Mmed thesis on the

SURVIVAL OF SOUTH-AFRICAN HIV INFECTED PATIENTS

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DECLARATION

DECLARATION

I, Frank A. Post, hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise), and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the University of Cape Town to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

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PUBLICATIONS IN PEER-REVIEWED JOURNALS THAT HAVE ARISEN FROM THE RESEARCH PRESENTED IN THIS THESIS

Pulmonary tuberculosis in HIV infection: radiographic appearance is related to CD4+ T-lymphocyte count. *Tubercle and Lung Disease* 1995;**76**:518-521.

Total lymphocyte count as a surrogate for CD4+ Lymphocyte count in African patients co-infected with HIV and Tuberculosis. *J Acquir Immunodef Syndr* 1996;**11**:411-412 (short report).

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HIV infection is not associated with an increased rate of drug-resistant tuberculosis. *South African Medical Journal* 1997;**87:**903 (short report).

Acquired immunodeficiency syndrome in Africa: survival according to AIDS defining event (in press).

Tuberculous pleural effusions in HIV positive patients (in press).

CONTENTS

SYNOPSIS

In sub-Saharan Africa, resource-limitation results in scarce availability of HIV prognostic tools such as $CD4^+$ T-Lymphocyte (CD4) count and HIV viral load. To facilitate counselling and clinical decisions in this setting, widely available and inexpensive markers of prognosis are required.

Chapter one gives an overview of the epidemiology and pathophysiology of HIV infection (with particular reference to sub-Saharan Africa), and its clinical manifestations. Staging systems for HIV infection and aspects of management in resource-poor environments are briefly discussed.

Chapter two describes the epidemiological, pathophysiological and clinical aspects of tuberculosis (TB) in HIV infected patients, the commonest opportunistic infection in sub-Saharan Africa. It further provides HIV and TB prevalence data from the Western Cape, South Africa.

In *chapter three* a study is presented demonstrating the usefulness of the total lymphocyte count (TLC) in combination with the World Health Organisation (WHO) clinical staging system to predict outcome in 831 HIV positive patients.

A TLC of 1250/μL was found to be the equivalent of a CD4 count of 200/μL. Patients with early HIV disease (WHO stage 1 & 2) had low annual rates of progression to AIDS : 3-4% if the TLC was above 1250/μL, 12-14% if the TLC was below 1250/μL. Annual progression to AIDS increased to 25% and 46% in patients with clinical stage 3 and a TLC above or below 1250/μL respectively. Patients with AIDS had 30-55% one-year mortality rates depending on the TLC.

Chapter four illustrates that pulmonary tuberculosis (PTB) in HIV infected patients presents with a radiographic spectrum reflecting the degree of HIV induced immune suppression. Chest radiographs and pre-treatment total lymphocyte counts provide prognostic information.

Upper zone cavitatory infiltrates typical of reactivation PTB were associated with a preserved CD4 count (mean 389/μL) and predicted a 100% two-year survival. Pleural effusions were associated with a mean CD4 count of 184/μL and predicted 65% two-year survival. Patients with atypical radiographic presentation, including lower and mid-zone infiltrates, hilar and mediastinal adenopathy or interstitial patterns, had low CD4 counts (mean 105/μL) and a 36% survival at two years.

Rather than classifying every patient with pleuro-pulmonary tuberculosis as WHO stage 3, incorporation of the prognostic value of the chest radiograph into the clinical staging system, such that typical reactivation PTB becomes stage 2, tuberculous pleural effusion stage 3 and atypical PTB stage 4, would enhance the prognostic accuracy of HIV related tuberculosis.

Chapter five demonstrates that patients with AIDS could be categorized according to one of three survival patterns, relating to the type of opportunistic illness. One-year survival rates were highest for extra-pulmonary tuberculosis

and herpes simplex virus infection (70%); intermediate for oesophageal candidiasis, cryptococcal meningitis, kaposi sarcoma and pneumocystis carinii pneumonia (45%); and poorest for the HIV wasting syndrome, AIDS-dementia complex and performance status 4 (20%). Despite the overall poor prognosis associated with the acquired immunodeficiency syndrome, a substantial proportion of patients survive, even in the absence of anti-retroviral therapy, for a number of years.

Chapter six concludes by proposing how the data presented in this thesis could be used in the clinical management of patients with HIV infection in a resource limited environment.

CHAPTER ONE

HIV INFECTION: THE AFRICAN PERSPECTIVE

1a INTRODUCTION

In 1981, an outbreak of Pneumocystis carinii pneumonia (PCP) and Kaposi sarcoma (KS) was described in American male homosexual patients [1,2]. These previously healthy men were noted to have very low numbers of circulating helper-T-lymphocytes [3]. The $CD4^+$T-lymphopenia rendered these patients susceptible to a wide spectrum of infections and malignancies.

In 1983, a virus to be classified among the lentivirus family of retroviruses, was identified as the agent responsible for the gradual $CD4^+$T-cell depletion [4,5]. This virus subsequently was renamed human immunodeficiency virus (HIV) type 1, and the clinically manifested susceptibility to opportunistic infections labelled acquired immunodeficiency syndrome (AIDS). It appeared that following seroconversion, HIV infection was characterized by a prolonged period of clinical latency prior to the onset of opportunistic infections and AIDS.

Although the initial epidemic was recognized in homosexual men in the United States, the majority of patients in resource-poor countries acquired HIV infection via heterosexual transmission. The number of HIV infected patients worldwide was estimated to have reached 30.6 million by late 1997, the majority of cases (approximately 20.8m) were living in sub-Saharan Africa [6]. Most African countries have reported a rise in HIV seroprevalence throughout the 1990's, and the projected cumulative figure for Africa is 40 million by 2000. HIV infection was also rapidly spreading through Asia, whereas the HIV epidemic appeared to have stabilized in the developed world [7].

A second human T-cell lymphotropic virus associated with the acquired immunodeficiency syndrome was first described in west Africa, and is now

known as HIV-2 [8]. Human immunodeficiency virus type 2 infection is rare outside the West-African region, and compared to HIV-1 less transmissible, associated with a lower rate of progression to AIDS and a lower mortality [9]. Over 10 subtypes of HIV-1 infection have been described since its discovery, and are categorized according to the degree of difference in their *env* coding region as major (M; up to 30% variance) or outlier (O, approximately 50% structural homology) [10]. The majority of HIV-1 infected individuals in sub-Saharan Africa carry subtype A, whereas in South Africa the dominant subtypes are C in heterosexually transmitted cases and subtype B in homosexually acquired infections [11]. The clinical implications of infection with particular subtypes of HIV, particularly the sensitivity of diagnostic tests, long-term response to anti-retroviral therapy and specificity of protection afforded by future vaccines remains unclear [10].

By 1990, the HIV prevalence in the general population of many African countries had reached 1-10%. Higher seroprevalence rates were reported in selected individuals such as young, sexually active persons and hospitalized patients (up to 30%) or sexually transmitted diseases (STD) clinic attendees, truck drivers and prostitutes (up to 60%). HIV incidence rates ranged from approximately 1% in the general population to more than 20% in the highest risk groups [12]. Consequently, health services in many African countries became overwhelmed with HIV positive patients, and HIV/AIDS a major cause of death in hospitalized patients. HIV infection also became an important cause of loss of productive work force, and by depriving elderly of their support system and causing children to become orphans, a contributor to socio-economic disintegration [13].

The principle mode of HIV transmission in sub-Saharan Africa is heterosexual intercourse. In this light, the high prevalence of STD's in Africans may have contributed to the rapid transmission of HIV throughout Africa [14]. In the absence of a cure for HIV infection, interventions aimed at the reduction of HIV transmission have been emphasized. These include the counselling of individuals at risk of acquiring HIV infection regarding HIV/AIDS, high risk sexual behaviour and the use of condoms, and the treatment of STD's [15]. Although successful in having increased the awareness of AIDS, these measures have not been able to prevent the spread of HIV infection amongst millions of Africans. Other interventions, such as the reduction of vertical transmission by administration of anti-retroviral therapy to pregnant women, have remained too expensive for most African countries. A significant reduction in HIV related morbidity and mortality in sub-Saharan Africa may only be realizable once an effective and affordable HIV vaccine becomes available.

1b PATHOGENESIS OF HIV INFECTION AND AIDS

Human immunodeficiency virus infection results in the majority of patients in a progressive depletion of mononuclear cells expressing the CD4 surface molecule. The loss of these important components of the immune system results in an increased susceptibility to a variety of micro-organisms.

After entering the host, human immunodeficiency virus infects cells that express CD4 molecules on their membrane (lymphocytes, monocytes, macrophages and dendritic cells). The CD4 molecule acts as receptor for HIV envelope glycoprotein, and attachment of HIV to CD4 and the chemokine receptors

CXCR4 (fusin) and CCR5 leads to introduction of viral RNA into the host cell [16]. The viral enzyme reverse transcriptase creates a DNA template, which becomes incorporated into host DNA. HIV DNA may remain latently present in the host genome, or be transcribed by host DNA polymerase, resulting in the production of viral genomic RNA and viral precursor proteins. Several enzymes, cleaved from the precursor proteins by viral protease, are required for the assemblance of the HIV virion within the host cell. Production of HIV virions may result in death of the host cell. The HIV virions, once released, will rapidly invade uninfected CD4 expressing mononuclear cells, thereby commencing a new cycle of HIV replication [17,18].

The production of billions of HIV virions each day results in a massive turnover of $CD4^+$T-lymphocytes. Initially, the loss of $CD4^+$T-cells is matched by a markedly increased rate of production. With time and for reasons unclear, a progressive decline in number and function of CD4 cells occurs [19]. This is reflected clinically by the increased susceptibility to infections caused by organisms normally contained or rapidly cleared by mononuclear cells.

Currently available anti-retroviral therapy is aimed at decreased HIV replication. Nucleoside analogues, such as zidovudine (AZT), didanosine (ddI), zalcitabine (ddC), lamivudine (3TC) and stavudine (d4T), and non-nucleoside reverse transcriptase inhibitors (NNRTI) such as nevirapine and decaviridine inhibit the viral protein reverse transcriptase and thus interfere with the production of a DNA template prior to insertion into host genome. Protease inhibitors such as indinavir and ritonavir interfere with virion assembly. Anti-retroviral agents have been shown to reduce HIV viral load and improve CD4 counts, particularly when

given in combination. Clinically, this is reflected by a reduction in number of opportunistic infections and improved survival [17,19].

1c CLINICAL MANIFESTATIONS OF HIV INFECTION

Acute HIV infection may, in 50-70% of patients, present as an infectious mononucleosis-like illness with fever, malaise, lymphadenopathy and rash, or in others remain asymptomatic. The "seroconversion illness" may be associated with significant immunosuppression, and opportunistic infections typical of AIDS may temporarily occur. A milder seroconversion illness is predictive of a subsequent more benign course of HIV infection [20].

A period of clinical latency follows seroconversion, during which generalized lymphadenopathy may be the only clinical clue to underlying HIV infection [21]. During asymptomatic HIV infection, an extremely high turnover of $CD4^+$T-cells is associated with a gradual reduction in the number of circulating T-lymphocytes. This period may last many years or even decades, and the HIV viral load, in combination with CD4 count, is commonly used to monitor progression of HIV induced immune suppression and predict long term outcome [18].

The first symptoms of HIV infection may relate to relatively minor illnesses, such as skin rashes, upper respiratory tract infection, or mild unintentional weight loss. Alternatively, patients can present with more serious complications such as prolonged fever or diarrhoea, weight loss more than 10%, thrush, severe bacterial infections or AIDS-defining illnesses. Symptomatic HIV infection is preceded by an increased rate of $CD4^+$T-lymphocyte depletion [18].

Once severe immune suppression is present (CD4 counts commonly below 200/μL), AIDS-defining opportunistic infections may occur with increased frequency. A variety of pathogens (including non-tuberculous mycobacteria, fungi, protozoa and viruses) that are an uncommon cause of disease in immunocompetent individuals, may lead to life threatening illnesses in patients with AIDS. Following successful treatment of these opportunistic infections, most patients will require lifelong chemoprophylaxis to prevent a clinical relapse. With progressive deterioration of cellular immunity, multiple opportunistic infections may occur simultaneously and eventually result in death of the HIV infected patient [18]. The reduced immune surveillance also predisposes patients with advanced HIV infection to malignancies, including non-Hodgkin lymphoma, anal and cervical sqamous cell carcinoma [22]. Kaposi sarcoma is not a true malignancy, and may be related to concurrent human herpes virus-8 (HHV-8) infection, which is particularly prevalent in homosexually acquired HIV infected patients [22].

Prior to combination anti-retroviral therapy, median survival of patients with AIDS was generally poor and averaged 10.4 months [23]. However, the use of HIV suppressive therapy in conjunction with multiple primary and secondary prophylaxis regimen appears to have improved the outcome for those who are able to afford these drugs.

The commonest presentation of AIDS in Africa is weight loss, asthenia, and fever. Diarrhoea, cough and skin rash are frequently reported. In comparison to AIDS in the developed world, pulmonary and extra-pulmonary tuberculosis, cryptococcal meningitis, toxoplasmosis and cryptosporidiosis appear to occur

with increased frequency in Africa, whereas pneumocystis carinii pneumonia (PCP) and non-tuberculous mycobacterial infections are less frequently reported [24]. The true prevalence of PCP in Africans remains controversial as sophisticated techniques are usually required to confidently make this diagnosis. Studies from Zimbabwe using fibre-optic bronchoscopy documented the presence of PCP in 20% of patients with respiratory tract disease [25,26]. In contrast, PCP was found in the alveolar lavage fluid of only 1 of 127 HIV positive patients with lung disease in Tanzania [27]. At Somerset Hospital, Cape Town, the shift in patient characteristics from homosexual white males to heterosexual African males and females over a 12 year period was accompanied by a significant reduction of PCP as AIDS defining diagnosis from 41 to 12% [28].

A post mortem study from West Africa revealed that tuberculosis was the commonest (54%) disease present in patients dying with AIDS, followed by cytomegalovirus (26%), pyogenic pneumonia and cerebral toxoplasmosis (21%), Kaposi sarcoma (13%) and non-specific enteritis (12%), whereas the prevalence of PCP, cryptococcosis and cryptosporidiosis was 4-5% [29]. An important finding was that tuberculosis contributed significantly to the wasting syndrome. The majority of deaths were due to infections, including tuberculosis, bacteraemia, toxoplasmosis and pyogenic pneumonia, and thus potentially treatable or preventable by inexpensive drug therapy [29].

1d STAGING OF HIV INFECTION AND MARKERS OF DISEASE PROGRESSION

Based on clinical and laboratory parameters, several classification systems for HIV infection have been proposed [30-32] (see addendum at the end of this chapter). The most useful system in the African context appears to be the World Health Organization proposed clinical staging system [30]. In this classification, HIV positive patients can be entered into one of four stages according to performance status and clinical illnesses. By allowing the use of presumptive diagnoses, total lymphocyte counts, and performance status, the WHO system has easy applicability in resource-poor settings. Each stage reflects the degree of immune compromise and carries prognostic value [33]. The Walter Reed system [31] requires CD4 counts and assessment of delayed hypersensitivity, and does not specify the type of opportunistic infection. The Centres for Diseases Control (CDC) system [32] classifies the type of opportunistic disease but makes no distinction between early and late events. The CDC classification was modified in 1993 to include patients with CD4 counts <200/μl, pulmonary tuberculosis, recurrent bacterial pneumonia and invasive cervical cancer in group C (AIDS defining conditions [34].

The $CD4^+$T-lymphocyte count is the most frequently used, and probably most useful of markers to monitor progression of HIV infection [35]. HIV viral load has also been shown to predict long term outcome in HIV infection. Access to CD4 counts or HIV viral load however is extremely limited in Africa. These markers are therefore of limited use to clinicians for management of HIV infected patients.

In resource-poor settings, the combination of WHO clinical stage and total lymphocyte count can be used to predict progression to AIDS (see chapter 3). In HIV positive patients with tuberculosis, the chest radiograph has important prognostic value (see chapter 4). The type of AIDS-defining illness and performance status are important determinants of survival in patients with AIDS (see chapter 5).

1e MANAGEMENT OF HIV INFECTION IN AFRICA

The rate of progression from asymptomatic to symptomatic HIV infection in Uganda was similar to reported figures from the developed world [36]. Survival of patients with AIDS attending the same HIV clinic in Cape Town, South Africa, compared for the 2 transmission patterns (which reflected race, education and socio-economic status), showed that African patients had similar survival to patients of European descent [37]. This supports the suggestion that access to medical care may be an important determinant of survival of African patients with HIV infection. As in the developed world, treating patients with HIV infection in Africa may be rewarding, both in human and economical terms, and HIV positive patients should therefore be provided with the same standard of care as HIV negative patients.

The majority of the millions of Africans latently infected with HIV will eventually develop symptomatic disease. The burden placed by HIV infection and AIDS on the existing medical facilities of sub-Saharan countries is already overwhelming, and can be expected to increase. Resources for treating HIV positive patients

will have to be rationed so as not to disproportionally impede the health care for HIV negative patients.

HIV positive patients would be best cared for in specialized AIDS clinics, as the outcome of HIV infected patients is improved when they receive care from doctors who have experience with HIV infection [38]. Patients could be monitored for the presence of treatable intercurrent illnesses, and receive ongoing counselling. Early outpatient intervention may avoid a costly hospital admission subsequently. The formulation of national guidelines for the investigation, (empirical) treatment, and referral of patients with symptomatic HIV infection that take the restraints on the country's health care resources into consideration, may facilitate management decisions and promote a more equal distribution of care. Home-based care, particularly for patients in the pre-terminal phase of their disease, will become increasingly important as the demand for hospital beds rises. Traditional medicine has a limited role to play in a curative strategy for the complications of HIV infection, but remains an important source of palliative care for terminally ill patients [39].

Relatively inexpensive intervention aimed at the reduction of HIV transmission by altering high risk sexual behaviour, treatment of concurrent sexually transmitted diseases, and the administration of specific anti-retroviral therapy such as zidovudine to pregnant women should be considered. Low cost preventive therapy is available for tuberculosis and bacterial infections. The logistics, both in infrastructural and financial terms, associated with isoniazid prophylaxis to prevent active TB may preclude its widespread implementation in

Africa. Co-trimoxazole prophylaxis however should be considered for significantly immunocompromised patients.

ADDENDUM

Table 1. List of clinical conditions by clinical stage*.

Clinical stage 1

1. Asymptomatic infection (ASY)
2. Persistent generalized lymphadenopathy (PGL)
3. Acute retroviral infection (ARI)

Performance scale 1: asymptomatic, normal activity

Clinical stage 2

4. Unintentional weight loss (WL), < 10% of body weight
5. Minor mucocutaneous (mcs) manifestations (e.g. seborrheic dermatitis, prurigo, fungal nail infections, oropharyngeal ulcerations, angular cheilitis)
6. Herpes zoster (HZV), within the previous 5 years
7. Recurrent upper respiratory tract infections (URTI) (e.g., bacterial sinusitis)

And/or performance scale 2: symptoms, but nearly fully ambulatory

Clinical stage 3

8. Unintentional WL, > 10% of body weight
9. Chronic diarrhoea (DIA), > 1 month
10. Prolonged fever (PYR) (intermittent or constant) > 1 month
11. Oral candidiasis (ORC) (erythematous or pseudomembranous)
12. Oral hairy leukoplakia (HLP)
13. Pulmonary tuberculosis (PTB) (typical or atypical), within the previous year
14. Severe bacterial infections (BAC) (e.g., pneumonia, pyomyositis)
15. Vulvovaginal candidiasis (VVC), chronic (> 1 month) or poorly responsive to therapy

And/or performance scale 3: in bed < 50% of normal daytime, but > normal, during previous month

Clinical stage 4†

16. HIV wasting syndrome (CAC)
17. *Pneumocystis carinii* pneumonia (PCP)
18. Toxoplasmosis of the brain (TOXO)
19. Cryptosporidiosis with diarrhoea (CRS), > 1 month
20. Isosporiasis with diarrhoea (ISO), > 1 month
21. Cryptococcosis (CRC), extrapulmonary
22. Cytomegalovirus (CMV) disease of an organ other than liver, spleen or lymph node
23. Herpes simplex virus (HSV) infection, mucocutaneous (> 1 month) or visceral (any duration)
24. Progressive multifocal leukoencephalopathy (PML)
25. Any disseminated endemic mycosis (MYC) (e.g., histoplasmosis, coccidioidomycosis)
26. Candidiasis of the oesophagus, trachea, bronchi or lungs (OEC)
27. Atypical mycobacteriosis, disseminated (MAI)
28. Non-typhoid *Salmonella* septicaemia (SAL)
29. Extrapulmonary tuberculosis (ETB)
30. Lymphoma (LYM)
31. Kaposi's sarcoma (KS)
32. HIV encephalopathy (ADC)

And/or performance scale 4: in bed > 50% of normal daytime during previous month

Proposed World Health Organization clinical staging system for HIV infection (ref 30)

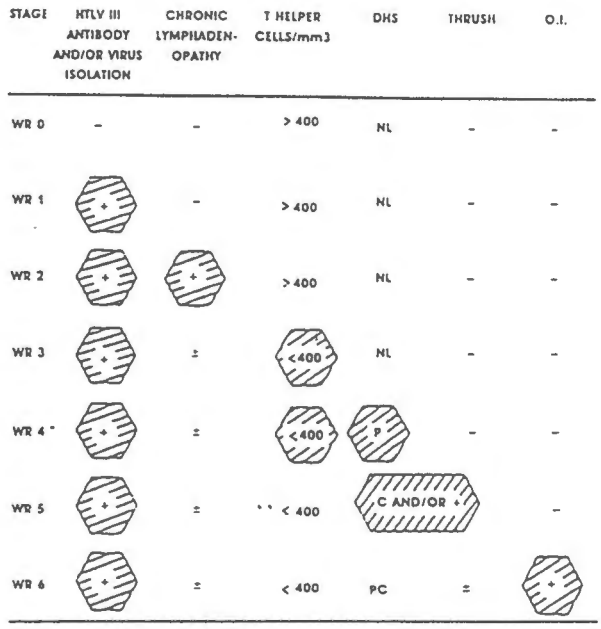

Figure 1. The Walter Reed Staging Classification for HTLV-III/LAV Infection.

The essential criteria for assignment to each stage are indicated by hatched hexagons. DHS denotes delayed hypersensitivity; NL, normal; P, partial cutaneous anergy, which is defined as an intact cutaneous response to only one of the four test antigens (see text); C, complete cutaneous anergy to the four test antigens; and O.I., opportunistic infection.

Walter-Reed classification system for HLTV-III/LAV infection (ref 31)

ADDENDUM (continued)

TABLE 5. Summary of classification system for human T-lymphotropic virus type III/ lymphadenopathy-associated virus

Group I.	Acute infection	
Group II.	"Asymptomatic infection"*	
Group III.	Persistent generalized lymphadenopathy*	
Group IV.	Other disease	
Subgroup A	Constitutional disease	
Subgroup B	Neurologic disease	
Subgroup C.	Secondary infectious diseases	
Category C-1	Specified secondary infectious diseases listed in the CDC surveillance definition for AIDS†	
Category C-2.	Other specified secondary infectious diseases	
Subgroup D	Secondary cancers†	
Subgroup E.	Other conditions	

*Patients in Groups II and III may be subclassified on the basis of a laboratory evaluation

†Includes those patients whose clinical presentation fulfills the definition of AIDS used by CDC for national reporting

Centers for Diseases Control classification system for HLTV type III/LAV infection (ref 32)

Table 4.1. Revised Classification System of HIV Disease
Centers for Disease Control and Prevention (January 1993)

CD4 Count	A	B	C
>500	A1	B1	C1
200–500	A2	B2	C2
<200	A3	B3	C3

Category A
- Asymptomatic HIV infection
- Persistent generalized lymphadenopathy
- Acute retroviral syndrome

Category B (formerly "ARC")
- Bacillary angiomatosis
- Candidiasis
  - Oral
  - Recurrent vaginal
- Cervical dysplasia
- Constitutional symptoms (e.g., fever or diarrhea) > 1 month
- Hairy leukoplakia, oral
- Herpes zoster
- Idiopathic thrombocytopenia purpura
- Listeriosis
- Pelvic inflammatory disease
- Peripheral neuropathy

Category C (AIDS-defining conditions)
- CD4 count less than 200 cells/mm³
- Candidiasis
  - Pulmonary
  - Esophageal
- Cervical cancer
- Coccidioidomycosis
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis
- Cytomegalovirus
- Encephalopathy, HIV
- Herpes simplex
  - Chronic (>1 month)
  - Esophageal
- Histoplasmosis
- Isosporiasis
- Kaposi's sarcoma
- Lymphoma
- *Mycobacterium avium*
- *Mycobacteria kansasii*
- *Mycobacteria tuberculosis*
- *Pneumocystis carinii*
- Pneumonia, recurrent
- Progressive multifocal leukemia
- Salmonellosis

Revised classification system of HIV Disease-Centers for Diseases Control (ref 34)

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CHAPTER TWO

TUBERCULOSIS IN HIV INFECTED PATIENTS

2a TUBERCULOSIS AND HIV IN SUB-SAHARAN AFRICA

Some 1700 million people worldwide, or one third of the human population, are infected with *Mycobacterium tuberculosis* (MTB). Annually, 8m people develop active tuberculosis (TB), resulting in 2.9m deaths. Africa, home to 12% of the world population, carried 64% of the global TB burden, 65% of the global human immunodeficiency virus (HIV) burden and almost 80% of the estimated 4M cases of HIV/TB co-infection in 1992. The interaction between human immunodeficiency virus and *Mycobacterium tuberculosis* has lead to a marked increase in the number of tuberculosis cases in sub-Saharan Africa [1].

HIV infection is an important risk factor for developing active tuberculosis. Studies comparing incidence rates of tuberculosis in HIV negative and HIV positive Africans indicate that HIV infection is associated with a 6-23 fold relative risk for developing active TB, as TB annual incidence rates ranged 0.2-0.8% in HIV negative and 5-8% in HIV positive persons. Based on these figures, it was estimated that in 1992 alone, HIV infection was responsible for an additional 150.000-250.000 cases of tuberculosis in Africa. Tuberculosis became by far the commonest opportunistic illness in HIV infected patients in Africa [1].

Approximately half of all Africans have acquired MTB infection by adolescence. As HIV infection became more prevalent in this population, many countries in sub-Saharan Africa reported an increase in tuberculosis case loads. Notification rates more than doubled over a five year period in Burundi, Malawi and Zambia. HIV prevalence in African patients with pulmonary TB was noted to be as high as 70%. The HIV related surge in TB case load has posed a major burden on the already stretched TB services of many sub-Saharan African countries [1].

Anti-tuberculous chemoprophylaxis given to HIV infected individuals may reduce the high tuberculosis incidence rate observed in these persons. An initial report from Haiti suggested that six months isoniazid reduced the number of clinical TB cases and possibly improved survival [2]. A larger Ugandan study showed that various prophylaxis regimen were able to offer protection against tuberculosis in PPD-positive HIV infected adults, however no survival benefit could be demonstrated [3]. A large Kenyan study in individuals with early and advanced HIV infection failed to show a significant beneficial effect of six months isoniazid preventive therapy, regardless whether patients were PPD-positive or negative [4]. To date, TB chemoprophylaxis has not been widely implemented in sub-Saharan Africa, because of expense of widespread HIV testing, the reluctance of persons undergoing HIV testing to be confronted with the result of the test, insufficiency of the existing TB infrastructure to supervise prophylaxis, anticipated high default rates that may lead to a rise in drug resistance, drug toxicity, the difficulty of confidently ruling out active tuberculosis prior to commencing prophylaxis, uncertainty about the duration of protection and the possible lack of efficacy in advanced HIV infection [5,6,7].

As HIV infection becomes more prevalent in sub-Saharan Africa, the number of TB cases is likely to rise even further. The increased patient load will necessitate more patients to receive ambulatory TB treatment. Highly efficacious rifampicin based short-course anti-tuberculous chemotherapy is the treatment of choice, as shorter duration of therapy may improve patient compliance and increased cure rates facilitate TB control. Ambulatory patients should receive this treatment under direct observation (DOTS), as drug resistance may be the

result of intermittent compliance to therapy. Supervision is facilitated by the use of a twice weekly administered modified rifampicin-based treatment regimen, and has been shown to achieve excellent cure rates [8]. In an attempt to limit costs, the use of non-professional people to supervise ambulatory TB treatment has been encouraged, and shown to be very successful in a rural South African community [9].

2b PATHOPHYSIOLOGY OF HIV RELATED TUBERCULOSIS

In immunocompetent individuals, following aerosol infection and phagocytosis by pulmonary macrophages, Mycobacterium tuberculosis will elicit both a cell-mediated immune and a delayed hypersensitivity reaction in lung tissue and regional lymph nodes. $CD4^+$ T-lymphocytes are important regulators of the induced immune response.

Cell-mediated immunity involves an incompletely understood interplay between Th_1 $CD4^+$ T-cells that produce interferon-γ and interleukin (IL)-2, cytokine-activated macrophages that produce tumour necrosis factor-α, IL-1 and IL-6, and cytotoxic $CD4^+$ $\gamma\delta$ T-cells. Cell mediated immunity leads to granuloma formation at the site of infection, and macrophage activation results in killing of phagocytosed mycobacteria. Delayed hypersensitivity, an important mechanism for clearing mycobacteria that escape killing by cell-mediated immunity, acts by macrophage lysis. This may result in the release of macrophage proteinases, nucleases and lipases into host tissue, which by causing local inflammation may lead to caseation and cavity formation [10,11]. Most persons with a competent immune system will thus contain MTB infection. A number of organisms may

remain dormant within macrophages, from which TB may reactivate, even decades later.

In HIV infection, most patients with time develop, in relation to dysfunction and depletion of $CD4^+$ T-cells, progressive impairment of both cell-mediated immunity and delayed hypersensitivity. This results in an increased rate of reactivation of latent tuberculosis, and an increased susceptibility to (re)infection with MTB. In early HIV infection, preserved immunity shows a reactive histological pattern and pauci-bacillary TB, similar to that in HIV negative patients. The immune response is sufficiently preserved for cavitation to occur, and sputum smears are typically positive at this stage. As HIV disease advances, granulomas show gradual depletion of $CD4^+$ T-cells and diminished caseation. Tuberculosis in severely immune compromised patients is characterized pathologically by multi-bacillary TB and absent granuloma formation [11], and clinically by frequent dissemination to extra-pulmonary sites [12]. The absence of cavity formation in advanced HIV infection underlies the frequent smear negativity.

2c CLINICAL ASPECTS OF HIV RELATED TUBERCULOSIS

Similar to TB in HIV negative patients, the lung is the commonest site of tuberculosis in HIV infection. Pulmonary TB may occur at all stages of HIV infection [13]. The clinical and radiographic presentation of pulmonary TB, including the diagnostic yield of smears, shifts from typical smear positive TB in early HIV infection to atypical, frequently smear negative TB with advanced immune compromise.

In early HIV infection, TB occurs in the setting of a relatively preserved immune response, and resembles TB in HIV negative individuals. Tuberculosis at this stage is predominantly pulmonary, and dissemination to extra-pulmonary sites occurs infrequently. The clinical and radiographic features are those of TB in HIV negative patients, with cavitating upper zone infiltrates on chest radiograph. Sputum smears are typically positive, and clinical signs of underlying immune compromise such as oral candidosis or kaposi sarcoma are usually absent. Generalized lymphadenopathy may be a clue to underlying HIV infection [14-17].

As HIV-induced immune suppression becomes more pronounced, the presentation of TB becomes increasingly more atypical, and concurrent extra-pulmonary tuberculosis more frequent. Lymph nodes, pleura, pericardium and abdomen are the more common sites of extra-pulmonary TB, meningitis and osteitis occur less frequently. Clinical examination at this stage may reveal thrush, oral hairy leukoplakia, or evidence of previous herpes zoster. Radiographically, a shift towards atypical patterns (adenopathy, interstitial infiltrates, and pleural effusions) reminiscent of primary infection occurs [15-17]. The sputum smear remains the most important diagnostic tool, but its yield may be reduced. Enlarged lymph nodes may reveal acid-fast bacilli and, if present on clinical examination, should be considered for diagnostic fine needle aspiration. Sputum culture is almost invariably positive and may confirm the diagnosis in retrospect.

In patients with AIDS, tuberculosis not infrequently recurs and may contribute significantly to morbidity and mortality [18]. At this stage, tuberculosis may be entirely or predominantly extra-pulmonary, and chest radiographs may be

normal, even in the presence of positive sputum smears and cultures [17]. Patients frequently present with features of severe immune compromise, a wasting illness and pyrexia. The diagnosis may be extremely difficult to confirm; mycobacterial blood culture and histological examination of liver or bone marrow may be required. Clinical outcome is poor, even in patients with a microbiological response.

Sputum culture has shown that tuberculosis in Africa is almost entirely due to M.tuberculosis infection, and that HIV infection is not associated with an increased rate of drug resistant TB [8,14,19]. Optimum treatment of TB in HIV positive patients is directly observed, short-course chemotherapy (2 months isoniazid + rifampicin + pyrazinamide + ethambutol, followed by 4 months isoniazid + rifampicin). Rifampicin-based chemotherapy has been shown to be more efficacious and better tolerated than conventional TB therapy [20]. Rifampicin allowed a reduction of treatment duration to 6 months without impairing cure rate, and was associated with very few treatment failures [8]. Lower rates of treatment completion have been reported in HIV positive patients with tuberculosis, mainly due to HIV-related mortality [8,21-23]. Atypical radiographic presentation, oral candidosis and low CD4 count were predictors of mortality in HIV related PTB [24].

2d HIV AND TB IN THE WESTERN CAPE, SOUTH AFRICA

The countrywide HIV prevalence for South African adults, based on the sampling of women attending ante-natal clinics, was estimated at 14.17% (95%CI 13.45-14.89) in 1996. This indicated a significant increase compared to 1995 (10.44%)

and 1994 (7.57%), and HIV prevalence was shown to be rising in all age groups. Within South Africa, large regional variation of HIV prevalence rates was observed, ranging from 3% in the Western Cape to more than 25% in the North West Province [25]. Data from the 1996 survey suggested that HIV infection is not equally distributed within the Western Cape population, as none of 35 Whites, 0.3% (2/787) of Coloureds and 4.7% (17/361) of Blacks tested positive for HIV at the time that overall HIV prevalence was 1.7% [26]. No HIV prevalence figures for males have been published to date. Caution is required when extrapolating HIV prevalence data obtained from antenatal surveys to the general population, as the reduced pregnancy rate of HIV positive women may result in underestimation of the magnitude of the HIV epidemic in this population [27].

Tuberculosis incidence and prevalence rates for the Cape Town area are more difficult to obtain. Population statistics for many of the townships where TB is highly prevalent are rough estimates, and the Black population is highly mobile. In 1995, the estimated overall tuberculosis incidence rate was 372/100.000, ranging from less than 25/100.000 for Whites and Asians to approximately 400 and 800/100.000 for Coloureds and Blacks respectively [28]. In certain high-density residential areas in Cape Town, incidence rates as high as 1339/100.000 have been reported [29].

Cape Town therefore is at the interface of two epidemics: tuberculosis prevalence and incidence rates are among the highest in the world, and HIV infection is rapidly spreading in this population. A surge of tuberculosis can be anticipated in the Black population as HIV infection becomes even more prevalent, and more HIV infected persons develop significant immune

compromise. Data from Somerset hospital (a local state hospital serving some of the communities with high HIV and TB prevalence rates) revealed a large increase in tuberculosis admissions between 1990 and 1995. This increase was entirely accounted for by HIV positive patients, whereas the number of HIV negative patients with TB remained unchanged [30]. The overall HIV prevalence rate of patients admitted to Somerset hospital with TB and prior unknown HIV status was 39% in 1995-1996: 37% in Coloured and 53% in Black patients. Tuberculosis in these hospitalized patients had developed in the presence of advanced HIV-induced immune suppression (median $CD4^+$ T-cell count 65/μL for both pulmonary or extra-pulmonary TB). Whereas drug-resistant TB was frequently encountered in the small number of White male homosexuals, HIV infection in the Black and Coloured patient population was not associated with an increased rate of (multi-) drug resistant tuberculosis [31].

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CHAPTER THREE

WHO CLINICAL STAGE AND TOTAL LYMPHOCYTE COUNT PREDICT THE RATE OF PROGRESSION OF HIV INFECTION

CD4 AND TOTAL LYMPHOCYTE COUNT: EQUAL PREDICTORS OF HIV DISEASE PROGRESSION?

SUMMARY

$CD4^+$T-lymphocyte (CD4) counts are a standard laboratory marker of disease progression in HIV infection, but expense precludes their use in large parts of the world. Total lymphocyte counts (TLC), in contrast, are widely available. We compared CD4 and TLC counts as predictor of developing AIDS or death in 831 HIV positive outpatients (582 males and 249 females with both homosexual (males, n=316) and heterosexual (n=515) transmission patterns. The first CD4 count <200/μL and first TLC <1250/μL predicted similar (p=0.52) survival, irrespective of clinical stage. For each clinical stage, a significant difference in progression to AIDS and mortality was predicted by a TLC above or below 1250/μL (p<0.03). Survival and progression to AIDS occurred at similar rates in patients with a TLC <1250/μL or a CD4 count <200/μL (p>0.1), and patients with a TLC >1250/μL or a CD4 count >200/μL (p>0.5). A TLC <1250/μL preceded the development of *Pneumocystis carinii* pneumonia (PCP) or cerebral toxoplasmosis in 76% of patients. In this longitudinal study, TLC and CD4 counts were equal predictors of disease progression. A TLC below 1250/μL could be considered an indication for commencing cotrimoxazole prophylaxis.

*(Q J Med 1996; **89**:505-508)*

INTRODUCTION

HIV infection can be monitored by laboratory [1,2] and clinical [3,4] markers of disease progression. The $CD4^+$T-lymphocyte (CD4) count is considered the best laboratory marker of progression of HIV infection [1], but lacks uniform reproducibility [5], is a crude predictor of HIV disease progression when taken by itself [6], and, because of expense, has limited availability in both resource-poor and developed countries [7].

In the absence of $CD4^+$T-lymphocyte counts, the use of total lymphocyte counts (TLC) has been advocated to predict CD4 count [8] and to stage HIV disease [4,9]. The use of the TLC as predictor of $CD4^+$T-lymphocyte count is limited by the presence of $CD4^+$T-lymphopenia in up to 30% of non-lymphopenic patients [8]. However, a low TLC was found to predict progression to clinical AIDS [2,10]. This longitudinal study compared total lymphocyte count with CD4 count as predictor of hard clinical end-points (developing AIDS and death) in lymphopenic and non-lymphopenic HIV positive patients.

METHODS

Computer-based medical records of Somerset and Groote Schuur Hospital HIV clinics, two principal Western Cape HIV out-patient clinics, were analysed. Patients had been staged clinically (retrospectively from 1984 to 1991, prospectively from 1992 onwards) at each visit according to the WHO clinical staging system [9], in which stage 4 is equivalent to the 1987 Centres for Diseases Control (CDC) definition of AIDS [11]. Most patients that presented with serious HIV related complications were admitted to hospital in an attempt to confirm the

diagnosis pathologically or microbiologically. Depending on the clinical condition of the patient and/or response to empiric therapy, spinal fluid sampling, liver and bone marrow biopsy, bronchosopy, CT scanning and occasionally brain biopsy was used to enhance diagnostic certainty. HIV encephalopathy was diagnosed in the appropriate clinical context and after the presence of concurrent opportunistic illnesses had been excluded, PCP and cerebral toxoplasmosis frequently remained a presumptive diagnosis. Paired CD4 and TLC values (n=1965) were available in 831 patients. CD4 counts were determined by flow cytometry and total lymphocyte counts by automated blood cell counter. Lymphopenia was defined as a TLC <1250/μL.

Survival was expressed as the Kaplan-Meier estimate of cumulative probability of survival and was calculated in months from the index visit (first visit at which CD4 or TLC occurred in the defined range) to the date of death (not censored) or last visit (censored). Similarly, AIDS free survival was calculated from the index visit to the date of initial AIDS diagnosis/death (not censored) or last visit (censored).

Survival curves were created for various degrees of lymphopenia (increments of 250 lymphocytes) and compared for closest fit to the curves of a CD4 count below 200 and 50/μL. Optimal match of the survival curve of a CD4 count <200/μL was achieved by a TLC <1250/μL. Probability of AIDS-free and overall survival was therefore determined for each clinical stage and a TLC above or below 1250/μL or a CD4 count above or below 200/μL. Statgraphics version 6.0 was used to create Kaplan-Meier plots and the log-rank test to establish statistical difference between survival curves.

RESULTS

Patients of the two HIV clinics represented both homosexual (n=316) and heterosexual (n=515) transmission pattern, male (n=582) and female (n=249) sex, and the three local population groups (whites n=280, blacks n=339 and mixed-race n=212). Intravenous drug abuse and haemophilia did not occur as risk factors for HIV infection in our patients. Mean age was 31.9 years (range 12-77), and increased with clinical stage (range 29.7-34.7 for stage 1 to 4, $p<0.02$). Mean age was higher for patients with CD4 counts below 200/μL (34.1 vs 30.4, $p<0.01$) and TLC below 1250/μL (33.2 vs 31.3, $p<0.01$) compared to patients with preserved CD4 or total lymphocyte counts.

A CD4 count <200/μL occurred in 81% (547 of 675) of total lymphocyte counts <1250/μL and a CD4 count >200/μL was present in 80% (1032 of 1290) of TLC >1250/μL. A total lymphocyte count <1250/μL was 68% sensitive and 89% specific for a CD4 count <200/μL. A TLC >1250/μL or a CD4 count >200/μL predicted the absence of clinical AIDS in 90% and 94% of patients respectively.

Survival of patients of any clinical stage whose total lymphocyte count had declined below 1250/μL was similar to the survival of patients with a first CD4 count below 200/μL (Figure 1). Survival of patients (n=132) with a first TLC below 750/μL was not statistically different ($p=0.37$) from patients (n=146) who had a CD4 count below 50/μL (45% at one year and 20% at two years). In lymphopenic patients (TLC <1250/μL) as well as patients with a CD4 count <200/μL, clinical stage was a major determinant of mortality (Figure 2**a,b**). Progression to AIDS and death occurred at significantly ($p<0.03$) higher rates in

lymphopenic patients than in non-lymphopenic (TLC >1250/μL) patients (Table 1). Mortality and progression to AIDS were not significantly different ($p>0.5$) between patients of similar clinical stage and a TLC <1250/μL or a CD4 count <200/μL (Figure 2**a-d**), nor between patients with a TLC >1250/μL and patients with a CD4 count >200/μL ($p>0.1$, data not shown).

Pneumocystis carinii pneumonia (PCP) was diagnosed in 51 patients and cerebral toxoplasmosis in 8. In the 12 months preceding the onset of PCP or toxoplasmosis, a TLC <1250/μL was present in 76% of these patients.

DISCUSSION

The $CD4^+$T-lymphocyte count is considered the best laboratory marker of progression of HIV infection [1], and serial CD4 count determinations are commonly performed to monitor the degree of HIV induced immunosuppression. Low CD4 counts are indicative of decreased cellular immunity and associated with increased risk of developing AIDS or death. In the absence of CD4 counts, the use of total lymphocyte counts has been advocated to predict CD4 count and to stage HIV disease [4,8,9]. The usefulness of the total lymphocyte count is best evaluated by direct comparison with CD4 count as predictor of hard endpoints such as AIDS and death. This study found CD4 and TLC to be equal predictors of progression of HIV infection. The routine use of total lymphocyte counts rather than CD4 counts would substantially reduce the costs associated with managing HIV infection.

The WHO staging system incorporates the use of TLC <1000, 1000-2000 and >2000/μL to replace CD4 counts <200, 200-500 and >500/μL in its laboratory axis [9]. In Rwandan HIV positive women, few of whom had severe lymphopenia, a TLC above or below 2000/μL had no prognostic value [12]. Our results suggest that a TLC of 1250 rather than 1000/μL should be the equivalent of a CD4 count of 200/μL, and the presence of a TLC above or below 1250/μL is associated with a significant difference in rates of progression of HIV infection.

In two previous studies, patients of various WHO clinical and/or laboratory stages were rearranged into 4 "modified stages", and survival was determined for each "modified stage" [4,12]. In our patients, TLC (and CD4 counts) added independent, prognostically meaningful information to the WHO clinical stage (Table 1). The stratification of patients by WHO clinical stage and absence or presence of lymphopenia is easily performed and practical for the management of HIV infection in resource-poor countries.

In advanced HIV infection, the total lymphocyte count declines as a result of progressive depletion of $CD4^+$T-lymphocytes, $CD8^+$T-lymphocytes and B-lymphocytes [13]. $CD8^+$T-lymphopenia was found to be an independent predictor of mortality [14], and the decrease in B-cells may further contribute to the immunodeficient state associated with advanced HIV infection. In our patients, severe lymphopenia (TLC <750/μL) predicted poor survival regardless of clinical stage and might reflect a high susceptibility to opportunistic infections. In one study, systemic *Mycobacterium avium* complex infection was restricted to patients with severe lymphopenia (mean 540/μL) [15].

Cotrimoxazole is effective prophylaxis against toxoplasmosis, PCP and bacterial infections, and is recommended for all patients with CD4 counts <200/μL [16]. Although PCP is less common in Africa, toxoplasmosis and bacterial infections are major causes of mortality [17]. As lymphopenia preceded the development of PCP or toxoplasmosis in 76% of our patients, a TLC <1250/μL could be considered a criterion for instituting cotrimoxazole prophylaxis.

A TLC >1250/μL was only 4% less sensitive than a CD4 count >200/μL as predictor of the absence of clinical AIDS. Using lymphopenia rather than CD4 T-lymphopenia as a criterion for commencing cotrimoxazole prophylaxis may thus select a slightly smaller group of patients at risk for developing PCP. Although we have shown the total lymphocyte count to be equal to the CD4 count for overall prognosis, its usefulness in individual patients as a criterion for commencing prophylaxis needs to be studied prospectively.

TABLE

One year Kaplan-Meier estimate of progression to clinical AIDS (WHO stage 1-3) and death (WHO stage 4), stratified by a total lymphocyte count (TLC) above or below 1250/μL.

	One-year progression to AIDS			One-year mortality
	Stage 1	**Stage 2**	**Stage 3**	**Stage 4**
TLC > 1250/μL	3%	4%	25%	30%
TLC < 1250/μL	14%	12%	46%	55%

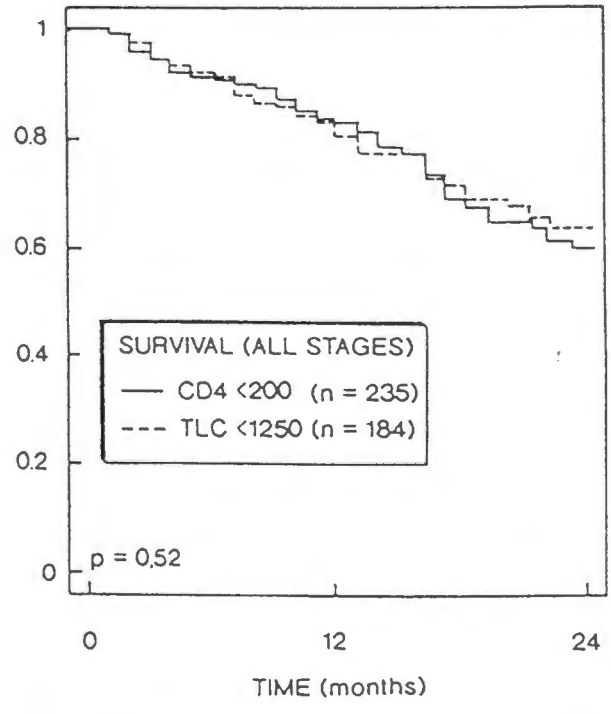

Figure 1. Overall survival for HIV-positive patients from the first CD4 count <200/μL or first lymphocyte count <1250/μL, regardless of WHO clinical stage.

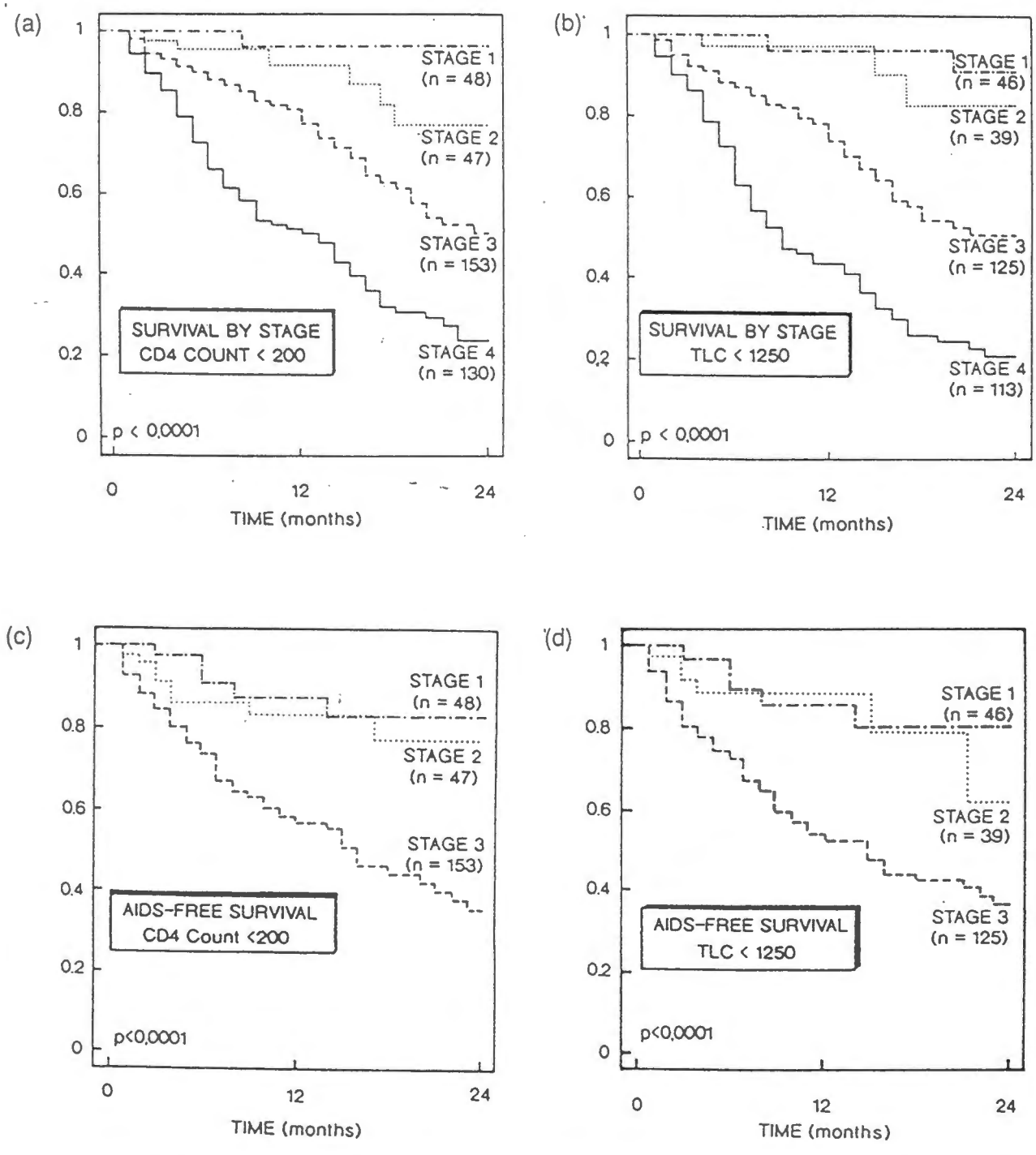

Figure 2. Overall survival and AIDS-free survival for patients with CD4 counts <200/μL and total lymphocyte counts <1250/μL. *p* values represent log-rank comparison of survival curves.

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CHAPTER FOUR

CHEST RADIOGRAPHS REFLECT IMMUNE STATUS IN HIV INFECTED PATIENTS WITH PULMONARY TUBERCULOSIS

4a PULMONARY TUBERCULOSIS IN HIV INFECTION: RADIOGRAPHIC APPEARANCE IS RELATED TO $CD4^+$ T-LYMPHOCYTE COUNT

4b SURVIVAL OF HUMAN IMMUNODEFICIENCY VIRUS-INFECTED PERSONS WITH PULMONARY TUBERCULOSIS

4c STAGING OF HIV POSITIVE PATIENTS WITH PULMONARY TUBERCULOSIS

4a PULMONARY TUBERCULOSIS IN HIV INFECTION: RADIOGRAPHIC APPEARANCE IS RELATED TO $CD4^+$ T-LYMPHOCYTE COUNT

(*Tubercle Lung Dis* 1995; **76**:518-521)

SUMMARY

Setting: An adult HIV outpatient clinic in Cape Town, South Africa.

Objective: To investigate the relationship between the radiographic appearance of pulmonary tuberculosis (PTB) in HIV infected patients and $CD4^+$ T-lymphocyte count.

Design: Pre-treatment radiographs of 150 patients with newly diagnosed PTB were reviewed. $CD4^+$ T-lymphocyte count was used as a marker of HIV disease progression.

Results: Upper zone infiltrate typical of PTB reactivation was present in 18 patients. This pattern was associated with early HIV infection (mean $CD4^+$ T-cell count 389) and had 78% positive predictive value for identifying patients with >200 $CD4^+$ T-lymphocytes/μL. Pleural effusion was present in 32 patients and occurred over a wide intermediate range of $CD4^+$ T-cell counts (mean 185). Lower or mid-zone infiltrates, adenopathy, interstitial pattern or normal radiograph occurred in 136 patients and were associated with advanced HIV disease (mean $CD4^+$ T-cell count 105). These patterns had 84%, 89%, 89% and 100% positive predictive value, respectively, for identifying patients with <200 $CD4^+$ T-cells/μL.

Conclusion: Pulmonary tuberculosis in African HIV positive patients presents with a spectrum of radiographic abnormalities, and specific patterns are predictive of

stage of HIV disease progression. In patients dually infected with HIV and PTB, chest radiographs are a useful adjunct to clinical staging.

INTRODUCTION

The interaction between the human immunodeficiency virus (HIV) epidemic and pulmonary tuberculosis (PTB) has been recognised in both the developed and developing world. In Sub-Saharan Africa, HIV seroprevalence of up to 67% has been reported among patients with newly diagnosed PTB [1,2]. The World Health Organisation (WHO) included PTB as one of the HIV clinical stage 3 criteria [3] and more recently it has been proposed that PTB should be an acquired immunodeficiency syndrome (AIDS) defining diagnosis [4]. In African HIV infected patients, however, PTB was found to be a poor marker of stage of disease. In areas of high PTB prevalence, individuals may be HIV seropositive and develop PTB without significant immunosuppression [5].

Patients dually infected with HIV and PTB frequently present with chest radiographic abnormalities that differ from those of PTB in HIV-negative individuals [6-10]. This study, conducted in an area with a high PTB prevalence of 1.134/100.000 [11] and an estimated 2.5% HIV seroprevalence [12], investigated the relationship between various radiographic patterns and $CD4^+$ T-lymphocyte counts.

METHODS

Medical records of adults attending Somerset Hospital HIV outpatient clinic in Cape Town, South Africa, from 1989-1994 were examined. Pre-treatment chest radiographs of 150 patients (103 M, 47 F, mean age 33, range 17-75) in whom

PTB was diagnosed were reviewed. These radiographs and those of 100 consecutive HIV clinic attendees without respiratory symptoms were reported on by a radiologist and categorised in a blinded fashion by 2 physicians independently. In case of disparity, the radiologist reviewed the films and was the final arbiter.

Radiographs with infiltrates localised predominantly in the upper lobes or apical segment of the lower lobes with or without cavitation were categorised as typical of reactivation (post-primary) PTB. In addition, radiographs were screened for the presence of pleural effusions, mediastinal and hilar adenopathy, lobar or segmental parenchymal infiltrates, and reticulo-nodular or miliary pattern. Fibro-cystic changes and pleural scarring were considered evidence of previous PTB. Patients without typical reactivation pattern could be included into more than one category.

A PTB diagnosis was confirmed on sputum in 104 patients (smear only n=40, smear and culture n=42, sputum culture with negative smear n=22). Pleural fluid adenosine deaminase (ADA) and pleural culture/histology (n=8), effusion ADA only (n=9), lymph-node histology (n=12), blood culture (n=3) or clinical and radiographic response (improvement in body weight, performance score, disappearance of pyrexia, cough or respiratory distress ; n=14) to 4 drug anti-tuberculous medication (Isoniazid, Rifampicin, Ethambutol and Pyrazinamide) suggested active PTB. Smear-positive sputum was not routinely cultured. In accordance with WHO recommendations [13], HIV seropositivity was confirmed by a combination of four positive ELISA assays on two separate blood samples. $CD4^+$ T-lymphocyte counts were determined by flow cytometry.

Statistical analysis

Sensitivity, specificity and positive predictive values were calculated with standard formulae [14]. $CD4^+$ T-lymphocyte counts were expressed as means ± standard deviation (SD). $CD4^+$ T-cell counts associated with various radiographic patterns were compared by *T* test. A two-sided level of significance of 0.05 was used to reject null hypotheses.

RESULTS

The distribution of chest radiographic patterns of PTB in 150 HIV positive patients and the mean $CD4^+$ T-lymphocyte count (±SD) associated with each pattern is shown in the Figure. Patients with pleural effusions had a significantly lower mean $CD4^+$ T-lymphocyte count when compared to those with radiographs typical of reactivation PTB ($p<0.01$). Adenopathy, lower or mid-zone parenchymal infiltrates and diffuse reticulo-nodular or miliary pattern were associated with significantly lower mean $CD4^+$ T-cell counts than either pleural effusions ($p<0.05$) or typical reactivation pattern ($p<0.01$). CD4 counts were similar for patients with pleural effusions with or without concomitant pulmonary infiltrates.

Radiographs with typical upper zone infiltrates with or without cavitation had 96% specificity and 78% positive predictive value for identifying subjects with >200 $CD4^+$ T-lymphocytes/μL. Cavitation occurred exclusively within upper zone infiltrates. Three patients had a normal chest radiograph, were sputum smear positive and had $CD4^+$ T-lymphocyte counts <200/μL. The specificity and positive

predictive values for the atypical radiographic patterns for identifying patients with <200 $CD4^+$ T-lymphocytes/μL are shown in the Table. Apical fibrocystic disease and pleural scarring, representing prior PTB, had no predictive value for HIV stage of disease (data not shown) and occurred in 12% of both the patient and control population.

Mycobacterial culture of sputum and pleural effusion was performed in 71 patients. *M. tuberculosis* was the pathogen cultured in 94% (64 of 68 patients), three cultures lost viability or became contaminated. Atypical mycobacteria (*M.kansasii, M.xenopi* and 2 undefined non-tuberculous mycobacteria) were isolated from sputum of four patients who had <200 $CD4^+$ T-cells/μL. These patients were excluded from analysis.

Sputum smear or culture positivity occurred in 73% of PTB patients with reticulo-nodular or miliary pattern. Of 100 HIV positive PTB negative controls, 75% had a normal chest radiograph, 12% showed evidence of previous PTB, 7% had parenchymal infiltrates and 6% a reticulo-nodular pattern. Hilar or mediastinal adenopathy was not present in these PTB negative patients and was thus not a feature of the persistent generalised lymphadenopathy of HIV infection.

DISCUSSION

This study documented that PTB occurred at all stages of HIV infection, and that there was a spectrum of chest radiographic presentation related to HIV stage of disease.

In Southern Africa, latent *M.tuberculosis* infection has been reported to be present in the majority of adults [1,2,15], and HIV seronegative adults typically develop

reactivation PTB with post-primary infiltrates and cavitation [10,15]. This pattern in our HIV positive patients was associated with early HIV disease as manifested by relatively preserved $CD4^+$ T-cell counts. Pleural effusion, although regarded as a marker of early clinical HIV disease [16,17], occurred throughout an intermediate range of lymphocyte counts and its presence was less helpful for prediction of HIV stage of disease.

In advanced HIV disease, both PTB reactivation and re-infection radiographically resemble primary tuberculosis, with features such as adenopathy and interstitial or non-cavitating parenchymal infiltrates [6,17,18]. These radiographic abnormalities occurred in our patient population despite historic or radiographic evidence of prior reactivation PTB. In contrast to miliary PTB in HIV negative patients [19], HIV positive patients with reticulo-nodular and miliary pattern have multi-bacillary PTB [1] confirmed in our patients by frequent sputum smear and culture positivity. In agreement with previous reports, adenopathy was the best predictor of low $CD4^+$ T-lymphocyte count [17,20].

A histopathological spectrum of *M.tuberculosis* infection in HIV disease analogous to that seen in *M.leprae* infection has been described [1]. This study reports a radiographic spectrum of pulmonary tuberculosis related to stage of HIV disease. In early HIV disease, a preserved cell mediated response results in paucibacillary PTB with apical fibrosis and cavitation. In advanced HIV infection, patients present with normal chest radiographs, interstitial patterns or adenopathy and advanced immunosuppression results in high bacterial load. The latter radiographic appearances of PTB could be regarded AIDS defining criteria in our HIV positive patients.

Although outpatient records were reviewed, patients had often required hospital admission or been referred from the community. The sample of patients might therefore be a reasonable representation of HIV-associated tuberculosis in our area. Tuberculosis in early HIV disease might have been under-represented, as specific abnormalities prompting HIV testing are often absent during early HIV infection. HIV serology is extremely sensitive [21], and multiple ELISA essays performed on our patients should ensure a high specificity. Consequently, the chance of false HIV seropositivity in our patients should be minimal.

In Sub-Saharan Africa, PTB is the commonest opportunistic infection in HIV disease and $CD4^+$ T-lymphocyte counts are frequently unobtainable. In this setting, radiographic criteria are a useful adjunct to clinical HIV disease staging. Prospective studies however will be required to confirm these findings in other population groups.

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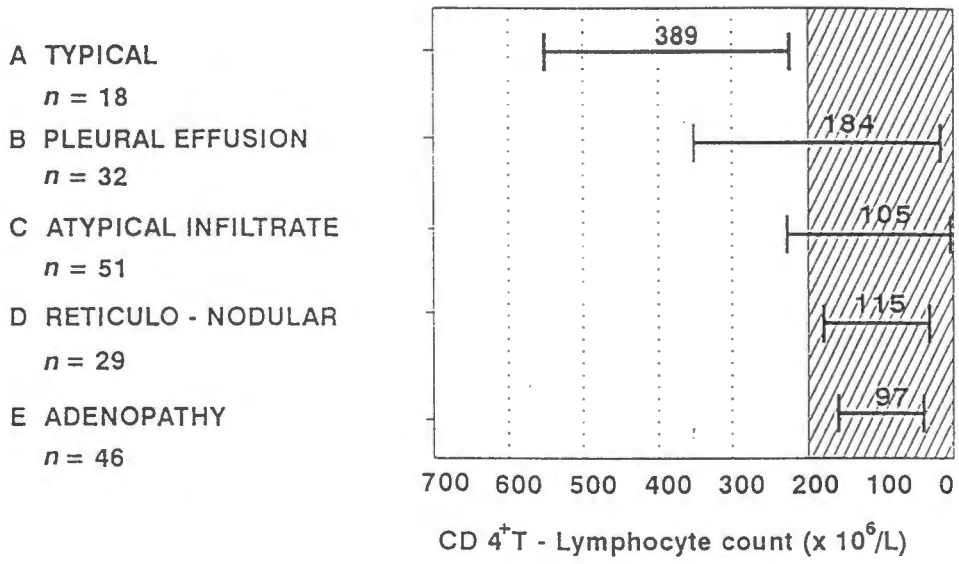

Figure. $CD4^+$ T-lymphocyte counts associated with PTB radiographic patterns in 150 HIV positive patients. $CD4^+$ T-cell numbers are shown as mean ±SD. Pattern A is defined by upper zone infiltrate with or without cavitation and pattern C by parenchymal infiltrate in mid or lower zone. Pattern A is associated with early HIV disease and patterns C, D, and E with advanced HIV infection. Patients may be included in one or more of categories B-E.

TABLE. The specificity and positive predictive value of atypical PTB radiographic patterns for identifying HIV positive patients with <200 $CD4^+$ T-cells/μL.

Radiographic pattern	Specificity	Positive predictive value
Normal radiograph (n= 3)	100%	100%
Reticulo-nodular (n=36)	88%	89%
Adenopathy (n=46)	85%	89%
Lower/midzone infiltrate (n=51)	76%	84%

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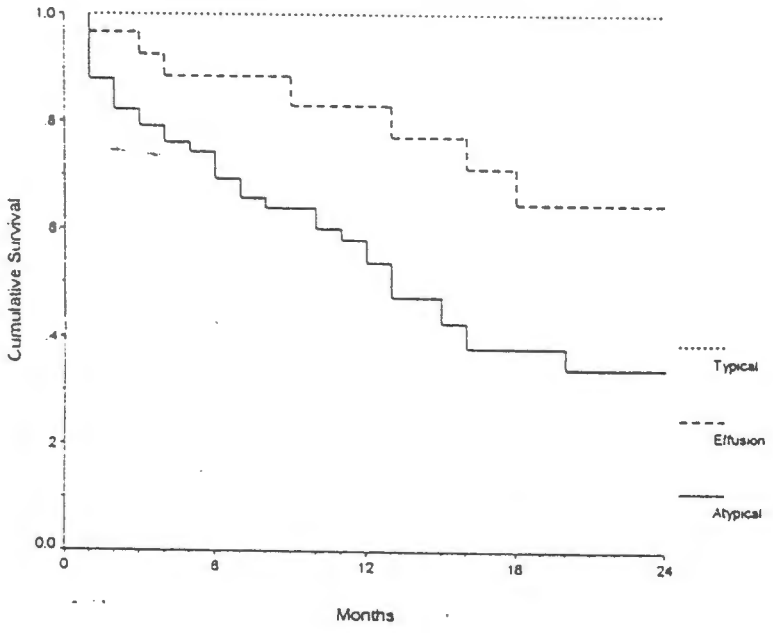
4b SURVIVAL OF HUMAN IMMUNODEFICIENCY VIRUS-INFECTED PERSONS WITH PULMONARY TUBERCULOSIS

(*Int J Tuberc Lung Dis* 1997; **1(1)**:87)

We have described the radiological features of 150 HIV-1 infected patients presenting with pulmonary tuberculosis to a Cape Town HIV clinic between 1989 and 1994 [1]. All patients had confirmed tuberculosis and received rifampicin-based short course chemotherapy (6 months RHZ for initial cases, 6 months RHZE for relapse cases). Treatment was both supervised (5 days per week) and self-administered (weekly supply of medication). Subsequent follow-up of this cohort demonstrated an overall mortality rate of 41/100 person years. However, different radiological presentations of pulmonary tuberculosis were associated with highly significant (logrank test $P < 0.001$) differences of Kaplan-Meier proportional survival (Figure). The total lymphocyte count was also found to be a major predictor of survival. Sixty-one percent of patients presented with lymphopaenia of <1250/μL, 39% had a total lymphocyte count >1250/μL. Lymphopaenic patients had a significantly higher mortality rate than those with a normal total lymphocyte count (65 vs 2/100 person years, χ^2 test $P < 0.001$).

The 2-year mortality rate of patients with HIV-1 infection and pulmonary tuberculosis described by Kassim et al. [2] was considerably lower (20.3/100 person years) than that reported by Small et al. [3] and ourselves. Each of these studies used rifampicin-based chemotherapy, but the different mortality rates could be explained on the basis of differences in study population. The CD4 lymphocyte count has been found to be a major determinant of mortality [4], but is frequently

unavailable in resource-poor countries. In contrast, chest radiographs and total lymphocyte counts are widely available and were powerful prognostic markers of mortality in our patients with HIV-1 related pulmonary tuberculosis. These variables have such strong impact on mortality that they should be reported and controlled for in comparative studies of response to tuberculosis chemotherapy in HIV-infected individuals.



Number of patients at risk

Time (months)	0	6	12	18	24
Typical	18	15	10	6	5
Effusion	32	19	14	12	10
Atypical	100	52	27	14	10

Figure. Kaplan-Meier estimated survival of HIV-infected patients with pulmonary tuberculosis, stratified by radiographic appearance. Typical presentation includes infiltrates limited to the upper lobes or apical segments of lower lobes. Effusion denotes pleural effusion. Atypical pattern includes lower and mid-zone infiltrates, adenopathy and/or interstitial infiltrates. Survival is significantly impaired in those patients presenting with pleural effusion or atypical patterns (logrank test $P < 0.001$).

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4C STAGING OF HIV POSITIVE PATIENTS WITH PULMONARY TUBERCULOSIS

Pulmonary tuberculosis in HIV positive patients presents with a radiographic spectrum, ranging from contained, cavitatory upper lobe infiltrates in patients with preserved cellular immune response and pleural effusions in patients with partial preservation of immunity to radiographic patterns of primary tuberculosis in patients with advanced HIV infection [1-3]. Survival for HIV positive patients presenting with PTB varies significantly with the degree of immunosuppression suggested by the chest radiograph [4]. Currently, all patients with pulmonary TB are included in WHO clinical stage 3. The prognostic accuracy of pulmonary tuberculosis in the WHO clinical staging system might be improved by incorporation of the prognostic information of chest radiographs.

In this retrospective analysis, we directly compared the survival of 150 HIV positive patients with proven pulmonary tuberculosis and radiographic patterns of either post-primary PTB (n=18), primary PTB (adenopathy, mid/lower zone or interstitial infiltrates, n=100) or tuberculous pleural effusion (n=32) with the survival of 831 HIV positive outpatients stratified by WHO clinical stage 1-4 (Table). Statgraphics version 6.0 was used to calculate Kaplan-Meier proportional survival, and the log-rank test to establish statistical difference between survival curves.

Statistical analysis showed survival to be similar for typical (post-primary) reactivation pattern and WHO clinical stage 2 (p=0.93), tuberculous pleural effusions and clinical stage 3 (excluding PTB, p=0.65), and atypical (primary)

radiographic patterns and AIDS (WHO stage 4, p=0.62). By classifying typical reactivation PTB as stage 2, pleural effusion as stage 3 and atypical pattern as stage 4, the prognosis of pulmonary tuberculosis in HIV positive patients is reflected by the WHO clinical stage.

Typical reactivation PTB in HIV positive patients occurs in the absence of significant HIV induced immune suppression. The atypical patterns, in contrast, are associated with advanced HIV infection and low CD4 counts [1-3]. They frequently coexist with or may be preceded by other opportunistic infections and/or AIDS defining illnesses. Patients diagnosed with 'atypical' pulmonary tuberculosis should, analogous to HIV positive patients with lymphopenia, be considered for cotrimoxazole prophylaxis [6].

TABLE : Proportional survival (Kaplan-Meier estimates) for HIV positive patients with tuberculosis and WHO clinical stage 1-4

SURVIVAL (months)	6	12	18	24
TYPICAL PTB	100%	100%	100%	100%
WHO STAGE ½	99%	98%	96%	95%
PLEURAL EFFUSION	88%	82%	68%	63%
WHO STAGE 3	89%	76%	69%	62%
ATYPICAL PTB	74%	54%	38%	34%
WHO STAGE 4	74%	51%	37%	30%

HIV-infected patients with pulmonary tuberculosis (n=150) are stratified by radiographic appearance and HIV positive outpatient clinic attenders (n=831) by WHO clinical stage. Typical PTB includes infiltrates limited to the upper lobes or apical segments of lower lobes. Atypical PTB includes lower and midzone infiltrates, adenopathy and/or interstitial infiltrates. WHO stage 4 equals acquired immunodeficiency syndrome (AIDS). Survival was similar for patients with typical radiographs and WHO stage 1 or 2 (p=0.93), pleural effusion and WHO stage 3 (p=0.65), and atypical PTB and WHO stage 4 (p=0.62).

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CHAPTER FIVE

TYPE OF AIDS-DEFINING ILLNESS PREDICTS MORTALITY IN PATIENTS WITH AIDS

Acquired immunodeficiency syndrome in Africa: survival according to AIDS defining event

SYNOPSIS

Survival of patients with AIDS is related to the degree of HIV-induced immunodeficiency. Laboratory markers to assess the severity of immune dysfunction are rarely available in Africa, and clinical decisions are frequently based on surrogate markers such as performance status and type of opportunistic illnesses. The prognostic value of these variables remains to be established for Africans.

Two hundred and eighty patients with AIDS, as defined by the proposed WHO clinical staging system, were stratified according to AIDS defining illness and CD4 count. Data was analyzed using Kaplan-Meier survival and Cox proportional hazard analyses. Median survival following the onset of AIDS was 11.5 months. Extra-pulmonary tuberculosis was the commonest AIDS defining illness.

Initial AIDS-defining diseases were stratified into early (extra-pulmonary TB and herpes simplex virus infection), intermediate (oesophageal candidiasis, *Pneumocystis carinii* pneumonia, Kaposi sarcoma and cryptococcal meningitis) and late diseases (HIV wasting syndrome and encephalopathy) according to median survival rates (>12, 6-12, <6 months; log-rank $p<0.00001$). The relative hazards for death associated with intermediate and late diseases (compared to early diseases) were 11.2 (95% CI: 2.5-50.3) and 25.0 (4.9-127.6) for patients with CD4 counts >200/μL, 2.4 (1.3-4.7) and 11.3 (4.4-28.8) with CD4 counts 50-200/μL, and 1.3 (0.7-

2.2) and 2.9 (1.6-5.0) for patients with CD4 counts <50/μL. A performance status score of 4 predicted 50% mortality at one month, irrespective of co-morbidity.

The type of AIDS-defining disease is an important determinant of survival, particularly in patients with relatively preserved CD4 counts. The stratification of patients by type of AIDS-defining illness and performance status may be useful for the management of patients with advanced HIV infection in resource-limited environments.

INTRODUCTION

The disease burden caused by human immunodeficiency virus (HIV) infection has been overwhelming health care facilities in many African countries [1]. It has been suggested that African patients with HIV infection have an increased rate of progression from asymptomatic HIV infection to the acquired immunodeficiency syndrome (AIDS) compared to patients in the developed world, and this difference has been related to limited access to medical care [1]. A recent longitudinal cohort study from Uganda however showed the rate of progression to AIDS in HIV positive patients to be comparable to figures previously reported from the Western world [2]. Survival of South African AIDS patients, provided with adequate medical care, was similar to European and American patients with AIDS [3].

Laboratory markers that reflect the degree of immunocompromise in HIV infection, such as $CD4^+$T-lymphocyte (CD4) count [4] and quantitative HIV viral load [5], are frequently unavailable in Africa. In this setting, prognostic information may be

obtained from clinical staging as proposed by the World health Organisation (WHO) clinical staging system and the total lymphocyte count [2,6,7].

Acquired immunodeficiency syndrome includes a variety of opportunistic diseases that may occur across a spectrum of immune dysfunction [8]. The prognosis of patients with AIDS varies accordingly and is influenced significantly by the type of AIDS defining illness [3,9,10]. Prognostic stratification based on AIDS-defining disease and performance status can be performed in the outpatient clinic and does not require sophisticated laboratory facilities. It is therefore widely applicable in resource-poor settings, and potentially useful to guide resource allocation and patient management. This study evaluated outcome of the commonest AIDS defining events and poor performance status in a cohort of South African HIV positive patients.

METHODS

All patients with an AIDS diagnosis (as defined by the proposed WHO clinical staging system [11], which is similar to the Centres for Diseases Control 1987 definition of AIDS [12]) attending the HIV outpatient clinics of the University of Cape Town medical school (at Somerset and Groote Schuur Hospitals) were selected from computer-based medical records. Survival was analyzed from the onset of AIDS, according to type of AIDS-defining illness, for diseases that occurred in at least 10 patients. Patients were stratified according to CD4 count (<50,51-200,>200/μL). CD4 counts performed within 3 months preceding the onset of AIDS-related illness were used for analysis.

All patients received co-trimoxazole prophylaxis, and treatment for tuberculosis (TB), herpes simplex infection (HSV), oesophageal candidiasis, *Pneumocystis carinii* pneumonia (PCP) and cryptococcal meningitis was available (Rifampicin based short course chemotherapy, valacyclovir, fluconazole, co-trimoxazole and amphotericin B / fluconazole respectively). Anti-retroviral therapy was not routinely available for patients with AIDS, and patients (n=83) who had received such therapy were excluded from analysis. Treatment regimens for opportunistic infections remained unchanged throughout the study period.

Survival was expressed as the Kaplan-Meier estimate of cumulative probability of survival and was calculated in months from the index visit (first visit at which the condition occurred) to the date of death or last visit (censored). Kaplan-Meier survival curves were created using the software package Statistica version 5, and evaluated for statistical difference by log-rank test. Relative hazards of death were calculated using the univariate Cox proportional hazard model of SAS statistical program (version 6, SAS institute, Cary NC, USA).

RESULTS

By April 1997, 280 patients had developed AIDS, 160 of whom had died . Both homosexual (n=109) and heterosexual (n=171) transmission pattern, and male (n=199) and female (n=81) sex were represented; intravenous drug abuse and haemophilia did not occur as risk factors for HIV infection in our patients.

The overall median survival from the onset of AIDS was 11.5 months. Initial AIDS-defining illnesses were stratified into early, intermediate and late events, according

to median survival rates (Table 1). No statistical difference was present between the survival curves of individual diseases within each stratum (p=0.90, 0.43, and 0.98 respectively). Kaplan-Meier survival for each of the three strata of opportunistic diseases is depicted in the figure. AIDS-defining illnesses were associated with a poorer outcome when they occurred after the onset of AIDS rather than as initial illness, but these differences only reached statistical significance for extra-pulmonary tuberculosis (data not shown). Performance status score 4 (in bed >50% of normal day time during the last month) predicted 50% one-month mortality, irrespective of co-morbidity .

Survival of AIDS patients was dependent on both CD4 count (p<0.00001) and AIDS-defining illness. The relative hazards of death associated with intermediate and late diseases relative to early diseases for the defined strata of CD4 counts are shown in Table 2. The influence of AIDS-defining illness on mortality was most striking in patients with preserved CD4 counts.

DISCUSSION

This study, performed in a resource limited environment, showed that the type of AIDS-defining disease was a major predictor of outcome, and that the prognostic information provided by the opportunistic disease was additive to the CD4 count. Stratification of patients according to AIDS-defining disease and performance status is easily performed, and therefore widely applicable in resource-poor settings. The prognostic information provided by these clinical parameters can be used for counselling and management of HIV infected patients.

Extra-pulmonary tuberculosis and HSV infection (lasting more than one month) as initial AIDS diagnoses were associated with the most favourable outcome and survival was comparable to reported figures from the developed world [9,10]. Extra-pulmonary tuberculosis was the initial AIDS diagnosis in one third of our patients, and associated with a relatively preserved CD4 count. Its frequent occurrence may explain the more favourable overall prognosis of patients with AIDS in Cape Town compared to Uganda [2,3].

Survival in our patients following cryptococcal meningitis was similar to patients with cryptococcosis in a large European study (7 vs 9 months) [10], and Kaposi sarcoma (KS) predicted similar outcome as in an American cohort (12 vs 12.3 months) [13]. The comparability of African and Western AIDS survival figures support the notion that access to care is an important determinant of survival of African AIDS patients [1].

Reports from sub-Saharan Africa suggest that wasting syndrome is common [1,2], and post-mortem studies have revealed that tuberculosis is highly prevalent in cachectic African AIDS patients [14]. HIV positive patients who presented to our clinics with a wasting illness were thoroughly investigated for tuberculosis by means of sputum smears and culture, histology of lymph node, liver or bone marrow, and blood culture. The resulting high frequency with which tuberculosis was diagnosed, and the relatively low prevalence of diarrhoeal illnesses in South African HIV positive patients [15] may offer an explanation for the small number of patients with unexplained HIV-wasting syndrome in this study.

The type of AIDS-defining disease [9,10], prior HIV or AIDS related morbidity [16], total lymphocyte count [5] and performance status [17] all provide useful prognostic

information in patients with advanced HIV infection. Prognostic stratification of HIV infected patients has particular relevance in resource-poor countries, to avoid irrational spending of scarce health care resources. Expensive investigations or therapy could be reserved for patients with favourable prognostic criteria. Survival figures of patients with performance status 4 or diseases such as HIV wasting syndrome or encephalopathy on the other hand support the institution of home-based terminal care for these patients.

TABLE 1

Median CD4 counts and survival (Kaplan-Meier estimates) for the commonest *initial* AIDS-defining illnesses

AIDS-defining illness	**median CD4 count (cells/μL)**	**median survival (months)**	**(n)**
early	***111***	***>24***	***(116)***
extra-pulmonary tuberculosis	111	>24	(97)
herpes simplex virus	114	>24	(19)
intermediate	***48***	***9***	***(105)***
kaposi sarcoma	118	12	(24)
oesophageal candidiasis	76	9	(32)
pneumocystis carinii pneumonia	39	7	(38)
cryptococcal meningitis	32	7	(11)
late	***64***	***2***	***(40)***
encephalopathy	121	3	(20)
wasting	45	1	(20)

Legend

Initial AIDS-defining illnesses were stratified into early, intermediate and late events according to median survival rates (>12,6-12,<6 months). n reflects the number of patients in each stratum.

TABLE 2 : Relative hazards for death associated with class of AIDS-defining illness, for defined strata of CD4 count (95% confidence intervals between brackets; values >1 imply (statistically significant) increases in risks of death for a particular AIDS defining illnesses relative to early AIDS defining diseases occuring in patients with similar CD4 counts)

CD4 count	**class of AIDS-defining illness**		
	early	**intermediate**	**late**
>200/μL	1	11.2 (2.5-50.3)	25.0 (4.9-127.6)
51-200/μL	1	2.4 (1.3- 4.7)	11.3 (4.4- 28.8)
0- 50/μL	1	1.3 (0.7- 2.2)	2.9 (1.6- 5.0)

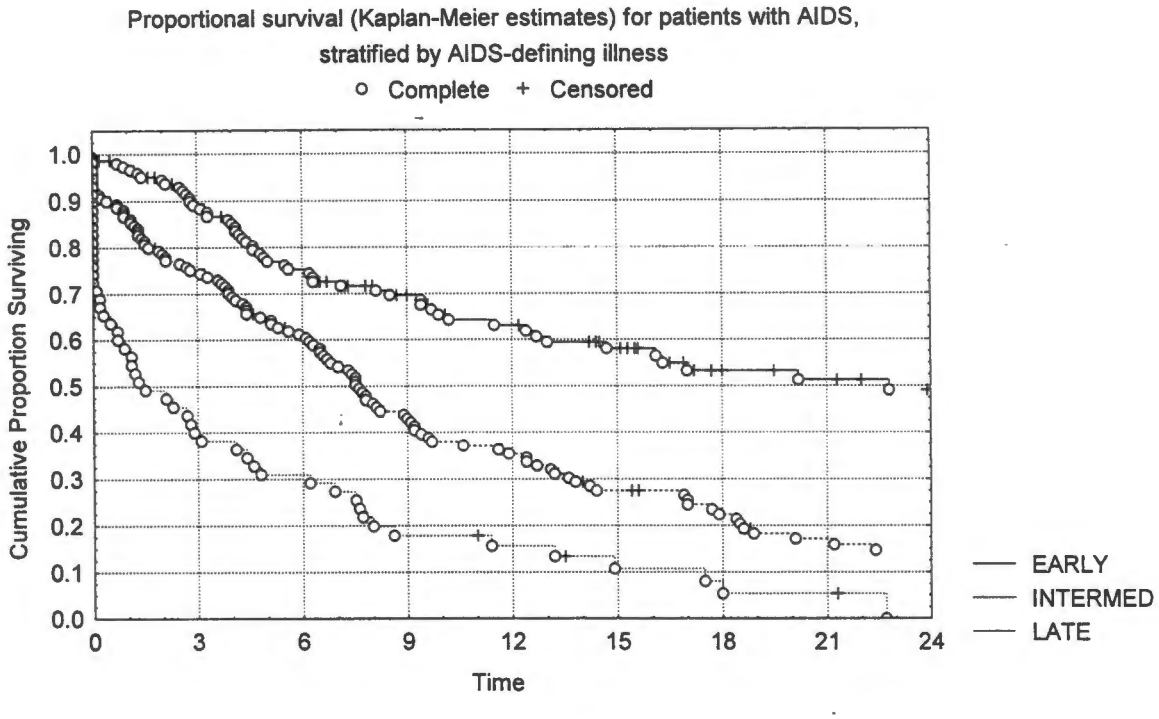
Legend

Hazards for death are expressed relative to the risk associated with early AIDS-defining illnesses (extra-pulmonary TB and herpes simplex) in the same CD4 count stratum. Intermediate illnesses include Kaposi sarcoma, oesophageal candidiasis, PCP and cryptococcal meningitis; late diseases encephalopathy and wasting. Figures between brackets are the accompanying 95% confidence intervals.

(AIDS-defining illness occurring as initial event or following the onset of AIDS are included)

The authors wish to gratefully acknowledge Ms M Visser for assisting with the statistical analysis

Figure



Legend

Survival for the eight commonest AIDS-defining illnesses could be stratified into one of three patterns; early diseases include extra-pulmonary TB and HSV, intermediate diseases KS, oesophageal candidiasis, PCP and cryptococcal meningitis, late diseases encephalopathy and wasting. Survival was significantly different for early, intermediate and late events ($p<0.00001$).

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CHAPTER SIX

CONCLUSIONS

CONCLUSIONS

Africa is disproportionally affected by both the human immunodeficiency virus (HIV) and tuberculosis (TB) epidemics. Health services in sub-Saharan African countries are overwhelmed by the huge number of patients suffering from HIV infection and acquired immunodeficiency syndrome, and many of these patients will develop active TB.

To facilitate counselling and rational distribution of scarce health care resources, inexpensive and readily available markers of HIV disease progression are required. This thesis explored the prognostic value of World Health Organisation clinical stage, total lymphocyte count, performance status and type of opportunistic infection in patients with HIV infection, and of chest radiographs in patients co-infected with tuberculosis. These parameters can be easily assessed during an outpatient clinic visit and do not require sophisticated equipment.

Early HIV infection (WHO clinical stage 1-2) carries a favourable prognosis, with annual rates of progression to AIDS below 15%. During early HIV infection therefore, patient management should be guided by clinical parameters. Total lymphocyte counts below 1250/μl predict a faster progression to AIDS, and patients with low lymphocyte counts are at increased risk of preventable opportunistic infections, including PCP and toxoplasmosis. Patients with total lymphocyte counts below 1250/μl should thus be considered for co-trimoxazole prophylaxis, as this intervention may improve outcome.

Tuberculosis is the commonest opportunistic infection in African HIV infected patients. As TB is eminently treatable and a major cause of HIV related morbidity

morbidity and mortality, its presence should be considered in all patients presenting with a respiratory, wasting or diarrhoeal illness. Chest radiographs in HIV positive patients with TB provide important prognostic information; typical reactivation pattern is encountered in patients with early HIV disease and predicts a favourable outcome. The atypical radiographic patterns were frequently associated with marked CD4+T-lymphopenia and clinically advanced HIV disease. These patients have a poor prognosis, are markedly immune suppressed and as such may benefit from co-trimoxazole prophylaxis. The three radiographic presentations of PTB (typical, effusion and atypical) predicted distinct survival patterns similar to WHO stage 1/2, 3 and 4 respectively. The prognostic value of the WHO clinical staging system would be enhanced if typical PTB in African HIV infected patients were to be classified as WHO stage 2, tuberculous pleural effusion as WHO stage 3, and the atypical presentation of PTB as WHO stage 4.

The prognosis of patients with acquired immunodeficiency syndrome is variable. It was shown that AIDS defining diseases could be categorized according to outcome as early, intermediate and late events. Whereas the early AIDS defining illnesses extra-pulmonary tuberculosis and herpes simplex infection had a relatively favourable outcome, poor performance status, HIV wasting syndrome and encephalopathy were associated with a very poor prognosis.

Further validation of the suggested predictors of outcome, and their use in clinical practice may indeed facilitate the targeting of scarce health care resources at patients with the most favourable prognosis. While patients with

early HIV infection should be considered for investigations and treatments offered to HIV negative individuals, those who present with the complications of advanced AIDS and other markers of poor prognosis are unlikely to benefit from such interventions, in which case referral for home-based terminal care may be more appropriate.

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