

Clinical Characteristics and Natural History of Human Immunodeficiency Virus Infected Patients Seen at a General Hospital in Singapore

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Abstract

The number of patients with human immunodeficiency virus (HIV) infection in Singapore has risen over the years. A considerable proportion of them present with acquired immunodeficiency syndrome (AIDS). In this study, we document the clinical characteristics and natural history of a consecutive series of 50 patients who were found to have HIV infection when they were seen at a tertiary care hospital. The majority were in the 30 to 49 age group and the most common mode of acquisition was heterosexual contact. The patients presented with a variety of symptoms to 11 different clinical departments. Fifty-eight per cent of the patients had AIDS-defining illnesses at presentation, with Pneumocystis carinii pneumonia being the most common. On follow-up, the most frequently occurring opportunistic infection that developed was Cytomegalovirus retinitis. Most patients had multiple subsequent admissions-for both AIDS-defining and non AIDS-defining conditions. The median CD4 count of the cohort at presentation was 72/mm³. The median survival was 399 and 822 days in those who had and those who did not have an AIDS-defining illness at presentation, respectively. Mortality was most commonly attributed to pneumonia. HIV infection has protean manifestations and patients may present to various speciality departments; hence, doctors need to be aware of the spectrum of disease in order to make a diagnosis.

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Key words: AIDS, Opportunistic infections, Survival, Tertiary care

Introduction

The number of persons diagnosed with human immunodeficiency virus (HIV) infection in Singapore has increased steadily over the past few years' (Fig. 1). A considerable proportion of these patients presented with acquired immunodeficiency syndrome (AIDS). At the Communicable Disease Centre (CDC), the national referral centre for the management of HIV infection in Singapore, Leo² found that about half of the patients had AIDS-defining illnesses (ADIs) at presentation. It is therefore not surprising that patients have been presenting with AIDS to a general hospital. Tay and Chan³ at the Singapore General Hospital (SGH), a 1500-bed hospital with both acute and tertiary care facilities, reported that the number of known HIV-positive patients was 0.047 per thousand discharges in 1991 and that the figure increased to 0.260 per thousand discharges in 1994.

The increasing importance of HIV infection and AIDS as clinical entities in a tertiary care setting led us to embark on this study. The main objectives of the study were:

- 1) to document the presenting features of HIV infection as they were seen in patients presenting to a general hospital with both acute care and tertiary level facilities,
- 2) to determine the clinical circumstances that led to the diagnosis of HIV infection in this setting, and
- 3) to chart the natural history of HIV infection in this cohort of patients over a minimum follow-up period of two years.

Materials and Methods

This study is a retrospective review of the clinical records of the first 50 consecutive patients who fulfilled

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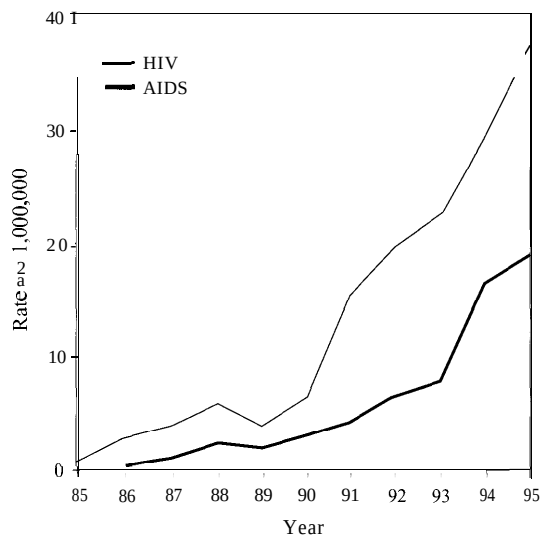


Fig. 1. Reported morbidity rate of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) in Singapore, 1985 to 1995 (Reproduced with permission from *Epidemiological News Bulletin* 1997; 23: 7-9).

the criteria for inclusion into the study. The names and identification numbers of the patients were provided by the HIV Reference Laboratory.

Inclusion criteria: All patients who tested positive for HIV infection at the HIV Reference Laboratory up to 31 December 1994 were eligible for inclusion into the study if their blood specimen had been sent from SGH. Known HIV-positive patients referred by CDC to SGH for specialist care, e.g. radiotherapy for cerebral lymphoma, were excluded. This is because the major aim of the study was to see how patients presented and were diagnosed to have HIV infection in a tertiary care setting.

Data collection: To obtain data on clinical presentation, case records from SGH were reviewed. Casenotes at SGH were reviewed for demographic data, sexual history, clinical features and the reason(s) for HIV testing. To obtain data on follow-up, case records up to 31 December 1996 in the CDC were reviewed. Demographic data and sexual history were checked against the information recorded in the CDC casenotes as history taking in the CDC was more focused given the already established diagnosis. Additional data collected on review of the CDC casenotes included clinical events, length of survival and cause of death (if applicable). Information on the survival of patients who had defaulted their follow-up were obtained from the Department of Clinical Epidemiology and the Registry of Births and Deaths, National Registration Department.

Definitions/Terminology

AIDS: In general, the 1993 CDCP (Centers for Disease Control and Prevention, Atlanta) Expanded Surveillance Case Definition was used to define AIDS.⁴

However, because the CD4 count was not available in all patients, CD4 <200/mm³ was not used as an AIDS-defining criterion in this study. A single episode of pneumonia in a year was not considered an ADI but if there were two or more episodes in a year, the second episode was considered an ADI. The Singapore Standard Occupational Classification was used to classify the patients' occupations.⁵

Unit presented to: This was the unit that the patient presented to with the illness that led to the discovery of HIV infection (called the index illness). Because of the re-organisation of the medical units in SGH in the period under study, the units that took in general medical admissions were collectively called "medical units" in this study.

Initial diagnosis: In trying to portray the patients as they presented and as they were investigated, we matched presenting symptoms of the index illness with the initial diagnosis made by the attending doctors and with the final diagnosis. The initial diagnosis in each case was the diagnosis entered after a doctor of at least Registrar grade had seen the patient. If the rank or seniority of the doctors seeing the patients could not be ascertained, the diagnosis entered on the morning after the admission was taken as the initial diagnosis. For cases seen only in the outpatient clinics, it was the diagnosis made at the first clinic visit.

Reason for HIV serology: The reason for ordering a HIV test was that recorded in the casenotes. Where this was not documented, the reason was classified as "clinical impression of HIV" if HIV infection or AIDS was entertained as a diagnostic possibility. If HIV infection or AIDS was not documented in the differential diagnoses of the attending doctors, a "best guess" reason was selected, depending on the clinical circumstances.

Intermittency of anti-retroviral therapy: Anti-retroviral therapy was considered to have been administered intermittently if there was a break of one week or longer in the continuity of consumption of the agent(s).

Survival: Survival was calculated from the date that HIV serology was sent.

Results

Fifty patients fulfilled the criteria for inclusion into the study. The SGH casenotes were incomplete for two patients and the CDC casenotes incomplete for one. Wherever this incompleteness affects the results, it will be mentioned and taken into account.

Year of Evaluation

The first patient was seen in 1986. One each was seen in 1988 and 1989. There was a marked increase in the number of patients diagnosed to have HIV infection at the SGH from 1993. This paralleled the dramatic in-

crease in the number of newly diagnosed HIV patients islandwide (Figs. 1 & 2).

Sex and Age Distribution, Marital and Occupational Status

Forty-nine (98%) of the patients were male. Their ages ranged from 19 to 64 years (Fig. 3). Thirty-four (68%) of the patients were single, ten (20%) were married, one was divorced and one widowed. The marital status was unknown in four others.

The patients' occupations are shown in Table I. One-quarter (24%) worked in the sales and service industry and another quarter (24%) worked in managerial and professional positions.

Nationality

Thirty-seven (74%) of the 50 patients were Singaporeans. Nine (18%) of them were from ASEAN countries (6 from Malaysia, 2 from Thailand and 1 from Indonesia) and four (8%) from farther afield (one each from the United Kingdom, Myanmar, Senegal and Seychelles).

Sexual Orientation and Multiplicity of Sexual Partners

Thirty-two (64%) were heterosexual, nine (18%) were homosexual and five (10%) were bisexual. In four (8%) of the patients, information on sexual orientation was not available.

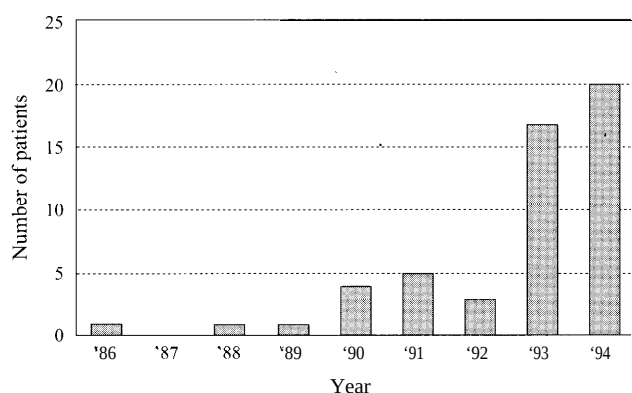


Fig. 2. No. of patients seen by year.

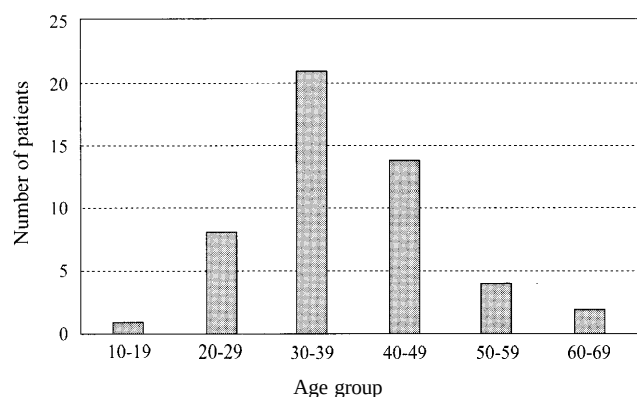


Fig. 3. Age distribution of patients.

TABLE I: CLASSIFICATION OF PATIENTS BY OCCUPATION

Occupational Classification	No. of patients (%)
Legislators, managers and senior officials	5 (10)
Professionals	7 (14)
Technicians and associate professionals	2 (4)
Clerical workers	0
Service workers, shop and market sales workers	12 (24)
Agricultural and fishery workers	0
Production craftsmen and related workers	3 (6)
Plant/Machine operators and assemblers	9 (18)
Cleaners, labourers and related workers	5 (10)
Not classifiable	7 (14)
Total	50 (100)

There were 33 (66%) patients who reported sexual contact with commercial sex workers. Thirteen (26%) patients denied visiting commercial sex workers. In four (8%) of the patients, this aspect of the sexual history was not documented. Overall, however, 44 (88%) of the patients reported multiple sexual partners.

Of the nine homosexuals, only two admitted to sexual contact with commercial sex workers.

Mode of Acquisition

Although 44 (88%) reported multiple sex partners, the mode of acquisition was determined to be sexual in 43 (86%) of the cases (Fig. 4). One patient with a history of sexual contact with female commercial sex workers in the 1970s was classified as having acquired the infection from blood transfusions in the United States in 1981. His physicians and an epidemiologist who investigated his case noted that he had been evaluated for lymphadenopathy and that his wife had become symptomatic only in the years subsequent to his transfusions.

Two patients in the cohort had received solid organ transplants. The transplant, performed overseas, was believed to be the mode of acquisition in one of them who denied all other risk factors for HIV infection. The other transplant recipient reported having had several sexual partners, including female commercial sex work-

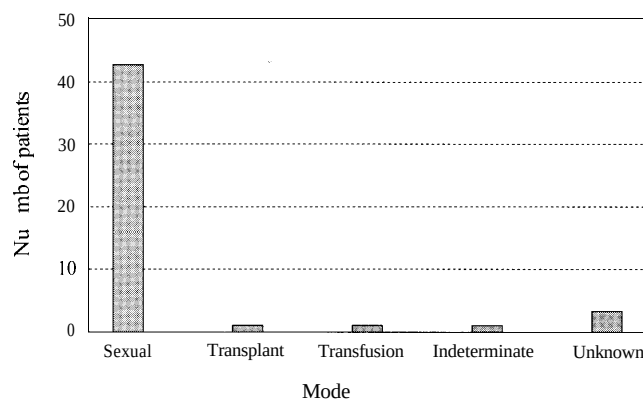


Fig. 4. Mode of acquisition

ers, and therefore his mode of acquisition was listed as indeterminate. The mode of acquisition was unknown in another four (8%) patients, the same four patients on whom information on sexual orientation was not available. One of them was admitted in a coma and died without regaining consciousness while another denied all risk factors for HIV infection. In another two non-Singaporean patients, the sexual histories had not been adequately documented before the patients returned to their home countries.

Unit Presented To, Clinical Presentation, Initial and Eventual Diagnoses

The units that the patients presented to are shown in Table II.

The commonest presenting symptoms were cough and dyspnoea, a lump in the neck or axilla (i.e. lymphadenopathy), and fever. The presenting complaints, initial diagnoses and eventual diagnoses are tabulated in Table III.

As can be seen from Table III, the most frequent diagnosis made by attending physicians in patients who presented with respiratory complaints was bronchopneumonia. In all four instances where the initial impression was bronchopneumonia (as well as in one more patient where the initial diagnosis was bilateral pneumonia), the eventual diagnosis was *Pneumocystis carinii* pneumonia (PCP).

The presenting complaint was neurological in origin in nine patients (Table III). The patient with bilateral leg weakness also had dyspnoea and received the correct diagnosis of Guillain-Barre syndrome.

Six patients presented with lymphadenopathy. After investigations including lymph node biopsy, the diagnosis was made of tuberculosis (TB) in two patients and HIV-related lymphadenopathy (persistent generalised lymphadenopathy) in four others.

Of the four patients who presented to the general surgical unit, one presented with severe *Salmonella* gastroenteritis, one with cervical and axillary lymphaden-

opathy, and two with an acute abdomen (one case of perforated appendix and one of acute pancreatitis).

Weight loss was the presenting complaint in three (6%) of the patients but an additional 25 patients admitted to having had significant weight loss on direct questioning.

It is interesting to note that the two patients in this series who presented with vomiting had cryptococcal meningitis. The patient who presented to the Burns unit had been admitted for Toxic Epidermal Necrolysis (TEN) believed to have resulted from carbamazepine prescribed for post-herpetic neuralgia.

Reason for HIV Serology

The commonest reason for doing HIV serology was the clinical impression that HIV infection was a possible or likely diagnosis in the patient-this occurred in 12 (24%) of the patients. A history of sexual contact with commercial sex workers prompted HIV testing in another 9 (18%) patients. The discovery of an ADI led to HIV testing in a further 5 (10%) of the patients. The other reasons for doing HIV serology are listed in Table IV.

Index of Illnesses in the SGH

Of the 50 patients, 29 (58%) had ADIs when they were seen at the SGH. Twenty-one (42%) had no ADI when they were evaluated in the SGH. One patient "presented" twice, once with generalised lymphadenopathy and the second time (three years later) with cerebral toxoplasmosis, having defaulted his appointments at the CDC. He was included as having had an ADI.

Seven conditions (Table V) accounted for all the AIDS indicator conditions seen in the SGH. These were PCP, cerebral toxoplasmosis, TB, cryptococcal meningitis, cryptosporidiosis, non-Hodgkin's lymphoma and Kaposi's sarcoma. Of the 29 patients, two had two ADIs and one had three ADIs, giving a total of 33 episodes of AIDS-defining diseases. If a CD4 count $<200/\text{mm}^3$ had been considered AIDS-defining, an additional five patients would have been classified as having AIDS.

Of the illnesses that were not AIDS-defining, the most common diagnosis was persistent generalised lymphadenopathy. Other conditions in this category included Guillain-Barre syndrome, mononeuropathy associated with lymphocytic pneumonitis, sinusitis and pneumonia. One patient, who presented to another hospital with *Salmonella* gastroenteritis, was referred to the SGH because he was discovered to have chronic lymphatic leukaemia (CLL). He was tested because he had a reversed CD4/CD8 ratio.

Prior Diagnosis of HIV Infection

Nine (18%) of the patients had previously been diag-

TABLE II: UNITS PRESENTED TO

Unit	No. of patients (%)
General Medicine	29 (58)
General Surgery	4 (8)
Haematology	4 (8)
Neurology/Neurosurgery	4 (8)
Ophthalmology	2 (4)
Nephrology	2 (4)
Burns	1 (2)
Obstetrics and Gynaecology	1 (2)
Cardiology	1 (2)
Otorhinolaryngology	1 (2)
Multiphasic Health Screening	1 (2)
Total	50 (100)

TABLE III: PRESENTING SYMPTOMS, INITIAL DIAGNOSES AND EVENTUAL DIAGNOSES

Symptom/Patients	Initial diagnoses	Eventual diagnoses
Cough and Dyspnoea		
	PTB	PTB
2	Bronchopneumonia	PCP
3	PCP	PCP
4	?Churg Strauss syndrome	Interstitial pneumonitis*
	Congestive cardiac failure	PCP
6	Bronchopneumonia	PCP
	Bilateral pneumonia	PCP
8	**	PCP
Fever		
9	TB lymphadenopathy	TB lymphadenopathy
10	Pyrexia of unknown origin (PUO)	HIV infection
11	Bronchopneumonia	PCP
12	Bronchopneumonia	PCP
13	PCP	PCP
14	HIV infection	PCP
15	PUO	HIV infection
16	Meningitis	Cryptococcal meningitis
17	HIV infection	HIV infection
Lymphadenopathy		
18	PTB	PTB
19	Lymphadenopathy for investigation	TB
20	TB	HIV infection
21	Lymphadenopathy for investigation	HIV infection
22	Haematologic malignancy	HIV infection
23	Lymphadenopathy for investigation	HIV infection
Headache		
24	Brain tumour	Cerebral toxoplasmosis
25	Brain tumour	Cerebral toxoplasmosis
Seizure		
26	Epilepsy	Cerebral toxoplasmosis
27	Stroke	Cerebral toxoplasmosis
Drowsiness		
28	Encephalitis	Pneumococcal meningitis
29	Miliary TB	Miliary TB (with meningitis)
30	Meningitis	Cryptococcal meningitis
Leg Weakness		
31 (unilateral)	?Churg-Strauss syndrome	HIV infection a/w mononeuritis
32 (bilateral)	GBS	HIV infection a/w GBS
Vomiting		
33	Chronic renal failure	Cryptococcal meningitis
34	Acute gastritis	Cryptococcal meningitis
Diarrhoea		
35	Diarrhoea for investigation	No microbial cause found
36	Diarrhoea for investigation	Cryptosporidiosis

1 & 18, 2 & 11, 7 & 12, 6 & 35 are the same patients

* no microbiologic aetiology found

** information not available

nosed to have HIV infection and therefore knew their underlying diagnosis when they were attended to by doctors in the SGH. However, only three of these nine (33%) revealed this to their attending doctors.

Earliest CD4 Counts

This parameter was evaluable only in 39 (78%) of the patients. Of the remaining 11 (22%), the CD4 count was not done in eight (16%) of the patients. Six of these eight were foreigners who subsequently returned to their home countries; another two died after relatively short

stays in the SGH. One patient's casenotes were incomplete and hence the earliest CD4 count could not be determined; in another patient, the absolute CD4 was never documented, although a percentage was recorded. The last patient deemed inevaluable was the patient with CLL whose CD4 was $1195/\text{mm}^3$.

The median CD4 count of the rest was $72/\text{mm}^3$, with a mean of $142/\text{mm}^3$.

Follow-up

Two patients died in the SGH and four returned to

TABLE IV: REASONS FOR ORDERING HIV TEST

Reason	No. (%)
Clinical impression of HIV	12 (24)
Sexual history	9 (18)
AIDS-defining illness	5 (10)
Confirming patient's history	3 (6)
Post-overseas transplant	2 (4)
Pre-bone marrow transplant	1 (2)
Needlestick injury protocol	1 (2)
Multiphasic health screen	1 (2)
Patient's request	1 (2)
Foreigner	1 (2)
Reversed CD4/CD8 ratio	1 (2)
Not documented	13 (26)
Total	50 (100)

TABLE V: THE INDEX OF ADIs IN SGH

Index of ADIs	No. of patients
PCP	11
Tuberculosis (pulmonary, extrapulmonary)	8
Cerebral toxoplasmosis	7
Cryptococcal meningitis	3
Non-Hodgkin's lymphoma	2
Cryptosporidiosis	1
Kaposi's sarcoma	1

their home countries after discharge from the SGH, hence, six (12%) were never seen at the CDC.

Of those referred to the CDC for further management, four of the patients returned to their home countries after being seen at the CDC only once. Three of them were stabilised as inpatients before discharge.

Six patients died in their first admission to the CDC after transfer from the SGH. Two of them did not have an ADI—one had complications associated with TEN and the other was thought to have aspirated. None of these six developed a new ADI in the interim between transfer and death. Therefore, long-term follow-up data were available for only 34 (68%) of the original 50 patients.

Subsequent ADIs on Follow-up

Eighteen patients developed 35 new ADIs during their follow-up. Sixteen did not develop a new ADI.

The most common ADI was cytomegalovirus (CMV) retinitis, which developed in 8 patients. Table VI shows new ADIs that developed in patients while on follow-up. The single patient who developed PCP had not been regular with follow-up. A CD4 count of 198/mm³ was documented about 6 months before he presented with PCP, which progressed to the acute respiratory distress syndrome (ARDS) and eventually proved fatal.

TABLE VI: NEW ADIs DEVELOPING ON FOLLOW-UP

New ADIs	No. of cases
CMV retinitis	8
MAI bacteraemia	6
Cerebral toxoplasmosis	6
Recurrent pneumonia	4
TB (pulmonary or extrapulmonary)	2
Cryptococcal meningitis	2
PCP	1
Non-Hodgkin's lymphoma	1
Candida oesophagitis	1
Wasting syndrome	1
HSV oral ulcer lasting >1/12	1
Isosporiasis	1
HIV encephalopathy	1
Total	35

Non-ADIs on Follow-up

The patients also developed illnesses that were not AIDS-defining. Excluding a rash, a total of 37 episodes of illnesses not requiring admission were documented in 19 patients. A skin rash seen and evaluated on an outpatient basis only was not included in the calculation as rashes are very common conditions in HIV patients which not all doctors document at every attendance. The most common illness treated on an outpatient basis was a chest infection, of which six cases were documented. *Salmonella* bacteraemia was treated with oral antibiotics in the outpatient setting in two patients. Other conditions similarly diagnosed and treated included herpes zoster, gastroenteritis and skin abscesses. Optic atrophy attributed to Ethambutol was diagnosed in one patient.

Non-ADIs that required hospitalisation were also documented. Twenty-three patients were admitted 36 times for such illnesses. A chest infection was again the most common, accounting for nine admissions in nine patients. This was followed by an adverse drug reaction—seven episodes requiring admission were documented in six patients. Other conditions that were not AIDS-defining but that required inpatient evaluation and care included *Salmonella* gastroenteritis, pyomyositis, peripheral neuropathy, oesophageal ulcer, subarachnoid haemorrhage, and myelopathy of undetermined aetiology.

Admissions after Transfer from SGH

Of the 44 patients who were referred to the CDC for further management, one has returned to his home country after one outpatient attendance. Seven more have never had any admissions, although one of them was lost to follow-up. Thirty-five patients were admitted a total of 114 times. One patient's casenotes were incomplete. As he had several admissions (precise number unknown), the number and duration of his admissions have been omitted from the results. How-

ever, it is significant that his last admission spanned 270 days. For the other patients, the length of stay ranged from one to 188 days, with a mean of 19 days and a median of 13 days. Of the 114 admissions, 36 (32%) were for illnesses that were not AIDS-defining (*vide supra*).

Anti-retroviral Therapy

Twenty-seven (54%) patients never received anti-retroviral therapy. Of the other 23, 17 received therapy only intermittently.

The reasons for never having received anti-retroviral therapy included return to home country, non-availability of such agents at that time, death soon after diagnosis and financial constraints. Of those who did receive the agents intermittently, the main reason for temporary or permanent discontinuation of the agents was the development of adverse effects; other reasons included inadequate finances, attempts at alternative therapy and a sense of hopelessness.

Survival

Of the 50 patients, 28 (59%) have died by the end of the study period in December 1996. Two (4%) died before coming to the CDC, as mentioned earlier. Eight (16%) have returned to their home countries and are lost to follow-up. Fourteen (28%) are alive. The Kaplan-Meier survival curves of the cohort are shown in Figures 5a and 5b. The median survival of the cohort was 428 days. The median survival of those who had an ADI at discovery of HIV infection was 399 days and that of those who did not have an ADI at diagnosis of HIV infection was 822 days.

Cause of Death

The most common cause of death was pneumonia, recorded in 12 patients. One patient died of PCP complicated by ARDS. Death was attributed to cerebral toxoplasmosis in four patients and to cryptococcal meningitis in three. The other causes of death are listed in

Table VII.

Discussion

This study documents the clinical characteristics and natural history of the first fifty consecutive patients with positive HIV serology results sent from the SGH, a hospital with both acute care and tertiary level facilities.

In the authors' experience, a few patients evaluated at the CDC for newly-diagnosed HIV infection have reported prior outpatient attendances and admissions in the SGH. However, reviewing the SGH records of all known HIV patients may not have led to a more accurate characterisation of the clinical presentation of HIV infection. HIV infection has a long and variable incubation period and it would not have been possible to determine the time of HIV infection and whether or not their symptoms at the time of evaluation in SGH were HIV-related.

In line with national⁶ and worldwide^{6,7} trends, the number of cases seen and diagnosed has increased over the years. The trend, as documented in Figure 2, parallels the national trend.⁶ This reflects the contribution of

TABLE VII: CAUSES OF DEATH

Cause of Death	No. of Patients
Pneumonia	12
Cerebral toxoplasmosis	4
Cryptococcal meningitis	3
Disseminated TB	1
<i>Pseudomonas aeruginosa</i> septicaemia	1
Neutropaenic sepsis	1
Cryptosporidiosis	1
MAI bacteraemia	1
Non-Hodgkin's lymphoma	1
Kaposi's Sarcoma	1
Subarachnoid haemorrhage	1
PCP with ARDS	1

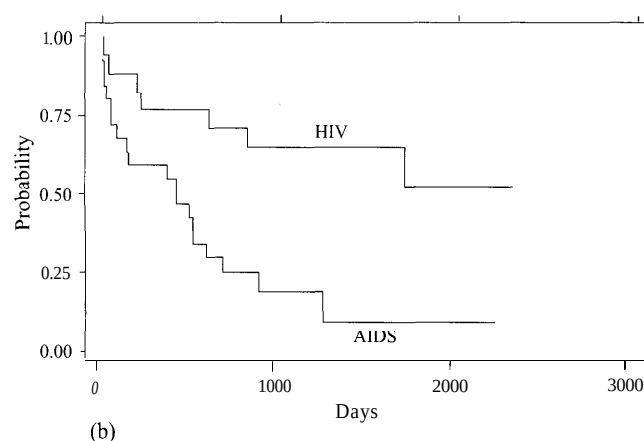
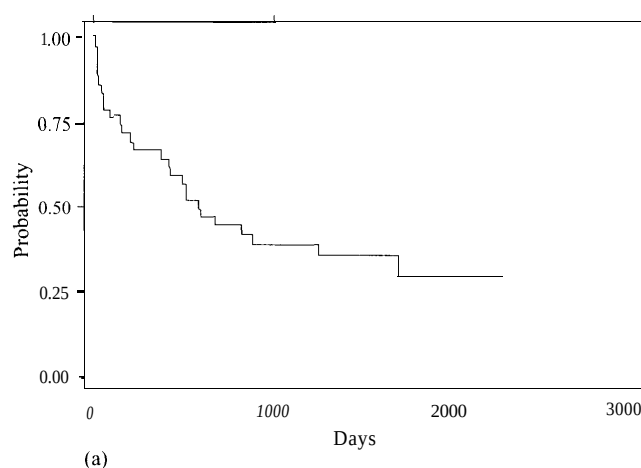


Fig. 5. Kaplan-Meier survival curve for (a) the entire cohort and (b) for subgroups with AIDS and without AIDS-defining illnesses (labelled HIV).

a large hospital to the number of cases nationwide. This also shows how a hospital with both acute and tertiary care facilities can be a microcosm of society in terms of disease incidence.

The occupations of the patients serve as a reminder that HIV is not a disease of any particular group of people. The absence of clerical, agricultural and fishery workers in this cohort reflects the small size of the cohort and the relative scarcity of agricultural and fishery workers in Singapore.

As in many parts of Asia, the most common mode of acquisition in this series of patients was heterosexual intercourse. Interestingly, in a study of the first 50 Singaporeans with HIV infection up to the mid-1990, majority had been infected through homosexual contact.⁸ This trend has changed and at the end of 1995, the main mode of acquisition among Singaporeans was heterosexual contact.⁹ Although intravenous drug users are not represented in this cohort, it is a documented form of transmission of HIV infection in Singapore.⁹ The absence of intravenous drug users in this cohort may be explained by the referral pattern—drug rehabilitation inmates or probationers who fall ill tend to be referred by their supervisors directly to the prison hospital, where the discovery of HIV infection leads to a direct referral to the CDC. Organ transplants overseas are known to account for a few local cases of HIV infection.⁹

HIV infection is well known to have protean manifestations and textbooks of HIV medicine have separate chapters dedicated to its manifestations in the different organ systems. The findings of this study are no exception, with patients presenting to many different clinical disciplines. Hence, doctors in a wide variety of specialties need to be aware of the clinical manifestations of HIV infection.

The presenting symptoms of HIV infection in its various stages are, however, common ones.⁹ Cough, breathlessness, fever, vomiting, headache, hemiparesis and lymphadenopathy, which were the most common presenting symptoms recorded in this series of patients, are everyday clinical problems for all doctors, especially doctors of first contact. With the emergence of HIV infection and AIDS as important clinical entities, it is only appropriate that HIV infection and its complications be included in the differential diagnosis of a large number of symptoms.

Interestingly, a history of high-risk sexual behaviour did not always correlate with the clinical suspicion of HIV infection. The formulation of a differential diagnosis that includes HIV infection and its complications in a patient with high-risk behaviour may have happened less readily in the earlier part of the period covered by the study. This, in part, was due to the incomplete understanding of the disease—the link between HIV

and TB, for example, was not clear in the early days of the AIDS epidemic.¹⁰ That awareness of HIV infection is increasing among doctors in Singapore is reflected in the increased requests for HIV serology received by the HIV Reference Laboratory from 1990 to 1994.¹¹⁻¹³

In this series, PCP was the most common illness that led to the diagnosis of HIV infection. This is not surprising, as prior to the advent of preventive therapy, PCP was the most common AIDS-defining illness in western countries¹⁴ and hospitalisation of first-episode cases was the rule.¹⁵ In this region too, PCP has been reported as the most common AIDS-defining event.^{2,16,17} The frequency of this condition has declined with the introduction of preventive therapy.¹⁸ In this small series, only one patient developed PCP while “on follow-up”—he had defaulted his therapy and appointments.

PCP carries a substantial mortality, with death occurring in 20% of typical cases and 50% of severe cases.¹⁵ It has been reported to be the most frequent cause of death in a cohort of patients followed up in Hong Kong from 1985 to 1995.¹⁹ In this series, there were no deaths from PCP when it was the presenting illness.

As in other parts of the world where TB is endemic,^{16,20,21} TB was a common ADI in this series and in local HIV patients as a whole.^{1,2} Indeed, the frequency of TB as an AIDS-indicator illness is rising in Singapore,² underlining the role of co-infection in causing morbidity.

Fever is a common problem in the HIV patient^{9,22,23} and this series was no exception. A superposed infection is the first consideration when evaluating a febrile HIV patient as treatment of an opportunistic infection may be life-saving. Very rarely, no cause other than HIV itself can be found for the fever,^{22,23} as shown in this series.

No patient presented with CMV disease or with *Mycobacterium avium intracellulare* (MAI) infection. These, however, were common illnesses in this cohort of patients on follow-up. This is in keeping with established knowledge of the natural history of HIV infection, where CMV disease and MAI infection (in particular, MAI bacteraemia), are diseases seen late in the course of HIV infection.^{9,18,24} In fact, at one time, MAI bacteraemia was considered a marker of the dying HIV patient and not thought of as a disease to be treated.²⁵

The numerous non AIDS-defining illnesses and their associated morbidity recorded in this cohort of patients illustrate that HIV-infected patients will continue to present to a variety of doctors, specialists and non-specialists alike. The underlying HIV infection may not be detected because the presenting illness is usually a common one. This is true even when the patient is already known to be seropositive as he or she may not reveal their underlying diagnosis to the attending doctors, as shown in this series. A high index of suspicion is essential, for the knowledge that HIV infection is an

underlying illness will affect the differential diagnosis entertained and the initial treatment prescribed.

The survival in this cohort of patients is comparable to that seen in several published studies,^{26,27} (also summarised by Mocroft et al²⁸). Because of the small number of patients, stratifying survival according to opportunistic infection at presentation may not have reflected the natural history of HIV infection accurately and therefore was not done. Comparative analysis of the survival benefit of different regimens of anti-retrovirals was also difficult to interpret because of the small numbers of patients in each subgroup (data not presented).

In this series, 42% of the patients who were evaluated in a tertiary hospital and found to have HIV infection did not have illnesses that were AIDS-defining. Given the availability of effective anti-retrovirals that could well change the natural history of the disease, recognising HIV infection early in its course is of crucial importance. While people at risk are urged to be tested early, the opportunity to diagnose HIV infection in a patient presenting with a HIV-related (albeit not AIDS-defining) condition must not be missed.

In summary, this study reports how HIV infection, with its protean manifestations, presented to doctors in many clinical specialties at a general hospital in Singapore. The natural history of HIV infection in this cohort was that of progressive immunodeficiency characterised by multiple opportunistic infections. Like other patients with moderate to advanced HIV infection, the patients suffered considerable morbidity and required substantial outpatient and inpatient care. Doctors in many fields of medicine will come into contact with HIV-infected patients and should include HIV infection and its complications in their approach to common medical problems.

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