients, 15.3%), and this reflects the increasing proportion of women seen at the hospital originating from sub-Saharan Africa. The median age at initial AIDS defining illness was 35.2 years (90% range 24.6 - 55.5), and the male patients were significantly older than the female (median ages 35.6 and 30.7 respectively, $p < 0.0001$, Wilcoxon).

The median CD4 count within three months of initial AIDS defining illness, which was available for 311 patients (80.8%), was 70/mm^3 (90% range 10 - 550/mm^3). During follow-up, a median of 9 CD4 lymphocyte counts for each patient were measured (90% range 1 - 31). The median time between measurements was just one month (90% range 1.2 - 24.7 months). In 74 patients, the CD4 lymphocyte count within three months of the initial AIDS diagnosis was not available. This was for a variety of reasons, the main one being that patients were first seen at the Royal Free Hospital some time after their initial AIDS defining diagnosis. Over 20% of patients (79 patients, 20.5%) had a CD4 count in excess of 200/mm^3 at their initial AIDS defining illness.

Table 6.2 and 6.3 illustrate the use of antiretrovirals and prophylaxis against *Pneumocystis carinii* pneumonia (PCP) during patient follow-up.

Table 6.2
Use of treatment during follow-up

Started Treatment	**Never**	**At/Before AIDS**	**After AIDS**
Antiretrovirals	113 (29.4)	174 (45.2)	98 (25.5)
Zidovudine	135 (35.1)	166 (43.1)	84 (21.8)
Didanosine	296 (76.9)	17 (4.4)	72 (18.7)
Zalcitabine	353 (91.7)	8 (2.1)	24 (6.2)
PCP Prophylaxis	77 (20.0)	165 (42.9)	143 (37.1)
Nebulised pentamidine	211 (54.8)	83 (21.6)	91 (23.6)
Cotrimoxazole	139 (36.1)	113 (29.4)	133 (34.5)
Dapsone	347 (90.1)	14 (3.6)	24 (6.2)
Clindamycin	372 (96.6)	0 (0.0)	13 (3.4)

The patterns of prescribing in 1994 was very different to what it would be now, with strategic combinations of therapy and the introduction of protease inhibitors. Dates of stopping treatment were not collected, and even if such data were available it would not be used to estimate the risk of death. The variable representing treatment is better described as 'ever started treatment', rather than 'on treatment', which is consistent with an intention-to-treat type approach. The most common antiretroviral used was zidovudine, but after an initial AIDS defining illness, both ddI and ddC were commonly

used. This may reflect their use in patients whose health is deteriorating on zidovudine, or that combination treatment was becoming more common.

Table 6.3

Duration of treatment (months)

	N	Mean	SD	Median	90% range
Antiretrovirals					
Total	272	23.6	16.3	21.6	2.5 - 52.4
Started At/Before AIDS	174	10.1	13.5	2.5	0.0 - 36.0
Started After AIDS	98	15.3	12.2	14.0	0.0 - 35.4
PCP Prophyiaxis					
Total	308	20.6	17.2	18.1	0.6 - 47.7
Started At/Before AIDS	165	9.9	16.7	3.9	0.0 - 33.0
Started After AIDS	143	14.4	11.8	13.1	0.0 - 36.8

SD; standard deviation

Prophylaxis against *Pneumocystis carinii* pneumonia tended to be evenly split between nebulised pentamidine and cotrimoxazole, reflecting the allergies which are commonly encountered during treatment with cotrimoxazole. Both dapsone and clindamycin were infrequently used. Among patients with AIDS who started treatment before an AIDS diagnosis, the median duration of treatment with either antiretrovirals or *Pneumocystis carinii* pneumonia prophylaxis was low (2.5 and 3.9 months respectively). In the patients with AIDS who had ever started treatment, the median duration of treatment following an AIDS diagnosis was much longer (14.0 and 13.1 months respectively). Among patients who started treatment, the median CD4 lymphocyte count at which treatment with antiretrovirals commenced was 100/mm^3 (90% range 10 - 350/mm^3) and was 110/mm^3 (90% range 10 - 320/mm^3) when patients started prophylaxis for *Pneumocystis carinii* pneumonia.

Table 6.4 combines the AIDS defining diagnoses into mild, severe and very severe. Patients with more than one diagnosis at initial AIDS defining illness were included in the most severe category of their multiple AIDS defining illnesses.

Table 6.4

Categorisation of AIDS defining illnesses

	AIDS Defining Illnesses			Total
	First (%)	Second (%)	Subsequent (%)	(%)
Mild	275 (71.4)	67 (36.0)	30 (18.4)	372 (50.7)
Severe	96 (24.9)	112 (60.2)	125 (76.7)	333 (45.3)
Very Severe	14 (3.6)	7 (3.8)	8 (4.9)	29 (4.0)
Total	385 (100)	186 (100)	163 (100)	734 (100)

The proportion of diagnoses which were mild steadily decreased as you move from first to second to subsequent diagnoses, while an opposite trend of increasing frequency of severe diseases was seen. The proportion of patients diagnosed with a very severe disease stayed constant.

6.5.1 Establishing Prognostic Factors and Appropriate Models

Table 6.5

Relative hazard of death associated with further AIDS defining illnesses

	Relative Hazard of Death	95% Confidence Interval	p - value
Unadjusted			
Per Disease[1]	2.14	1.89 - 2.43	0.0001
CD4 Count[2]	2.29	1.76 - 3.00	0.0001
Adjusted[3]			
Per Disease	1.75	1.51 - 2.01	0.0001
CD4 Count	1.79	1.39 - 2.30	0.0001

1 The number of diseases (regardless of severity of diagnosis) was modelled as a time dependant covariate, and the relative hazard represents the increased hazard of death associated with the development of each additional AIDS defining illness

2 per 100/mm^3 difference in the CD4 lymphocyte count, also modelled as a time dependant covariate

3 Mutually adjusted for each other

Table 6.5 shows the relative hazard of death associated with the CD4 lymphocyte count and with the diagnosis of AIDS defining illnesses, regardless of whether the illness was mild, severe or very severe. The relative risk of death doubled, on average, each time a new AIDS defining illness occurred (RH 2.14; 95% CI 1.89 - 2.43, $p < 0.0001$) or each time the CD4 lymphocyte count dropped by 100/mm^3 (RH 2.29; 95% CI 1.76 - 3.00, $p < 0.0001$). Patients who have experienced more AIDS defining illnesses would be expected to have lower CD4 lymphocyte counts, and the adjusted figures showed that the number of AIDS defining illnesses and CD4 lymphocyte count were both important independent prognostic factors when determining the relative risk of death.

There are many different ways to model the relationship between CD4 lymphocyte count and the relative hazard of death. Table 6.6 presents some of the different models. In all cases, the CD4 lymphocyte count was modelled as a time dependent covariate.

Table 6.6

Different modelling strategies for the CD4 lymphocyte count

Model	**Relative Hazard of Death**	**95% Confidence Interval**	**p - value**	**Log-Likelihood[1]**
Per 50% difference in latest count	1.70	1.51 - 1.91	0.0001	89.00
Per 100/mm^3 difference in latest count	2.29	1.76 - 3.00	0.0001	80.73
Per 100/mm^3 difference in minimum count to date	2.54	1.87 - 3.45	0.0001	79.45
Per 100/mm^3 difference in mean of last 5 counts	1.96	1.59 - 2.42	0.0001	71.89
Per 100/mm^3 difference in median of last 3 counts	1.92	1.56 - 2.37	0.0001	66.57
Per 100/mm^3 difference in mean of last 2 counts	1.88	1.53 - 2.31	0.0001	62.56

[1] This is the difference in log-likelihood between Cox models with and without a variable representing CD4 lymphocyte count.

The test statistic shown was the difference in log-likelihood between the null model and the model with CD4 lymphocyte count included and provided a measure of the fit of the model. The higher this test statistic, the better the fit of the model. In common with previous chapters, the logarithm of the CD4 lymphocyte count provided the best fitting model. The relative risk of death increased by 70% for each 50% difference in the CD4 lymphocyte count (RH 1.70; 95% CI 1.51 - 1.91, $p < 0.0001$). It was interesting to note that the models of the latest CD4 lymphocyte count and the minimum CD4 lymphocyte count to date provided an almost identical fit. Using the mean or median of the last two, three or five CD4 lymphocyte count measurements did not improve the fit of the models. Although the logarithm of the CD4 lymphocyte count provided the best fitting model, the minimum CD4 lymphocyte count was used to make the score simple to calculate and use. Using the minimum CD4 count in this way also meant that patients would not be able to move in the reverse direction through the grades if their CD4 lymphocyte count began to rise. This reflected the belief at the time of deriving the score that AIDS was an irreversible disease process. This is discussed further in Chapter 6.6.

Having established that both CD4 lymphocyte count and the number of AIDS defining illnesses were both independently related to the relative risk of death, the relationship between the severity of the disease and relative risk of death was further investigated. Initially, the first AIDS defining illness was distinguished from subsequent AIDS defining illnesses. The results of this model are shown in Table 6.7. The number of subsequent diagnoses was fitted as a time dependant covariate. Hence the unadjusted relative risk is the increase in the risk of death each time a patient experiences a mild, severe, or very severe diagnosis after the initial AIDS defining illness. After adjustment for the minimum CD4 lymphocyte count to date, patients diagnosed with either a severe or very severe illness as an initial AIDS defining illness were at a significantly higher risk of death relative to patients in whom the initial AIDS defining illness was mild (RH 1.57 and 3.33; 95% CI 1.07 - 2.31 and 1.67 - 6.64, p-value 0.023 and < 0.0001 respectively). For subsequent diagnoses, the risk of death increased significantly for each additional mild, severe or very severe diagnosis experienced. The results of Table 6.7 show that, for example, a severe diagnosis increased the relative risk of death by approximately the same amount whether it occurred as the first or subsequent AIDS defining illness (RH 1.57 versus 2.10). Although there was a suggestion of a worse prognosis for each of the groups of illnesses when diagnosed during follow-up, the model was kept as simple as possible and simply counted the number of diagnoses of each severity.

Table 6.7

Relative hazard of death following mild, severe and very severe diagnoses

	Unadjusted			Adjusted for CD4 Lymphocyte Count		
	Relative Hazard of Death	**95% Confidence Interval**	**p - value**	**Relative Hazard of Death**	**95% Confidence interval**	**p - value**
Initial AIDS Defining illness						
Mild	1.00	-	-	1.00	-	-
Severe	1.72	1.22 - 2.30	0.0018	1.57	1.07 - 2.31	0.023
Very Severe	3.61	1.93 - 6.75	0.0001	3.33	1.67 - 6.64	0.0001
Subsequent Diagnoses						
Per Mild Diagnosis	1.57	1.22 - 2.02	0.0004	1.32	1.01 - 1.73	0.042
Per Severe Diagnosis	2.50	2.14 - 2.93	0.0001	2.10	1.75 - 2.53	0.0001
Per Very Severe Diagnosis	15.45	8.47 - 28.25	0.0001	12.59	6.30 - 25.17	0.0001
CD4 Count[1]	2.54	1.87 - 3.45	0.0001	1.90	1.39 - 2.60	0.0001

[1] per 100/mm^3 difference in the minimum CD4 lymphocyte count

6.5.2 Derivation of the Scoring System

The results of Table 6.8 strongly suggest that the minimum CD4 lymphocyte count since AIDS (RH 1.93; 95% CI 1.59 - 2.34, $p < 0.0001$) and the type and severity of AIDS defining illnesses were of independent importance for assessing the relative risk of death. That is, they both provide substantial information about the risk of death independently of one another.

Table 6.8

Relative hazard of death - combining initial and subsequent diagnoses

	Relative Hazard of Death	**95% Confidence Interval**	**p - value**	**Natural Log**
Unadjusted				
Per Mild Diagnosis	1.62	1.33 - 1.97	0.0001	
Per Severe Diagnosis	2.49	2.14 - 2.90	0.0001	
Per Very Severe Diagnosis	8.47	5.38 - 13.34	0.0001	
Adjusted[1]				
Per Mild Diagnosis	1.40	1.13 - 1.75	0.0027	0.3365
Per Severe Diagnosis	2.08	1.74 - 2.48	0.0001	0.7324
Per Very Severe Diagnosis	6.89	4.11 - 11.55	0.0001	1.9301
Minimum CD4 Count ($100/mm^3$)	1.93	1.59 - 2.34	0.0001	0.6575

[1] Each relative hazard is adjusted for all other variables in the model

The relative risk of death increased by 40% (RH 1.40; 95% CI 1.13 - 1.75, $p = 0.0027$) for each mild disease diagnosed, by 108% for each severe diagnosis (RH 2.08; 95% CI 1.74 - 2.48, $p < 0.0001$) and by 589% (RH 6.89; 95% CI 4.11 - 11.55, $p < 0.0001$) when a very severe condition (i.e. lymphoma) developed.

The natural logarithms of the adjusted relative hazards, shown in Table 6.8, were used to derive the score which reflects the risk of death. Mathematically, the score can be

written as;

$$\text{Score} = \log(RR_m) \times N_m + \log(RR_s) \times N_s + \log(RR_{vs}) \times N_{vs} - \log(RR_{CD4}) \times \text{min CD4}$$

where N_m, N_s, and N_{vs} denote the number of mild, severe or very severe conditions experienced to date

$\log(RR_m)$, $\log(RR_s)$, $\log(RR_{vs})$ and $\log(RR_{CD4})$ denote the natural logarithm of the relative hazards obtained from fitting the number of mild, severe or very severe diagnoses, or a one cell difference in the minimum CD4 lymphocyte count achieved to date, using a Cox proportional hazards model and time dependant covariates

and min CD4 denotes the minimum CD4 lymphocyte count (/mm^3) measured following an AIDS diagnosis.

This score was then divided by $\log(RR_{CD4})$, so that the multiplier for the CD4 lymphocyte count was -1. This simplifies the score without affecting the power to discriminate between the prognosis of individual patients. The coefficients were also rounded to give

Score =		300 per very severe diagnosis
	+	100 per severe diagnosis
	+	40 per mild diagnosis
	-	minimum CD4 count since AIDS diagnosis (/mm^3)

For those patients who transferred their care to the Royal Free, a full history of CD4 lymphocyte counts was not necessarily available. In these patients, a score was not calculated until the first CD4 lymphocyte count was available. At this date, the history of diagnoses was used to construct the score.

6.5.3 Score Cut-offs Used to Define the AIDS Grades

The AIDS grades were defined *a priori*, and were constructed to be as easy to remember and use as possible. Table 6.9 summarises both the score and AIDS Grades; AIDS Grade I was defined as a score of less than zero, AIDS Grade II was defined as a score between zero and 99 and AIDS Grade III was defined as a score of 100 or more. Patients' scores and hence their grades cannot decrease over time, as the minimum CD4 count since AIDS diagnosis was used. A patients' score was updated each time a new illness was diagnosed or the minimum CD4 lymphocyte count dropped.

Table 6.9

Definition of AIDS grades and the score

Score =	300 per very severe diagnosis
+	100 per severe diagnosis
+	40 per mild diagnosis
-	minimum CD4 (/mm^3) since AIDS diagnosis
AIDS Grade I	Score < 0
AIDS Grade II	Score 0 - 99
AIDS Grade III	Score 100 +

6.5.3.1 An Example

Figure 6.1 shows the AIDS defining illnesses, CD4 lymphocyte count and score as they change over time in a single patient. At an initial AIDS defining illness of cutaneous Kaposi's sarcoma, the patient's score was -55, and the patient was classified as Grade I. One mild condition had been diagnosed and the CD4 count was 95/mm^3:

$$\text{Score} = [300 \times 0] + [100 \times 0] + [40 \times 1] - 95 = -55$$

New CD4 counts during the first month following the initial AIDS defining illness did not fall below 95/mm^3, hence the score remained unchanged. A CD4 count of 80/mm^3 two months following the initial AIDS diagnosis resulted in an updated score of -40, and the patient remained in AIDS Grade I:

$$\text{Score} = [300 \times 0] + [100 \times 0] + [40 \times 1] - 80 = -40$$

A CD4 count of 50/mm^3 after 7 months, together with a diagnosis of oesophageal candidiasis , a mild diagnosis, changed the score to +30, and the patient moved into AIDS Grade II;

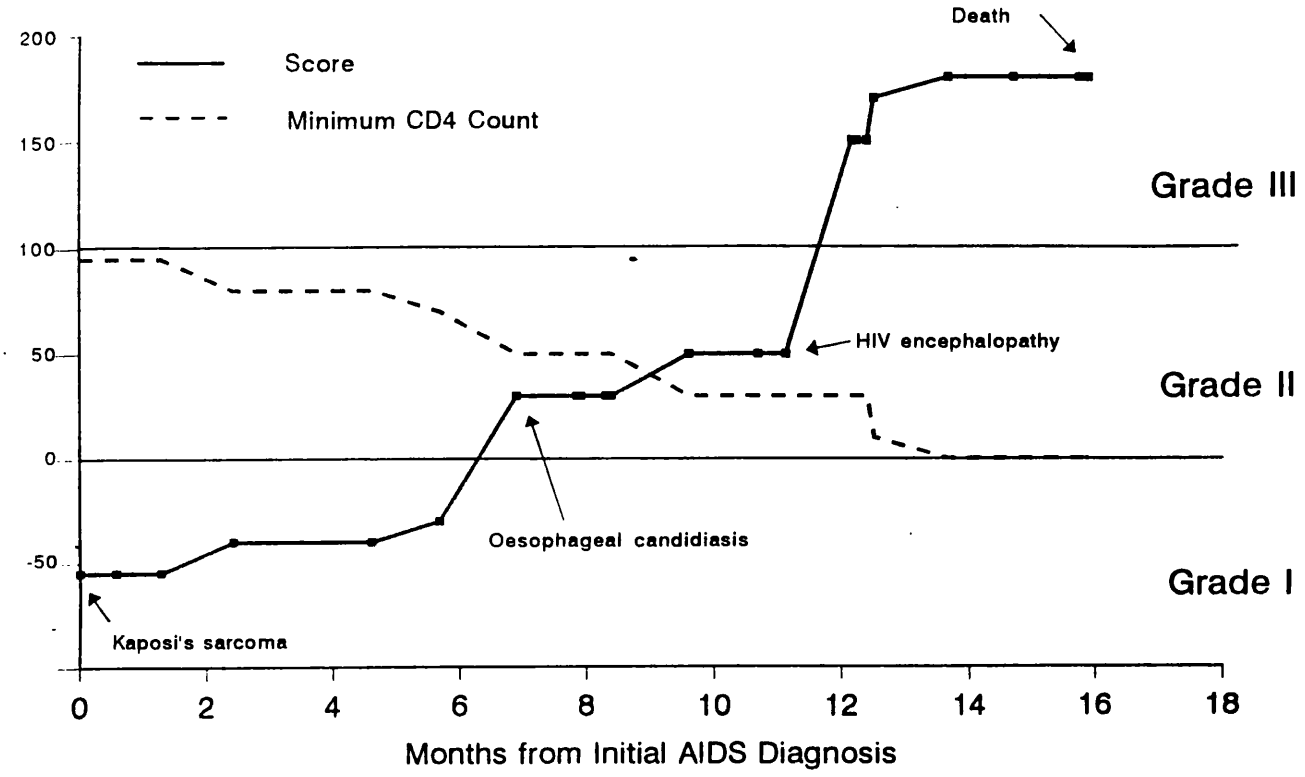
$$\text{Score} = [300 \times 0] + [100 \times 0] + [40 \times 2] - 50 = +30$$

At 12 months after an initial AIDS diagnosis, the patient was diagnosed with HIV encephalopathy, a severe diagnosis, and the CD4 count had dropped further to 30/mm^3. Thus the patient moved to Grade III and his score was +150:

Score = [300 x 0] + [100 x 1] + [40 x 2] - 30 = + 150

No further AIDS defining illnesses were defined, and the patient died in AIDS Grade III 16 months following his initial AIDS defining illness.

Figure 6.1
The score after an AIDS diagnosis



6.5.4 Validation of the Scoring System

6.5.4.1 The Royal Free Hospital Cohort

Table 6.10 shows the death rates, number of person-years at risk and deaths in each of the AIDS Grades for the Royal Free Hospital Cohort, the group of patients from which the score was derived. Using the patient example above, this patient contributed 7 months follow-up to AIDS Grade I, 5 months to AIDS Grade II and 4 months in AIDS Grade III. The patient died in AIDS Grade III, and hence the death was allocated to this Grade. As would be expected, the gradient of increasing risk of death through the different Grades was very strong. The score was also modelled as a time dependent covariate in a Cox

proportional hazards model; the relative risk of death increased by 83% per 100 unit increase in the score (RH 1.83; 95% CI 1.64 - 2.03, $p < 0.0001$).

Table 6.10

Death rates in the Royal Free Hospital cohort

Score	**< 0** **Grade I**	**0 - 99** **Grade II**	**100 +** **Grade III**
Person Years at risk	178.1	222.8	90.1
Deaths	21	86	97
Death rate (per 10 person-years)	1.18	3.86	10.77
95% Confidence Interval	0.7 - 1.7	3.0 - 4.7	8.6 - 12.9

6.5.4.2 The Chelsea and Westminster Cohort

The score was also validated on the much larger group of patients from the Chelsea and Westminster Hospital. A total of 4429 AIDS defining illnesses were diagnosed in 1884 patients with AIDS in whom the CD4 lymphocyte count had been measured on at least one occasion following an AIDS diagnosis. The relationship between the score and the risk of death was highly statistically significant; the relative risk of death associated with an increase in the score of 100 units was 1.84 (RH 1.84; 95% CI 1.77 - 1.92, $p < 0.0001$). The death rates in each grade, shown in Table 6.11, show a remarkable agreement with those shown in Table 6.10

Table 6.11

Death rates in validation cohort : Chelsea and Westminster Hospital

Score	**< 0** **Grade I**	**0 - 99** **Grade II**	**100 +** **Grade III**
Person Years at risk	966.0	1012.2	625.0
Deaths	97	403	648
Death rate (per 10 person-years)	1.00	3.98	10.37
95% Confidence Interval	0.8 - 1.2	3.6 - 4.4	9.6 - 11.2

6.5.4.3 The Royal Free Hospital Haemophilia Cohort

Although the validation discussed above showed that the score and grading system had similar prognostic value in a different group of patients, patients from the Royal Free and the Chelsea and Westminster Hospital Cohorts were quite similar, that is, they are both predominantly cohorts of young homosexual men. Men with haemophilia have different demographic characteristics and suffer from different opportunistic infections, and for this reason the score and staging system was also validated on a separate cohort of patients from the Royal Free Hospital Haemophilia Cohort[305]. Although a much smaller number of patients in this cohort have AIDS (37 patients in whom the score could be evaluated), the relationship between the score and risk of death was again highly significant. The relative risk associated with an increase in the score of 100 units was 1.78 (RH 1.78; 95% CI 1.32 - 2.39, $p < 0.0001$). The person years at risk and the death rates in each of the AIDS Grades are shown in Table 6.12.

Table 6.12

Death rates in validation cohort : Royal Free Hospital Haemophilia cohort

Score	**< 0** **Grade I**	**0 - 99** **Grade II**	**100 +** **Grade III**
Person Years at risk	17.5	42.9	15.7
Deaths	2	12	16
Death rate (per 10 person-years)	1.14	2.80	10.19
95% Confidence Interval	0.0 - 2.7	1.2 - 4.4	5.2 - 15.2

6.5.5 Improving the Score

Other cofactors may also predict death, in particular age and treatment. Table 6.13 shows the relative hazard of death associated with a number of potential cofactors. These estimates were obtained by adding each of the cofactors to the model presented in Table 6.8 to determine if their inclusion resulted in a better fitting model and hence a more appropriate score. Gender and year of diagnosis were not significantly related to the relative risk of death. After counting the number and severity of diagnoses and adjusting for the CD4 lymphocyte count, patients who belonged to the 'other' exposure

Table 6.13

Improving the score

Variable[1]	Relative Hazard of Death	95% Confidence Interval	p - value
Male	1.00	-	-
Female	0.91	0.56 - 1.48	0.70
Homo/Bisexual	1.00	-	-
Heterosexual	1.05	0.62 - 1.77	0.87
Intravenous drug users	0.92	0.50 - 1.73	0.81
Other	2.53	1.44 - 4.64	0.0013
1990 and earlier	1.00	-	-
1991 and 1992	1.24	0.87 - 1.75	0.23
1993 and later	1.66	0.91 - 3.03	0.10
Age (per 10 yr increase)	1.26	1.07 - 1.49	0.0069
Antiretrovirals	0.54	0.35 - 0.83	0.0051
PCP prophylaxis	0.45	0.28 - 0.70	0.0005

[1] Each variable has been fit in turn to the adjusted Cox proportional hazards model shown in Table 6.8. Treatment was included in the model as a time dependant covariate.

category remained at a significantly higher risk of death relative to homosexuals or bisexuals (RH 2.53; 95% CI 1.44 - 4.64, p = 0.0013). As discussed briefly in Chapter 4, the majority of patients in this group may not survive long enough for an exposure group to be established, and their poor survival may be an artefact of their late presentation, and as such, it would not be appropriate to adjust for this in the score. After adjustment for the number and severity of AIDS defining illnesses and CD4 lymphocyte count, older patients were at a significantly higher relative risk of death, while patients who started treatment with antiretrovirals or prophylaxis against *Pneumocystis carinii* pneumonia were at a significantly lower relative risk of death.

A final model which incorporates the prognostic information provided by age and

treatment is shown in Table 6.14.

Table 6.14

Model incorporating age and treatment

	Relative Hazard of Death	95% Confidence Interval	p - value	Natural Log
Per Mild Diagnosis	1.41	1.13 - 1.77	0.0027	0.3436
Per Severe Diagnosis	2.11	1.75 - 2.53	0.0001	0.7467
Per Very Severe Diagnosis	6.99	4.17 - 11.76	0.0001	1.9445
100/mm^3 drop in minimum CD4 count	2.20	1.60 - 3.03	0.0001	0.7885
Age (per 10 year increase)	1.28	1.08 - 1.52	0.0051	0.2469
Antiretroviral Treatment	0.60	0.38 - 0.94	0.027	-0.5108
PCP prophylaxis	0.53	0.33 - 0.85	0.0008	-0.6349

A revised score, calculated in the same way as discussed in section 6.7, is shown below;

Score = 250 per very severe diagnosis
+ 100 per severe diagnosis
+ 40 per mild diagnosis
+ 3 x age at AIDS diagnosis
- 60 if started antiretroviral treatment
- 80 if started *Pneumocystis carinii* prophylaxis
- minimum CD4 count since AIDS diagnosis (/mm^3)

Practically, this improved score would be considerably more difficult to calculate and incorporate into clinical practice and would also enable patients to move back through the AIDS grades if they started treatment. If a score was constructed in this way, such that patients could reverse through grades, it may be more appropriate to use the latest CD4 lymphocyte count rather than the minimum count since AIDS, and this is discussed further in Chapter 6.6.

6.6 Discussion

In this chapter, I have developed a staging system for patients with AIDS which has practical applications in clinical decision making, such as ordering invasive tests or selecting which patients should benefit from scarce resources. In addition, the prognostic score could be used to select a uniform group of patients (in terms of prognosis) for participation in clinical trials. The staging system helps to explain the considerable heterogeneity of survival among AIDS patients, and has been validated on four separate groups of patients to date with close agreement[306,325-326]. The staging system has all the attributes of a clinically useful prognostic staging system[327]; it is based on an objective criterion (risk of death); it places patients in a single category at any given time point and all patients are able to be allocated to a clinical stage; it does not allow patients to move from a higher to a lower grade, and each grade carries a risk of death which is substantially different from the other grades. Further, all the information required is easily gathered with a high degree of accuracy[328].

Since the original score was published in 1995, two further validations have been performed, as shown in Table 6.15[325-326]. One of these validations was performed on a group of Italian intravenous drug users and the other was of Scottish intravenous drug users. Again, both validations showed that the score discriminated between patients in different Grades and provided accurate prognostic information.

Table 6.15

Death rates in published validation cohorts

Score	**< 0**	**0 - 99**	**100 +**
	Grade I	**Grade II**	**Grade III**
Edinburgh City Hospital Cohort[325]			
Person Years at risk	132.9	149.1	97.4
Deaths	14	45	116
Death rate (per 10 person-years)	1.1	3.0	11.9
Italian Seroconversion Study[326]			
Person Years at risk	120.7	145.1	26.6
Deaths	29	43	31
Death rate (per 10 person-years)	2.4	3.0	11.7

A common problem with many staging systems is that they are not validated on further groups of patients[315], or when they are, the scoring system is less predictive[329-330]. Validating the system on the patients from which it was derived will inevitably produce prognostic discrimination between groups. The grading system developed here was validated on two distinct cohorts of patients, with remarkably consistent results.

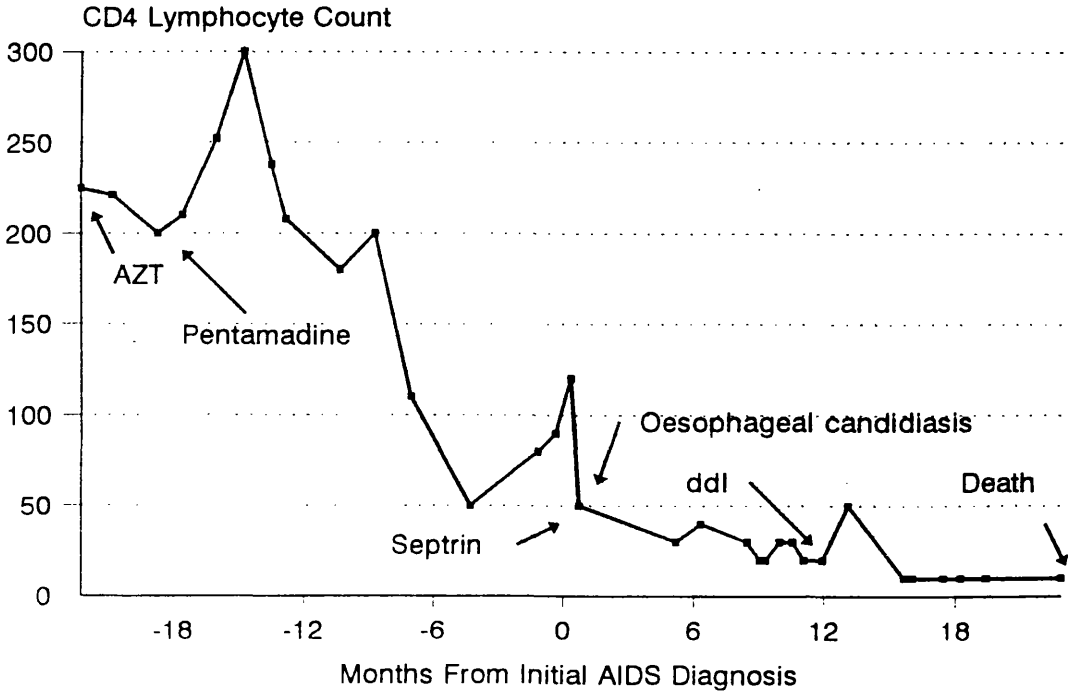
6.6.1 The CD4 Lymphocyte Count

There has been some uncertainty as to whether the CD4 lymphocyte count would provide important prognostic information about the risk of death once information about AIDS defining illnesses was accounted for. The results of this chapter show that CD4 lymphocyte counts remain a predictor of survival throughout the lifetime of patients with AIDS. Many clinicians discontinue measurement of this marker after an AIDS diagnosis, even though it has been shown to be a prognostic marker for death[193,210]. Further, in 1993, de Gruttola *et al* showed that the most recent CD4 lymphocyte count was the most prognostic of death[331].

Unfortunately, the CD4 count is not a perfect measure of the immune status of a patient. Figure 6.2 illustrates the CD4 lymphocyte counts both before and after an AIDS diagnosis in one patient, chosen because they had at least eighteen months follow-up before and after an AIDS diagnosis.

Figure 6.2

CD4 lymphocyte counts during patient follow-up



Major events during follow-up, such as starting treatment or the diagnosis of opportunistic infections are also indicated on the illustration. This patient is not typical of patients seen at the Royal Free Hospital due to the frequency of follow-up visits both before and after an AIDS diagnosis, but it illustrates the variable nature of the CD4 lymphocyte count. Various methods to smooth the CD4 counts, including the mean and median of the last few measurements led to a decrease in the relative risk of death when compared to using the most recent or minimum CD4 count, suggesting that important information may have been lost, as discussed by Sabin in 1995[238]. The problem of variability in CD4 lymphocyte counts has been well documented[251,253,332], but remains as a problem because it is the current gold-standard against which other potential prognostic markers are compared.

6.6.2 AIDS Defining Illnesses

This staging system used estimates of previously published survival times to grade the severity of AIDS defining illnesses. These survival estimates are consistent with those shown in Chapter 3, which is also based on the AIDS in Europe data, and also Chapter 5, where survival after each AIDS defining illness was reported. They are also consistent with other large studies based on surveillance data[63,70,90]. However, further work by Hutchinson *et al* on the staging system suggested that HIV encephalopathy may be a very severe diagnosis[333]. In Chapter 5, survival after this diagnosis was almost six months and seemed to carry a more favourable prognosis than that of a lymphoma. The differences in survival among patients with HIV encephalopathy between the Edinburgh Cohort and the patients from the Royal Free and Chelsea and Westminster Hospitals Cohort may be partly attributable to the higher proportion of intravenous drug users in the Edinburgh Cohort[333].

The original published score used AIDS defining illnesses according to the Centers for Disease Control 1987 criteria[14]. Pulmonary tuberculosis and recurrent pneumonia were added to the surveillance definition of AIDS in 1993[15], and were subsequently included in the derivation of the score as mild diseases. The results of Chapter 5 suggested that both of these diagnoses had survival times similar to that of oesophageal candidiasis, Kaposi's sarcoma and *Pneumocystis carinii* pneumonia. No patients to date in either cohort have been diagnosed with invasive cervical carcinoma, so it is difficult to place this in the current severity groupings.

6.6.3 Practical Applications of the Staging System

This grading system could have a clear application in the design of clinical trials, where there is a need for a means of classifying stages of AIDS on the basis of a firm criterion, such as risk of death[57,334-335]. The grading system developed in this Chapter could be used for defining entry or endpoint criteria, or both. For example, classification in AIDS Grade III could be used as an appropriate entry criteria for some trials of late interventions, with mortality as the endpoint. Patients recruited to the trial would be a homogeneous group, all with a poor prognosis. In other trials it might be more appropriate to use an AIDS Grading, together with death as an endpoint. There is some concern that AIDS is an unsuitable endpoint in some trials which recruit AIDS free patients[57], and this could be partly addressed by using progression to AIDS Grade I or II as an endpoint. Such approaches could shorten the duration of clinical trials. Use of the Grades or score in this way might be criticised as it incorporates the CD4 lymphocyte count as well as clinical progression. Use of the CD4 lymphocyte count as an endpoint in clinical trials has been heavily debated, as changes in the CD4 lymphocyte count do not necessarily explain treatment differences[56,336-338]. However, the results of this analysis suggest that changes in the CD4 lymphocyte count are as important as the occurrence of some AIDS defining illnesses for determining the risk of death, which are currently accepted as endpoints in clinical trials.

Resource allocation and planning may also benefit from the adoption of this grading system. The cost of caring for patients with AIDS has been estimated to be up to £16,000 per year[40-41], but would vary substantially between the three Grades in terms of hospitalisation and treatment. Knowledge of the numbers of patients in each grade, together with an estimate of future survival times would give a more accurate picture of the resources required than could be gained from knowing the total number of patients with AIDS.

6.6.4 Adjustments to the Score

Further variables, such as gender and year of diagnosis, were added to the score to determine if their addition resulted in a score which more accurately reflected the risk of death. Age was found to add to the information provided by the score, and confirms the results of Chapter 4 and other published studies which have shown that age is an important prognostic factor in patients with AIDS[58,63,73-74,134]. It may not be appropriate to include this in the score, as this should reflect the stage of disease rather than the demographic characteristics of the patient. In a clinical setting, a patient aged 50 would

be expected to have a poorer prognosis than a patient aged 20 with the same score, or who belonged in the same Grade. In a clinical trials application, stratification at enrolment by age may be appropriate.

Patients who had started treatment with antiretrovirals or prophylaxis against *Pneumocystis carinii* pneumonia were found to be at a significantly reduced relative risk of death; Hutchinson *et al* suggested that the grading system could be improved by accounting for antiretroviral use, but have not investigated the relationship between prophylaxis against *Pneumocystis carinii* pneumonia and death[325]. The proposed staging system does not account directly for disease specific prophylaxis, even though prophylaxis against *Pneumocystis carinii* pneumonia has been shown to reduce the risk of death in patients with AIDS[154,173]. Table 6.14 suggests that prophylaxis against *Pneumocystis carinii* pneumonia could add further information to the prognostic score, but this would further complicate the score.

The revised score which took account of the additional prognostic factors of age and treatment was necessarily more complicated than the simple score proposed which counts the number and severity of each disease. The original idea of the score was that it was to be as simple as possible and capture as much prognostic information as possible. With the addition of each extra explanatory variable, the score becomes more complicated, and hence it is less likely to be used.

6.6.4.1 Measurement of HIV-1 Viral Load

The staging system may also need to be modified to incorporate prognostic information from HIV RNA viral load, which has been shown to provide important prognostic information in a variety of patients and settings. Until recently, methods for determining virus replication were hampered by poor sensitivity and reproducibility[339]. Recent data indicate that the amount of HIV-RNA in the plasma accurately reflects the extent of viral replication in an infected person[340-343]. Studies have also suggested that HIV-1 RNA in plasma is a good predictor for the development of AIDS, independent of the CD4 lymphocyte count[344-352]. The relationship between viral load and death has not been investigated so thoroughly, but early reports suggest that it may have prognostic power independent of the CD4 lymphocyte count when death is an endpoint[37,353]. However, these studies have only considered the prognostic value of baseline viral load rather than viral load measured throughout follow-up, and the relationship between death and viral load may change when updated values are used.

6.6.4.2 New Treatment Options

It should be remembered that the patients included in this thesis will have had minimal exposure to the new drugs which have been developed in recent years. The clinical care and prognosis of patients with HIV and AIDS has been substantially altered by the development of a new class of drugs called protease inhibitors[354]. The four available protease inhibitors are saquinavir, ritonavir, indinavir and nelfinavir. All four drugs have clearly been shown to be effective in short term studies[355-358]. Ritonavir and saquinavir have both individually been shown to increase survival in patients with advanced immunodeficiency[359-360].

The introduction of new treatments has raised the question of the reversibility of HIV infection, that is, can patients with AIDS get better? The current grading system makes no provision for patients to medically improve. However, initial evidence suggests that patients may shown significant signs of recovery from serious AIDS defining illnesses[361], that hospitalisations and new AIDS defining events have been dramatically reduced[362], and even that death rates may be falling[363]. The long term benefits of these drugs remains to be seen, but based on current evidence, it would seem appropriate to allow patients to recover to a certain extent. There are several ways this idea could be incorporated into the score. The score could be constructed based on the number of AIDS defining illnesses diagnosed in the past one or two years[364], or the score could be modified to use the latest CD4 lymphocyte count or viral load measurement, which will reflect virological and immunological improvement.

6.7 Summary

The results of this chapter have formally confirmed that the risk of death after an initial AIDS defining illness increases as more new diseases occur. In addition, it provides evidence that the CD4 lymphocyte count remains an independent prognostic marker of survival throughout the lifetime of patients with AIDS. A prognostic staging system has been developed and validated on two cohorts, one with almost 2000 patients with AIDS and a small cohort of haemophilic patients. The agreement between the derivation and validation cohort was striking, and further to the original publication of the staging system, it has been validated on two further cohorts of patients infected predominantly via drug use.

CHAPTER 7 - ANTIHERPES VIRUS TREATMENT AND THE RISK OF KAPOSI'S SARCOMA

7.1 Introduction

In contrast to the previous Chapters in this thesis, this Chapter concentrates on one specific AIDS defining diagnosis, Kaposi's sarcoma, and the risk of this disease in patients from the Chelsea and Westminster Cohort of patients. In common with the analysis presented in Chapter 5, patients without an AIDS diagnosis were also included in these analyses. The analyses consider whether patients treated with the antiherpes virus drugs, foscarnet, ganciclovir and acyclovir are at a reduced risk of Kaposi's sarcoma. These results are compared to those reported by others, and alternative statistical analyses are considered, which may account for the differences observed.

7.2 Literature Review

Kaposi's sarcoma was first described by Moritz Kaposi, a Hungarian dermatologist, in 1872. In its classical form, this rare lesion was a pigmented sarcoma, appearing on the lower legs of predominantly older Jewish and Eastern European men[38]. In the 1960's, Kaposi's sarcoma emerged as a late complication of immunosuppression in patients undergoing organ transplantation, where the tumours were often found to regress spontaneously when immunosuppressive therapy was discontinued[365]. A third variety of non-AIDS Kaposi's sarcoma occurs in sub-Saharan Africa, where Kaposi's sarcoma has been endemic for many years. The disease may resemble the more classical form, or take a more aggressive course similar to that seen in AIDS patients[38]. In 1980, the first cases of Kaposi's sarcoma in young homosexual men heralded the arrival of AIDS-associated Kaposi's sarcoma[2].

Kaposi's sarcoma lesions in AIDS patients are usually multiple, progress rapidly and may affect practically any area of the skin or organs[23]. The tumours often begin as small flat dusky red or violet areas of skin discolouration, progressing in weeks or months to raised painless firm nodules[38]. In contrast to classical Kaposi's sarcoma, AIDS associated Kaposi's sarcoma has an aggressive course, and up to 50% of patients have lymph-node or gastrointestinal involvement at the time of diagnosis[125].

Initially, it was reported that up to 60% of homosexual men with AIDS had Kaposi's sarcoma, but this figure is thought to have declined in recent years[64,366-368]. This decline

has been attributed to less complete reporting or to changes in sexual practises among homosexual men[286,369]. In addition, there is some evidence that patients are now diagnosed with Kaposi's sarcoma at an older age and at more advanced stages of immunodeficiency[212,369]. In Chapter 4 of this thesis, almost 20% of initial AIDS defining illnesses were of Kaposi' sarcoma, and this figure illustrates that this disease remains a common problem in patients infected with HIV.

Various studies have suggested that an infectious agent may be the cause of Kaposi's sarcoma. Chang *et al* found herpes-virus like DNA sequences in Kaposi's sarcoma tissue from a patient with AIDS[287]. Since this discovery, these DNA sequences have been found in nearly all biopsy specimens from patients with classical Kaposi's sarcoma, endemic Kaposi's sarcoma and AIDS associated Kaposi's sarcoma[289,370-374]. This virus has been named Kaposi's sarcoma-associated herpes virus (KSHV), or human-herpes virus 8 (HHV-8). The discovery of this herpes virus has lead to suggestions that the drugs active against humanherpes virus (cytomegalovirus infections and recurrent herpes simplex infections), such as foscarnet, ganciclovir and acyclovir, may be effective in the prevention of Kaposi's sarcoma[375-377]. These studies have reported inconsistent results, which may be due to a lack of statistical power or simple differences in the method of statistical analysis. A reduction in the risk of Kaposi's sarcoma would have implications in patient management, costs and quality of life.

Cytomegalovirus is one of the most common viruses causing life threatening infections in patients with AIDS[274]. In patients with AIDS, cytomegalovirus manifests itself primarily by causing retinitis[378-380] and gastroenteritis[381-383]. Foscarnet and ganciclovir are the currently licensed treatments for cytomegalovirus infections. Foscarnet was licensed in 1991 and has been shown *in vitro* to be a potent inhibitor of humanherpes virus and has been shown to be effective in the treatment of cytomegalovirus retinitis in patients with AIDS in two randomised controlled trials[384-385]. Ganciclovir was licensed in 1991; a number of studies have also shown that ganciclovir, another inhibitor of viral DNA polymerase, is effective in suppressing active cytomegalovirus infection, eliminating cytomegalovirus from blood and urine, and significantly reducing the size of retinal lesions to slow the progression of cytomegalovirus retinitis[386-387]. Acyclovir has been shown to be highly effective and well tolerated in the treatment and prophylaxis of herpes simplex virus infections[388-389] and could therefore play a role in the suppression of Kaposi's sarcoma.

In addition to the three drugs described above, cidofidir is a relatively new nucleoside analogue that has been shown to be highly active against cytomegalovirus[390] and effective in the treatment of cytomegalovirus retinitis[391-392]. However, this treatment was rarely used at the Chelsea and Westminster hospital in the period up to July 1995, and no data about this treatment has been included.

7.3 Anti Herpesvirus Treatments at the Chelsea and Westminster Hospital

As discussed in Chapter 2.3.1, the treatment policies described here reflect those in use prior to July 1995. At the Chelsea and Westminster Hospital, no patients are offered primary prophylaxis against cytomegalovirus infections. Patients with a diagnosis of cytomegalovirus are treated with foscarnet, 90mg/kg twice daily for 14-21 days or ganciclovir 5mg/kg twice daily. Treatment for gastrointestinal manifestations is stopped on the patient's recovery. Secondary prophylaxis against retinitis is with foscarnet 90mg/kg once daily or ganciclovir 5mg/kg daily, 5-7 days per week. From 1994, patients have been given 1 g oral ganciclovir daily as secondary prophylaxis against cytomegalovirus retinitis. All patients with recurrent herpes virus infections are treated with acyclovir 400mg twice daily, and all patients are offered acyclovir 400mg twice daily when their CD4 lymphocyte count drops below 100/mm^3. Patients who participated in a primary prophylaxis study of high dose acyclovir were allowed to remain on the study medication.

7.4 The Patient Population

Between 1982 and July 1995, a total of 3688 patients were diagnosed with HIV at the Chelsea and Westminster Hospital. Patients who were diagnosed with Kaposi's sarcoma within one month of their initial visit were excluded from this analysis, but patients with any other AIDS defining illnesses were included. In total, 599 patients were diagnosed with Kaposi's sarcoma (16.2%), 510 were diagnosed with cytomegalovirus of any site (13.8%) and 46 were diagnosed with recurrent herpes simplex virus disease (1.2%), as illustrated in the Venn diagram, Figure 7.1. Of patients diagnosed with cytomegalovirus, 296 were diagnosed with cytomegalovirus retinitis, 324 patients were diagnosed with gastrointestinal manifestations of cytomegalovirus, and 110 patients were diagnosed with both forms of cytomegalovirus.

Figure 7.1

Diagnoses made during follow-up

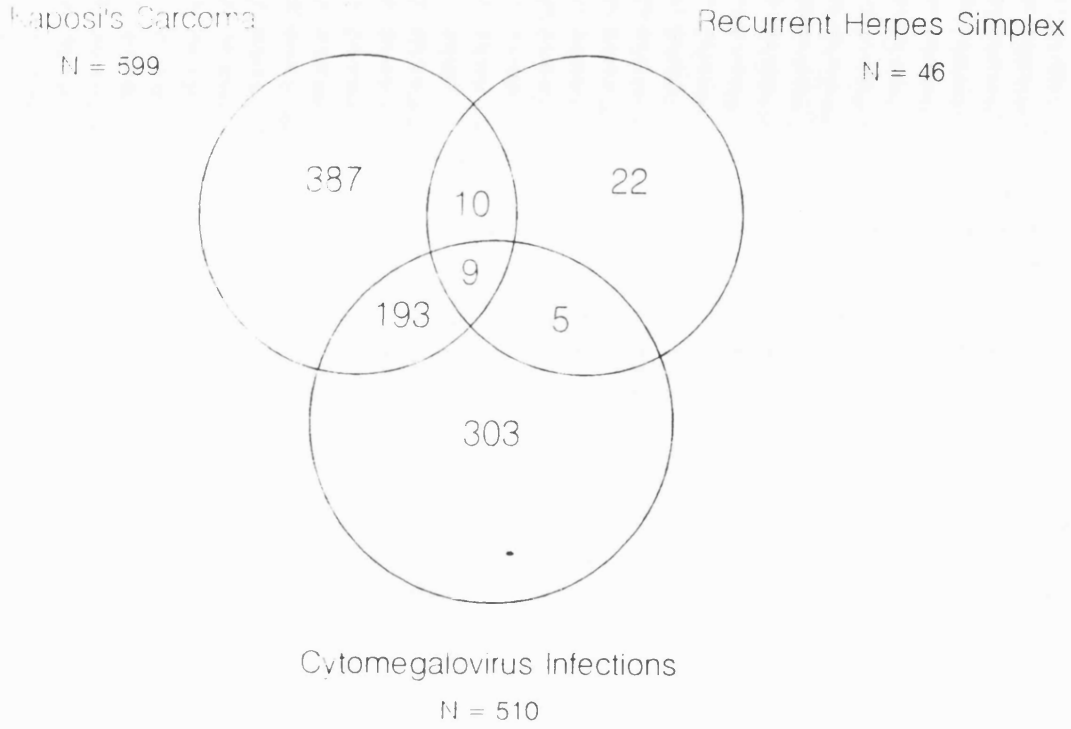
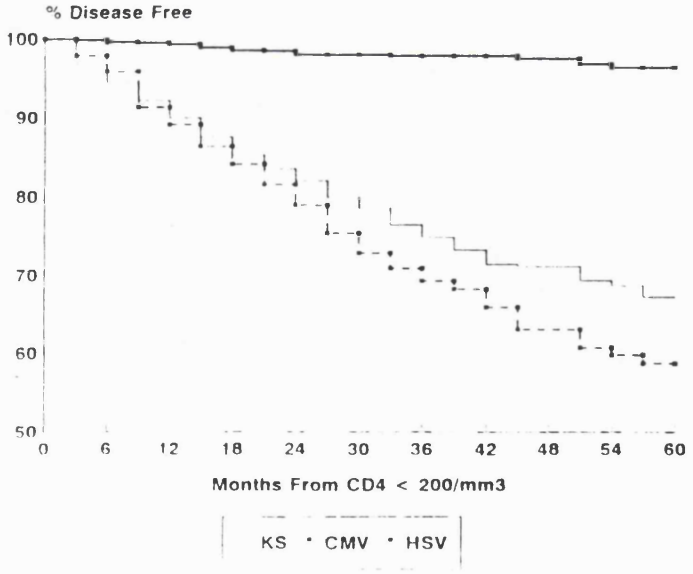


Figure 7.2 shows the proportion of patients who were disease free in the months following their first CD4 lymphocyte count below 200/mm^3.

Figure 7.2

Kaplan-Meier progression: Months from the first CD4 lymphocyte count below 200/mm^3



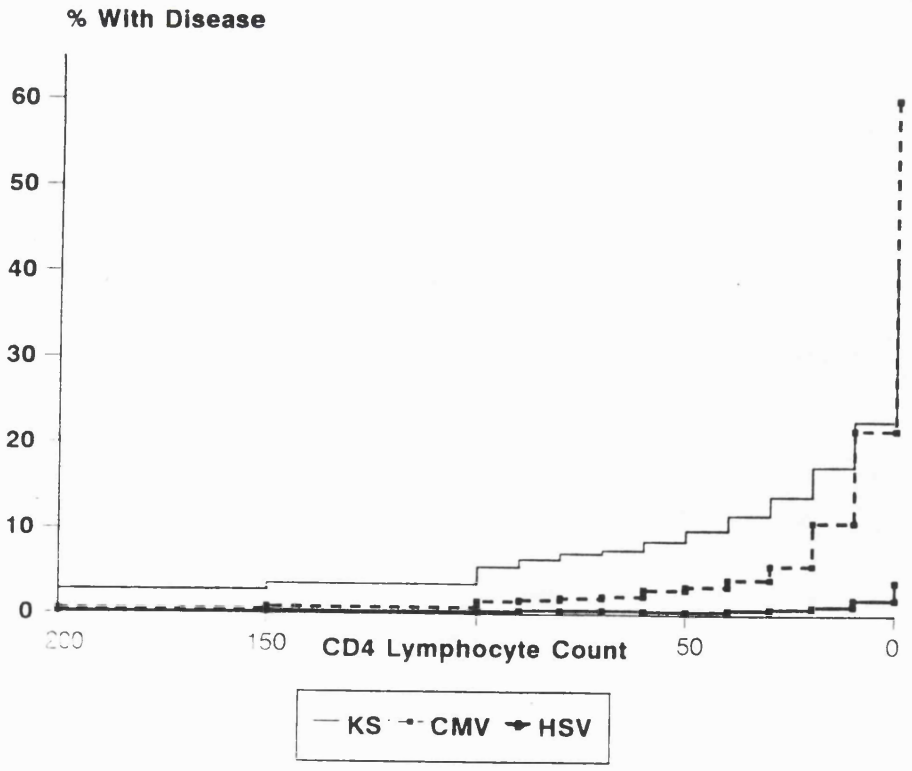
KS; Kaposi's sarcoma, CMV; cytomegalovirus infections (including retinitis), HSV; recurrent herpes simplex virus

Kaplan-Meier estimates suggested that at two years, 2% of patients had been diagnosed with recurrent herpes simplex infections, 18% had a diagnosis of Kaposi's sarcoma and 19% had a diagnosis of cytomegalovirus (of any site). At four years, these proportions had increased to 3.5%, 31.3% and 39.3% respectively.

The results of Chapter 5 suggested that the probability of developing each disease was highly dependent on the CD4 lymphocyte count, and this is illustrated in Figure 7.3. In all three diseases, the proportion of patients with disease, estimated by Kaplan-Meier progression curves, increased as the CD4 lymphocyte count decreased, although the pattern was distinct for each diagnosis. At CD4 lymphocyte counts of 50/mm^3, less than 1% of patients were estimated to develop recurrent herpes simplex, 2.5% were estimated to have developed cytomegalovirus of any site and 10% were estimated to have Kaposi's sarcoma. As the CD4 lymphocyte count declined further to zero, the corresponding percentages were 3.9%, 60.2% and 40.2% respectively. The difficulties of interpreting these illustrations and figures, discussed in Chapter 5.7.4 and in more detail by Hoover *et al* should be remembered[296-297].

Figure 7.3

Kaplan-Meier progression: Probability of diagnosis according to lowest CD4 lymphocyte count



KS; Kaposi's sarcoma, CMV; cytomegalovirus infections (including retinitis), HSV; recurrent herpes simplex virus

The majority of the patients were male (3487, 94.5%), belonged to the homosexual or bisexual exposure category (3409, 92.4%), and were diagnosed with HIV before 1990 (2678, 72.7%). A brief description of the patients is shown in Table 7.1. The demographic characteristics of the patients included in this Chapter were very similar to the demographics in previous Chapters.

Table 7.1

A description of the patient population

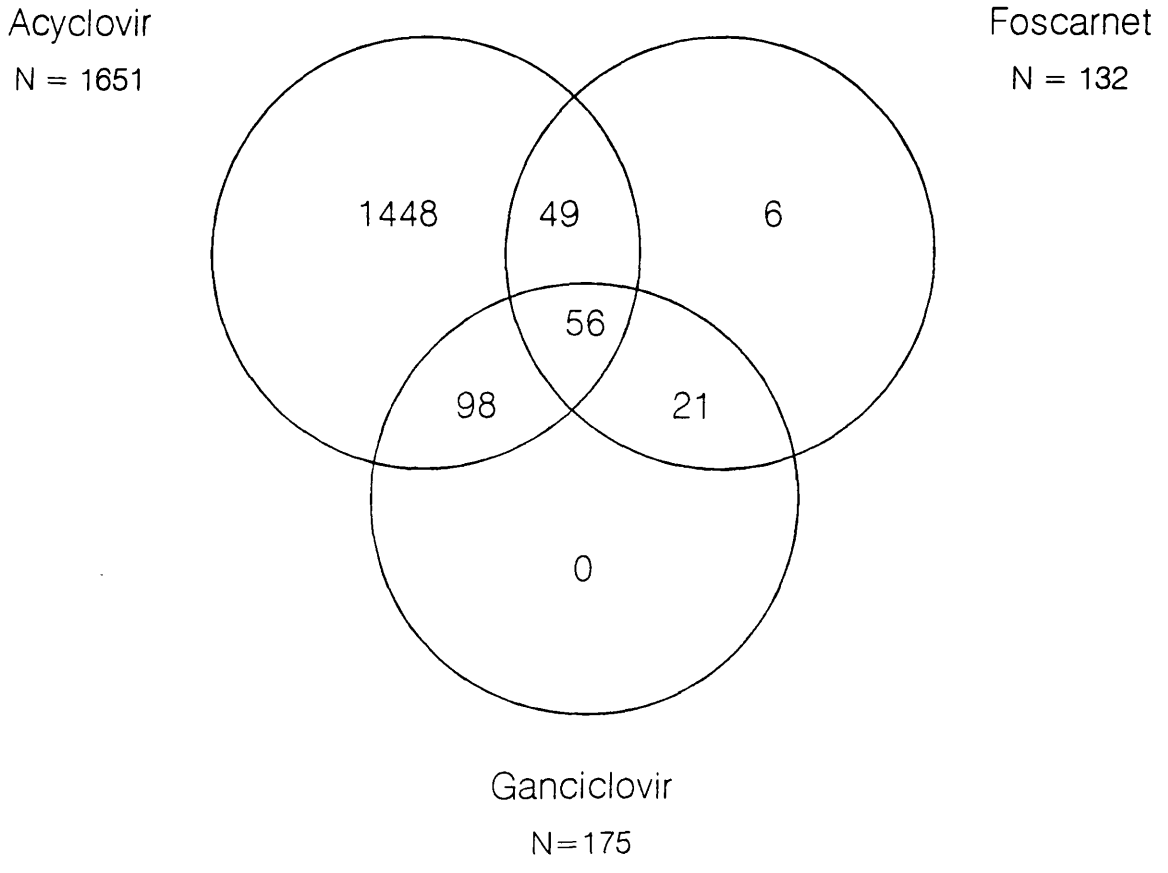
		N	%
Exposure Category	Homosexual/Bisexual	3409	92.4
	Intravenous Drug Users	104	2.8
	Heterosexual	37	1.0
	Other	138	3.7
Gender	Male	3487	94.5
	Female	201	5.5
Year of HIV Diagnosis	1987 or earlier	1621	44.0
	1988 - 1990	1057	28.7
	1991 - 1993	461	12.5
	1994 or later	549	14.9
CD4 Lymphocyte Count at First Visit	50/mm^3 or less	617	16.7
	51 - 100/mm^3	275	7.5
	101 - 200/mm^3	467	12.7
	201 - 500/mm^3	1538	41.7
	501/mm^3 or more	791	21.4
Age group	25 years or less	847	23.0
	26 - 35 years	1725	46.8
	36 - 45 years	801	21.7
	46 - 55 years	263	7.1
	Over 55 years	52	1.4

The median CD4 lymphocyte count at initial visit was 288/mm^3 (90% range 11 - 482/mm^3), and the median age at diagnosis of HIV was 31.8 years (90% range 20.5 - 48.4). At diagnosis of HIV infection, male patients were significantly older than female (mean ages 31.9 and 29.1 respectively, $p < 0.0001$, Wilcoxon), while intravenous drug users were significantly younger than other exposure groups (mean ages 27.8 and 31.9 years respectively, $p < 0.0001$, Kruskall-Wallis test). In addition, intravenous drug users had significantly higher CD4 lymphocyte counts at first visit when compared to other exposure groups (median 329/mm^3 and 295/mm^3 respectively, $p < 0.0001$ respectively). There was also a clear increase in the median CD4 lymphocyte count at initial visit; this rose from 286/mm^3 in patients diagnosed with HIV during 1987 or earlier, to 300/mm^3 in patients diagnosed HIV positive after 1990 ($p < 0.0001$, Wilcoxon).

During patient follow-up, 2349 patients (63.7%) had at least one CD4 lymphocyte count measured below 200/mm^3, 1899 (51.5%) had a CD4 lymphocyte count of below 100/mm^3 and 1592 (43.2%) had at least one CD4 lymphocyte count below 50/mm^3. During this period, patients received a variety of antiviral treatments; this is shown in Figure 7.4.

Figure 7.4

Treatment with antiherpes-virus drugs during patient follow-up



As in previous Chapters, no data is provided regarding stopping treatment and the duration of treatment shown in Table 7.2 reflects this fact. A similar proportion of patients received antiretroviral treatment or *Pneumocystis carinii* pneumonia prophylaxis. Among patients who started antiretroviral treatment, the most common treatment was zidovudine. No data was available detailing what type of *Pneumocystis carinii* pneumonia prophylaxis was administered. The duration of treatment with antiretrovirals and *Pneumocystis carinii* pneumonia prophylaxis was considerably longer than the duration of treatment with either foscarnet or ganciclovir.

Table 7.2

Treatment with *Pneumocystis carinii* pneumonia prophylaxis, antivirals and antiretrovirals

	N	Duration of Treatment (months)			
		Mean	Standard Deviation	Median	90% Range
Antiretrovirals	1931	26.6	20.5	22.2	0.9 -2 64.2
Zidovudine	1880	26.9	20.6	22.6	1.0 - 64.7
Didanosine	370	19.2	15.9	15.2	0.8 - 56.8
Zalcitabine	348	11.9	8.8	10.4	0.3 - 27.9
Lamivudine	81	1.1	1.8	0.7	0.0 - 3.0
PCP prophylaxis	1745	19.0	16.4	15.0	0.6 - 55.4
Antivirals					
Acyclovir	1651	19.9	16.7	15.7	0.6 - 55.3
Ganciclovir	175	7.3	13.6	4.7	0.2 - 21.8
Foscarnet	132	7.9	9.1	5.3	0.6 - 27.5

7.4.1 The Risk of Developing Kaposi's Sarcoma

Table 7.3 shows the unadjusted and adjusted relative hazard of developing Kaposi's sarcoma associated with each of the three antiherpes virus drugs, CD4 lymphocyte count, prophylaxis against *Pneumocystis carinii* pneumonia and antiretroviral treatment, previous cytomegalovirus disease, recurrent herpes infections of other AIDS defining illnesses, year of diagnosis with HIV, gender, age and exposure category.

Table 7.3

Relative hazard of Kaposi's sarcoma associated with the use of antiherpes-virus therapy

	Univariate Model		Multivariate Model	
	Relative Hazard (95% Confidence Interval)	**p**	**Relative Hazard (95% Confidence Interval)**	**p**
Age (10 yr increase)	1.39 (1.27 - 1.52)	0.0001	1.11 (1.00 - 1.22)	0.050
Female[1]	0.11 (0.04 - 0.39)	0.0002	0.12 (0.02 - 0.54)	0.0063
Homo/Bisexual[2]	3.50 (1.93 - 6.35)	0.0001	1.56 (0.78 - 3.13)	0.21
HIV Positive 1988-1990[3]	1.36 (1.11 - 1.67)	0.0035	0.99 (0.78 - 1.26)	0.96
HIV Positive 1991-1993[3]	2.09 (1.47 - 2.97)	0.0001	1.22 (0.83 - 1.79)	0.32
HIV Positive 1994-1995[3]	2.19 (1.63 - 2.94)	0.0001	1.21 (0.87 - 1.70)	0.26
CMV Diagnosis[4]	5.74 (4.36 - 7.55)	0.0001	2.84 (2.04 - 3.94)	0.0001
HSV Diagnosis[4]	6.49 (3.56 - 11.83)	0.0001	2.54 (1.38 - 4.70)	0.0029
Other AIDS Diagnosis[4]	5.79 (4.92 - 6.82)	0.0001	1.59 (1.28 - 1.97)	0.0001
Antiretroviral treatment[4]	3.04 (2.56 - 3.60)	0.0001	1.31 (1.04 - 1.66)	0.023
PCP prophylaxis[4]	4.01 (3.37 - 4.77)	0.0001	1.58 (1.21 - 2.05)	0.0007
CD4 count[4*]	1.75 (1.66 - 1.84)	0.0001	1.30 (1.26 - 1.35)	0.0001
Acyclovir[4]	2.64 (2.18 - 3.19)	0.0001	1.22 (0.97 - 1.53)	0.096
Foscarnet[4]	2.15 (0.89 - 5.21)	0.089	0.38 (0.15 - 0.94)	0.036
Ganciclovir[4]	2.62 (1.30 - 5.28)	0.0070	0.38 (0.18 - 0.81)	0.012

p; p - value, CMV; cytomegalovirus (including retinitis), HSV; recurrent herpes simplex virus, PCP; *Pneumocystis carinii* pneumonia

1 Risk of Kaposi's sarcoma in females compared to males

2 Risk of Kaposi's sarcoma in homosexual or bisexual men compared to other exposure categories

3 Risk of Kaposi's sarcoma in patients diagnosed HIV positive in given year compared to patients diagnosed with HIV in 1987 or earlier

4 Variable fitted as a time dependant covariate

* The relative risk is per 50% difference in the CD4 count

Before adjustment, all factors were related to the development of Kaposi's sarcoma; in particular, the relative risk of Kaposi's sarcoma was significantly raised in older patients and in patients who belonged to the homosexual and bisexual exposure categories. Patients with a lower CD4 lymphocyte count were also at a higher relative risk of developing Kaposi's sarcoma, as were patients with a prior AIDS diagnosis. However, as shown in Chapter 5, patients diagnosed with cytomegalovirus for example, tended to have much lower CD4 lymphocyte counts than patients who were not diagnosed with an AIDS defining illness. Kaposi's sarcoma also occurs at lower CD4 lymphocyte count, and this is why patients who started treatment with antivirals were also at a higher relative risk of Kaposi's sarcoma.

The multivariate analysis attempts to remove this confounding due to disease stage by adjusting for the disease stage and AIDS defining illnesses which may have occurred. After this adjustment, an apparently protective effect of foscarnet and ganciclovir was revealed. Treatment with either foscarnet (RH 0.38; 95% CI 0.15 - 0.94, p = 0.036) or ganciclovir (RH 0.38; 95% CI 0.18 - 0.81, p = 0.012) was associated with a significantly lower relative risk of subsequently developing Kaposi's sarcoma.

7.4.2 An Alternative Model

In order to reconcile these results with those presented by other workers, the analysis presented above was repeated. The model was altered to be consistent with those models used by other workers. In particular, the CD4 lymphocyte count was not transformed and no separate adjustment was made for cytomegalovirus or recurrent herpes simplex infections. All other variables, with the exception of year of diagnosis, gender, exposure category and age were fitted as time dependent covariates. The results of this model are shown in Table 7.4.

With this method of analysis, the conclusions would be substantially different and more consistent with previously published work. Foscarnet and ganciclovir were associated with a lower relative risk of developing Kaposi's sarcoma, but not significantly so (RH 0.53 and 0.63; 95% CI 0.21 - 1.31 and 0.31 - 1.30, p = 0.17 and 0.21 respectively).

Table 7.4

An alternative model

	Relative Hazard (95% Confidence Interval)	p-value
Age (10 yr increase)	1.05 (0.95 - 1.16)	0.33
Female[1]	0.12 (0.03 - 0.57)	0.0073
Homo/Bisexual[2]	1.54 (0.77 - 3.13)	0.22
HIV Positive 1988-1990[3]	1.03 (0.81 - 1.30)	0.83
HIV Positive 1991-1993[3]	1.34 (0.91 - 1.99)	0.14
HIV Positive 1994-1995[3]	1.35 (0.96 - 1.89)	0.081
AIDS Diagnosis[4]	2.47 (2.03 - 3.00)	0.0001
Antiretroviral treatment[4]	1.14 (0.91 - 1.43)	0.27
PCP prophylaxis[4]	1.30 (1.00 - 1.68)	0.049
CD4 count[4*]	1.59 (1.48 - 1.71)	0.0001
Acyclovir[4]	1.23 (0.98 - 1.56)	0.079
Foscarnet[4]	0.53 (0.21 - 1.31)	0.17
Ganciclovir[4]	0.63 (0.31 - 1.30)	0.21

PCP; *Pneumocystis carinii* pneumonia

1 Risk of Kaposi's sarcoma in females compared to males

2 Risk of Kaposi's sarcoma in homosexual or bisexual men compared to other exposure categories

3 Risk of Kaposi's sarcoma in patients diagnosed HIV positive in given year compared to patients diagnosed with HIV in 1987 or earlier

4 Variable fitted as a time dependant covariate

* The relative risk is per 100/mm^3 difference in the CD4 count

In the multivariate analysis, after adjusting for disease stage, it could be argued that patients who were diagnosed with cytomegalovirus and consequently treated with antiviral agents were at a reduced risk of Kaposi's sarcoma because the diagnosis of cytomegalovirus reduced their survival time and hence the time available to be diagnosed with Kaposi's sarcoma. As most patients with cytomegalovirus disease were treated with foscarnet or ganciclovir, this might suggest that ganciclovir and foscarnet reduced the risk

of Kaposi's sarcoma. For this confounding to explain these results, patients with cytomegalovirus disease would have to be at a lower risk of Kaposi's sarcoma compared to those patients without cytomegalovirus disease but with similar CD4 lymphocyte counts and a similar history of AIDS defining illnesses. To further investigate this potential bias, consider the risk of two other diagnoses, oesophageal candidiasis and *Pneumocystis carinii* pneumonia in patients treated with foscarnet and ganciclovir. The results of the multivariate analyses are shown in Table 7.5. These two diagnoses were chosen as they were classified as mild when deriving the staging system in Chapter 6, as was Kaposi's sarcoma.

It can be seen that foscarnet and ganciclovir were not associated with a significant reduction in the relative risk of either oesophageal candidiasis or *Pneumocystis carinii* pneumonia, and in most cases, treatment with antivirals was associated with a non-significant increase in the relative risk of either disease. It should also be noted that there was no relationship between acyclovir and the relative risk of either oesophageal candidiasis or *Pneumocystis carinii* pneumonia.

Table 7.5

The relative hazard of oesophageal candidiasis and *Pneumocystis Carinii* pneumonia associated with the use of antiherpes-virus therapy

	Oesophageal candidiasis		***Pneumocystis carinii* pneumonia**	
	RH (95% CI)	**p**	**RH (95% CI)**	**p**
Age (10 yr increase)	0.93 (0.83 - 1.04)	0.22	1.10 (1.00 - 1.21)	0.062
Female[1]	0.28 (0.12 - 0.63)	0.0024	0.81 (0.38 - 1.75)	0.60
Homo/Bisexual[2]	0.50 (0.27 - 0.91)	0.023	0.96 (0.52 - 1.75)	0.89
HIV Positive 1988-1990[3]	1.24 (0.95 - 1.62)	0.11	0.84 (0.67 - 1.07)	0.15
HIV Positive 1991-1993[3]	1.23 (0.86 - 1.76)	0.27	0.57 (0.40 - 0.82)	0.0022
HIV Positive 1994-1995[3]	0.71 (0.48 - 1.05)	0.088	0.73 (0.53 - 1.01)	0.057
CMV Diagnosis[4]	1.23 (0.88 - 1.72)	0.23	1.55 (1.11 - 2.17)	0.01
HSV Diagnosis[4]	0.77 (0.34 - 1.74)	0.53	0.98 (0.46 - 2.10)	0.97
Other AIDS Diagnosis[4]	1.45 (1.18 - 1.78)	0.0004	1.51 (1.24 - 1.83)	0.0001
Antiretroviral treatment[4]	1.62 (1.29 - 2.05)	0.0001	0.78 (0.63 - 0.98)	0.031
PCP prophylaxis[4]	1.55 (1.22 - 1.98)	0.0004	2.04 (1.60 - 2.58)	0.0001
CD4 count[4*]	1.39 (1.33 - 1.45)	0.0001	1.39 (1.34 - 1.45)	0.0001
Acyclovir[4]	1.00 (0.80 - 1.24)	0.97	1.47 (0.66 - 3.29)	0.35
Foscarnet[4]	0.84 (0.43 - 1.64)	0.60	1.64 (0.89 - 3.03)	0.11
Ganciclovir[4]	1.48 (0.80 - 2.72)	0.21	1.08 (0.87 - 1.33)	0.50

RH; relative hazard, CI; confidence interval, p; p - value, CMV; cytomegalovirus (including retinitis), HSV; recurrent herpes simplex virus, PCP: *Pneumocystis carinii* pneumonia

1 Risk of diagnosis in females compared to males

2 Risk of diagnosis in homosexual or bisexual men compared to other exposure categories

3 Risk of diagnosis in patients diagnosed HIV positive in given year compared to patients diagnosed with HIV in 1987 or earlier

4 Variable fitted as a time dependant covariate

* The relative risk is per 50% difference in the CD4 count

7.5 Discussion

The results from this Chapter suggest that foscarnet and ganciclovir, anti-herpes virus drugs, may reduce the risk of Kaposi's sarcoma. Table 7.6 summarises the results available from published studies which have addressed this question. The reports from these studies were short and the exact statistical methods that were used were not explicitly stated. Consistent with the results of this analysis, both Jones *et al*[376] and Glesby *et al*[375] report a reduced risk of Kaposi's sarcoma associated with the use of foscarnet, significantly reduced in the paper by Jones *et al.* In addition, all three previous studies reported that acyclovir did not reduce the risk of Kaposi's sarcoma. The analysis in this Chapter is the first that has reported a reduction in the risk of Kaposi's sarcoma associated with the use of ganciclovir.

Table 7.6

Summary of results of antiherpes-virus treatment and the risk of Kaposi's sarcoma

Study	N	Relative Hazard of Kaposi's Sarcoma Associated With Treatment (95% Ci)		
		Acyclovir	Foscarnet	Ganciclovir
Glesby *et al*[375]	935	0.84 (0.56 - 1.26)	0.40 (0.05 - 3.10)	0.56 (0.22 - 1.44)
Jones *et al*[376]	20228	1.4 (1.2 - 1.5)	0.3 (0.1 - 0.6)	1.0 (0.8 - 1.3)
Costagliola *et al*[377]	16229	1.34 (1.01 - 1.78)	1.36 (0.40 - 2.37)	0.98 (0.40 - 2.37)
This Study	3688	1.22 (0.97 - 1.53)	0.38 (0.15 - 0.94)	0.38 (0.18 - 0.81)
Alternative analysis	3688	1.23 (0.98 - 1.56)	0.53 (0.21 - 1.31)	0.63 (0.31 - 1.30)

CI; confidence interval

The alternative analysis which did not transform the CD4 lymphocyte count and made no separate adjustment for cytomegalovirus or recurrent herpes simplex infections produced

results which suggested a protective, but non-significant, effect of antiherpes virus drugs. These results were more consistent with those of Glesby *et al*[375]. Given that the other reports in this area have been short, it is difficult to determine the extent to which these differences in statistical analysis could account for the different results. A multivariate analysis attempted to remove the confounding due to the disease stage of the patient to reveal the treatment effect, given that patients who started treatment were those that were sickest. After this adjustment, the potential preventative effect of anti-herpes virus treatment was revealed. If the adjustment for disease stage was not adequate, this preventative effect may remain masked to a certain degree, as shown in the alternative analysis.

7.5.1 Other Factors Related to the Development of Kaposi's Sarcoma

The results of Table 7.3 suggest several other factors which were related to the risk of developing Kaposi's sarcoma. In contrast to some other reports[115,212], older patients were at an increased risk of this diagnosis (RH per 10 yr increase 1.11; 95% CI 1.00 - 1.22, p = 0.050), consistent with a report from Veugeulers *et al* that increasing age is associated with an increased risk of neoplasms[235]. As reported and discussed in Chapter 5, females were at a significantly reduced risk of Kaposi's sarcoma when compared to males. Patients who belonged to homosexual and bisexual exposure category were, unexpectedly, not at a significantly increased risk of Kaposi' sarcoma, and this may be attributable to some homosexual or bisexual patients who were classified as the 'other' exposure category. An increased risk of Kaposi's sarcoma in patients diagnosed with cytomegalovirus has been reported by other workers[280,393], and this could be due to the high incidence of cytomegalovirus in homosexual and bisexual men[182-183] and a possible role of sexual transmission.

As reported by many others, a low CD4 lymphocyte count was highly predictive of the risk of Kaposi's sarcoma[124,212,280,394]. The results of Chapter 5 concur with this result, as the incidence of Kaposi's sarcoma increased progressively across all CD4 lymphocyte count strata. Few previous studies have assessed the relationship between treatment with antiretrovirals, prophylaxis against *Pneumocystis carinii* pneumonia and the risk of Kaposi's sarcoma. Those that have reported no direct relationship[212,369]. In the multivariate analysis, patients beginning either treatment were at a higher risk of Kaposi's sarcoma, and the exact reasons for this are unclear. The adjustment for disease stage through CD4 lymphocyte count and AIDS defining illnesses may not be sufficient. The possible biases of treatment effects and predicting disease in patients who are at an

increased risk of death have been discussed recently[296-297,395], and suggest that perhaps further adjustment for disease stage may be necessary, by adjusting for additional symptoms of HIV as they arise. This data was not available in the Chelsea and Westminster Cohort.

7.6 Summary

The results of this analysis suggest that patients treated with foscarnet and ganciclovir were at a lower risk of Kaposi's sarcoma than patients who were not treated, but that acyclovir did not offer any protective effect. These findings add weight to the argument that a human herpes virus is associated with the development of Kaposi's sarcoma. In addition, the recent work by Kedes *et al*[396] measured the ability of antivirals to block the release of Kaposi's sarcoma herpes virus; replication of the virus was insensitive to acyclovir, but sensitive to ganciclovir and foscarnet. This study was retrospective and not one of randomised treatments, and so lacks the same credibility of a randomised controlled trials of antiherpes virus treatment. However, the results are encouraging and the issue merits further investigation.

CHAPTER 8 - CLOSING REMARKS

8.1 Summary of Results

This thesis has presented data on almost twelve thousand patients infected with HIV, of which nine thousand patients had developed at least one AIDS defining illness. Approximately half of these patients were recruited to a European study of an AIDS patients, the remainder were HIV infected patients from two centres in London. These large patient groups have provided the ideal opportunity to study the relationship between survival, AIDS defining events, the CD4 lymphocyte count and other factors associated with disease progression. To summarise these results, age, CD4 lymphocyte count at the time of AIDS diagnosis and throughout follow-up, and type of AIDS defining illness, including those made after the initial AIDS defining illness were the strongest predictors of future survival. The risk of each AIDS defining illness was highly dependent on the CD4 lymphocyte count, and varies considerably between diagnoses.

Survival after an AIDS diagnosis differed quite markedly according to the AIDS defining illnesses that were present. A ranking of AIDS defining illnesses, in terms of prognosis, was established and was found to be generally consistent across strata such as year of diagnosis, whether antiretroviral treatment had begun or according to whether the diagnosis was an initial AIDS defining illness or a subsequent diagnosis. Furthermore, the estimates of median survival after each diagnosis were similar in different patient groups.

Most large studies of survival of patients with AIDS in the UK tend to be based on surveillance data, rather than prospectively collected observational data. The Royal Free and Chelsea and Westminster Hospital Cohorts have seen almost 25% of the UK population of AIDS patients, and complete follow-up information is available. Median survival after an initial AIDS diagnosis was estimated to be 20 months, and while there was no evidence of improvement in survival in recent years, AIDS is now being diagnosed in patients who are more immunosuppressed, which may suggest that time between HIV infection and death has increased. Patients diagnosed with AIDS after 1987 were much more likely to survive the first three months following an AIDS diagnosis, compared to patients diagnosed before this time, but long-term survival remained poor. Patients who were older or who had a lower CD4 lymphocyte count at intial AIDS defining illness were at a much higher risk of death.

The CD4 lymphocyte count has been considered to be central to disease progression in HIV infection. The median CD4 lymphocyte count at which each diagnosis is made was found to vary quite widely, from 11/mm^3 in patients diagnosed with cytomegalovirus retinitis to 102/mm^3 in those patients diagnosed with extrapulmonary tuberculosis. The incidence of disease also varied quite considerably as the CD4 lymphocyte count declined. Generally, the incidence increased as the CD4 count dropped. Diseases which were common as initial AIDS defining illnesses, such as Kaposi's sarcoma and oesophageal candidiasis had a relatively high incidence at higher CD4 lymphocyte counts, while diseases such as cytomegalovirus retinitis had a very low incidence until the CD4 lymphocyte count had declined below 25/mm^3. As more prophylactic agents are developed to treat patients with advanced immunodeficiency, results such as these could be of great importance for determining the optimal time to start prophylaxis, which will be a trade off between expense, quality of life and the risk of disease.

The heterogeneous survival of patients with AIDS may be related to several factors; much of the work in this thesis shows that certain diseases have a worse prognosis and that the CD4 lymphocyte count is strongly associated with survival. The number of diseases, severity of disease, and CD4 lymphocyte count were all independently related to the risk of death. By simply counting the number of mild, serious and very serious diseases made and utilising the CD4 lymphocyte count, I have developed a grading system for patients with AIDS; patients can be classified into AIDS grade I, II or III with a distinct risk of death in each AIDS grade. This grading system is very simple to use and has now been validated on four cohorts of patients with remarkable agreement, although as more data about HIV viral load and new treatments becomes available it may be necessary to update the grading system.

Kaposi's sarcoma remains one of the most common AIDS defining illnesses, and may be a visual reminder to the patient that they are clinically deteriorating. Foscarnet and ganciclovir are antiherpes virus drugs used to treat cytomegalovirus, another common infection associated with advanced immunodeficiency. Treatment with these drugs was associated with a lower risk of Kaposi's sarcoma.

8.2 The Future

The area of HIV research moves rapidly, and it was inevitable that over the three years that this thesis has been written, there have been many developments. The data

included in this thesis was collected prior to July 1995, and the results should be taken in this context.

Treatment of patients with HIV and AIDS has advanced particularly rapidly over the past few years, and very few of the patients included in this thesis will have had access to the new protease inhibitors at the cut-off date for analysis. These new drugs are providing hope that HIV is reversible. Survival in patients with AIDS who have started on these new drugs can be expected to increase and clinicians are optimistic that the hospital beds, now mainly empty, will remain that way. Patients with a history of AIDS defining illnesses appear to be getting better and returning to work. However, the new protease inhibitors also have major disadvantages which could limit their use. They all have considerable side effects, such as diarrhoea, nausea, gastrointestinal discomfort, vomiting, fatigue, and taste disturbances. The dosing regimens are complicated; for example, saquinavir must be taken with meals, preferably with a high fat content, while indinavir must be taken at eight hourly intervals, one hour before or two hours after meals and patients are required to drink at least 1.5 litres of water a day to reduce the risk of kidney stones. The development of resistance and subsequent loss of drug activity is a major threat to the long-term use of the protease inhibitors; a drug-holiday or non-compliance can have serious consequences.

Therefore the use of protease inhibitors with existing antiretrovirals has resulted in widespread optimism that HIV can become a long-term chronic disease. It is worth remembering however that these new therapies may not be available to developing countries in the near future, where the majority of people with HIV and AIDS now live. Many questions about treatment remain unanswered;

What is the best time to start therapy?
Should clinicians treat early or late?
Are all combination regimens equally effective?
Will less closely monitored patients comply with therapy?
Who will pay for the combination therapies?

Before any new and potentially expensive laboratory markers are used for monitoring patients infected with HIV, it is important to establish if the new marker adds information to that provided by the CD4 lymphocyte count. The role of HIV viral load as a prognostic marker is currently being evaluated by many researchers, and will be evaluated at the

Royal Free and Chelsea and Westminster Hospitals in the future. Viral load will probably be used in conjunction with CD4 lymphocyte count to enable clinicians to make informed decisions about the prognosis and treatment of a patient. For example, patients wth a high CD4 lymphocyte count but a high viral load may benefit from early intervention to reduce their viral load, or an increase in viral load may be used to indicate that the current treatment regimen is not working and needs to be changed.

Clinical trials in HIV infection which assess the value of new treatments or compare treatment regimens are often constrained to follow-up a large number of patients over a long period of time to obtain a sufficient number of endpoints (i.e., AIDS or death) for comparisons to be made. Both changes in viral load and CD4 lymphocyte count are now used to assess the efficacy of new treatments. It remains to be seen whether a decrease in the viral load, or a treatment induced rise in CD4 lymphocyte counts results in an improvement in patient prognosis. The scoring system I developed has already been successfully adapted for use in one clinical trial, which allowed the timely presentation of results. The score and grading system will be further developed to use prognostic information from viral load, and the issue of reversibility of HIV will be addressed.

To conclude, this thesis has presented a selection of work based on three large cohorts of patients with HIV and AIDS. Many of the results could be generalised to other patient groups and some of the work has been published (Appendix 4). The collaboration between the Royal Free and Chelsea and Westminster Hospitals has proved to be highly successful. As follow-up data on existing patients and relevant data on new patients is collected, I hope that the Cohorts will continue to provide answers to clinical questions in the future.

TABLE OF CONTENTS - APPENDICES

INITIAL VISIT FORM

Hosp No.: ☐☐☐☐☐☐☐☐ Date of Visit: ☐☐-☐☐-☐☐

Date of Birth: ☐☐-☐☐-☐☐ Sex: ☐ M ☐ F

Surname:..... First Name..... Other (Aliases).....

UK Resident? ☐ Y ☐ N ☐ Unknown Country of birth: .....

Patient Address:

.....

.....

.....

.....

Postcode:.....

Tel:.....

DHA:.....

Next of Kin's Address:

.....

.....

.....

.....

Postcode: .....

Tel: .....

Relationship: .....

GP Address:

.....

.....

.....

Postcode:.....

PAS Code:.....

Tel: .....

Can GP be informed of patient's HIV status? ☐ Y ☐ N

First Centre of Treatment for HIV/AIDS

Where was the initial diagnosis of HIV or AIDS made?

Royal Free	☐	Barnet general	☐	
JPH/Middx/UCH	☐	Chase Farm	☐	
St Mary's	☐	Hammersmith	☐	
Whittington	☐	Other London	☐	.....
St Thomas's	☐	Other UK	☐	.....
Guy's	☐	USA/Canada	☐	
Kobler/Westminster	☐	Continental Europe	☐	
King's	☐	Africa	☐	
Bart's	☐	Asia	☐	
North Middlesex	☐	Australia/NZ	☐	
Royal Northern	☐	Abroad:Other	☐	.....
Edgeware general	☐	Other	☐	.....

Ethnic Origin

White	☐
Black (African)	☐
Black (Caribbean)	☐
Asian	☐
Other/Mixed	☐

Marital Status

Tick one or more boxes

Married	☐
Single	☐
Reg cohabitator, M	☐
Reg cohabitator, F	☐
Widow/seperated/divorced	☐

Circumstances leading to presentation

Date of **first positive** HIV antibody test ☐☐-☐☐-☐☐

Where was this test performed? .....

Why was this test performed?

Investigation of symptoms/illness ☐ Notified by partner ☐

Perceived risk ☐ Other *(specify)* ☐ .....

Date of **last negative** test (if applicable) ☐☐-☐☐-☐☐

Where was this last negative HIV test performed? .....

Was a flu-like 'seroconversion' illness noted? (If yes, date) ☐ Y ☐ N ☐☐-☐☐-☐☐

Further Details on Presentation/Seroconversion

Patient Risk Factors

Please indicate which is the **major** risk factor by ticking **one** box. Please give dates of exposure where possible

Primary risk factors	**Tick**	**Details of risk: e.g. dates, abroad, with HIV +ve partner etc.**
1. IVDU	☐	
2. Blood transfusions	☐	
3. Blood products	☐	
4. Sexual relationships:homosexual	☐	
5. Sexual relationships:heterosexual	☐	
7. Vertical transmission	☐	
8. Occupational	☐	
9. Other	☐	
0. Unknown	☐	

Sexual Orientation

Please tick the most appropriate box:

Homosexual ☐

Heterosexual ☐

Bisexual ☐

Unknown ☐

Current Partner Details

Patient has a regular partner currently	☐ Y	☐ N	
If yes, partner is	☐ M	☐ F	
Partner is HIV positive	☐ Y	☐ N	☐ Unknown
If yes, partner has AIDS	☐ Y	☐ N	☐ Unknown
Patient has other partner	☐ Y	☐ N	

Other Details
e.g., *methods of contraception, type of sex. HIV status of partners, etc.*

Patient History

Past Medical History
Please include any relevant information on STD's

History of Previous AIDS Diagnoses
Please list the prior AIDS defining conditions (if any), with dates, (if possible) that this patient has had, prior to care at the Royal Free.

	Date(mm/yy)		Date(mm
.....	☐☐-☐☐	.....	☐☐
.....	☐☐-☐☐	.....	☐☐

Medication and Trial History

Patient is currently using no medication ☐
Patient is not currently enrolled in any trials ☐

Please list the drugs **(and dosage)** that the patient is currently using, and list the trials the patient is currently participating in.

.....	.....
.....	.....
.....	.....

Cigarette smoking and alcohol consumption

Have you ever smoked cigarettes? ☐ Y ☐ N

If **yes**, do you currently smoke cigarettes? ☐ Y ☐ N

If **yes**, how many per day? ☐☐

Average alcohol consumption: (units/week) ☐☐

Social and Economic Information
e.g., paid employment, housing, etc.,

Clinical Examination

	Normal	Abnormal		Normal	Abnormal
General	☐	☐	Skin	☐	☐
Mouth	☐	☐	Lymph nodes	☐	☐
Chest	☐	☐	Cardiovascular	☐	☐
Abdomen	☐	☐	Fundi	☐	☐
Neurological	☐	☐	Other *(specify)*	☐	☐

Weight: ☐☐☐.☐ kg (at this visit)

Comments:

Investigations Booked	Referrals

Clinical Diagnoses

Please write the clinical diagnoses made at this initial visit in the space provided below.

Non-AIDS defining	AIDS defining
.....	.....
.....	.....
.....	.....

If the patient has AIDS, has the patient been reported to CDSC ☐ Y ☐ N

Medication and Trial Changes

Please specify changes to patient medication or participation in trials

There are no changes to patient medication ☐

There are no changes to participation in trials ☐

Medication/Trials Alterations	Comments
.....	.....
.....	.....
.....	.....

Summary

Follow-up Details

Next appt: ..... Dr Name: .....

Signature of Dr. ..... Post: .....

Has the patient changed address or GP? ☐ Y ☐ N

HOSPITAL NO ..... **SURNAME** .....

VISIT DATE ...../...../..... **Booked O/P** ☐ **Walk-In** ☐ **Daycase** ☐

WEIGHT ..... kg **CD4 COUNT** ...../mm^3 **DATE** ...../...../.....

CURRENT HISTORY/ ONGOING PROBLEMS

CLINICAL EXAMINATIONS

	Normal	Abnormal
General	☐	☐
Mouth	☐	☐
Chest	☐	☐
Abdomen	☐	☐
Neurological	☐	☐
Skin	☐	☐
Lymph nodes	☐	☐
Cardiovascular	☐	☐
Fundi	☐	☐
Other (please specify)	☐	☐

New non-AIDS diags

New AIDS diags

ALL MEDICATIONS

INVESTIGATIONS/ TREATMENTS

REFERRALS

Enrolled trials:

Current stage:

Asymp ☐ Symp ☐

AIDS ☐

Notified to CDSC?

☐ Y ☐ N

Outcome of appt?

☐ Follow-up appt

☐ Admit

Doctor's Name ..... Post .....

EUROAIDS 1979 - 1989

Center/patient number _____-_____

DATA COLLECTION FORM

- Complete form for all AIDS patients at your center diagnosed from 197 to 1989.
- Number patients consecutively (keep a list for later identification).
- Fill in month and year for questions concerning time (if time unknow use code 99). Encircle correct number(s) for questions concerning variou possibilities. If way of diagnosis is unknown leave box open. Do not fil in boxes on the right - reserved for codification.
- Always fill in section A ("baseline data") and question number 1 in eac of the sections.
- Chech last page for definitions of the various diseases.

Time completing form (m-y): [ ][ ]

Name of investigator: _____

EUROAIDS 1979 - 1989

Center/patient number _____-_____

A. Baseline data

1. Time of birth (m-y) :	[ ][ ] or age(y) [ ]	[ ][1]
2. Sex :	/1/ male /2/ female	[ ][2]
3. Ethnic background :	/1/ white /2/ black /3/ asian /4/ other, specify_____ /5/ no information available	[ ][3]
4. Risk group :	/1/ homosexual-bisexual /2/ i.v. drug abuser /3/ haemophiliac /4/ transfusion recipient /5/ heterosexual contact, Africa /6/ heterosexual contact, other /7/ born to HIV positive mother /8/ other, specify : _____ /9/ no information available	[ ][4]
5. Follow up status :	/1/ still follow up at same center /2/ follow up at another center /3/ lost to follow up /4/ died	[ ][5]
6. Time, latest follow up (m-y):	[ ][ ]	[ ][6]
7. Time of AIDS diagnosis (m-y):	[ ][ ]	[ ][7]
8. Time of death (m-y):	[ ][ ]	[ ][8]
9. Autopsy:	/1/ yes /2/ no /3/ no information available /4/ still alive	[ ][9]

B. HIV antibody status

1. Information available : /1/ yes, fill out
/2/ no, go to section C

2. HIV antibody, first positive test (m-y):	[ ][ ]	[ ][10]
3. HIV antibody, last negative test (m-y):	[ ][ ]	[ ][11]

EUROAIDS 1979 - 1989

Center/patient number _____-_____

C. Therapy

1. Information available : /1/ yes, fill out
/2/ no, go to section D

2. Zidovudine initiated (m-y): [ ][ ] [ ][12]
(if no zidovudine, write 00)

3. Zidovudine discontinued permanently (m-y): [ ][ ] [ ][13]
(if no zidovudine, write 00)

4. Primary PCP prophylaxis initiated (m-y): [ ][ ] [ ][14]
(if no primary prophylaxis, write 00)

5. Primary PCP prophylaxis:
/1/ co-trimoxazole (800/160 mg daily)
/2/ co-trimoxazole (1600/320 mg daily)
/3/ co-trimoxazole (other dosage)
/4/ pentamidine inhalation
/5/ other_____
/6/ unknown [ ][15]

6. Primary PCP prophylaxis discontinued permanently (m-y): [ ][ ] [ ][16]

D. Immunological data at AIDS diagnosis

1. Information available : /1/ yes, fill out
/2/ no, go to section E

2. Lymphocyte count (x 10^6cells/L): [ ] [ ][17]

3. CD4 lymphocytes (%): [ ] [ ][18]

4. CD8 lymphocytes (%): [ ] [ ][19]

5. IgG (g/L, or :) [ ] [ ][20]

6. IgA (g/L, or :) [ ] [ ][21]

E. Pneumocystis carinii pneumonia

1. Information available : /1/ yes, fill out
/2/ no, go to section F

	Time onset (m-y)	Way of diagnosis (tick a box): definitive	presumptive	autopsy	
2. First episode	[ ][ ]	[ ]	[ ]	[ ]	[ ][22]
3. Second episode	[ ][ ]	[ ]	[ ]	[ ]	[ ][23]

4. Total number of episodes: [ ] [ ][24]

5. Has patient received secondary PCP prophylaxis
/1/ no
/2/ yes drug_____ dosage_____
/3/ no information available [ ][25]

6. Secondary PCP prophylaxis discontinued permanently (m-y): [ ][ ] [ ][26]

7. Has patient on secondary prophylaxis at time of second episode:
/1/ no
/2/ yes drug_____ dosage_____
/3/ no information available [ ][27]

EUROAIDS 1979 - 1989

Center/patient number _____-_____

F. Other opportunistic infections

1. Information available : /1/ yes, fill out
/2/ no, go to section G

	Time onset (m-y)	Way of diagnosis (tick a box): definitive	presumptive	autopsy	
2. AIDS dementia complex	[ ][ ]	[ ]	NA	NA	[ ][28]
Candidiasis:					
3. Trachea, bronchi lungs	[ ][ ]	[ ]	NA	[ ]	[ ][29]
4. Oesophageal	[ ][ ]	[ ]	[ ]	[ ]	[ ][30]
5. Cryptococcosis, extrapulm.	[ ][ ]	[ ]	NA	[ ]	[ ][31]
6. Cryptosporidiosis, > 1 m	[ ][ ]	[ ]	NA	[ ]	[ ][32]
Cytomegalovirus:					
7. Chorioretinitis	[ ][ ]	NA	[ ]	NA	[ ][33]
8. Pneumonitis	[ ][ ]	[ ]	NA	[ ]	[ ][34]
9. Oesophagitis	[ ][ ]	[ ]	NA	[ ]	[ ][35]
10. Colitis	[ ][ ]	[ ]	NA	[ ]	[ ][36]
11. Adrenalitis	[ ][ ]	[ ]	NA	[ ]	[ ][37]
12. Other : _____	[ ][ ]	[ ]	NA	[ ]	[ ][38]
Herpes simplex virus:					
13. Ulcers >1 m	[ ][ ]	[ ]	NA	[ ]	[ ][39]
14. Other localization: _____	[ ][ ]	[ ]	NA	[ ]	[ ][40]
15.Histoplasmosis, extrapulm.	[ ][ ]	[ ]	NA	[ ]	[ ][41]
16.HIV wasting syndrome	[ ][ ]	[ ]	NA	NA	[ ][42]
17.Isoproriasis, >1 m	[ ][ ]	[ ]	NA	[ ]	[ ][43]
18.Lymphoid interstitial pneumonitis (<13 y)	[ ][ ]	[ ]	[ ]	[ ]	[ ][44]
19.M. avium complex, extrapulm.	[ ][ ]	[ ]	[ ]	[ ]	[ ][45]
20.M. tuberculosis, extrapulm.	[ ][ ]	[ ]	[ ]	[ ]	[ ][46]
21.Mycobacterium other extrapulm. (species_____)	[ ][ ]	[ ]	[ ]	[ ]	[ ][47]
22.Progressive multifocal leukoencephalopathy	[ ][ ]	[ ]	NA	[ ]	[ ][48]
23.Salmonella (non-typhoid) bacteraemia, recurrent	[ ][ ]	[ ]	NA	[ ]	[ ][49]
24.Toxoplasmosis,brain (>1m age)	[ ][ ]	[ ]	[ ]	[ ]	[ ][50]
Other AIDS defining opportunistic infections:					
25._____	[ ][ ]	[ ]	NA	[ ]	[ ][51]
26._____	[ ][ ]	[ ]	NA	[ ]	[ ][52]
27._____	[ ][ ]	[ ]	NA	[ ]	[ ][53]

Center/patient number _____-_____

G. Other disease

1. Information available : /1/ yes, fill out
/2/ no, go to section H

	Time onset (m-y)	Way of diagnosis (tick a box): definitive	presumptive	autopsy	
Herpes zoster :					
2. 1. episode	[ ][ ]	[ ]	[ ]	[ ]	[ ][49]
3. 2. episode	[ ][ ]	[ ]	[ ]	[ ]	[ ][50]
4. M. tuberculosis, pulm.	[ ][ ]	[ ]	NA	[ ]	[ ][51]

H. Malignancies

1. Information available : /1/ yes, fill out
/2/ no, go to section I

Kaposis sarcoma:					
2. Cutaneous	[ ][ ]	[ ]	[ ]	[ ]	[ ][52]
3. Lymphnode	[ ][ ]	[ ]	NA	[ ]	[ ][53]
4. Oral cavity	[ ][ ]	[ ]	[ ]	[ ]	[ ][54]
5. Gastrointestinal	[ ][ ]	[ ]	[ ]	[ ]	[ ][55]
6. Liver	[ ][ ]	[ ]	NA	[ ]	[ ][56]
7. Pulmonary	[ ][ ]	[ ]	[ ]	[ ]	[ ][57]
Malignant lymphoma:					
8. Non-Hodgkin B-cell	[ ][ ]	[ ]	NA	[ ]	[ ][58]
9. Primary brain	[ ][ ]	[ ]	NA	[ ]	[ ][59]
10. Hodgkin	[ ][ ]	[ ]	NA	[ ]	[ ][60]
Other malignancies:					
11.	[ ][ ]	[ ]	NA	[ ]	[ ][61]
12.	[ ][ ]	[ ]	NA	[ ]	[ ][62]

I. Main causes of terminal disability.

/1/ No information available
/2/ opportunistic infection,specify_____
/3/ Kaposi's sarcoma
/4/ malignant lymphoma
/5/ AIDS dementia complex
/6/ Wasting
/7/ bacterial infection,specify_____
/8/ suicide
/9/ other,specify_____ [ ][63]

DEFINITIVE AND PRESUMPTIVE WAY OF DIAGNOSIS OF AIDS DEFINING DISEASES.

AIDS dementia complex :
- Definitive : Disabling cognitive and/or motor dysfunction, or milestone loss in a child, and no other cause by CSF exam and brain imaging or by autopsy.

Candidiasis (trachea,bronchi,lung):
- Definitive/autopsy : Gross inspection at endoscopy/autopsy or by microscopy (histology or cytology).

Candidiasis (oesophageal) :
- Definitive/autopsy : Gross inspection by endoscopy/autopsy or by microscopy (histology or cytology).
- Presumptive : Recent onset retrosternal pain on swallowing and confirmed oral or pharyngeal candidiasis.

Cryptococcosis, extrapulm :
- Definitive/autopsy : Microscopy, culture of, or antigen detection, in affected tissue.

Cryptosporidiosis, > 1 m :
- Definitive/autopsy : Microscopy. Duration of diarrhoea for over 1 m.

Cytomegalovirus retinitis :
- Presumptive : Loss of vision and characteristic appearance on serial ophthalmoscopy, progressing over seri months.

Cytomegalovirus (pneumonia, oesophagitis, colitis, adrenalitis, other organs) :
- Definitive/autopsy : Microscopy (histology or cytology).

Herpes simplex virus (ulcers > 1 m) :
- Definitive/autopsy : Microscopy, culture of, or antigen detection in, affected tissue. Ulcers could have persist for over 4 weeks.

Herpes simplex virus (other localization) :
- Definitive/autopsy : Microscopy, culture of, or antigen detection in, affected tissue.

Histoplasmosis (extrapulm.) :
- Definitive/autopsy : Microscopy, culture of, or antigen detection in, affected tissue.

HIV wasting syndrome :
- Definitive : Weight loss (over 10% of baseline) with no other cause, and 30 days or more of either diarrho or weakness with fever.

Isosporiasis, > 1 m :
- Definitive/autopsy : Microscopy (histology or cytology). Duration of diarrhoea for over 1 month.

Kaposi's sarcoma (cutaneous, oral cavity):
- Definitive/autopsy : Histology.
- Presumptive : Characteristic erythematous/violaceous plaque-like lesion on skin or mucous membranes.

Kaposi's sarcoma (gastrointestinal) :
- Definitive/autopsy : Histology.
- Presumptive : Characteristic lesion(s) at endoscopy with no other cause.

Kaposi's sarcoma (liver) :
- Definitive/autopsy : Histology.

Kaposi's sarcoma (pulmonary) :
- Definitive/autopsy : Histology.
- Presumptive : Typical chest x-ray appearance (nodules or interstitial infiltrates), no pathogen identifie and no antibiotic response in a patient with Kaposi's sarcoma elements elsewhere.

Lymphoid interstitial pneumonitis (< 13 y) :
- Definitive/autopsy : Histology.
- Presumptive : Bilateral reticulonodular pulmonary interstitial infiltrates for over 2 months and no pathog identified and no antibiotic response.

Malignant lymphoma :
- Definitive/autopsy : Histology.

Mycobacterium (avium complex, tuberculosis, other, extrapulm.) :
- Definitive : Culture
- Presumptive : Acid fast bacteria (species not identified by culture) on microscopy of stool specimen normally sterile body fluid/tissue, not lung, skin, cervical or hilar nodes.

Pneumocystis carinii pneumonia :
- Definitive : Microscopy (histology or cytology)
- Presumptive : Recent onset dyspnoea on exertion or dry cough, and diffuse bilateral infiltrates on chest ray. and pO_2 < 70 mmHg and no evidence of bacterial pneumonia.

Progressive multifocal leukoencephalopathy :
- Definitive : Microscopy (histology or cytology).

Salmonella (non typhoid) bacteraemia, recurrent :
- Definitive : Culture.

Toxoplasmosis, brain :
- Definitive : Microscopy (histology, cytology).
- Presumptive : Resent onset focal neurological abnormalities or reduced level of consciousness, and mass effe lesion on scan, and serological evidence or specific therapy response.

Royal Free and Chelsea and Westminster Hospitals Collaborative Group

Royal Free Hospital

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Appendix

The multicentre study group on **AIDS IN EUROPE** (national coordinators in parenthesis). Belgium **(N Clumeck)**, S DeWit, B Sommereijns, Saint-Pierre Hospital, Brussels. **Denmark (J O 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 Kosmidis)** 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-Ishai, 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 Calongni, Arcispedale S. Maria Nuova, Regio Emilia; A Cargnel, Osp. Sacco, Milano; M Arlotti, R Ciammarughi, Osp. Infermi Rimini, Rimini; A Colomba, Osp. Casa del Sole, Palermo; F DeLalla, Osp. Civile, Vicenza; P Fassio, OO.RR. di Bergami, Bergami; A Ferlini, Osp. Infermi Faenza, Faenza; F Fiaccadori, G Pasetti, Osp. Riuniti, Parma; F Giannelli, Osp. Niguarda cà Granda, Milano; W Grillone, Osp. Amedeo di Savoia, Torino; A Lazzarin, A D'Arminio Monforte, Osp. L. Sacco, Milano; E Mignani, Osp. S. Andrea, La Spezia; A Nunnari, Patologia Medica Università, Catania; L Ortona, Università Cattolica del Sacro Cuore, Rome; G Panichi, Università di Sassari, Sassari; S Pauluzzi, Policlinico Monteluce, Perugia; N Piersantelli, Osp. Galliera, Genova; S Ranieri, Osp. S. Maria delle Croci, Ravenna; P Ricciardiello, Osp. Maggiore, Novara; B Roscioli, Osp. S. Maria Maddalena, Trieste; M Soranzo, Osp. Amedeo di Savoia, Torino. **Luxembourg (R Hemmer)**, Centre Hospitalier, Luxembourg. **Netherlands (S Danner)**, D Bloemkolk, Academisch Ziekenhuis bij de Universitet van Amsterdam. **Portugal (F Antunes)**, Hospital Santa Maria; R Proenca, Hospital Curry Cabral, Lisbon. **Spain (J González-Lahoz)**, L Martinez-Blanco, Instituto Carlos III, Madrid; B Clotet, Hospital Germans Trias i Pujol, Barcelona; J Gatell, E Buira, J Miró, Hospital Clinic I Provincial, Barcelona. **Sweden (P Pehrson)**, Karolinska Insitutet, Stockholm. **Switzerland (R Lüthy)**, B Ledergerber, C Olsson, Swiss HIV cohort study, Zürich; M Glauser, Centre Hospitalier Universitaire Vaudois, Lausanne; B Hirschel, Hospital Cantonal Universitaire de Geneve, Geneve. **United Kingdom (A Johnson)**, S Hawkes, A Phillips, UCL Medical School; S Barton, J Morcinek, St. Stephen's Clinic, Chelsea and Westminster Hospital; A Pinching, D Coleman, St. Mary's Hospital, London.

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APPENDIX 3 - THE COX PROPORTIONAL HAZARDS MODEL

3.1 Introduction

The Cox proportional hazards model has been the main statistical technique used in the analysis of data in this thesis. Altman[397] and Andersen[398] have both written good reviews of the model and problems commonly encountered when fitting the model. This section gives a short summary of the statistical ideas which form the basis of the model.

Let an individual i, i=1, 2, ..., N, be observed from time 0 to an event or censoring time, T_i, and let D_i be the censoring indicator for the ith individual, which takes the value 1 if T_i is an event and 0 if T_i is a censored time. It is of interest to study the relationship between the variables $(0,T_i)$ and a set of covariates $z_1, z_2, ...z_q$.

The hazard function, written $\lambda_i(t)$, defines the probability that an individual i experiences an event at time t, given that they have been event-free up to that time point. The cumulative survival function at time t, $S_i(t)$, often estimated using the methods of Kaplan and Meier[42], expresses the cumulative probability of being event free to that time point, and is related to the cumulative hazard function, $H_i(t)$, by:

$$S_i(t) = \exp(-H_i(t)) \quad (1)$$

$$= \exp\left(-\int_0^t \lambda_i(u)\,du\right) \quad (2)$$

It is possible to make univariate comparisons of the effects of covariates on survival using the log-rank test[43]. More normally, however, it is often the independent effects of multiple covariates on survival that is of particular interest.

3.2 The basic model

The proportional hazards model was proposed by David Cox in 1972[399], who suggested that the hazard function could be expressed as

$$\lambda_i(t) = \lambda_0(t) \exp\{\beta_1 z_{i1} + \beta_2 z_{i2} + ... + \beta_q z_{iq}\} \quad (3)$$

or, in vector form;

$$\lambda_i(t) = \lambda_0(t) \exp(\beta \mathbf{z}_i) \quad (4)$$

where $\lambda_0(t)$ is some baseline hazard function, $\mathbf{z}_i$ is the vector of covariate values z_{ij}, j=1, 2, ..., q, measured on individual i at baseline (at time zero), and β is the vector of unknown model parameter values, β_j, j=1, 2, ..., q, which are to be estimated.

The ratio of the hazards for two individuals i and k with covariate values z_{ij} and z_{kj} respectively, is given by;

$$\frac{\lambda_i(t)}{\lambda_k(t)} = \exp\{\beta(\mathbf{z}_i - \mathbf{z}_k)\} \qquad (5)$$

This is known as the relative hazard and, since it is independent of t, the value is constant over time. The hazards for the two individuals are therefore proportional. This value is also independent of the baseline hazard, $\lambda_0(t)$.

When there are no ties among the event times, the estimation of the parameters β_i, i=1, 2, ..., q, is performed by maximising the partial likelihood $L(\beta)$, given by

$$L(\beta) = \prod_i \left[\frac{\exp(\beta \mathbf{z}_i)}{\sum_{k \ni R_i} \{\exp(\beta \mathbf{z}_k)\}} \right]^{D_i} \qquad (6)$$

where R_i is the set of subjects at risk at each event time, T_i, and D_i is the censoring indicator. Each element in the likelihood is the probability that an individual, i, has an event at time T_i, given that only one individual fails at T_i. Where tied event times occur an approximation suggested by Peto is often used[400].

3.3 The time-updated model

The model discussed above is based on covariates measured at baseline. Hence, the estimates of the relative hazards are expressed in terms of the individuals baseline value of the covariates. However, many covariate values may change over the follow-up period and repeated measurements are often available for analysis. These covariates are known as 'time-updated' or 'time-dependent' covariates. The Cox model can be extended to incorporate time-dependent covariates.

Suppose

$$\lambda_i(t) = \lambda_0{}^u(t) \exp(\beta^u \mathbf{z}_i(t)) \qquad (7)$$

where $\mathbf{z}_i(t)$ are the updated covariates for subject i at time t. Estimation of the

parameters β^u is carried out by maximising the logarithm of the partial likelihood.

Estimates of the baseline hazard function, $\lambda_o{}^u$, can be made if desired[43,401]. However, these estimates are normally based on the baseline values of the covariates, and hence the estimate of this hazard is of little relevance when considering time-updated covariates.

3.4 Significance testing and confidence intervals

In large samples, the distribution of the parameters β can be approximated by a normal distribution with mean, variances and covariances which can be estimated from the second derivative of the logarithm of L(β) Hence confidence intervals and hypothesis tests for β can be performed in the usual way. Given a parameter estimate β_j, and standard error for this estimate, a 95% confidence interval can be calculated as

$$\beta_j \pm 1.96 \text{ x std err } (\beta_j) \tag{8}$$

and the ratio of β_j to its standard error can be compared to a normal distribution in order to test whether it is significantly different from zero.

3.5 The assumption of proportional hazards

This model relies on the fact that the ratio of hazards in equation (5) is independent of time. This assumption can be tested, both for fixed and time-updated covariates. This assumption is tested by incorporating the interaction between the covariate of interest and the logarithm of time in the model[399]. If the parameter estimate for this interaction term is significantly different from zero then there is evidence that the relative hazards are not proportional over time. Alternatively, the follow-up period can be split into intervals and the relative hazard estimated separately in each time period. These estimates can be visually inspected to see if the hazard appears to change over the different time periods[397].

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Survival of AIDS Patients According to Type of AIDS-Defining Event

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Mocroft A J (HIV Research Unit, Dept Primary Care and Population Sciences, Royal Free Hospital School of Medicine, Rowland Hill Street, London NW3 2PF, UK), Lundgren J D, d'Arminio Monforte A, Ledergerber B, Barton S E, Vella S, Katlama C, Gerstoft J, Pedersen C and Phillips A N for the AIDS IN EUROPE Study Group. Survival of AIDS patients according to type of AIDS-defining event. *International Journal of Epidemiology* 1997; **26**: 000–000.

Background. There are known to be wide differences in the prognosis of patients with a diagnosis of AIDS. In this study of 6578 patients with AIDS from 17 European centres, we develop a ranking of AIDS-defining illnesses, and determine how well this ranking holds after adjustment for potential confounding variables.

Methods. Survival from each AIDS-defining event was calculated and ranked using Kaplan-Meier estimation of median survival. Cox proportional hazards models with each disease modelled as a time dependant covariate were used to determine the risk of death after each diagnosis, before and after adjustment for potential confounders.

Results. Median survival after an initial AIDS-defining diagnosis of progressive multifocal leukoencephalopathy and malignant lymphoma was particularly poor (2 and 5 months respectively), while the longest median survival occurred after initial AIDS-defining illnesses of Kaposi's sarcoma and extrapulmonary tuberculosis (17 and 22 months respectively). Patients diagnosed with a primary brain lymphoma had shorter median survival times than patients with a penpheral lymphoma (median survival of 1 month and 4 months respectively, $P < 0.0001$). In general, median survival in patients with cutaneous Kaposi's sarcoma (skin, oral) was between two and four times longer than patients with systemic involvement. The ranking of diseases was found to be generally similar after adjustment for all potential confounders.

Conclusions. AIDS-defining events can be grouped into three categories with median survival after diagnosis of ≤6 months, 6–12 months and >12 months. The assigned rankings of disease would not be altered by prognostic factors such as age or CD4 lymphocyte count. These results have important implications in the design of clinical trials and patient management.

Keywords: AIDS, survival, ranking, CD4 lymphocyte count, age

There are known to be wide differences in prognosis between patients who have been given a clinical diagnosis of AIDS.[1–9] Despite the fact that in clinical trials of antiretroviral therapy for patients infected with HIV, the major outcome variable is often based on clinical events,[10–12] few studies have considered the impact of further AIDS-defining events which occur after the primary diagnosis.[13–14] Thus in most commonly performed analyses, a patient with a series of serious opportunistic events would be considered to have a more favourable outcome than a second patient experiencing a single comparatively mild disease, if the second patient's event occurred earlier during follow-up.[15]

Clearly, if a clinical endpoint of disease progression is to be used in trials, there is a need to rank the opportunistic events that constitute disease progression,[15–16] considering both primary and secondary events. To our knowledge, there are few studies that have attempted to rank disease severity.[2,11,17] In this study of 6578 AIDS patients from 17 European centres, we develop a ranking of opportunistic diseases based on the typical survival experience of patients in whom they occur. We further investigate whether the ranking remains after adjustment for age, exposure category, CD4 lymphocyte count, whether or not the opportunistic infection occurred as a first diagnosis or during subsequent follow-up, and use of antiretrovirals.

We also take advantage of this large data set to conduct an investigation of subsequent survival according to site of Kaposi's sarcoma, which has been considered

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to be an early outcome of human immunodeficiency virus infection,[18] which to our knowledge has not previously been investigated. We further investigated survival according to site of systemic-AIDS related lymphoma, a later manifestation associated with much shorter survival times.[19]

PATIENTS AND METHODS

The AIDS in Europe study, which has been described elsewhere,[1] has collected clinical, therapeutic and CD4 cell count measurements from 6578 AIDS patients from 52 centres in 17 European countries. In brief, centres provided data on all patients diagnosed with AIDS (or a preselected group in 23 Italian centres) between 1979 and 31 December 1989. The 23 Italian centres each enrolled only a predefined proportion of patients according to month of birth; supervised by the Istituto Superiore di Sanita in Rome. AIDS was diagnosed according to the revised criteria from the Centers for Disease Control (CDC) from 1987.[20] Information was collected from patient notes on a standardized data collection form. These were checked by scientific staff for logistical errors. The collection of data was performed by retrospective review of case notes between May 1991 and August 1992. All time variables were collected as month and year, thus patients who died in the same month as an event would be recorded as having a survival time of zero. Similarly, events diagnosed at the time of AIDS diagnosis or within the first month of diagnosis were recorded as occurring at the time of the AIDS diagnosis.

For the present analysis, a total of 6548 patients were included, for whom all clinical, therapeutic and demographic information was available. Survival from each AIDS-defining event, irrespective of whether this event was the first or subsequent AIDS-defining event, was calculated using Kaplan-Meier estimation using SAS.[21] AIDS-defining events were ranked according to median survival. Where diseases shared similar median survival times they were ranked according to the number of patients diagnosed with each disease. Kaplan-Meier estimation of median survival time with stratification for the confounding variable and multivariate Cox proportional hazards models were used to investigate the ranking of diseases where further investigation of a possible confounding factor was required. The relative hazards of death from a multivariate Cox proportional hazards model were ranked to investigate the consistency of the ranking of disease after adjustment for age, gender, exposure category, region of Europe, CD4 lymphocyte count at initial AIDS-defining illness and treatment with antiretrovirals.

TABLE 1. *A description of the patient population*

Region of Europe	South[a]	Central[b]	Northern[c]	All
No. of subjects	2116	1938	2524	6578
No. of centres	33	8	11	52
Median age (years)	30	35	37	34
Men (% of total)	88	86	98	91
Homosexual (% of total)	29	60	88	60
Intravenous drug users (% of total)	62	19	4	27
Median CD4 cell count (/mm^3)	78	89	90	86
No. with CD4 count	794	1355	904	3053

[a] Greece (2), Israel (3), Italy (24), Portugal (2) and Spain (2).
[b] Belgium (1), France (1), South Germany (1), Hungary (1), Luxembourg (1), Switzerland (3).
[c] Denmark (3), Ireland (1), Finland (1), North Germany (1), Netherlands (1), Sweden (1), UK (3).
Numbers in parenthesis indicate number of centres participating within each country.

In addition to calculating survival from any malignant lymphoma, survival from a primary brain lymphoma and a lymphoma presenting outside the central nervous system were considered separately. Similarly, in order to study whether different types of organ involvement of Kaposi's sarcoma was associated with a different prognosis, a subgroup analysis was performed. In this analysis, centres who had not provided information on which organs were involved when Kaposi's sarcoma was diagnosed were excluded. A total of 809 diagnoses of Kaposi's sarcoma were recorded in the remaining 2674 patients.

RESULTS

A total of 13 764 AIDS-defining events were observed among 6548 patients. A brief description of the patient population is shown in Table 1, and includes demographic data and CD4 lymphocyte count at initial AIDS diagnosis. The median age at diagnosis tended to be higher in Southern Europe, as did the proportion of patients who were intravenous drug users (IDU). The majority of patients were male.

The median survival after a given diagnosis, measured in months, is shown in Table 2, together with the 25–75 percentiles. The differences in survival between diagnoses was highly statistically significant ($P < 0.0001$). Tests for differences in survival between each pair of diseases were not performed due to the large number of possible combinations. Only 17 patients

TABLE 2. *Median survival time (months) for each AIDS-defining event*

Disease[a]	No.	Median survival (25–75 percentile)	Ranking[b]
Progressive multifocal leukoencephalopathy (PML)	104	2 (1–5)	1
Malignant lymphoma	401	3 (1–8)	2
AIDS dementia complex	697	4 (1–12)	3
Cytomegalovirus (exc. retinitis)	641	4 (0–12)	4
Mycobacterium avium, extrapulmonary	401	4 (2–12)	5
Other *mycobacterium*, extrapulmonary	107	5 (1–11)	6
Candidiasis, pulmonary	78	5 (1–11)	7
Cytomegalovirus retinitis	804	6 (3–13)	8
Cryptosporidiosis	432	6 (2–16)	9
Cryptococcosis	308	6 (1–15)	10
Toxoplasmosis	1028	8 (3–17)	11
HIV wasting syndrome	463	8 (2–20)	12
Salmonella septicaemia	123	10 (4–20)	13
Herpes simplex, not skin	59	10 (2–21)	14
Oesophageal candidiasis	1869	12 (5–23)	15
Herpes simplex ulceration	367	12 (5–23)	16
Pneumocystis carinii pneumonia	3293	14 (5–25)	17
Kaposi's sarcoma	1919	15 (7–26)	18
Tuberculosis, extrapulmonary	695	19 (7–37)	19

[a] Diseases are ranked according to median survival. In the case of similar median survival times, diseases are ranked according to number of patients.
[b] Survival for each disease is calculated regardless of whether it was the first or subsequent AIDS event.

were diagnosed with either isosporiasis or histoplasmosis, and these diagnoses were therefore excluded from further analyses. A diagnosis of progressive multifocal leukoencephalopathy (PML) was associated with a very poor median survival of 2 months, while in contrast, patients diagnosed with extrapulmonary tuberculosis had the most favourable prognosis, a median survival of 19 months. It should be noted that a patient who died within the same month as diagnosis of an AIDS-defining illness was recorded as having zero survival. This proportion of patients varied according to the severity of the disease, and ranged from 25% of patients diagnosed with PML to 5% of patients diagnosed with Kaposi's sarcoma. Excluding patients with zero survival extended the median survival times by 1–2 months, but the rankings of diseases presented in Table 2 were unaltered. An alternative ranking of diseases was obtained based on the estimated relative risk of death from a Cox proportional hazards model, with each disease fitted as a time dependant covariate. These ranks were similar to those presented in Table 2 (data available from author on request).

The overall rankings of diseases, as assigned in Table 2, were found to be generally maintained when events were stratified according to whether the diagnoses occurred as a first event or during subsequent follow-up (Table 3). The diseases are shown in the same order as presented in Table 2. Median survival was shorter when a diagnoses occurred during follow-up, compared to the median survival of the disease as an initial AIDS-defining event. It can be seen from Table 3 that lower ranked diseases, such as extrapulmonary tuberculosis and oesophageal candidiasis, occurred much more commonly as an initial AIDS event, while diseases caused by *Mycobacterium avium* and cytomegalovirus occurred with a greater frequency during follow-up.

Age at diagnosis of AIDS has been shown to be an important prognostic factor following an AIDS diagnosis. In a Cox proportional hazards model, although there was a strong relationship between age and death (relative hazard [RH] per 10-year age difference 1.18, 95% confidence interval (CI) : 1.14–1.21, $P < 0.0001$) the adjusted ranks of the diseases from this model were unaltered. A further potential confounding variable was exposure category, as deaths in intravenous drug users may be less likely to be related to AIDS than in homosexual men. After adjustment for exposure category in a Cox proportional hazards model, the rankings of the diseases were again identical.

Table 4 presents the relative risk of death for each of the AIDS-defining events, after adjustment for factors which may be related to survival, including age, exposure category, gender, region of Europe and treatment with antiretrovirals, modelled as a time

TABLE 3 *Survival for each AIDS-defining event after stratification for time of AIDS event*

Disease	Initial AIDS event		During follow-up	
	No.	Median survival	No.	Median survival
Progressive multifocal leukoencephalopathy (PML)	47	2	57	2
Malignant lymphoma	228	5	173	1
AIDS dementia complex	235	5	402	3
Cytomegalovirus (exc. retinitis)	240	7	401	3
Mycobacterium avium, extrapulmonary	104	8	297	4
Other *mycobacterium*, extrapulmonary	40	8	67	4
Candidiasis, pulmonary	48	6	30	5
Cytomegalovirus retinitis	154	8	650	6
Cryptosporidiosis	226	8	216	5
Cryptococcosis	158	9	150	4
Toxoplasmosis	512	11	516	6
HIV wasting syndrome	328	12	135	3
Salmonella septicaemia	70	15	53	7
Herpes simplex, not skin	30	17	29	5
Oesophageal candidiasis	1212	14	657	8
Herpes simplex ulceration	199	15	168	9
Pneumocystis carinii pneumonia	2517	17	776	7
Kaposi's sarcoma	1394	17	525	8
Tuberculosis, extrapulmonary	571	22	124	8

The AIDS-defining conditions are listed according to the rankings from Table 2.

TABLE 4 *Relative risk of death after each AIDS-defining illness*

Disease	Relative hazard	95% confidence interval	*P*-value
Progressive multifocal leukoencephalopathy (PML)	4.28	3.46–5.28	0.0001
Malignant lymphoma	3.63	3.25–4.06	0.0001
AIDS dementia complex	2.72	2.49–2.97	0.0001
Cytomegalovirus (exc. retinitis)	2.21	2.01–2.42	0.0001
***Mycobacterium avium*, extrapulmonary**	2.14	1.91–2.41	0.0001
Other *mycobacterium*, extrapulmonary	1.87	1.51–2.31	0.0001
Candidiasis, pulmonary	1.99	1.54–2.56	0.0001
Cytomegalovirus retinitis	1.76	1.61–1.92	0.0001
Cryptosporidiosis	2.14	1.91–2.39	0.0001
Cryptococcosis	2.04	1.79–2.32	0.0001
Toxoplasmosis	2.05	1.89–2.22	0.0001
HIV wasting syndrome	2.06	1.85–2.31	0.0001
Salmonella septicaemia	1.69	1.38–2.07	0.0001
Herpes simplex, not skin	1.06	0.80–1.42	0.67
Oesophageal candidiasis	1.36	1.27–1.45	0.0001
Herpes simplex ulceration	1.34	1.18–1.52	0.0001
***Pneumocystis carinii* pneumonia**	1.37	1.25–1.49	0.0001
Kaposi's sarcoma	1.56	1.46–1.68	0.0001
Tuberculosis, extrapulmonary	1.14	1.02–1.27	0.020

The multivariate model has been adjusted for age, gender, exposure category, and region of Europe. Treatment was included in the Cox proportional hazards model as a time dependant covariate.

dependant covariate. These are presented in the same order as shown in Table 2, and the rankings of the diseases remains generally consistent, although there is some shuffling of the comparative severity of the diseases. In addition, some of the diseases, such as salmonella septicaemia, were not diagnosed in many patients, and the confidence intervals around the estimates were wider than those around the more common diseases, such as Kaposi's sarcoma. With the exception of herpes simplex ulceration (not skin), all diagnoses significantly raised the risk of death. Another important potential confounder is CD4 lymphocyte count at AIDS diagnosis, which was available for 3053 patients (46.4%). The model presented in Table 4 was repeated in those patients for whom CD4 count was available, and the order of the relative hazards was consistent with those shown in Table 4 (data available from author on request).

The median survival after a diagnosis of lymphoma was universally poor (3 months overall), as illustrated in Table 5. Patients diagnosed with a primary brain lymphoma had a much shorter median survival time of one month, significantly shorter than the median survival of 4 months in patients with all other types of lymphoma ($P < 0.0001$). The proportion of patients with zero survival was significantly higher in patients with a primary brain lymphoma (43% versus 18%), although the exclusion of these patients did not increase the estimate of median survival, possibly due to the smaller size of the groups. Even after stratification for whether or not the primary brain lymphoma occurred as an initial AIDS-defining event or during follow-up, median survival remained at one month.

Table 6 shows median survival times after a diagnosis of Kaposi's sarcoma, stratified by site of involvement. The observed differences in survival were highly statistically significant ($P < 0.0001$). By far the most common site was skin, which had the most favourable prognosis. Median survival after a diagnosis of pulmonary Kaposi's sarcoma was particularly poor, with an overall median survival time of 3 months, which dropped to 2 months when the diagnosis was made during follow-up. In general, median survival in patients with cutaneous Kaposi's sarcoma (skin, oral) was between two and four times longer than patients with systemic involvement (gastrointestinal tract, pulmonary, glandular). The frequency of patients with zero survival was much lower in cutaneous Kaposi's sarcoma (4%) compared to systemic Kaposi's sarcoma (34%), and excluding these patients had no effect on survival after a diagnosis of cutaneous Kaposi's sarcoma, and increased survival in patients with systemic Kaposi's sarcoma by one month for all sites.

TABLE 5 *Median survival (number of patients) after a diagnosis of malignant lymphoma*

Type	Overall	At AIDS	After AIDS
All	2 (401)	5 (228)	1 (173)
Peripheral	4 (322)	5 (208)	2 (114)
Primary in brain	1 (88)	1 (21)	1 (67)

TABLE 6 *Median survival (number of patients[a]) after a diagnosis of Kaposi's sarcoma*

Site of Kaposi's sarcoma	Overall	At AIDS	After AIDS
One site[b]	13 (809)	16 (574)	7 (235)
Skin	13 (709)	15 (496)	8 (213)
Oral	10 (301)	14 (134)	7 (167)
Gatrointestinal tract	5 (170)	9 (52)	2 (118)
Glandular	4 (57)	9 (24)	0 (33)
Pulmonary	3 (156)	7 (22)	2 (134)

[a] Survival from a first diagnosis of Kaposi's sarcoma, irrespective of location.
[b] Only patients from centres who completed information on site of Kaposi's sarcoma were included (2764 patients).

DISCUSSION

This study has examined survival from an AIDS-defining event and ranked survival from worst to best prognosis. The AIDS in Europe study is amongst the largest study worldwide of unselected AIDS patients in whom AIDS events during follow-up were also recorded. Using information from these patients, this study has examined survival after an AIDS diagnosis, stratifying by whether the diagnosis was an initial or subsequent event. Even after adjustment for age, exposure category, gender, CD4 lymphocyte count and region of Europe, the results show a clear ranking of diseases. The median survival estimates from this study agree with results from other studies; Luo *et al.*[2] grouped diseases into two classes based on median survival times, these two classes mirror the rankings shown in this patient group. In addition there are many studies showing the favourable prognosis for patients diagnosed with Kaposi's sarcoma[3–4,7–9] and *Pneumocystis carinii* pneumonia, particularly since the introduction of zidovudine and prophylaxis against *Pneumocystis carinii* pneumonia.[2,6–8]

Several comments can be made about specific diagnoses included in Table 2. HIV wasting syndrome, ranked twelfth with a median survival of 8 months, may cover a variety of aetiologies, including disseminated

disease that remains undetected. In addition, the diagnoses of Herpes simplex virus (duration of greater than one month) depends to a large extent on the awareness of the treating physician. Effective antiviral drugs to treat Herpes simplex, such as acyclovir, have been available since 1984.

A multivariate model which adjusted for all potential confounding variables showed generally consistent rankings. Although factors such as age and CD4 lymphocyte count were strongly related to survival, as previously published,[2,6,9,22–24] their relationship with survival was generally consistent for all AIDS-defining illnesses. Although the ranking of diseases was not identical to those from a Kaplan-Meier univariate analysis, three broad classifications of disease would still incorporate the same diseases. For example, based on the results of Table 2 which presented estimates of median survival regardless of whether the disease occurred as an initial AIDS-defining illness or during follow-up, the diseases could be grouped into three categories, very severe with survival <6 months (ranks 1–7), severe with survival 6–12 months (ranks 8–14), and mild in diseases where survival >12 months (ranks 15–19). Categorization of diseases in this way may have important implications for entry and endpoint criteria in clinical trials,[15] where there is a need for classifying stages of AIDS on the basis of a firm endpoint such as survival. In a clinical trials setting, patients could be classified as reaching an endpoint when they progress to a disease in a group more severe than the one in which they started. Similarly, progression to a more severe disease, as measured by a lower rank, could be a possible endpoint. Such an approach could shorten the duration of clinical trials and allow more trials including patients at an advanced stage of AIDS.

Differences in survival according to the location of a malignant lymphoma are not surprising based on the published literature.[19,25] However, differences in survival according to the location of Kaposi's sarcoma in such a large group of patients has not, to our knowledge, previously been documented. The differences in survival may be due to one of several factors; namely that systemic Kaposi's sarcoma tends to develop later than cutaneous Kaposi's sarcoma and at lower CD4 counts,[26] and also that systemic Kaposi's sarcoma may be more life threatening to the extent that only palliative treatment is available. Such treatment includes chemotherapy, resulting in further immunosuppression, perhaps leading to an increased risk of developing another opportunistic disease.

Possible biases of this study include differences in how the disease was diagnosed at the various centres, and differences in the ability to diagnose the diseases over time. These data predate the increasing trends in prophylaxis against some opportunistic infections. However, they provide estimates of survival and the rankings of diseases before the widespread introduction of such therapies, and may be of use as historical controls when data regarding efficacy of these new treatments is published. A further drawback of these data is that the first occurrence of each disease only (except when malignant lymphoma and Kaposi's sarcoma were stratified by site of involvement) was included in the analysis. The determination of precisely when a disease recurs is difficult, and will depend on how aggressively the disease was treated initially and subsequent maintenance therapy.

This study used AIDS diagnoses in line with the 1987 CDC criteria. In 1993 these criteria were revised to incorporate additional AIDS-defining events[27] of pulmonary tuberculosis, recurrent bacterial chest infections and invasive cervical carcinoma. Only as time progresses will information on the severity of these diseases become available. Clinical experience in the management of bacterial pneumonia suggests that this event is easily manageable, but the risk of developing bacterial pneumonia is inversely related to CD4 count.[28] However, with the present knowledge, we believe that both pulmonary tuberculosis and bacterial pneumonia should be classified as having a relatively good prognosis. The epidemiological knowledge of cervical carcinoma in AIDS patients is poor at present, and so this disease is difficult to place in the current rankings.

To conclude, using a large group of unselected AIDS patients in whom all AIDS-defining events have been recorded, we have ranked AIDS-defining events according to median survival. We have shown that such rankings are generally maintained after adjustment for CD4 lymphocyte count, treatment with antiretrovirals, gender, exposure category, age and region of Europe. In addition, we have presented results illustrating survival according to site of Kaposi's sarcoma.

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Factors affecting survival in patients with the acquired immunodeficiency syndrome

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Keywords: Survival, AIDS, demographic factors, CD4 count, AIDS-defining illness, treatment

Introduction

The first recognized cases of AIDS occurred in the United States in 1981 when occurrences of previously rare diseases, such as *Pneumocystis carinii* pneumonia (PCP) and Kaposi's sarcoma, were observed in a few homosexual men [1–4]. The number of patients with AIDS has grown rapidly since the first reported cases: the World Health Organization (WHO) has estimated that over 4.5 million cases of AIDS had occurred world-wide by the middle of 1994, compared with a total of 1 169 811 cases actually reported to the WHO [5]. The number of cases reported world-wide is an underestimate because of underdiagnosis, underreporting and delays in reporting. An increasing proportion of AIDS cases occur in developing countries. The WHO predicts that within 10 years, 90% of AIDS cases will occur in developing countries [6]. In the United States and Europe the predominant groups of people affected by the epidemic remain those infected through either homosexual sex or injecting drug use [7].

Infection with HIV and subsequent development of AIDS represent a public health problem of immense magnitude to many countries in the world. Provision of healthcare for those infected depends upon monitoring and predicting the prevalence of HIV and AIDS, which requires an accurate understanding of survival patterns. Such understanding can provide a basis for determining accurate prognostic information for individual patients and their physicians. Monitoring the survival times of patients with AIDS can also help with the assessment of the impact of new treatments as they become available. AIDS results in a considerable cost, not only in terms of human suffering but also in health services funding. Studies of HIV and AIDS patients in the UK have given an estimate costing for caring for each AIDS patient of between £14 000 and £16 000 [8–9], taking account of hospital and drug costs alone. Other, perhaps more hidden, costs include time spent off work and the effect of the increase in deaths, amongst the younger population, on productivity and services. A clear understanding of the prognosis of patients with AIDS, and the factors that influence survival, allows an insight into the pathophysiology of this disease and the development of interventions which may improve survival of future patients.

There have been numerous studies that consider survival in patients with AIDS. In this review we attempt to summarize the available evidence that concerns the influence of various demographic, clinical and immunological variables on the prognosis of patients with AIDS.

Survival following an AIDS diagnosis

Reported survival times for patients following an AIDS diagnosis are summarized in Table 1. These studies are ranked by the number of patients included in the study. Generally, median survival has been estimated to be between 12 and 18 months. There is an obvious difference in survival between that reported in studies in developing countries [19,32] and those in developed countries. This poorer survival in the former could be an artefact of later diagnosis resulting from a lack of awareness or access to healthcare, but serves to illustrate the desperate situation of people with AIDS in the developing world. Even within developed countries, there is considerable variation in survival after an AIDS diagno-

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Table 1. Median survival (months) in published studies of patients with AIDS.

Study (year of publication)	Reference	Country of origin	n	Median survival (months)	Alive (%)	
					12 months	24 months
Piette (1992)	10	USA	43795	12.7	49.1	18.4
Blum (1994)	11	USA	23324	13.7	54.7	31.9
Piette (1991)	12	USA	23271	11.5	n/a	n/a
Lundgren (1994)	13	Europe	6578	17.0	n/a	n/a
Rothenberg (1987)	14	USA	5833	11.4	48.8	28.2
Lemp (1990)	15	USA	4233	12.5	51.6	20.2
Whitmore-Overton (1993)	16	UK	3984	16.7	n/a	n/a
Chang (1993)	17	USA	3699	11.5	48.8	29.0
Luo (1995)	18	Australia	3204	14.3	57.2	26.4
Chequer (1992)	19	Brazil	2135	5.1	32.0	21.0
Seage (1993)	20	USA	1931	13.5	54.0	23.0
Payne (1990)	21	USA	1015	17.0	65.4	35.1
Jacobson (1993)	22	USA	891	16.4	62.3	33.4
Osmond (1994)	23	USA	761	15.9	n/a	n/a
Stehr Green (1989)	24	USA	716	11.7	49.2	28.9
Reeves (1988)	25	UK	663	12.4	n/a	n/a
Buira (1992)	26	Spain	629	26.0	n/a	n/a
Whyte (1990)	27	Australia	554	10.4	n/a	n/a
Monforte (1992)	28	Italy	547	12.0	n/a	n/a
Friedland (1991)	29	USA	526	9.5	39.0	8.0
Bachetti (1988)	30	USA	505	11.0	44.0	18.0
Bindels (1991)	31	Netherlands	409	16.0	56.1	33.0
Kitavaporn (1996)	32	Thailand	329	7.0	39.2	19.9
Pederson (1990)	33	Denmark	231	13.0	53.0	29.0
Greco (1986)	34	Italy	222	n/a	35.7	22.7
Swanson (1994)	35	Australia	185	11.8	n/a	n/a
Carlson (1991)	36	NZ	179	13.4	54.0	23.0
Ghirardini (1995)	37	Italy	176	17.0	n/a	n/a
Marasca (1986)	38	UK	168	13.5	n/a	n/a
Eskild (1992)	39	Norway	166	11.0	n/a	n/a
Bindels (1995)	40	Netherlands	160	18.0	62.0	37.0
Eskild (1990)	41	Norway	100	9.3	n/a	n/a
Low (1996)	42	UK	96	20.0	n/a	n/a

n/a, Estimates not available.

sis, which may be explained by differences in demographic and socioeconomic factors, such as age, gender or access to care, and clinical or immunological factors.

Demographic factors

Demographic factors, such as age, gender, ethnic origin, exposure category and socioeconomic status, may play a role in survival after an AIDS diagnosis. Although it is not always possible to alter such factors, their relationship with survival may provide clues to the underlying pathogenesis of infection with HIV. In addition, identification of the relationships between demographic factors and survival is important for predicting individual patients' prognosis.

Whereas some reports have questioned whether age is an important cofactor [22,33,35], most agree that older people are more likely to experience shortened survival following a diagnosis of AIDS [12–18,24–27,30–31,43–45]. The underlying reason for this association, which is also found when considering the time from HIV infection to development of AIDS [46–48], is not known but may relate to a poorer capacity for lymphocyte production in older persons [49], or may be a marker for a characteristic that makes it more difficult for older people to resist the pathological effect of HIV [50–51].

Thinking has been divided on whether ethnicity affects survival after an AIDS diagnosis and this may be due to the under representation of the minority ethnic groups in some studies. Historically, early studies from the United States that were of sufficient size to consider survival differences between racial groups showed that African American and Hispanic patients had poorer survival [11–12,14,43,52–53] than Caucasians after an AIDS diagnosis, although this may simply have reflected poorer access to care [53]. Minority ethnic groups may reside in an area where there is less medical care and treatment, or their disease may go unnoticed for longer, making it more life threatening and serious when it is finally diagnosed. In contrast, the majority of more recent studies show no survival differences according to race [17,20,22,34,54]. Studies of African patients who live in London have suggested no marked differences in survival compared with estimates from developed countries [42]. In common with the studies from Brazil and Thailand [19,32], survival in patients with AIDS in Africa is generally thought to be poorer as compared with that in developed countries, probably reflecting limitations in

access to treatment and care and the high incidence and poor control of other infectious diseases, such as tuberculosis [55–56].

The majority of early studies suggested poorer survival after AIDS diagnosis in women than in men [11–12,14,25–27]. However, more recent studies suggest that there is no difference in survival between the sexes [13,17,35,57–61]. Again, the findings of the earlier studies may have reflected poorer access to healthcare for women or the effects of their lack of time and of other family pressures [62–63], or it may reflect the potential effects of pregnancy [64]. In the early years of the epidemic, HIV in women was often diagnosed concurrently with AIDS [14]. The apparent improvement in survival now observed in women may be due to community education on risk behaviour [65], and an alternative explanation for the earlier poor survival may be that, even when HIV was diagnosed in women, they had limited access to approved and experimental therapy [66]. A likely reason for the early reports of gender differences in mortality may be differences in ethnicity and socioeconomic circumstances, rather than due to biological differences in mortality.

Comparison of survival in different exposure groups is often complicated by confounding with other factors, such as geographical differences [13], or the AIDS-defining diseases which may be preferentially diagnosed in some exposure groups. Kaposi's sarcoma has been shown to occur more commonly in homosexual men [67], to develop at higher CD4 counts [68–69], and have a more favourable prognosis than other AIDS defining illnesses [12–18,20,22,25,27,29–30,38,40,44,52]. Any group of patients that is more likely to develop Kaposi's sarcoma may be expected to have longer survival after the initial AIDS-defining diagnosis than patients who develop other AIDS indicator illnesses. Equally, any differences in survival between men and women may also be attributable to the AIDS-defining diseases which are commonly diagnosed. Differences in survival after an AIDS diagnosis in different exposure categories have been suggested, although the results are rarely consistent [13,15,17–19,26–27,29,33–34,54]. There has been a suggestion of higher mortality in injecting drug users (IDU) with AIDS, arising from drug overdose and violence, including homicide and suicide [70]. In addition, compared with other exposure categories, IDU have been reported to experience a faster rate of CD4 lymphocyte decline [71], which could explain a shorter survival time in this group.

Patients infected with HIV from lower socioeconomic groups have been shown to have a poorer survival, which is independent of access to care [61,72–73]. Further factors investigated, but found to have no relationship with survival, include the number of sexual partners after diagnosis of AIDS [45,74], depression [75], continued smoking, drug use and alcohol intake [75].

CD4 lymphocyte count

The CD4 lymphocyte count at initial diagnosis of AIDS may be related to the patient's count prior to seroconversion to HIV, whereby persons with higher CD4 lymphocyte counts at seroconversion later develop AIDS at a higher count [76]. AIDS normally occurs when the CD4 count has dropped to below 200×10^6/l [44,68,76–78] and 50% of patients have been shown to have a CD4 count of below 50×10^6/l at their initial AIDS-defining diagnosis [68,79]. Death tends to occur when the CD4 count is close to zero [80–83]. Many of the studies of survival after an initial AIDS-defining diagnosis show that patients with a higher CD4 count at diagnosis have a more favourable prognosis [13,18,22–23,33,44,61–62,83–87].

The ranking of AIDS-defining illnesses

Few studies have specifically addressed the ranking of AIDS-defining diseases and survival after each diagnosis [18,69]. A natural order of AIDS-defining diseases, based on the average CD4 lymphocyte count at which they occur, has been suggested [68–69]. This order ranges from diseases such as lymphomas, tuberculosis and Kaposi's sarcoma, which typically occur at higher CD4 lymphocyte counts [18,69,88–89], to diseases such as cytomegalovirus (CMV) disease and *Mycobacterium avium* complex (MAC), which are infrequently observed in patients with CD4 lymphocyte counts above 50×10^6/l [69,90–94].

Some rankings of disease may be implied from studies of the natural history of patients with AIDS. Diseases such as lymphoma have a particularly poor prognosis [18,22,27,31,40,44] as does CMV disease [18,22,29,44,95] and infection with MAC [95–96], the latter two of which tend to occur during the advanced stages of AIDS, as mentioned earlier [68–69,97]. Mortality after a second episode of PCP was initially reported to be higher compared to a first episode [98], but more recent evidence has shown similar survival rates for first and subsequent episodes [99]. Luo *et al.* [18] divided diseases into two classes: 'mild' and 'severe', and formally confirmed that, on average, survival in patients with greater than one illness was reduced, as suggested by a number of earlier studies [14–15,27,38]. Diagnoses such as oesophageal candidiasis and extrapulmonary tuberculosis have the longest median survival times [13,18,32,95,100], whereas the severity of disease resulting from an infection such as cryptosporidiosis is highly variable [18,29,44,95]. Such variation may be related to the degree of immunosuppression at diagnosis [101–102].

Those studies that have considered survival after the diagnosis of a second AIDS-defining illness, occurring subsequently to the first, have reported that the diagno-

sis of a second AIDS-defining illness during follow-up increased the risk of death considerably [85,103–104]. The treatment of a second AIDS-defining illness may be more complicated: this could be due to drug intolerance [35,105], the effects of drugs on concomitant disease [106], problems with patient compliance [107], or simply a more aggressive disease pattern.

Staging systems for patients with AIDS

In practice, staging systems for patients with HIV and AIDS could be of use in many situations. They may help a clinician in advising their patient over planning for the future, for example, to determine if this patient is well enough to go on a trip for 6 months, or to determine if the patient is eligible for a hospice place, given that the hospice will only accept a patient with a life expectancy of under 3 months. Staging systems are also potentially of use for providing guidance in making diagnostic and therapeutic decisions and they allow appropriate prognostic stratification for clinical trials and also identify intermediate measures of disease progression that can be used to speed up the assessment of promising therapies in such trials.

Several classification systems have been proposed which stage patients with HIV [108–112]. Such classification systems have used a range of clinical and laboratory criteria to stage patients. The disadvantages of some of these staging systems, as reviewed by Rabeneck *et al.* in 1991 [113], is that they are not necessarily based on severity of illness, and a large number of people cannot be classified. These staging systems often placed all patients with AIDS into one group, when the heterogeneity in survival between patients with AIDS meant that a finer distinction might be more useful, particularly in clinical trials [114].

There have been several attempts to subdivide patients with AIDS according to prognosis. Justice *et al.* [115] proposed a staging system based on physiological deficits, such as nutritional deficit, haematocrit levels and white blood cell count, rather than demographic or diagnostic features. Turner *et al.* [95] proposed a severity index based on survival criteria developed from current expert opinion: it created three AIDS-defining diagnosis groups and then determined the risk of subsequent complications and risk of death. The most recently proposed staging system is based on a score which takes account of the number and type of AIDS-defining illnesses and the CD4 lymphocyte count [104]. This score and grading system was independently validated on two cohorts of patients, one comprised mainly of homosexual men and the other a group of haemophiliacs, and also on an Italian cohort, which comprised mainly intravenous drug users [116]. The proposed grading system also showed that the CD4 lymphocyte count after an AIDS diagnosis continued to provide important prognostic information about the risk of death even after adjusting for the number and type of AIDS-defining illnesses that occur.

Other potential cofactors of disease progression

The relationship between survival after AIDS and several other factors has also been investigated. Such factors include knowledge of HIV status prior to the diagnosis of AIDS, which provides conflicting results [39,117], and the realistic acceptance of a terminal disease which has been proposed to significantly decrease survival in patients with late stage disease [118]. Regular follow-up care following diagnosis has been shown to increase survival [119], and this is probably attributable to antiretroviral treatment and disease-specific prophylaxis.

Coinfection with viruses and survival after HIV diagnosis

The relationship between survival and coinfection with other viruses such as CMV and hepatitis is unclear. Several reports have suggested that there is no clear evidence of poorer survival occurring in patients coinfected with either hepatitis B or hepatitis C [120–122], whereas studies of children suggest a poorer survival amongst children coinfected with hepatitis [123], in particular hepatitis B [124]. Studies of the role of coinfection with CMV are difficult to perform as up to 90% of homosexual men are infected [125], and among homosexual men infected with HIV, seropositivity for CMV infection approaches 100% [126]. In a group of haemophiliacs with HIV, seropositivity for CMV was associated with a poorer survival [127].

The relationship between treatment and survival in AIDS patients

The nucleoside analogue reverse transcriptase inhibitor, zidovudine (ZDV) was found, in 1985, to have activity against HIV *in vitro* [128]. In 1987 Fischl *et al.* showed that ZDV improved survival in patients with AIDS and AIDS-related complex [129]. Several uncontrolled studies have also shown an improved survival in AIDS patients when treated with ZDV [52,84,130]. Treatment with this drug is complicated by many problems. There is some concern that the efficacy of ZDV may be short lived [131–135], and after a variable period of time most patients resume the immunological and clinical decline seen before therapy started. Studies have shown that drug resistance may be a factor in further disease progression [136–137]. The use of ZDV is often limited by side

effects such as anaemia, neutropenia, nausea and vomiting [138–139], or by poor patient compliance [107]. The advantageous effect of early therapy at higher CD4 lymphocyte counts on survival and the appropriate time to initiate therapy remains controversial [140–141].

Didanosine (ddI) was the second drug to be licensed to treat patients with HIV. The approval was based on small Phase I trials in which there was an improvement in weight, CD4 lymphocyte counts and other laboratory markers [142–144]. There is now strong evidence of a benefit to survival, over and above that provided with ZDV alone, when patients with no prior antiretroviral treatment are treated with either ddI or zalcitabine (ddC) in combination with ZDV [145–148]. The addition of ddI or ddC to ongoing ZDV therapy is of uncertain benefit [147–149]. In addition, ddC has been shown to provide some survival benefit over ddI in patients with late-stage disease in whom treatment with ZDV has failed [150]. A further antiviral treatment that has been associated with improved survival in patients treated with ZDV is the anti-herpesvirus drug aciclovir [151–153]. Most recently, the inclusion of the protease inhibitor ritonavir in treatment with antiretrovirals has been shown to prolong survival in patients with very advanced HIV infection [154].

It seems likely that use of prophylaxis against individual AIDS-defining diseases, such as PCP, toxoplasmosis, MAC and CMV disease has a benefit in terms of reduced mortality, as well as reducing the incidence of specific AIDS-defining diseases, but few trials have been sufficiently large to prove such survival benefits and therefore this issue has not been specifically addressed.

Temporal changes in survival

Perhaps one of the more important factors which should be considered is the evidence that average survival following a diagnosis of AIDS has increased over time [11,15–17,22–23,44,84,100,155–156]. Over the first few years of the epidemic it seems that this was the case, with improvements in survival accompanying the introduction of ZDV in 1987 [84,129,157], and prophylaxis against PCP [158,159], which continues to be the most frequent opportunistic infection present at initial AIDS-defining diagnosis in developed countries [160–161]. Other important factors which may have played a role in extending average survival time include the change of the surveillance definition of AIDS in 1987 and 1993 [162–163], increased awareness and support for AIDS patients over time [16,164], improvements in diagnosis and earlier detection of disease [20,22].

There is some evidence to show that the average CD4 lymphocyte count at initial AIDS-defining diagnosis has declined quite markedly over time, from counts in the region of 100×10^6/l early in the epidemic to levels around 50×10^6/l observed in recent studies [13,26,165], attributed to the widespread use of antiretroviral therapy and primary prophylaxis against PCP [22,72] which has been shown to delay the initial AIDS-defining condition [132,141,166–168]. If the onset of AIDS has been delayed substantially, further improvements in survival time in patients with AIDS may only occur as more efficient treatments for the opportunistic infections and underlying immunodeficiency are developed. Whereas median survival times have shown some improvement over time the prognosis three and five years after diagnosis has remained poor [13].

Table 2. Summary of factors associated with survival in patients with AIDS.

	References
Strong evidence for an association	
Age	12–18,22,24–27,30–31,33,35,43–45
Initial AIDS-defining illness	12–18,20,22,25,27,29–32,38,40, 44,52,69,87,95–96,100
Number and type of subsequent AIDS-defining illnesses	14–15,27,38,85,98–99,103–104
CD4 lymphocyte count at diagnosis	13,18,22–23,33,44,61–62,83–86
Loss of CD4 cells after diagnosis	80,86,104
Inadequate evidence	
Pregnancy	64
Socioeconomic circumstances	61,72–73
Knowledge HIV status prior to AIDS diagnosis	39,117
Acceptance of a terminal disease	118
Regular follow-up care	119
Coinfection with other viruses	120–124,127
Case load of treating hospital	16,165
Number sexual partners following AIDS diagnosis	45,74
Depression	75
Smoking	75
Recreational drug use	75
Alcohol intake	75
Evidence against an association	
Gender	11–14,17,25–27,35,57–61
Ethnic origin (within developed countries)	11–12,14,17,20,22,34,42–43,52–54
Exposure category	13,15,17–19,26–27,29,33–34,54

Conclusion

It is clear that major advances in the understanding of the epidemiology and natural history of infection with HIV and AIDS have been made over the past 15 years. The survival of patients with AIDS has improved over time due to better awareness and treatment, and various factors that may play a role in survival have been investigated and established. Table 2 summarizes the factors thought to be related to survival, together with those factors which, based on current evidence, do not appear to have a strong association with survival. Age, CD4 lymphocyte count at the time of diagnosis and throughout follow-up, and type of AIDS-defining illness, including those made after the initial AIDS-defining diagnosis, are currently the strongest predictors of future survival. The relationship between HIV viral load in this context has not yet been extensively evaluated. With future advances in treatment survival times and the quality of life for patients with AIDS may continue to improve.

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Appendix

A recent article by Darby *et al.* based on the UK Haemophilia Cohort has provided additional evidence that age at infection with HIV is an important determinant of survival. After adjustment for year of seroconversion, haemophilia type and severity, the mortality of patients who seroconverted above the age of 55 was almost five times higher than patients who seroconverted below the age of 15.

Darby SC, Ewart DW, Giangrande PLF, Spooner RJD, Rizza CR, for the UK Haemophilia Centre Directors' Organization. **Importance of age at infection with HIV-1 for survival and development of AIDS in UK haemophilia population.** *Lancet* 1996, **347**:1573–1579.

Survival after diagnosis of AIDS: a prospective observational study of 2625 patients

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Abstract

Objective: To estimate median survival and changes in survival in patients diagnosed as having AIDS.
Design: Prospective observational study.
Setting: Clinics in two large London hospitals.
Subjects: 2625 patients with AIDS seen between 1982 and July 1995.
Main outcome measures: Survival, estimated using lifetable analyses, and factors associated with survival, identified from Cox proportional hazards models.
Results: Median survival (20 months) was longer than previous estimates. The CD4 lymphocyte count at or before initial AIDS defining illness decreased significantly over time from 90×10^6/l during 1987 or earlier to 40×10^6/l during 1994 and 1995 ($P<0.0001$). In the first three months after diagnosis, patients in whom AIDS was diagnosed after 1987 had a much lower risk of death (relative risk 0.44, 95% confidence interval 0.22 to 0.86; P=0.017) than patients diagnosed before 1987. When the diagnosis was based on oesophageal candidiasis or Kaposi's sarcoma, patients had a lower risk of death than when the diagnosis was based on *Pneumocystis carinii* pneumonia (0.21 (0.07 to 0.59), P=0.0030 and 0.37 (0.16 to 0.83), P=0.016). Three months after AIDS diagnosis, the risk of death was similar in patients whose diagnosis was made after and before 1987 (1.02 (0.79 to 1.31), P=0.91). There were no differences in survival between patients diagnosed during 1988-90, 1991-3, or 1994-5.
Conclusions: In later years, patients were much more likely to survive their initial illness, but long term survival has remained poor. The decrease in CD4 lymphocyte count at AIDS diagnosis indicates that patients are being diagnosed as having AIDS at ever more advanced stages of immunodeficiency.

Introduction

Although much has been published about the survival of patients with AIDS, large studies tend to be based on surveillance data from the United States.[1-4] Although data from surveillance studies can estimate survival in large numbers of patients, such studies are limited to basic data collection and follow up. A large British study based on surveillance data that were published in 1993 reported the bias that can occur as a result of reporting delays and underreporting, which are common problems with surveillance data.[5] The estimates of median survival from this study may well have changed because of improvements in treatment or the change, in 1993, of the definition of AIDS used in surveillance.[6] Rogers *et al* have more recently published a study based on British surveillance data describing the influence of covariates such as age and calendar year of diagnosis.[7] A current estimate of the prognosis of patients with AIDS would help in planning future research and allocation of resources.

A total of 12 565 cases of AIDS were reported between 1982 and March 1996 in England and Wales; 8713 of these patients (69%) are known to have died.[8] Our two hospitals have dedicated HIV units that, between them, have seen 2625 patients with AIDS—over a fifth of those in Britain—between 1982 and July 1995, the end date of the present study. Data were collected prospectively on patients throughout this period, and therefore the aim of our study was to provide an up to date estimate of survival in a large, unselected group of patients, and to identify whether survival has improved over time.

Patients and methods

We included all patients from the Chelsea and Westminster Hospital diagnosed as having AIDS between January 1982 and July 1995 and all patients from the Royal Free Hospital (RFH) diagnosed with AIDS between January 1986 and August 1994. AIDS was diagnosed according to the definition in use at the time. For example, patients receiving a diagnosis of pulmonary tuberculosis in 1994 would be classified as AIDS patients, but if the diagnosis had been made in 1991, before the revision of the surveillance definition,[8] they would not be classified as AIDS patients. Demographic data, details of all AIDS defining illnesses, treatment, and immunological data are prospectively collected and maintained on a separate database at each site. Prospective data collection began in 1986 at the Chelsea and Westminster and 1990 at the Royal Free Hospital; retrospective data for all patients with HIV who had ever been seen at either clinic was added at this time. Only the factors known at the time of initial AIDS diagnosis were included in this analysis, and no adjustments were made for CD4 lymphocyte counts during follow up or further AIDS defining illnesses.

Statistical methods

Estimates of median survival were obtained by using a lifetable analysis.[9] Patient survival was measured from the month of diagnosis of initial AIDS defining illness until death. Patients who did not die during the study were censored at the time of their last clinic attendance. Some patients had been diagnosed as having AIDS before their first visit to either hospital. These patients were included in the study, but their survival was left-truncated (survival was calculated from the time of their initial AIDS defining illness, but they were not included in the risk set until the date they were first seen at either hospital). The relative risks of death were obtained by using Cox propor-

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tional hazards models. With the exception of the lifetable analysis, all data were analysed with SAS 6; all P values are two sided.

To compare survival in different years, patients diagnosed in 1987 or earlier were placed in one group, representing those to whom treatment was not generally available when AIDS was diagnosed; those whose illness was diagnosed after 1987 were placed in a separate group. Patients whose illness was diagnosed after 1987 were split into further groups, but as survival within each group was similar these were combined. Tests of the proportional hazards assumption showed that the effect of year of diagnosis decreased with time. From the lifetable analysis it was clear that the risk of death in the first three months after AIDS diagnosis for patients diagnosed after 1987 was much lower than that of patients diagnosed before 1987. Therefore the relative risk of death in the first three months after AIDS diagnosis was compared with the risk of death after three months. This was modelled by two separate Cox proportional hazards models. The first estimated the relative risk of death in the first three months of follow up; thus patients who were followed up for more than three months were censored at three months. The second model estimated the relative risk of death after three months. In this model patient follow up started three months after a diagnosis of AIDS, so patients who survived for less than three months or who were lost to follow up within three months were not included. There was no evidence that the proportional hazards assumption did not hold in either model (P=0.15 and P=0.78 respectively).

Table 1 Characteristics of patients with AIDS seen at the Royal Free and Chelsea and Westminster Hospitals

	No (%) of patients	No (%) of deaths	Survival	
			Median (months)	P value
All patients	2625 (100)	1613 (61.5)	20	
Centre:				
Royal Free Hospital	385 (14.7)	204 (53.0)	21	0.92
Chelsea and Westminster Hospital	2240 (85.3)	1409 (62.9)	20	
Sex:				
Male	2497 (95.2)	1552 (62.2)	19	0.80
Female	125 (4.8)	58 (46.4)	21	
Exposure category:				
Homosexual/bisexual	2206 (84.0)	1356 (61.5)	21	
Heterosexual	92 (3.5)	64 (69.6)	13	
Intravenous drug users	94 (3.6)	45 (47.9)	23	0.0001
Other	184 (7.0)	114 (62.0)	20	
Unknown	49 (1.9)	34 (69.4)	7	
Age at diagnosis of AIDS:				
≤25 years	118 (4.5)	64 (54.2)	28	
26-35 years	1105 (42.1)	638 (57.7)	24	
36-45 years	917 (34.9)	582 (63.5)	20	0.0001
46-55 years	377 (14.4)	245 (65.0)	17	
>55 years	108 (4.1)	84 (77.8)	10	
Year of diagnosis:				
1987 or earlier	339 (12.9)	285 (84.1)	19	0.73
1988 or later	2286 (87.1)	1328 (58.1)	21	
CD4 count at diagnosis:				
Unknown	1002 (38.2)	633 (63.2)	20	
$<50 \times 10^6/l$	753 (28.7)	504 (66.9)	18	
$50\text{-}99 \times 10^6/l$	311 (11.8)	200 (64.3)	21	0.0001
$\leq 100 \times 10^6/l$	559 (21.3)	279 (49.4)	38	
Initial AIDS defining illness:				
Oesophageal candida	382 (14.6)	206 (53.9)	24	
Kaposi's sarcoma	490 (18.7)	288 (58.8)	22	
Pneumocystis carinii pneumonia	802 (30.6)	509 (63.5)	22	0.0001
Other single disease	708 (27.0)	417 (58.9)	17	
2 Or more diseases consecutively	243 (9.3)	193 (79.4)	16	

Results

In total, 2625 patients were diagnosed as having AIDS during the study period: 385 (14.7%) from the Royal Free Hospital and 2240 (85.3%) from the Chelsea and Westminster Hospital (table 1). The median duration of follow up after diagnosis of AIDS was 15.4 (90% range 2.3-52.8) months, during which time 1613 patients (61.5%) died. The first diagnosis of AIDS was made at the Chelsea and Westminster Hospital in 1982; the first diagnosis at the Royal Free was in 1986.

The population was, on average, quite young; the median age at AIDS diagnosis was 35.7 (range 2.1-72.2) years. Male patients were significantly older than female patients (median age 35.9 *v* 30.2 years; P<0.0001, Wilcoxon test). Patients from the homosexual/bisexual exposure category were the oldest patient group (median age 36.2 years) and intravenous drug users were the youngest (median age 31.7 years). In the Royal Free Hospital cohort the proportion of female patients was significantly higher than in Chelsea and Westminster Hospital cohort (45/382 (11.6%) *v* 81/2240 (3.6%); P<0.0001, χ^2 test), and the proportion of patients in the homosexual/bisexual exposure category was significantly lower (252/385 (65.5%) *v* 1954/2240 (87.2%); P<0.0001, χ^2 test). Overall, the proportion of female patients with AIDS increased over time, from 1.3% (four patients) before or during 1987 to 7% (31 patients) in 1994 and 1995 (P<0.0001, χ^2 test).

The most common single initial AIDS defining illness was *Pneumocystis carinii* pneumonia (802 cases, 30.6%), followed by Kaposi's sarcoma (490 cases, 18.7%) and oesophageal candidiasis (382 cases, 14.6%). No other single illness was used for diagnosis in over 100 patients; 243 patients (9.3%) were diagnosed with two or more AIDS defining illnesses simultaneously. Kaposi's sarcoma was significantly more likely to be diagnosed in men than women (477/2497 (19.1%) *v* 12/125 (3.6%); P<0.0001, χ^2 test), as was oesophageal candidiasis (370 (14.8%) *v* 12 (9.6%); P<0.0001, χ^2 test). The median CD4 lymphocyte count within three months of the initial AIDS defining illness, available for 1623 (61.8%) patients, was $56\times10^6/l$ (90% range $6\times10^6/l$-$416\times10^6/l$), and was significantly higher among patients from the Royal Free Hospital (median $62\times10^6/l$ *v* $54\times10^6/l$ at Chelsea and Westminster; p=0.0169; Wilcoxon test). The CD4 lymphocyte count at the initial AIDS defining illness decreased significantly over time, from $90\times10^6/l$ in patients whose illness was diagnosed during 1987 or earlier to $61\times10^6/l$ during 1988-90 (P<0.0001, Wilcoxon test).

Median survival overall was 20 months (table 1); only one in 15 patients remained alive five years after diagnosis. Age was strongly related to survival after diagnosis (fig 1). Median survival in patients aged 25 or less at initial diagnosis was 28 months; in patients aged over 55 at diagnosis it was 10 months.

Figure 2 shows the relation between survival and year of diagnosis. In the first three months of follow up,

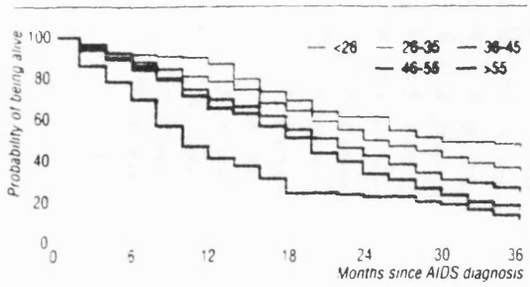

Fig 1 Lifetable progression rates: age at AIDS diagnosis

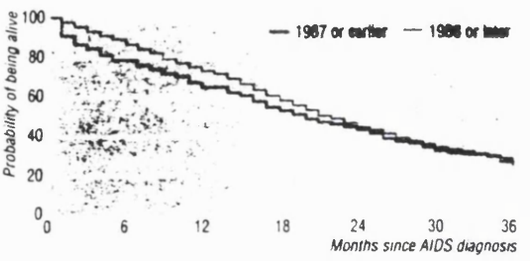

Fig 2 Lifetable progression rates: year of AIDS diagnosis

168 patients (6.4%) died and 127 (4.8%) were lost to follow up. The survival curves for those in whom AIDS was diagnosed before or during 1987 and after 1987 diverge rapidly; 15.9% of patients (54/339) in whom AIDS was diagnosed before or during 1987 had died within three months of diagnosis compared with 5.2% of patients (19/2286) in whom AIDS was diagnosed after this date. The survival curves converge as survival increases, and two years after diagnosis there is little difference in survival between patients in whom AIDS was diagnosed before or during 1987 and after 1987. As the survival curves converge, patients in whom AIDS was diagnosed after 1987 must be at a slightly higher risk of death after three months than those diagnosed before this time. When we broke the period after 1987 into three groups (1988-90, 1991-3, and 1994-5) we found no differences in survival between the groups either during the first three months or afterwards.

To overcome the problem of the converging survival curves, we divided follow up time into two distinct periods and obtained the relative risk of death in each period, as described in the methods. Table 2 shows the results of a multivariate analysis that included all cofactors in the model. We found no significant differences in survival in either time period according to the hospital of diagnosis or sex. Compared with the risk of death for homosexuals or bisexuals, only patients for whom exposure category could not be determined had a significantly greater risk of death. This increased risk was consistent in both time periods and may correspond to a later presentation in this group of patients (relative risk 3.75 during first three months after diagnosis (95% confidence interval 1.20 to 11.75), P=0.024; relative risk 2.60 after first three months (1.41 to 4.79), P=0.0021). The age effect was strong in both periods and CD4 lymphocyte count was strongly related to risk of death. The relative risk of death for a patient with a 50% lower CD4 count at baseline was 1.41 (1.22 to 1.64; P<0.0001) during the first three months and 1.59 (1.50 to 1.68; P<0.0001) after three months.

In the three months immediately after diagnosis of AIDS, patients whose defining illness was Kaposi's sarcoma or oesophageal candidiasis were at a significantly lower risk of death than those whose defining illness was *Pneumocystis carinii* pneumonia (0.21 (0.07 to 0.59), P=0.003 and 0.37 (0.16 to 0.83), P=0.016). After this time, patients with either of these diagnoses were at a similar risk of death to patients whose diagnosis was based on *Pneumocystis carinii* pneumonia. When diagnosis was based on a single disease other than oesophageal candidiasis, Kaposi's sarcoma, or *Pneumocystis carinii* pneumonia, patients had a higher risk of death in both time periods than did patients whose diagnosis was based on *Pneumocystis carinii* pneumonia (1.43, P=0.11 and 1.30, P>0.005). Risk of death was also higher, but not significantly higher, for patients whose diagnosis was based on two or more diseases.

In the three months after diagnosis of AIDS, patients in whom AIDS was diagnosed after 1987 had a significantly lower risk of death than patients in whom AIDS was diagnosed before this date (0.44; 0.22 to 0.86). As discussed above, when the diagnosis was made after 1987 the patients had a slightly higher risk of death after three months than when the diagnosis was made before 1987 (1.02; 0.79 to 1.31, P=0.91). To further examine the differential effects in the two periods, we considered the interaction between the main covariates and duration of follow up time, modelled as time dependent covariates. This creates a binary variable that takes the value zero for a patient with less than three months' follow up and switches to a value of one after three months' follow up. The interaction with

Table 2 Multivariate analysis examining all cofactors relating to survival of patients with AIDS seen at two London clinics

	Within 3 months of diagnosis of AIDS		After 3 months	
	Relative risk of death (95% CI)	P value	Relative risk of death (95% CI)	P value
Centre:				
Royal Free Hospital	1.00		1.00	
Chelsea and Westminster Hospital	1.17 (0.67 to 2.01)	0.58	1.02 (0.84 to 1.24)	0.82
Sex:				
Male	1.00		1.00	
Female	1.49 (0.63 to 3.51)	0.36	0.81 (0.52 to 1.25)	0.34
Exposure category:				
Homosexual/bisexual	1.00		1.00	
Heterosexual	2.39 (0.96 to 5.62)	0.082	1.01 (0.64 to 1.59)	0.96
Intravenous drug users	0.97 (0.23 to 4.14)	0.96	1.22 (0.73 to 2.01)	0.45
Other	0.82 (0.39 to 1.74)	0.60	1.35 (0.74 to 1.74)	0.53
Unknown	3.75 (1.20 to 11.75)	0.024	2.60 (1.41 to 4.79)	0.0021
Age (per 10 year increase)	1.58 (1.30 to 1.92)	0.0001	1.41 (1.30 to 1.52)	0.0001
CD4 count (per 50% decrease)	1.41 (1.22 to 1.64)	0.0001	1.59 (1.50 to 1.68)	0.0001
AIDS defining illness:				
Pneumocystis carinii pneumonia	1.00		1.00	
Oesophageal candida	0.21 (0.07 to 0.59)	0.0030	0.91 (0.74 to 1.12)	0.37
Kaposi's sarcoma	0.37 (0.16 to 0.83)	0.020	1.09 (0.88 to 1.34)	0.43
Other single diagnosis	1.43 (0.92 to 2.22)	0.11	1.30 (1.08 to 1.57)	0.005
2 Or more diseases	1.16 (0.60 to 2.24)	0.65	1.25 (0.98 to 1.59)	0.070
Year of diagnosis:				
1987 or earlier	1.00		1.00	
1988 or later	0.44 (0.22 to 0.86)	0.017	1.02 (0.79 to 1.31)	0.91

Table 3 Survival in published studies of patients with AIDS, including the present study

Study (year of publication)	Country of origin	No of subjects	Median survival (months)	% Alive at 12 months	% Alive at 24 months
Piette *et al* (1992)[11]	United States	43 795	12.7	49.1	18.4
Blum *et al* (1994)[6]	United States	23 324	13.7	54.7	31.9
Piette *et al* (1991)[7]	United States	23 271	11.5	NA	NA
Lundgren *et al* (1994)[12]	Europe	6578	17.0	NA	NA
Rothenberg *et al* (1987)[3]	United States	5833	11.4	48.8	28.2
Lemp *et al* (1990)[4]	United States	4233	12.5	51.6	20.2
Whitmore-Overton *et al* (1993)[5]	United Kingdom	3984	16.7	NA	NA
Chang *et al* (1993)[13]	United States	3699	11.5	48.8	29.0
Luo *et al* (1995)[14]	Australia	3204	14.3	57.2	26.4
Mocroft *et al* (1997)	United Kingdom	2625	20.0	70.8	40.5
Chequer *et al* (1992)[15]	Brazil	2135	5.1	32.0	21.0
Seage *et al* (1993)[16]	United States	1931	13.5	54.0	23.0
Payne *et al* (1990)[17]	United States	1015	17.0	65.4	35.1

NA=estimate not available.

year of diagnosis (after 1987 or before 1987) was highly significant (P<0.0001), supporting the view that patients whose diagnosis was made after 1987 were at a lower risk of death in the three months after an AIDS diagnosis than were patients whose diagnosis was made after this date.

Discussion

This large cohort of patients with AIDS has helped to confirm cofactors of disease progression. Table 3 summarises published studies of more than 1000 patients with AIDS,[1-5 11-17] ranked by the number of patients studied. Our study is one of the largest studies based on data collected prospectively at a clinic rather than on surveillance data. The estimate of median survival is longer than has previously been suggested and the proportion of patients alive one and two years after diagnosis is considerably higher than that reported in other studies. In addition to the increase in median survival, the proportion of patients who survived for three years (21.8%; 19.6 to 24.0%) was higher than that found by Lundgren *et al* (16%) in a large observational study of AIDS patients diagnosed between 1979 and 1989 across Europe.[12] Changes in the surveillance definition of AIDS[6 18] and improvements in antiretroviral treatment and prophylaxis for *Pneumocystis carinii* pneumonia[19-21] are both likely to have contributed to the improved survival seen in this patient group.

Patients for whom exposure category was not known had an increased risk of death, even after confounding variables were adjusted for. These patients may form a unique group who were too ill at presentation to be questioned about risk behaviour. Such patients may present with a wide variety of serious medical problems, or may not be well enough to be offered standard treatment with its associated side effects.[22 23]

Survival and AIDS defining illnesses

In the three months after diagnosis of AIDS, patients whose diagnosis was based on Kaposi's sarcoma and oesophageal candidiasis were at a significantly lower risk of death than those whose diagnosis was based on *Pneumocystis carinii* pneumonia, which may suggest that these are milder diseases which can initially be treated and are less likely to be terminal when first diagnosed. This is consistent with results from other studies, where patients with these as the initial AIDS defining illness had the longest median survival.[12 14 24 25] After three months, patients with other single AIDS defining illnesses had a significantly higher risk of death. Diseases in this category included lymphomas, toxoplasmosis, cytomegalovirus disease, and infection with non-tuberculosis mycobacterium, all of which have a poor prognosis[12 14 15 24] and, with the exception of lymphomas, tend to be diagnosed at lower CD4 lymphocyte counts.

Improvements in survival in later years

Many studies have indicated that survival in AIDS patients has improved over time.[2 4 5 12 15 25] Our results do not directly show an increase in survival in later years, but they show that in the first three months after diagnosis, patients whose diagnosis was made in later years had a significantly lower risk of death, and this may be due to improvements in treating the initial AIDS defining illness.[26] In 1987 and before, patients often died of their initial AIDS defining illness, and a significant proportion of patients would die within three months. Rothenberg *et al*[3] stated in 1987 that almost 12% of patients died within a month of their initial AIDS diagnosis[3]; this compares with 3.3% in our patients in whom AIDS was diagnosed after 1987. A later study showed that, before 1987, almost one quarter of patients died within three months of their initial AIDS defining illness; during 1987-90 this proportion had dropped to 14%.[5] In our study, from three months after diagnosis there was no difference in the risk of death according to year of diagnosis. Lundgren *et al* showed that although short term survival was improving during the 1980s, the long term prognosis of patients with AIDS was poor.[12]

Declining CD4 lymphocyte count at diagnosis of AIDS

In this as in other studies[12 27-29] the average CD4 lymphocyte count at the initial AIDS defining illness has declined over time, suggesting that AIDS is now being diagnosed later and patients are more immunocompromised when AIDS is diagnosed. In addition, the

Key messages

- Estimates of the prognosis of AIDS patients help with allocation of resources and future research
- Historically, surveillance data have been used to estimate survival in large patient groups
- In an unselected group of 2625 patients with AIDS, median survival (20 months) was longer than previously estimated; the CD4 count at diagnosis decreased significantly over time
- After 1987, patients were much more likely to survive an initial AIDS defining illness, but long term prognosis remained poor
- There has been little change in prognosis since 1987; this may be due to AIDS being diagnosed at ever more advanced stages of immunodeficiency

pattern of AIDS defining illnesses has been changing: Kaposi's sarcoma and *Pneumocystis carinii* pneumonia have become less common as AIDS defining illnesses, and diseases associated with more advanced immunosuppression, such as cytomegalovirus diseases, have become more common.[27 30] This has been attributed to the widespread use of antiretroviral therapy and prophylaxis against *Pneumocystis carinii* pneumonia,[5 29] which has been shown to delay the initial AIDS defining condition.[27 29 31] If the onset of AIDS has been delayed substantially then survival after a diagnosis of AIDS may be expected to decrease. Survival after diagnosis of aids was longer in our study than previously reported, which may indicate that the time between seroconversion and death is increasing.

Measuring survival after diagnosis of AIDS depends on recognition of the disease, and improvements in survival over recent years have been attributed to an increased awareness and support for patients with AIDS[5] and earlier detection of disease.[29] An alternative approach to identify possible improvements in survival time is to monitor survival after a given CD4 lymphocyte count—$200\times10^6/l$, for example—is reached. Issues such as treatment, AIDS defining illnesses, and the role of potential cofactors in improving survival can also be addressed. This has been discussed in part by the recent study by Enger *et al*[31] and will be further investigated in our cohort of patients.

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ONE HUNDRED YEARS AGO

Found drunk

When the police in Denmark find anyone in the streets drunk and incapable they take him in a cab to the station, where he gets sober under a surgeon's care. On recovering sobriety the police take him home. A bill for the services of the cabman, the surgeon, and the police agents for special duty is then presented to the host of the establishment where the patient took his last drink. In Turkey if a Turk falls down in the street while intoxicated and is arrested, he is sentenced to the bastinado, which punishment is repeated as far as the third offence. After the third bastinadoing he is considered to be incorrigible, and is called "Imperial," or "privileged" drunkard. If arrested after that he has only to give his name and address, and state that he is a "privileged" drunkard, when he is released and conducted home, the bill for these kindnesses being rendered to him for payment next day. (*BMJ* 1897;i:35.)

Staging system for clinical AIDS patients

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Summary

Although there are wide differences in prognosis between patients with AIDS they are often thought of as a single homogeneous group. We think a simple staging system that accounts for important prognostic factors including type and number of AIDS diseases and the CD4 lymphocyte count is required.

We followed 363 AIDS patients at the Royal Free Hospital and reported the occurrence of 680 AIDS-defining diseases (ADDs). We measured CD4 counts at approximately monthly intervals. Severity of AIDS diseases was defined a priori on the basis of survival in the AIDS in Europe study of 6578 AIDS patients: mild—oesophageal candidiasis, Kaposis sarcoma (cutaneous), *Pneumocystis carinii* pneumonia, extrapulmonary tuberculosis; severe—all other ADDs except lymphoma; very severe—lymphoma. The risk of death increased by 15% (p=0·08) for each mild condition experienced, by 89% (p<0·0001) for each new severe condition and by 535% (p<0·0001) when a lymphoma developed. Estimates from the Cox model were used to derive a score reflecting the risk of death. Patient experience was divided into three categories. Patients in AIDS Grade I had an average death rate of one per 10·1 years, compared with one per 2·8 years in AIDS Grade II and one per 1·1 years in AIDS Grade III. Similar rates were seen in an independent validation study on 1230 AIDS patients at different hospital.

Our grading system should be useful for patient management, clinical trial design, surveillance, and resource management.

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Introduction

The risk of death varies greatly between patients who have been given a clinical diagnosis of AIDS (a diagnosis not based solely on the CD4 count falling below 200/mm³). This risk almost certainly depends on the type and number of AIDS defining diseases (ADDs) which have occurred,[1–7] and possibly the CD4 count.[8,9] The heterogeneity between AIDS patients means that it is not helpful to think of AIDS as a discrete homogeneous state; a finer distinction would be more useful in many circumstances, for example when designing entry and endpoint criteria in clinical trials.[10–12]

The most objective and intuitively appealing approach for deriving such a staging system is to divide patients according to the risk of death. To derive such a system, follow-up data on AIDS patients are needed with information on all new AIDS diagnoses and regular CD4 counts up to time of death. Few studies have analysed these aspects of follow-up.[1,5,7] Although AIDS staging systems have been proposed and discussed in the past,[7,13,14] none has used information on CD4 counts and new ADDs.

During our study, 363 patients with AIDS were followed for up to 6 years after their initial AIDS diagnosis. We have recorded occurrences of all ADDs and measured CD4 counts at approximate monthly intervals. We have made use of these comprehensive data, along with published results from the AIDS in Europe study of 6578 AIDS patients,[1] to derive a staging system for AIDS patients. We then looked at two different groups of AIDS patients[15] with different risk behaviour and clinical history to validate the system.

Patients and methods

363 AIDS patients were seen on at least one occasion at the Royal Free Hospital by one consultant (MAJ). The patients were diagnosed with AIDS between June, 1986 and February, 1994 and had a total of 680 ADDs during follow-up. AIDS was diagnosed according to the Centers for Disease Control 1987 criteria.[16] Date of birth, ethnic origin, and first ADD were obtained from notification forms sent to the Communicable Disease Surveillance Centre (CDSC) in the UK. Exposure category, CD4 counts, and date of death were obtained from the HIV/AIDS unit database. Zidovudine use, subsequent ADDs, and the date of last visit to the centre were found by a retrospective search through all patient notes by one person (AJM). Only the first occurrence of each ADD was recorded for each patient. This search also serves as a way to cross check initial ADD, date of birth, and date of death with those appearing on the CDSC reporting form. In the event of contradictory information from patient notes and CDSC forms, confirmation from the consultant (MAJ) was sought. Where possible, dates of death for patients lost to follow-up were obtained from the CDSC. CD4 lymphocyte counts were

measured monthly throughout follow-up for most patients. Patient follow-up was censored at date of last hospital visit, or Feb 28, 1994, whichever occurred first.

Policies for use of antiretroviral therapy and Pneumocystis carinii pneumonia (PCP) prophylaxis

Primary prophylaxis for PCP began in 1988 with nebulised pentamidine (300 mg, monthly), which continued until the end of 1991. Since then co-trimoxazole has been used (960 mg per day), except for patients who were intolerant for co-trimoxazole and were treated with pentamidine. Secondary PCP prophylaxis followed the same protocol as primary prophylaxis, except that patients were nebulised with pentamidine fortnightly. Zidovudine treatment began in 1987, and tended to be at high doses (1000 mg per day). Currently, patients are treated with zidovudine at lower doses (400–600 mg per day), and sometimes in combination with other drugs (didanosine [ddI], zalcitabine [ddC]). For patients not participating in trials, treatment with both antiretroviral therapy and primary PCP prophylaxis usually commenced when a patient became symptomatic, or when a patient's CD4 count fell below 200/mm³.

CD4 analysis

A whole blood lysis method was used and the percentage of CD4 lymphocytes was expressed as absolute CD4 counts on the basis of lymphocyte counts. A monoclonal CD4 antibody, RFT4, was used, as described previously.[17] More recently, absolute CD4 counts have been directly obtained in an ORTHO Cytoron-Absolute (ORTHO Diagnostics, High Wycombe, UK). Flow cytometer quality control was monitored in the UK National External Quality Assurance Scheme.

Statistical methods

We used chi-squared tests to measure the associations between different groups of categorical variables. *t* tests were used to test whether differences existed between continuous variables, except where a variable was not normally distributed. In such cases non-parametric tests were used. All data analyses were done with SAS.[18]

Before analysing our data we used previous published results to grade the severity of ADDs. The AIDS in Europe study of 6578 AIDS patients[1] reported more favourable survival times after an initial AIDS diagnosis for patients with PCP (20 months), Kaposi's sarcoma (21 months), oesophageal candidiasis (19 months), and extrapulmonary tuberculosis (28 months). Less favourable survival times (13 months for all other single diagnoses) were reported for other diagnoses. This study also reported a particularly poor prognosis for patients with lymphoma (6 months). The survival estimates in the AIDS in Europe study are also consistent with results from other large studies using surveillance data.[4,19,20] On the basis of their prognosis attached, three groups of ADD were defined; 1) mild: oesophageal candida, cutaneous Kaposi's sarcoma, PCP, and extrapulmonary tuberculosis; 2) severe: all other ADDs excluding lymphoma; 3) very severe: lymphoma.

Cox proportional hazards models were used to mathematically model the risk of death as the CD4 count declined and more ADDs were experienced. Both minimum CD4 count since AIDS and number of mild, severe, or very severe ADDs experienced were modelled as time-dependent covariates (recurrences of the same ADD were ignored, because of problems of defining whether a disease is a continuation of the first episode or a new episode). Thus, changes in a person's risk of death when their CD4 count drops or a new ADC occurs can be modelled. Other variables, such as zidovudine use, were added to the model to see if they improved the fit of the model. The logarithms of the adjusted relative hazards obtained from the Cox model that best fitted the data were used to derive a score, which reflects the risk of death.

This score was categorised to give three grades of AIDS, AIDS Grade I (least severe), II, and III (most severe). Cut-off points of the score to create the grades were chosen a priori (ie, before calculation of the results in tables 4, 5, and 6) to make the grades as simple and as easy to remember as possible. The score was validated on a large group of AIDS patients seen at a clinic in another hospital (The St Stephen's Clinic), who had median patient follow-up of 16 months (range 0–130 months) and median CD4 count at initial AIDS diagnosis of 56/mm³ (range 5–405), and a group of AIDS patients with haemophilia at the Royal Free Hospital.[15]

All patients	Patient population	
	Number	Percentage
	363	100
Sex		
Male	321	88·4
Female	42	11·6
Age group		
<30	89	24·5
30–39	147	40·5
40–49	86	23·7
Above 50	41	11·3
Exposure category		
Homo/bisexual	258	71·1
Heterosexual	52	14·3
IVDU	27	7·4
Other	26	6·9
Ethnic origin		
White	270	80·8
Black	45	13·5
Other	19	5·7
Initial diagnosis		
Mild	247	68·0
Severe	101	27·8
Very severe	15	4·1
Zidovudine use		
Never	72	21·2
At/after AIDS	150	44·1
Before AIDS	118	34·7

IVDU=intravenous drug user.

Table 1: **Demographic characteristics of patient population**

Results

363 patients were followed for a median time of 17 months since their initial AIDS diagnosis (range 1–73 months). By Feb 28, 1994, 159 (43·8%) patients had died. No vital status was available for 23 patients (6·3%), 19 of whom were temporary visitors to the UK when the diagnosis was made. Table 1 shows the patient characteristics. 321 (88·4%) patients were male, 258 (71·1%) were homosexual or bisexual males, 52 (14·3%) were heterosexual, and 27 (7·4%) were intravenous drug users. Most of the patients, 270 (80·8%), were white. The median age at initial AIDS diagnosis was 35·5 years (range 7–68 years); the male patients were significantly older than the female patients (median ages 35·6 and 30·9, respectively, p=0·0002, Wilcoxon).

The median CD4 count (per mm³) at initial AIDS diagnosis, available for 233 patients (64·2%), was 73 (range 0–980). The median time between CD4 counts was one month (range 0·2–22). The patients for whom CD4 count at initial AIDS diagnosis was not available were from a different hospital, but were subsequently cared for at this centre. These patients were similar demographically to those for whom the initial diagnosis of AIDS was made at this centre.

268 patients (73·8%) used zidovudine. Of these, 118 (32·5%) were already using zidovudine when an initial AIDS diagnosis was made. 72 patients (19·8%) had never used zidovudine, and information on zidovudine use was not available for a further 23 (6·3%) patients. The median

	Relative risk of death (95% confidence interval)		Log* of adjusted relative risk
	Unadjusted	Adjusted*	
Mild disease	1·45 (1·18–1·79)	1·15 (0·97–1·47)	0·140
Severe disease	2·28 (1·94–2·68)	1·89 (1·58–2·25)	0·637
Very severe disease	7·63 (4·70–12·38)	6·35 (3·70–10·90)	1·848
Minimum CD4 count per 100/mm³ decrease†	2·56 (1·80–3·64)	1·88 (1·39–2·54)	0·631

*Natural logarithm. †Each relative hazard is adjusted for all other variables (mild, severe, very severe ADDs, CD4 count).

Table 2: **Results from Cox proportional hazards model**

total duration of zidovudine use was 22 months and did not differ by age, gender, exposure group, ethnic origin, or initial diagnosis. Those patients who commenced zidovudine before having an initial AIDS diagnosis had significantly lower CD4 counts (per mm³) at their initial AIDS diagnosis (median 49, range 0–460) than those who commenced zidovudine after their diagnosis (median 183, range 0–680, p=0·0005, Wilcoxon). The median CD4 count at which zidovudine treatment commenced, irrespective of whether this was before or after an initial AIDS diagnosis, was 95 (range 0–640).

Derivation of the scoring system

The relative risk obtained from fitting a Cox proportional hazards model to the data, shown in table 2, strongly indicated that the minimum CD4 lymphocyte count since AIDS (relative risk 1·88 per 100 cells decrease; 95% CI 1·39–2·54; p<0·0001) and the type and severity of ADDs were of independent importance for assessing risk of death—ie, they both provided substantial information on risk of death independent of each other. The risk of death increased by 15% (relative risk 1·15; 95% CI 0·97–1·47; p=0·09) for each mild condition experienced, by 89% (relative risk 1·89; 95% CI 1·58–2·25; p<0·0001) for each severe condition, and by 535% (relative risk 6·35; 95% CI 3·70–10·90; p<0·0001) when a very severe condition (ie, lymphoma) developed.

Models were also fitted in which the first ADD was distinguished from subsequent ADDs of each severity grouping. These indicated that, for example, a severe ADD increased the risk of death by approximately the same amount whether it occurred as the first, or subsequent ADD (data available from the author on request). For this reason we elected to concentrate on the simple model which merely counts the number of ADDs of each severity that have occurred.

The logarithm of the adjusted relative risks in table 2 were used to derive the score shown in table 3. The weighting factors for the three severity gradings of ADDs were derived by dividing the logarithm of the relative risks in table 2 by 0·0063 (the logarithm of the relative hazard for a drop in the minimum CD4 count of 100/mm³ was 0·63 [table 2]; therefore, the logarithm of the relative hazard for a drop in the minimum CD4 count of 1/mm³

Score	
300 per very severe diagnosis	
+ 100 per severe diagnosis	
+ 20 per mild diagnosis	
− minimum CD4 (/mm³) since AIDS	
Grading system	
AIDS Grade I	Score <0
AIDS Grade II	Score 0–99
AIDS Grade III	Score ≥100

Table 3: **The score and grading system**

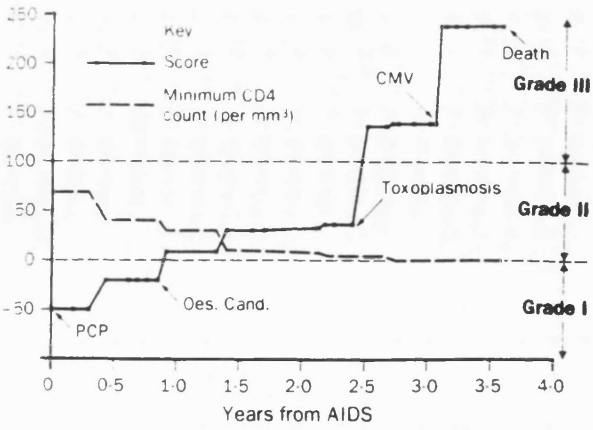

Figure: **Score after an AIDS diagnosis for one patient**

was calculated to be 0·0063) and rounding (ie, 300=1·85/0·0063, 100=0·64/0·0063, and 20=0·14/0·0063). The risk of death increased by 79% (relative risk 1·79; p<0·0001, 95% CI 1·58–2·02) per 100 unit increase in score. Other variables, such as zidovudine use, did not increase the predictive power of the score and therefore were not included. As some patients began their care at this centre after their initial AIDS diagnosis, a full history of CD4 counts was not available. For these patients, a score was not calculated until the first available CD4 measurement.

Using the score to define the AIDS grades

We defined AIDS Grade I as a score below zero, AIDS Grade II as a score between zero and 100 and AIDS Grade III as a score above 100. It should be noted that patients' scores, and hence their grades, cannot become lower over time because the minimum CD4 count since the diagnosis of AIDS, rather than the latest CD4 count, is used in the score. The score was updated each time a new CD4 count became available or the patient experienced a new ADD to reassess the risk of death. Figure 1 shows the increase in score for one patient, calculated each time a new CD4 count became available. At an initial AIDS diagnosis of PCP, the patient's score was −50. One mild condition had been experienced and the CD4 count was 70/mm³ (score=[300×0]+[100×0]+[20×1]−70=−50). It followed that the patient would be classified as Grade I. New CD4 counts at months three and four did not fall below 70/mm³; thus the score and grade remained unchanged. A CD4 level of 40/mm³ five months after an initial AIDS diagnosis resulted in an updated score of −20 (score=[300×0]+[100×0]+[20×1]−40=−20). However, the patient was still categorised as AIDS Grade I because the score remained below zero. A CD4 count of 30/mm³ after 11 months, together with the occurrence of oesophageal candidiasis, a mild diagnosis, changed the score to +10 and the patient moved to AIDS Grade II (score=[300×0]+[100×0]+[20×2]−30). At 28 months, the occurrence of a new ADD, toxoplasmosis, which is classified as a severe condition, added a further 100 to the score. The patient's minimum CD4 count also dropped to 3 mm³. Thus the patient moved to Grade III (score=[300×0]+[100×1]+[20×2]−3=137). The patient suffered a further severe ADD (cytomegalovirus) at 37 months, which again increased the score by 100 points, and the patient died a few months later.

Score	<0 AIDS Grade I	0–99 AIDS Grade II	100 AIDS Grade III
Person-years at risk	[illegible]	[illegible]	[illegible]
Deaths	[illegible]	[illegible]	[illegible]
Death rate (per 10 person-years)	[illegible]	[illegible]	[illegible]

Table 4: **Death rates in Royal Free Hospital Study Cohort**

Score	<0 AIDS Grade I	0–99 AIDS Grade II	100 AIDS Grade III
Person-years at risk	328·5	579·6	361·3
Deaths	65	229	322
Death rate (per 10 person-years)	0·8	4·0	8·9

Table 5: **Death rates in validation cohort: Chelsea and Westminster Hospital**

The number of person-years, the number of deaths experienced and the rate of deaths in each of the AIDS Grades are shown in table 4. The number of person-years contributed by the patient illustrated in figure 1 was 0·83 years (10 months) in AIDS Grade I, 1·5 years (18 months) in AIDS Grade II, and 1·25 years (15 months) in AIDS Grade III. The death of this patient occurred in AIDS Grade III, and so was allocated to this Grade. As would be expected, the gradient of increasing risk of death through the different grades of AIDS is strong.

Testing of the system on independent groups of AIDS patients

The score was then validated on a much larger group of patients from another hospital (St Stephen's Clinic, Chelsea & Westminster Hospital). A total of 3131 ADDs have been diagnosed in 1230 AIDS patients in whom the CD4 count was measured at least once. The relation between the score and the risk of death was highly statistically significant; the relative risk associated with an increase in the score of 100 points was 1·86 (1·75–1·97). The person-years of experience and death rates calculated in AIDS grades I, II, and III are shown in table 5.

The score and staging system were also validated on a separate cohort of AIDS patients from the Royal Free Hospital Haemophilia cohort.[15] Although a much smaller number of patients in this cohort have AIDS (31 patients in whom the score could be evaluated), the relation between the score and risk of death was again highly significant. The relative risk associated with an increase in the score of 100 points was 1·83 (1·31–2·57). The person-years of risk and the death rates calculated in AIDS grades I, II, and III are shown in table 6.

Discussion

This study formally confirmed the strong clinical impression that the risk of death after an initial AIDS diagnosis increases as more new diseases occur. Until now there has been uncertainty as to whether the CD4 count remained important for assessing patient risk of death once information about ADDs was accounted for. Many clinicians discontinue measurement of CD4 counts after AIDS diagnosis. It is important, therefore, to note that our study showed that CD4 counts remain an independent predictor of survival throughout the lifetime of AIDS patients. We have used this new information together with estimates of survival from the AIDS in Europe study,[1] to derive a staging system for patients with AIDS. The staging system has the attributes of a useful clinical staging system:[24] it is based on an objective criteria (risk of death); it places patients in a single category at any given point in time; it does not allow patients to move from a higher to a lower grade and each grade carries a risk of death which is substantially different from the risk of death in adjacent grades (tables 4, 5, and 6). Furthermore, the grading system was independently tested on two different groups of AIDS patients. The results obtained were remarkably consistent. The first validation took information from 1230 AIDS patients with more than 1700 patient-years of follow-up, whereas the second patient group was comparatively small and drawn from a different risk group, male patients with haemophilia who had different ADDs.

Further variables were added to the score to determine if their addition resulted in a score which more accurately reflected the risk of death, but none was identified. In particular, use of zidovudine, included as a time-dependent covariate to remove the bias that patients who lived longest had more opportunity to receive zidovudine, did not lead to an improved score. Age at initial AIDS diagnosis marginally improved the fit of the model ($p=0·049$, log-likelihood test), but was not included in the final score, as we wished this to reflect the stage of disease only. Age would have to be considered as a covariate, albeit a minor one, when using the score. For example, if the AIDS Grades were used as entry criteria for a clinical trial, stratification at enrolment by age may be appropriate. In a clinical situation a patient aged 50 would expect to have a slightly poorer prognosis than a patient aged 20 with the same score, or who belonged in the same grade.

This study used ADDs diagnosed according to the 1987 CDC criteria. In 1993, these criteria were revised to incorporate additional ADDs.[22] New information on the severity of the additional ADDs will become available only as time progresses. On the basis of current clinical impression, recurrent bacterial pneumonia and pulmonary tuberculosis should probably be classified as mild ADDs, according to our severity groupings. Currently, invasive cervical carcinoma is a rare phenomenon. Those that occur should be classified as a severe diagnosis.

The score was constructed by taking the minimum CD4 count recorded since AIDS diagnosis. This action ensured that it was not possible to have a decreasing score, or to move to a lower AIDS grade. For a disease such as AIDS, which is currently fatal, we thought this was the most appropriate approach. Although CD4 measurements are subject to a great deal of variation,[15,25] different CD4 measures (ie, latest count available, mean of last two, three, or five measurements) changed the score and the rates of death in different grades only marginally (data not shown).

Score	<0 AIDS Grade I	0–99 AIDS Grade II	100 AIDS Grade III
Person-years at risk	19·3	33·2	11·4
Deaths	2	9	12
Death rate (per 10 person-years)	1·1	2·7	10·5

Table 6: **Death rates and validation cohort: Royal Free Hospital Haemophilia Cohort**

This staging system is based on the clinical appearance of opportunistic disease. With the development of more effective treatment strategies for life-threatening severe ADDs it may be appropriate to reclassify certain AIDS diseases as mild instead of severe at some time in the future. A further issue is that the proposed staging system does not account for disease-specific prophylaxis. Such prophylaxis is increasingly being used to prevent opportunistic infections. We assessed the effect of PCP prophylaxis but did not find an independent effect on mortality once other factors in the score were accounted for (data not shown). If disease-specific prophylaxis reduces the risk of death then it does so via its ability to prevent the disease in question. Since in our score/staging system we are accounting for whether or not the disease occurs, prophylactic treatment is not directly relevant.

Previous studies[1-9] have concentrated on fixed factors, such as transmission category, gender, and initial AIDS diagnosis, to study survival. The relative risks obtained from our data concur with those from earlier studies regarding disease severity where the relative risks were higher in those with more severe diagnoses. Although these studies have provided important information about the natural history of the disease, we should appreciate that AIDS is a dynamic disease, and risk of death will depend on factors that change after the initial diagnosis is made. Few studies have measured CD4 counts after an initial AIDS diagnosis as regularly as in this group of patients, or collected information on all ADDs. This study has used both of these, in a cohort of patients seen by one consultant at one healthcare establishment. Consequently, diagnosis of ADDs, treatment, access to care, and treatment policies have been standardised as far as possible.

This grading system has a clear application in clinical trials where there is a need for a means of classifying stages of AIDS on the basis of a firm, objective criterion, such as risk of mortality.[10-12] The grading system could be used for defining entry criteria, endpoint criteria, or both. For example, classification in AIDS Grade III could be an appropriate entry criteria for some trials of late interventions, with mortality as the endpoint. In other trials it might be appropriate to use an AIDS grading, together with death, as an endpoint. Concern that progression to AIDS is an unsuitable endpoint in some trials[12] recruiting AIDS-free patients, could be at least partly addressed by using AIDS Grade II or III (combined with mortality) as the endpoint. It would also be possible to use the raw score that we have derived—without classifying into grades—as an endpoint in some trials. These approaches could shorten the duration of some clinical trials. Use of AIDS Grade II or III or the score as an endpoint in a trial might be criticised as it incorporates the CD4 count as well as clinical disease. Use of the CD4 count in this way has been questioned.[24-26] We have shown that relatively small changes in CD4 count are as important for determining risk of death as the occurrence of certain more minor ADDs (table 2), that are currently accepted as suitable endpoints.

Resource allocation and planning might also benefit from the adoption of our proposed grading system. The cost of patient care may vary substantially between the three grades shown. Knowledge of the numbers of patients in each of these AIDS grades, together with an expectation of future survival times, would give a more detailed picture of resources required than could be gained from knowing the total number of patients with AIDS. Similarly the grading system would help in certain surveillance exercises, where a more detailed picture of AIDS patients is required.

In summary, we have developed a grading system for AIDS patients that may represent a valuable aid to patient management, clinical trial design, surveillance, and clinic resource allocation.

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Angiomagnetic resonance imaging of iliofemorocaval venous thrombosis

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Summary

Although magnetic resonance imaging has been proposed for the diagnosis of deep venous thrombosis (DVT), its role in diagnostic strategy remains to be defined.

We compared prospectively magnetic resonance angiography (MRA) with two-dimensional time-of-flight with contrast venography (CV) and colour duplex sonography (CDS) in 25 patients with DVT of the pelvis confirmed by CV. All patients were examined by CV (gold standard) and MRA and 17 by CDS. These studies were compared for DVT diagnosis in the pelvis and inferior vena cava and analysis of thrombotic spread. MRA was positive in 25 patients whose DVT was diagnosed by CV (100% sensitivity). MRA sensitivity and negative predictive value were 100%, specificity 98·5% and positive predictive value 97·5% for the diagnosis of thrombosis at each anatomic level. There were discrepancies between MRA and CV (2 false-positive results for 2 venous segments) and between CDS and CV (2 false-positive and 3 false-negative results). CV was uninterpretable for 8·8% of segments and CDS was often technically limited to the pelvic level, whereas all venous segments explored were analysable in MRA. MRA gave excellent results for positive diagnosis and DVT spread. MRA is a potentially valuable technique for assessing iliofemorocaval venous thrombosis.

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Introduction

Doppler ultrasound is now used when deep venous thrombosis (DVT) is first suspected. This examination has a sensitivity of 95% and a specificity of 98% for femoropopliteal DVT.[1] However, the iliocaval area is not easily accessible to doppler ultrasound.[2] Thus, in case of doubt about the presence of a clot in any anatomic region, contrast venography (CV) is done. Although CV has been accepted as the diagnostic gold standard because of its accuracy, it causes the patient discomfort and may be responsible for adverse effects in at-risk patients, such as those with nephrotoxicity and allergy.[3] Contrast medium is irritating to the venous endothelium and has been implicated as a cause of post-venography DVT. Moreover, incomplete venous filling and the impossibility of puncturing the dorsal foot vein during CV have led to inadequate studies in 5% of cases.[4]

In magnetic resonance imaging (MRI), DVT features have been reported with spin-echo MRI,[5,6] gradient-echo MRI,[7,8] and comparative spin-echo and gradient-echo MRI.[9,10] Erdman et al,[5] found that MRI revealed DVT with a sensitivity of 90% and a specificity of 100% in 36 patients. In 26 patients with DVT, Spritzer et al[6] showed a sensitivity of 100% and a specificity at 92·9% for gradient-echo MRI. Arrivé[10] used combined spin-echo and gradient-echo MRI and found a specificity of 95% and a sensitivity of 82%. MRI seems to provide excellent diagnostic accuracy for thrombosis.

The role of MRI in DVT diagnostic strategy remains to be defined. We compared magnetic resonance angiography (MRA) with two-dimensional time-of-flight CV and colour duplex sonography (CDS) in 25 consecutive patients with DVT in the pelvis to evaluate the usefulness of MRA compared with conventional examinations.

Patients and methods

25 patients (9 male, 16 female; mean age 60 years, range 20–85) with pelvic DVT were included. All were examined by CV and MRA, 17 had CDS. The interval between MRI and venography ranged from 0 to 8 days (mean: 3 days). All patients were on

Anti-herpesvirus treatment and risk of Kaposi's sarcoma in HIV infection

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Objective: With the recent identification of a new herpesvirus in patients with Kaposi's sarcoma (human herpesvirus-8 or Kaposi's sarcoma-associated herpesvirus), there have been several reports on the use of anti-herpesvirus therapy (foscarnet, ganciclovir and aciclovir) and risk of developing Kaposi's sarcoma. We therefore investigated the association between use of anti-herpesvirus drugs and Kaposi's sarcoma in a large unselected group of patients with AIDS.

Patients and methods: We studied a group of HIV-positive patients at the Chelsea and Westminster Hospital, for whom details on all AIDS-defining diagnoses made during follow-up, treatment and regular CD4 counts were available. Cox proportional hazards models with time-dependant covariates were used to assess the association between treatment with aciclovir, foscarnet and ganciclovir and risk of Kaposi's sarcoma.

Results: A total of 3688 patients have been followed up for a median period of 4.2 years, during which time 598 patients (16.2%) developed Kaposi's sarcoma. After adjustments for sex, exposure category, age, treatment with antiretrovirals or *Pneumocystis carinii* pneumonia prophylaxis, the development of AIDS-defining conditions (including separate adjustment for the development of cytomegalovirus and herpes simplex virus) and CD4 count, there was a decreased risk of developing Kaposi's sarcoma with foscarnet [relative hazard (RH), 0.38; 95% confidence interval (CI), 0.15–0.95; $P = 0.038$] and with ganciclovir (RH, 0.39; 95% CI, 0.19–0.84; $P = 0.015$), but not with aciclovir (RH, 1.10; 95% CI, 0.88–1.38; $P = 0.40$).

Conclusions: These results suggest that both foscarnet and ganciclovir may have some activity in preventing the occurrence of Kaposi's sarcoma, but that aciclovir has no benefit. Further studies of the effect of these drugs on the risk of Kaposi's sarcoma is warranted.

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Keywords: Kaposi's sarcoma, disease progression, foscarnet, ganciclovir, aciclovir

Introduction

Kaposi's sarcoma (KS) was first described by Moritz Kaposi, a Hungarian dermatologist, in 1872, and in its classical form this rare lesion appears as a pigmented sarcoma usually appearing on the lower legs of predominantly older Jewish and Eastern European men [1]. In 1980, the first cases of KS in young homosexual men heralded the arrival of AIDS-associated KS [2]. In contrast to classical KS, AIDS-associated KS has an aggres-

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sive course, and up to 50% of patients have lymph-node or gastrointestinal involvement at the time of diagnosis [3].

The identification of a new herpesvirus (human herpesvirus-8 or KS-associated herpesvirus (KSHV)) as a possible causal factor in the development of KS [4–7] has led to analyses aimed at assessing whether the use of drugs active against herpesviruses can prevent the development of KS. Jones *et al.* [8] used a Cox proportional hazards model to determine the association between aciclovir, ganciclovir and foscarnet and the subsequent risk of KS in a large US follow-up study based on medical records. They found a significantly reduced risk of developing KS associated with the use of foscarnet, but not with aciclovir or ganciclovir, after adjustment for CD4 lymphocyte count, age, race, sex, exposure group, other AIDS opportunistic illnesses and antiretroviral treatment. In contrast, a similar analysis from France found no reduced risk with any of the three drugs [9]. Surprisingly, both studies found a significantly increased risk of KS associated with use of aciclovir. A further study from the Multicentre AIDS Cohort Study found a reduced risk of KS among patients treated with foscarnet or ganciclovir, but the result was not significant [10].

In this study, we provide further evidence on this important issue with an analysis of the risk of KS among 3688 patients followed at the Chelsea and Westminster Hospital in London. We also identify several issues relating to the way in which the analysis is performed which could help to explain apparent inconsistencies with and between the previous studies.

Patients and methods

Patients

All HIV-positive patients seen at the Chelsea and Westminster Hospital between July 1985 and 31 July 1995 (the cut-off date for this analysis) were included in this study if they did not have a diagnosis of KS either at their initial visit or within 1 month of this first visit. AIDS was diagnosed according to the classification in use at the time, and thus patients have not been retrospectively diagnosed with AIDS. Diagnoses made after 1993 are diagnosed according to the 1993 revised clinical criteria from the Centers for Disease Control and Prevention [11]. Patients with no clinical diagnosis and a CD4 lymphocyte count of below 200×10^6/l are not included as AIDS patients. Demographic data, clinical events and treatment are recorded and maintained on a database system which is regularly updated. Dates of stopping treatment are not recorded and all analyses presented consider only whether a patient has ever started treatment, consistent with an intention-to-treat analysis. CD4 counts were measured at regular intervals on these patients and added to the database.

Treatment policies

Currently, no patients are offered primary prophy for cytomegalovirus (CMV). Patients with diagn CMV syndromes are treated with foscarnet 90 mg twice daily for 14–21 days or ganciclovir 5 mg/kg tv daily. Treatment for gastrointestinal CMV diseas stopped once a patient has recovered, but secondary p phylaxis is usually given for CMV retinitis with foscar 90 mg/kg once daily, or with ganciclovir 5 mg/kg o daily, 5–7 days per week. From 1994, patients have b given 1 g oral ganciclovir daily for secondary prop laxis. All patients with recurrent herpes infections treated with aciclovir 400 mg twice daily, and all patie are offered aciclovir 400 mg twice daily when their C cell count drops below 100×10^6/l, as a possible effect the suppression of herpesviruses may occur [12]. Patie who participated in a primary prophylaxis study of hig dose aciclovir were given the option of remaining on t study medication.

Statistical methods

A Cox proportional hazards model was used to assess th association between the use of aciclovir, foscarnet ar ganciclovir and the risk of developing KS. The surviv time for each patient was measured as the time fror their initial visit to the Chelsea and Westminster Hospi tal until the development of the first KS lesion, las patient visit, death, or 31 July 1995, whichever occurre first. Treatment with aciclovir, ganciclovir and foscarnet together with antiretrovirals and *Pneumocystis carini* pneumonia (PCP) prophylaxis, was fitted as a time-dependent covariate taking the value '0' until a patient started treatment and remaining at '1' thereafter. The CD4 lymphocyte count was also fitted as a time-dependent covariate. In common with previous analyses with AIDS as endpoint [13,14], it was found that a logarithmic transformation of the CD4 lymphocyte count provided a better fitting model. We also adjusted for the occurrence of other AIDS-associated illnesses. In particular, the occurrence of CMV disease or herpes simplex virus (HSV) disease were fitted separately, again as time-dependent covariates, taking the value '0' before the occurrence of disease and '1' thereafter.

All analyses were performed using SAS statistical software [15]. Tests of the significance of the variables included in the Cox proportional hazard models were performed using the Wald test. Tests of the proportional hazards assumption found no evidence of non-proportionality.

Results

A total of 3688 patients have been followed up for a median period of 4.2 years (range, 0.1–10.0 years), during which time 598 patients (16.2%) developed KS. CMV disease was diagnosed in 510 patients (13.8%). Of these, 296 patients were diagnosed with retinitis, 324

Table 1. The relative hazard of Kaposi's sarcoma associated with the use of anti-herpesvirus therapy.

	Univariate model		Multivariate model	
	RH (95% CI)	*P*	RH (95% CI)	*P*
Age (10-year increase)	1.39 (1.27–1.52)	0.0001	1.00 (0.90–1.13)	0.94
Female	0.11 (0.04–0.39)	0.0002	0.10 (0.02–0.49)	0.0048
Homo-/bisexual	3.50 (1.93–6.35)	0.0001	1.15 (0.51–2.58)	0.74
CMV diagnosis	5.74 (4.36–7.55)	0.0001	1.67 (1.19–2.34)	0.0033
HSV diagnosis	6.49 (3.56–11.83)	0.0001	1.68 (0.89–3.14)	0.11
Other AIDS diagnosis	5.79 (4.92–6.82)	0.0001	1.30 (1.02–1.64)	0.031
Antiretroviral treatment	3.04 (2.56–3.60)	0.0001	1.01 (0.80–1.27)	0.94
PCP prophylaxis	4.01 (3.37–4.77)	0.0001	1.42 (1.10–1.82)	0.0065
CD4 count*	1.75 (1.66–1.84)	0.0001	1.58 (1.47–1.71)	0.0001
Aciclovir	2.64 (2.18–3.19)	0.0001	1.10 (0.88–1.38)	0.40
Foscarnet	2.15 (0.89–5.21)	0.089	0.38 (0.15–0.95)	0.038
Ganciclovir	2.62 (1.30–5.28)	0.0070	0.39 (0.19–0.84)	0.015

*Relative hazard is per log-unit decrease in CD4 count. RH, Relative hazard; CI, confidence interval; CMV, cytomegalovirus; HSV, herpes simplex virus; PCP, *Pneumocystis carinii* pneumonia.

patients were diagnosed with gastrointestinal disease, and 110 patients had a diagnosis of both. A much smaller number of patients were diagnosed with HSV: 46 patients (1.2%). The majority of the patients were men (n = 3487; 94.5%) and homosexual or bisexual (n = 3409; 92.4%). The median age at first visit was 30.2 years (range, 14.6–67.3 years), and the men were significantly older than the women (median ages of 30.4 and 27.1 years, respectively; $P < 0.0001$, Wilcoxon). The median CD4 count at initial visit was 288×10^6/l (range, 0–2520×10^6/l), which did not vary significantly according to sex or exposure category. During follow-up, 2349 patients (63.7%) had at least one CD4 lymphocyte count below 200×10^6/l, 1899 (51.5%) had a CD4 count below 100×10^6/l and 1592 (43.2%) had a CD4 count below 50×10^6/l.

During patient follow-up 1650 patients (44.7%) were treated with aciclovir, 132 (3.6%) were treated with foscarnet but not ganciclovir, 201 (5.5%) with ganciclovir but not foscarnet, and 77 patients (2.1%) were treated with both ganciclovir and foscarnet. Generally, patients were treated with aciclovir at an earlier stage before treatment with either ganciclovir or foscarnet began. Seventeen patients took foscarnet before aciclovir, and 16 patients took ganciclovir before aciclovir. A large proportion of patients were also treated with antiretrovirals and PCP prophylaxis; 1930 patients (52.3%) were treated with antiretrovirals, of which the majority were treated with zidovudine (n = 1879). A slightly lower proportion (n = 1744; 47.3%) started PCP prophylaxis during follow-up.

Table 1 shows the relative hazard (RH) of developing KS associated with each of the three anti-herpesvirus drugs, along with CD4 lymphocyte count, use of antiretroviral therapy and PCP prophylaxis, age, exposure group, sex, previous CMV disease, previous HSV disease and any other previous AIDS-defining diseases. The RH are shown with and without mutual adjustment. After adjustment, it can be clearly seen that treatment with either foscarnet [RH, 0.38; 95% confidence interval (CI), 0.15–0.95] or ganciclovir (RH, 0.39; 95% CI, 0.19–0.84) was associated with a significantly lower risk of subsequently developing KS. A low CD4 count was, as expected, strongly associated with the risk of KS.

These analyses were repeated considering only homosexual and bisexual men, and only considering patients who were first seen after 1990 when the methods used for the collection of routine data such as these were changed. Analyses were also repeated excluding patients who were seen prior to foscarnet becoming available in 1987 and the launch of ganciclovir in October 1988, and by separately modelling CMV gastrointestinal disease and CMV retinitis, which may involve different lengths of treatment. In all cases results were similar to those presented above (data not shown).

Although not all patients who developed CMV disease were treated, foscarnet and ganciclovir were highly correlated with CMV disease, which may lead to a problem of multicollinearity. This occurs when the model cannot separately estimate the effect of treatment with foscarnet and ganciclovir and the development of CMV disease, because they are highly correlated. To address this problem, we looked at the risk of developing KS after treatment with ganciclovir or foscarnet (modelled as a single variable). We adjusted for the development of AIDS as a time-dependent covariate, but with no separate adjustment for CMV disease. The relative risk of developing KS associated with treatment in this model was 0.39 (95% CI, 0.20–0.73; $P = 0.004$).

A further issue was that patients who reach a certain stage of HIV disease may no longer be at risk of developing KS. For example, it may be that a patient infected with KSHV will develop KS at a particular level of immunodeficiency. If KS does not develop during patient follow-up it may indicate that this patient was not infected with KSHV. This scenario was extremely unlikely given that the risk of developing KS continued to increase as the CD4 lymphocyte count decreased (Table 1). A further model, which included the untrans-

formed CD4 lymphocyte count as a time-dependent categorical variable (> 200, 101–200, 51–100 and ≤ 50×10⁶/l), showed that the risk of KS in patients with a CD4 count of 50×10⁶/l or less was over twice that of patients with a CD4 count of 51–100×10⁶/l (RH, 2.11; 95% CI, 1.66–2.70; $P = 0.0001$). As in the other models, treatment with either foscarnet or ganciclovir was associated with a significantly reduced risk of KS (RH, 0.39; 95% CI, 0.21–0.75; $P = 0.005$).

Table 2. The relative hazard of Kaposi's sarcoma associated with the use of anti-herpesvirus therapy: an alternative modelling strategy.

	Multivariate model	
	RH (95% CI)	*P*
Age (10-year increase)	0.96 (0.86–1.08)	0.51
Female	0.10 (0.02–0.52)	0.0057
Homo-/bisexual	1.15 (0.51–2.59)	0.73
AIDS diagnosis	1.41 (1.14–1.75)	0.0018
Antiretroviral treatment	0.86 (0.68–1.07)	0.18
PCP prophylaxis	1.14 (0.89–1.45)	0.31
CD4 count*	1.71 (1.53–1.86)	0.0001
Aciclovir	1.21 (0.96–1.51)	0.11
Foscarnet	0.54 (0.22–1.35)	0.19
Ganciclovir	0.68 (0.33–1.40)	0.29

*Relative hazard is per 100×10⁶/l drop in CD4 count. RH, Relative hazard; CI, confidence interval; PCP, *Pneumocystis carinii* pneumonia.

We also repeated our main analysis without adjusting for CMV and HSV disease separately from other diseases and fitting the unlogged CD4 count to investigate the extent to which these changes in the modelling process could alter the results. All variables, with the exception of sex, age and exposure category, were fitted as time-dependant covariates in the same way as described above. The adjusted RH are shown in Table 2. Here, the RH of the CD4 count can be interpreted as the risk of developing KS associated with each 100×10⁶/l drop in the CD4 count after adjustment for all other variables. Using this alternative model would appreciably alter our conclusions; foscarnet and ganciclovir are associated with a lower risk of developing KS (RH, 0.54 and 0.68, respectively), but the result is no longer significant.

Discussion

Results from this analysis suggest that both foscarnet and ganciclovir may have activity in preventing the occurrence of KS in HIV infection, but that aciclovir has no effect. Our findings on foscarnet are consistent with those from Jones *et al.* [8] who found a RH of 0.3 (95% CI, 0.1–0.6), but not with those from Costagliola *et al.* [9] who obtained a RH of 1.36 (95% CI, 0.40–2.37). In contrast to our study, both studies found no association between ganciclovir use and risk of KS. The differences in results from different studies may lie, in part, in the way in which the analysis was performed. All three studies have followed patients with a wide initial range of CD4 count, the presence of CMV, HSV or any other AIDS diagnosis is naturally positively associated with a higher risk of KS, since they tend to occur at low CD4 counts [16]. This means that foscarnet and ganciclovir use are associated with a raised risk of KS, as can be seen in the univariate analysis in Table 1. The multivariate analysis attempts to remove this confounding due to disease stage by adjusting for the patients' stage of disease through the CD4 lymphocyte count and diagnosis of AIDS-defining diseases. After this adjustment in our analysis the potential preventive effect of the therapy was revealed. If the adjustment for stage of disease is inadequate, then this potential preventive effect would remain masked. The analysis in Table 2 indicates how an analysis where the CD4 count was fitted as an unlogged variable and CMV and HSV diseases were not fitted separately leads to estimates of treatment effects closer to one (i.e., no effect). The reduced RH shown in Table 2 are consistent with those of Glesby *et al.* [10], who showed a non-significant reduction in risk of 0.56 with ganciclovir (95% CI, 0.22–1.44) and 0.40 with foscarnet (95% CI, 0.05–3.10). Given the brevity of reports from the other studies, it is not possible to tell how much these considerations could affect their findings [9,10].

Our study has the benefit of a considerably longer follow-up period, and that the dates of all AIDS-defining illnesses and treatment were routinely recorded. All the patients were cared for at a single institution, so treatment policies and access to care were relatively uniform. Our findings of a reduced risk of KS after treatment with foscarnet and ganciclovir, both anti-herpesvirus treatments, add weight to the argument that a human herpesvirus is associated with the development of KS. We found no reduced risk of KS in patients who were treated with aciclovir, and this may be due in part to the routine use of aciclovir to treat recurrent herpes infections and subsequent resistance.

In conclusion, our study has shown that patients treated with either foscarnet or ganciclovir are at a reduced risk for the development of KS. There is a potential for confounding of treatment and disease, because patients who develop CMV disease are likely to be those who are treated with ganciclovir or foscarnet. However, for this confounding to explain our findings, those patients with CMV disease would have to be at a lower risk of KS compared with those patients without CMV disease but with similar CD4 lymphocyte counts. In addition, it should be remembered that this study was retrospective and not one of randomized treatments, and thus lacks the power that a randomized study of anti-herpesvirus treatment would have. As Costagliola *et al.* [9] remind us, none of these analyses are of randomized comparisons, so caution is required in their interpretation.

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Appendix

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