Natural History of Human Immunodeficiency Virus Disease in Southern India

N. Kumarasamy,[1] Suniti Solomon,[1] Timothy P. Flanigan,[3] R. Hemalatha,[1] S. P. Thyagarajan,[2] and Kenneth H. Mayer[3]

[1]Y. R. Gaitonde Center for AIDS Research and Education and [2]Department of Microbiology, Dr.ALM Post Graduate Institute of Basic Medical Sciences, University of Madras, Chennai, India; and [3]Miriam Hospital, Brown University, Providence, Rhode Island

There are few reports of the natural history of human immunodeficiency virus (HIV) infection from Asia. In a retrospective analysis of 594 patients (72.9% male; baseline CD4 cell count, 216 cells/μL) receiving care at YRG Center for AIDS Research and Education, a tertiary HIV referral center in southern India, the mean duration of survival from serodiagnosis was 92 months. Ninety-three percent of the patients acquired infection through heterosexual contact. The most common acquired immune deficiency syndrome–defining illnesses were pulmonary tuberculosis (49%; median duration of survival, 45 months), *Pneumocystis carinii* pneumonia (6%; median duration of survival, 24 months), cryptococcal meningitis (5%; median duration of survival, 22 months), and central nervous system toxoplasmosis (3%; median duration of survival, 28 months). Persons with a CD4 lymphocyte count of <200 cells/μL were 19 times (95% confidence interval [CI], 5.56–64.77) more likely to die than were those with CD4 cell count of >350 cells/μL. Patients who had ⩾1 opportunistic infection were 2.6 times more likely to die (95% CI, 0.95–7.09) than were those who did not have an opportunistic infection. Antiretroviral therapy for patients with low CD4 lymphocyte counts improved the odds of survival (odds ratio, 5.37; 95% CI, 1.82–15.83).

The first case of HIV infection in India was detected in 1986 [1], and early reports suggested that the epidemic was most prevalent in female sex workers, truck drivers, and patients attending sexually transmitted disease clinics [2]. Subsequently, the prevalence of HIV infection among women attending antenatal clinics and married monogamous women was reported from India [3–5]. It is estimated that the number of people living with HIV infection in India could be 3–4 million [6].

HIV infection is marked by a progressive decrease in the number of circulating $CD4^+$ T helper cells, which, over a period of years, leads to immunologic decline and death due to opportunistic infections and neoplasms [7, 8]. Although the clinical course of HIV infection varies considerably from patient to patient, with progression to AIDS taking anywhere from <1 to ⩾10 years, the reason for this variability remains unclear. The spectrum of opportunistic infections differs from region to region [9–12]. Survival with AIDS has been shown to vary greatly, but, in general, the median duration of survival after an AIDS diagnosis in developed countries before the era of HAART was estimated to be 12–18 months [13]. Studies reveal that specific AIDS-defining illnesses, CD4 cell counts, and HIV RNA levels predict the survival of persons with HIV disease [14, 15]. The widespread use of effective chemoprophylaxis for opportunistic infections and, more recently, the use of antiretroviral therapy have resulted in a delay in the onset of AIDS, longer survival,

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Reprints or correspondence: Dr. N. Kumarasamy, YRG Center for AIDS Research and Education, 1 Raman St., T Nagar, Chennai-600017 India (nkumarasamy@eth.net).

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and a change in the pattern of opportunistic infections in the developed world [16, 17].

It is estimated that 90% of HIV-infected persons worldwide live in developing countries [18]. There have been very few reports of the natural history and patterns of survival of persons with AIDS from developing countries and resource-poor settings [19–21]. We report the prevalence of specific opportunistic infections, their correlation with CD4 lymphocyte counts, and durations of survival in relation to demographic variables and the use of antiretroviral therapy in a clinic-based population receiving care in the largest HIV care facility in southern India.

MATERIALS AND METHODS

We describe 594 patients for whom CD4 cell counts were available, who had ⩾2 study visits, and who presented for clinical care at the YRG Center for AIDS Research and Education Medical Center in Chennai, India, during the period of June 1996 through June 2001. YRG CARE was founded in 1993 as a nonprofit organization to provide voluntary counseling, HIV testing, programs on HIV prevention among youth, and medical and psychosocial care for persons living with HIV infection. This is the largest tertiary referral HIV care center in southern India, and it provides care for >2000 HIV-infected persons every year.

Specific opportunistic infections were diagnosed on the basis of standard clinical definitions and by laboratory procedures [22]. CD4 lymphocyte counts were determined by flow cytometry (Becton Dickinson). Serological markers of hepatitis B virus (HBV; hepatitis B surface antigen) and hepatitis C virus (HCV; antibody to HCV) were tested by ELISA (Wellcozyme; Murex Diagnostics). Standard clinical algorithms were used in clinical management of initiation of prophylactic and therapeutic interventions. Patients were given 1 double-strength tablet of trimethoprim-sulfamethoxazole (TMP-SMZ; 160 mg TMP and 800 mg SMZ) orally once daily to prevent *Pneumocystis carinii* pneumonia when the CD4 lymphocyte count was <200 cells/μL [23] or independent of CD4 lymphocyte count if they had developed any opportunistic infection. Patients were advised to initiate antiretroviral therapy when their CD4 lymphocyte count was <350 cells/μL if they were able to afford treatment [24]. The mean duration of follow-up for the study subjects from the date of HIV serodiagnosis was 18 months (range, 3–147 months); the median duration of follow-up was 14.5 months. The date of HIV serodiagnosis was obtained from the laboratory results after counseling and testing. The HIV diagnosis was confirmed by 2 different antibody tests.

Data were entered by use of a standardized collection form that documented age, sex, demographic variables, mode of HIV transmission, date of HIV detection, presenting symptoms and opportunistic infections, CD4 lymphocyte counts, total lymphocyte counts, and use of TMP-SMZ prophylaxis and antiretroviral drugs. Study participants were seen every 3 months as part of clinical care in addition to visits when they were symptomatic. The primary end point in this analysis was death, and the secondary end points were incident opportunistic infections.

Data entry, database management, and analysis were done with use of SPSS, version 9.5 (SPSS). Descriptive statistics were used to calculate the frequency, mean, median, and standard deviation. For all normally distributed variables, Student's *t* test was used to determine the significant mean difference in various groups. For nonnormally distributed variables, the Mann-Whitney *U* test was used. Survival times were calculated from the date of the participant's initial HIV detection to the last day of study follow-up for each participant. Kaplan-Meier survival analysis was performed to determine the mean and median durations of survival in relation to the demographic variables, opportunistic infections, TMP-SMZ prophylaxis, CD4 cell count, and antiretroviral therapy. Log-rank statistics were used to test the equality of the survival distributions for all of the variables. Univariate and multivariate Cox regression analyses for all factors relating to survival of patients were done.

RESULTS

The median age of the study subjects at the time of HIV diagnosis was 32 years (range, 18–72 years), and the median CD4 lymphocyte count at baseline was 216 cells/μL. Of the 594 patients studied, 72.9% were male, and the median CD4 lymphocyte count was 162 cells/μL, compared with 358 cells/μL for female subjects (27.1%; $P < .001$). Ninety-three percent of these persons acquired HIV infection through heterosexual intercourse, 4.6% via blood transfusion, and 2.4% via injection drug use. More than half (56.9%) of the study subjects were 26–35 years old (table 1).

Pulmonary tuberculosis (49.3%) was the most common AIDS-defining illness observed in this cohort, and the median CD4 lymphocyte count at the time of diagnosis was 111 cells/μL. The other prevalent AIDS-defining infections are as follows: extrapulmonary tuberculosis (11.0% of patients; median CD4 cell count, 122 cells/μL), *P. carinii* pneumonia (6.1% of patients; median CD4 cell count, 87 cells/μL), cryptosporidiosis (4.7% of patients; median CD4 cell count, 133 cells/μL), cryptococcal meningitis (4.7% of patients; median CD4 cell count, 91 cells/μL), CNS toxoplasmosis (3.4% of patients; median CD4 cell count, 135 cells/μL), and cytomegalovirus retinitis (3.2% of patients; median CD4 cell count, 51 cells/μL). Eighty percent of subjects had >1 opportunistic infection when they initially

Table 1. Characteristics of study patients in survey of HIV infection in India.

Characteristic	No. (%) of patients	Median CD4 cell count, cells/μL	No. (%) of deaths	Duration of survival, months		P[a]
				Median	Mean	
Sex						
Male	433 (72.9)	162	67 (91.8)	50	58	<.001
Female	161 (27.1)	358	6 (8.2)	147	58	
Mode of transmission						
Heterosexual contact	552 (93.0)	218	67 (91.8)	147	92	.96
Blood transfusion	27 (4.6)	138	2 (2.7)	30	32	
Injection drug use	14 (2.4)	217	4 (5.5)	82	56	
Age, years						
16–25	85 (14.3)	468	4 (5.5)	92	39	.04
26–35	338 (56.9)	218	39 (53.4)	147	103	
36–45	122 (20.5)	129	23 (31.5)	44	51	
>45	49 (8.2)	99	7 (9.6)	40	42	
HIV-associated condition[b]						
Pulmonary tuberculosis	293 (49.3)	111	58 (79.5)	45	77	<.001
Oropharyngeal candidiasis	324 (54.5)	107	70 (95.9)	45	76	<.001
Extrapulmonary tuberculosis	66 (11.1)	122	15 (20.5)	40	85	.07
Herpes zoster	51 (8.6)	160	10 (13.7)	51	58	.60
Pneumocystis carinii pneumonia	36 (6.1)	87	21 (28.8)	24	54	<.001
Herpes simplex	34 (5.7)	219	4 (5.5)	51	92	.19
Cryptosporidiosis	28 (4.7)	133	9 (12.3)	40	73	.33
Cryptococcal meningitis	28 (4.7)	91	19 (26.0)	22	23	<.001
Oral hairy leukoplakia	24 (4.0)	129	3 (4.1)	45	41	.68
CNS toxoplasmosis	20 (3.4)	135	10 (13.7)	28	64	.01
Cytomegalovirus retinitis	19 (3.2)	51	4 (5.5)	45	67	.74
Papular pruritic eruption	66 (11.1)	95	16 (21.9)	49	77	.49
Tinea	29 (4.9)	143	6 (8.2)	147	92	.66
Recurrent bacterial respiratory infection	9 (1.5)	180	—	—	—	—
Coinfection						
Hepatitis B virus (n = 116)	7 (6.0)	98	1 (6.7)	31		.82
Hepatitis C virus (n = 43)	4 (4.8)	91	2 (13.3)	33		.001
Total	594 (100)	216	73 (12.3)	147.13	92	

[a] For comparison with the median duration of survival.
[b] Durations of survival were calculated for each HIV-associated condition compared with persons who did not have that condition.

presented for care; thrush and/or pulmonary tuberculosis were often seen in patients with other infections. Six percent of the patients were coinfected with HBV, and 4.8% were coinfected with HCV (table 1). Fourteen percent of HBV-infected and 25% of HCV-infected patients had received blood transfusion; 50% of HCV-infected patients were injection drug users.

Of the 594 subjects studied, 73 (13.2%) died during follow-up. The overall mean duration of survival for the study patients was 92 months. Female patients had a higher median duration of survival than did male patients (147 months vs. 50 months; $P < .001$). Persons who acquired HIV infection through heterosexual contact had survival rates comparable with those who became infected via other routes.

The median duration of survival for patients who presented with or developed opportunistic infections was compared with that of those who did not. The median duration of survival for persons who presented with or developed oropharyngeal candidiasis was 45 months ($P < .001$), and the median duration

Table 2. Findings of univariate Cox regression for all factors relating to survival of patients with AIDS in a survey in India.

Variable	OR (95% CI)	*P*
Sex		
Male	4.08 (1.64–10.14)	.002
Female[a]	1.0	
Mode of transmission		
Heterosexual contact[a]	1.0	
Blood transfusion	0.87 (0.21–3.57)	.85
Injection drug use	1.23 (0.45–3.4)	.69
Age, years		
16–25	0.61 (0.22–1.71)	.35
26–35[a]	1.0	
36–45	1.8 (1.06–3.05)	.02
>45	1.54 (0.68–3.45)	.29
CD4 lymphocyte count, cells/μL		
<200	8.19 (2.53–26.47)	<.001
200–350	2.19 (0.49–9.79)	.31
>350[a]	1.0	
HIV-associated illness		
Pulmonary tuberculosis		
Yes	3.52 (1.96–6.32)	
No[a]	1.0	<.001
Oropharyngeal candidiasis		
Yes	13.94 (4.38–44.32)	<.001
No[a]	1.0	
Extrapulmonary tuberculosis		
Yes	1.7 (0.95–3.06)	.07
No[a]	1.0	
Herpes zoster		
Yes	0.76 (0.37–1.51)	.42
No[a]	1.0	
Pneumocystis carinii pneumonia		
Yes	4.47 (2.67–7.51)	<.001
No[a]	1.0	
Herpes simplex		
Yes	0.48 (0.15–1.51)	.21
No[a]	1.0	
Cryptosporidiosis		
Yes	1.48 (0.71–3.12)	.3
No[a]	1.0	
Cryptococcal meningitis		
Yes	6.98 (4.1–11.97)	<.001
No[a]	1.0	
Oral hairy leukoplakia		
Yes	0.79 (0.25–2.54)	.70
No[a]	1.0	
Toxoplasmosis		
Yes	2.57 (1.27–5.2)	.01
No[a]	1.0	
Cytomegalovirus retinitis		
Yes	1.23 (0.39–3.9)	.73
No[a]	1.0	
Papular pruritic eruption		
Yes	1.24 (0.69–2.2)	.47
No[a]	1.0	
Tinea		
Yes	0.82 (0.33–2.06)	.68
No[a]	1.0	
Coinfection		
Hepatitis B virus		
Yes	1.27 (0.16–10.02)	.82
No[a]	1.0	
Hepatitis C virus		
Yes	7.84 (1.61–38.22)	.01
No[a]	1.0	

[a] Referent.

of survival for those who had pulmonary tuberculosis was 45 months ($P < .001$). The median duration of survival was lower for persons who had CNS toxoplasmosis (28 months; $P = .007$), *P. carinii* pneumonia (24 months; $P < .01$), or cryptococcal meningitis (22 months; $P < .001$) (table 1).

Univariate analysis showed that male patients died sooner than did female patients (OR, 4.08; 95% CI, 1.64–10.14). Persons who received their diagnosis at age 36–45 years died sooner than did those who were 26–35 years old (OR, 1.8; 95% CI, 1.06–3.05; $P = .02$). However, patients in other age strata did not seem to have significant increased risk of death. Persons with CD4 lymphocyte counts of <200 cells/μL died sooner than did those with counts of >350 cells/μL at baseline (OR, 8.19; 95% CI, 2.53–26.47). The following opportunistic infections were associated with increased risk of death: pulmonary tuberculosis (OR, 3.52; 95% CI, 1.96–6.32), oropharyngeal candidiasis (OR, 13.94; 95% CI, 4.38–44.32), *P. carinii* pneumonia (OR, 4.47; 95% CI, 2.67–7.51), cryptococcal meningitis (OR, 6.98; 95% CI, 4.1–11.97), and CNS toxoplasmosis (OR, 2.57; 95% CI, 1.27–5.2). Herpes zoster, herpes simplex, and oral hairy leukoplakia were not associated with changes in mortality (table 2).

On multivariate analysis, the sex difference for survival disappeared. Persons with CD4 lymphocyte counts <200 cells/μL were 18.97 times (95% CI, 5.56–64.77) more likely to die than were those with >350 CD4 cells/μL, and persons who had ≥ 1 opportunistic infection were 2.6 times (95% CI, 0.95–7.09) more likely to die than were those who did not. The OR of death for persons with CD4 lymphocyte counts <200 cells/μL who were not receiving TMP-SMZ prophylaxis was 2.96 (95% CI, 1.30–6.77), compared with persons who received TMP-SMZ prophylaxis with comparable CD4 lymphocyte counts. Persons with CD4 lymphocyte counts of <350 cells/μL who

Table 3. Findings of multivariate Cox regression analysis relating to survival of patients with AIDS after adjusting for sex, mode of transmission, age, CD4 lymphocyte count, presence of any opportunistic infection (OI), use of trimethoprim-sulfamethoxazole (TMP-SMZ) prophylaxis, and antiretroviral therapy.

Variable	OR (95% CI)	*P*
Sex		
Male	1.95 (0.75–5.12)	.17
Female[a]	1.0	
Mode of transmission		
Sexual	0.76 (0.23–2.53)	.65
Parenteral[a]	1.0	
Age group, years		
⩽45	1.37 (0.41–4.56)	.61
>45[a]	1.0	
CD4 lymphocyte count		
<200	18.97 (5.56–64.77)	<.001
200–350	3.07 (0.68–13.87)	.14
>350[a]	1.0	
Presence of any OI		
Yes	2.60 (0.95–7.09)	.06
No[a]	1.0	
TMP-SMZ prophylaxis		
Yes[a]	1.0	
No	2.96 (1.30–6.77)	.01
Antiretroviral therapy		
Yes[a]	1.0	
No	5.37 (1.82–15.83)	.002

[a] Referent.

were not receiving antiretroviral therapy were 5.37 times (95% CI, 1.82–15.83) more likely to die than were those who received antiretroviral therapy (table 3).

In our study, 29% of the subjects received antiretroviral therapy. The median duration of survival for subjects who initiated antiretroviral therapy when their CD4 lymphocyte counts were <200 cells/μL ($n = 141$) was 45 months; for those with comparable CD4 lymphocyte counts who did not receive antiretroviral therapy ($n = 71$), the median duration of survival was only 33 months ($P < .001$; figure 1).

DISCUSSION

HIV infection has become a global epidemic far more extensive than what was predicted even a decade ago [18], and the pace of the epidemic is accelerating in India. In our study population, the ratio of male to female patients was 2.6 to 1, which is similar to rates from other parts of India [6]. The most common mode of transmission in the study is heterosexual intercourse, which confirms the findings of earlier studies from India [6, 12, 25]. The median CD4 lymphocyte count and duration of survival in the study was higher for female patients than male patients, because many of the female patients were asymptomatic and were tested after their husbands had initially presented for care. In an earlier study from our group, the vast majority of HIV-infected women acquired infection from their husbands [5]. The sex difference in survival duration disappeared when we controlled for CD4 lymphocyte count. Oropharyngeal candidiasis and tuberculosis were the most common opportunistic infections in the study, which was consistent with earlier reports from India [12, 26, 27], and the spectrum appears different from reports from the developed world before the era of antiretroviral therapy [9, 10, 28].

This study was the first attempt to assess the contribution of different cofactors that could be associated with the survival of Indians infected with HIV. The mean duration of survival for the study participants from the date of HIV serodiagnosis was 92 months, which is higher than that noted in other reports from developing countries [18–20]. The development of opportunistic infections (pulmonary tuberculosis, oropharyngeal candidiasis, *P. carinii* pneumonia, cryptococcal meningitis, and CNS toxoplasmosis) was associated with decreased durations of survival, which was similar to observations in other cohorts [29–32]. The effects of opportunistic pathogens in accelerating the progression of HIV infection and death are complex. Several

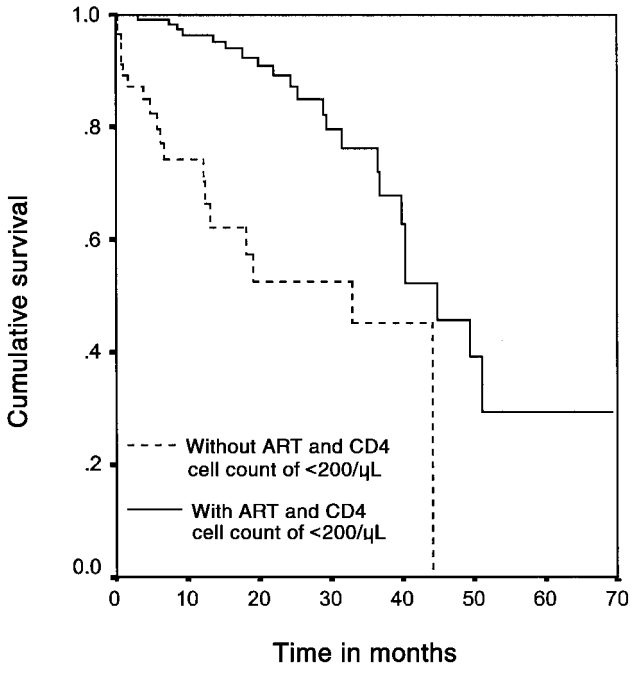

Figure 1. Cumulative survival rate for persons with baseline CD4 cell counts of <200 cells/μL who did or did not receive antiretroviral therapy (ART). The mean duration of survival for persons who received ART ($n = 141$) was 46 months (median, 45 months); for those who did not receive ART, the mean duration of survival was 27 months (median, 33 months; $P < .001$).

of these microbes can up-regulate HIV expression, particularly *Mycobacterium tuberculosis* [33], partially by increasing cytokines that in turn may have an impact on disease progression. Therefore, chemoprophylaxis and early diagnosis and treatment of opportunistic infections are important for control of HIV replication and disease progression. In this study, mortality was not associated with herpes zoster, herpes simplex, or oral hairy leukoplakia, which generally occurred early in the course of HIV disease. The prevalence of HBV infection in the study is similar to the prevalence in the general population in India [34], and the prevalence of HCV infection in the study was higher than that found in the general population [35].

In our study, persons who were not undergoing prophylaxis with TMP-SMZ when their CD4 lymphocyte counts were <200 cells/μL tended to have faster progression to death. The benefits of TMP-SMZ prophylaxis were well studied by Dworkin et al. [36], who showed that TMP-SMZ prophylaxis was associated with significant protection from *P. carinii* pneumonia, toxoplasmosis, salmonellosis, *Haemophilus* infection, and staphylococcal infection in persons with HIV infection. The affordability of TMP-SMZ and the great benefit in preventing HIV-associated mortality and morbidity make this an important tool for management of HIV infection in India.

In this study, persons who had CD4 cell counts of <200 cells/μL were 19 times more likely to die than were those with CD4 lymphocyte counts of >350 cells/μL. Persons with CD4 cell counts of 200–350 cells/μL were 3 times more likely to die than were persons who had CD4 lymphocyte counts of >350 cells/μL. The relationship between CD4 lymphocyte count and AIDS-associated mortality has been well documented [37]. Persons with CD4 cell counts of <350 cells/μL who were not receiving antiretroviral therapy had a more rapid progression to death in our study, similar to findings in cohorts from the developed world. Persons receiving antiretroviral therapy had increased durations of survival, even if they had advanced disease. Our findings are consistent with the survival benefits associated with receipt of antiretroviral therapy that have been described by other investigators [38, 39]. The results of the current study support benefits of antiretroviral therapy in an Indian cohort similar to those observed elsewhere. Unfortunately, only 29% of the patients in this cohort received any antiretroviral therapy during the study, even though the majority would have met the criteria to initiate antiretroviral therapy. The lack of availability of life-prolonging therapies resulting from their unaffordability poses major public health challenges to India and the world.

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