Short Term Survival after Anti-Retroviral Therapy Initiation among Aids Patients from South India

Sreenivasan Srirangaraj[1,2]* and Dasegowda Venkatesha[1]

[1]Department of Microbiology, Mysore Medical College and Research Institute, Mysore-570001, Karnataka, India
[2]Department of Microbiology, Mahathma Gandhi Medical College and Research Institute, Pondicherry-607402, India

Abstract

Background: The one-year survival rate of adults with the Acquired Immunodeficiency Syndrome (AIDS) after Anti Retroviral Therapy (ART) initiation and data on the efficacy of generic ART has not been well documented in India. The other objective was to see if opportunistic Infections were a significant risk factor for mortality.

Methodology: Survival was studied in a prospective observational cohort study of 108 ART-naïve patients with AIDS in a South Indian state by Kaplan Meier estimates. Efficacy of different generic ART regimens was evaluated by Cox-regression analysis and multiple logistic regression analysis was performed to assess the role of opportunistic infections in mortality.

Results: The overall survival rate was 94.25% at 6 months and 88.46% at one year after ART initiation among persons who initiated therapy with CD4 counts < 200 cells/ cu.mm. There was no difference in survival between those on Efavirenz-based or nevirapine-based regimens. The mortality rate at the end of one year was 9% (nine deaths), out of which four deaths occurred within the first 90 days of ART initiation. Pulmonary Tuberculosis was a significant risk factor for mortality (OR = 4.768, $p \leq 0.05$).

Conclusion: Generic ART is beneficial in a majority of AIDS patients in resource-limited settings. Pulmonary Tuberculosis is an important risk factor for mortality in AIDS patients on ART.

Keywords: AIDS; ART; Mortality; Pulmonary tuberculosis; Survival

Introduction

Combination antiretroviral therapy (ART) with three or more medications for patients with the Acquired Immunodeficiency Syndrome (AIDS) has reduced morbidity and mortality [1]. The positive impact of antiretroviral therapy (ART) on HIV viral load decrease, CD4 count increase and improved survival is well documented in the developed world [1-4]. The largest populations of persons with HIV are living in resource-poor areas, where much less was known about the effect of ART on the clinical course and survival of HIV-infected persons. However, after the scaling up of ART by various international initiatives, a number of studies have come up from the developing world [5-8]. Comparatively, there are fewer published studies from India on this aspect [9]. Generic ART forms the backbone of treatment of AIDS patients in India. This is provided free of cost to the patients under the National AIDS Control Programme (NACP) [10]. The present study was therefore conducted to calculate the probability of survival among AIDS patients after one year of ART initiation, to determine the efficacy of different generic ART regimens and to see if opportunistic infections (OIs) are a significant risk factor for mortality after ART initiation.

Materials and Methods

Study design and setting

A prospective observational cohort study was conducted from August 2006 to August 2007, involving 108 ART-naïve AIDS patients attending our ART Centre at K. R. Hospital, Mysore, India. This study was approved by the ethics Committee of our institution.

After taking an informed consent for HIV testing, individuals voluntarily attending the Integrated Counseling and Testing Centre (ICTC) at the Department of Microbiology, Mysore Medical College and Research Institute, Mysore (or any of the Government designated ICTCs), underwent pre-test counselling by male or female ICTC counsellors, followed by HIV testing per strategy III of the National AIDS Control Organization (NACO) guidelines (for HIV testing) [11]. After post-test counselling, those found HIV positive were referred to the ART Centre, K. R. Hospital, Mysore Medical College and Research Institute, Mysore, where they underwent pre-ART counselling. After clinical evaluation, informed consent was taken from these patients and they were enrolled into the study if they satisfied the inclusion criteria.

Inclusion criteria

The inclusion criteria were as follows: individuals should be above 18 years of age, proven to be HIV-positive, and should not be on prior anti-retroviral therapy. Those individuals found to be HIV-seronegative and those on prior ART were excluded.

The CD4/CD3 enumeration was done using the single-platform BD FACS Calibur™ machine (Becton, Dickinson and Company, San Jose, United States of America), by strictly following the manufacturer's instructions.

Follow-up

For each patient, the clinic visit prior to initiating a new ART regimen served as the baseline, during which the CD4 counts were recorded. After initiation of ART, these patients were followed up monthly until the end of the study period.

*Corresponding author: Dr. Srirangaraj.S, Assistant professor, Department of Microbiology, Mahatma Gandhi Medical College and Research Institute, Pondicherry-607402, India, Tel: 0413-2615996, Mobile No: 09787095587; E-mail: rangaraj1980@indiatimes.com

Treatment

Those found eligible for ART as per the WHO guidelines [12], were started on anti-retroviral therapy. The anti-retroviral drugs were supplied and given free of cost by NACO under the NACP. First-line antiretroviral-therapy regimens followed WHO guidelines. The first-line antiretroviral- therapy regimens used in this cohort were Zidovudine –based or Stavudine-based. Zidovudine based regimens consisted of Zidovudine, Lamivudine and Nevirapine/Efavirenz. Stavudine-based regimens consisted of Stavudine, Lamivudine and Efavirenz/Nevirapine.

Statistical analysis

A database entry, including patient demographics, dates of patient visits, clinical diagnoses listed at each visit and all antiretroviral medications was established for each cohort in this study attending our ART centre.

Comparison of categorical data between groups was evaluated by Fisher's exact test. Survival after the initiation of ART was estimated using the method of Kaplan and Meier. For patients who did not reach the end point, the data were censored at the date of the last visit. Efficacy of different generic ART regimens was evaluated by Cox-regression analysis.
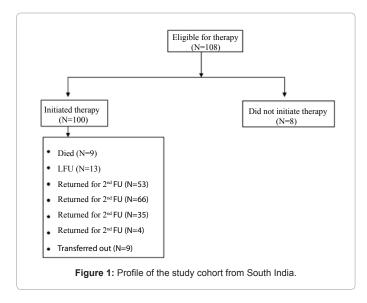
Multiple logistic regression analysis was performed to assess the role of Opportunistic infections (OIs) in mortality. All statistical analyses were performed using SPSS software (version 16.0, SPSS, Chicago, USA). All statistical tests were two-sided and $p \leq 0.05$ was considered statistically significant.

Results

Profile of the study cohort

Of the 108 ART-naïve AIDS patients, ART was initiated in a 100 patients. Eight (7.41% percent) of them met the criteria for antiretroviral therapy but were lost to follow-up before therapy could be initiated. A total of 13 patients were lost to follow-up (LFU) and a further 9 were transferred out from our ART centre to another ART centre in the surrounding districts. Figure 1 shows the profile of our study cohort.

Table 1 shows the baseline demographic and clinical characteristics

Figure 1: Profile of the study cohort from South India.

Characteristic	Value
Female sex — no. (%)	37(34.26%)
Age — no. (%) 21–30 yr 31–40 yr 41–50 yr	36(38.88%) 53(57.24%) 19(20.52%)
Rural residence	70(64.8%)
Risk factor for contracting HIV infection- heterosexual route	90(83.4%)
Marital status — no. (%) Married Single Widowed	74(68.6%) 13(12.0%) 21(19.4%)
Income < $1/day — no. (%)	96(88.89%)
WHO Clinical staging Stage1 Stage2 Stage3 Stage4	4(3.7%) 32(29.6%) 50(46.3%) 22(20.4%)
Baseline CD4 T-cell count — per mm3 Median Inter-quartile range	124 65-185
Initial antiretroviral-therapy regimen* — no. (%) d4T+3TC+NVP d4T+3TC+EFV ZDV+3TC+NVP ZDV+3TC+EFV	33(33%) 12(12 %) 42(42%) 13(13%)

Table 1: Baseline demographic and clinical characteristics of patients in Mysore receiving ART.

of patients in our study. In this cohort, 71 (65.74%) were males and 37 (34.26%) were females. 90(83.4%) acquired HIV infection via heterosexual transmission, and the median age was 35 years [inter--quartile range- 30-39years]. The median CD4 cell count at baseline was 124 cells/cu.mm. The most common first-line regimen was zidovudine (AZT), lamivudine(3TC) and nevirapine (NVP) administered to 42 patients (42%) as a fixed-dose combination. PCP prophylaxis was given to all the patients free of cost.

Mortality

Of the hundred patients started on ART, the mortality rate at the end of one year was 9% (nine deaths), out of which four deaths occurred within the first 90 days of ART initiation. Of these nine deaths, two were due to Steven –Johnson syndrome, two were due to Tuberculosis, one each due to Cerebral toxoplasmosis, Cryptococcal meningitis and Nevirapine –rash and two were due to unknown causes.
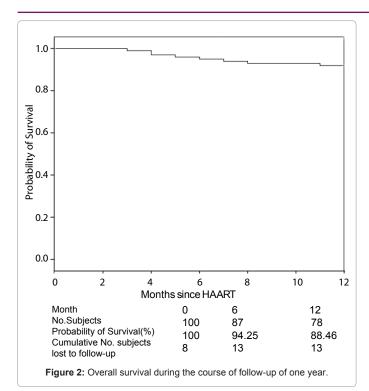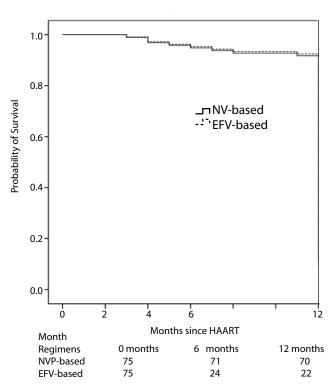
CD4 T-Cell Response

The median increase in the CD4 T-cell count at six months was 184.5 cells per cubic millimeter (interquartile range, 165 to 258 per cubic millimeter). The CD4 T-cell count at six months was greater than the baseline value in 62 of 66 patients (93.93 percent) and remained the same or decreased from baseline in 4 (6.07 percent). The median increase in the CD4 T-cell count at 12 months was 187 cells per cubic millimeter (interquartile range, 168.75 to 217 per cubic millimeter).

Survival analysis

Figure 2 illustrates overall survival during the course of follow-up of one year. The overall survival rate was 94.25% at the end of six months of HAART and 88.46% at the end of one year of ART initiation.

Though patients on Efavirenz -based regimens tended to show better survival when compared with those on Nevirapine-based regimens, this difference was not statistically significant (hazard ratio [HR] = 1.104, 95% confidence interval [CI]: 0.671 to 1.815; P = 0.698; Figure 3).

Figure 2: Overall survival during the course of follow-up of one year.

Month	0	6	12
No.Subjects	100	87	78
Probability of Survival(%)	100	94.25	88.46
Cumulative No. subjects lost to follow-up	8	13	13

Figure 3: Survivorship analysis among patients treated with Efavirenz (EFV)-based regimens and Nevirapine (NVP)-based regimens. Time to death (HR = 1.104, 95% confidence interval [CI]: 0.671 to 1.815; P = 0.698; not significant).

Month Regimens	0 months	6 months	12 months
NVP-based	75	71	70
EFV-based	75	24	22

Role of OIs in mortality

The multivariate logistic regression analysis done to assess the role of OIs in mortality showed that Pulmonary Tuberculosis was a highly significant risk factor for mortality (OR = 4.768, p = 0.05).

Although statistical significance was not noted, abdominal tuberculosis (OR=6.340, p = 0.174) negatively affected survival. Table 2 shows the opportunistic infections at first admission and mortality multivariate regression analysis.

Discussion

Four of the nine deaths (44.44%) which occurred after HAART initiation were due to opportunistic infections. This indicates the dominant role played by OIs in causing mortality in AIDS patients.

With an annual incidence of two million cases, India has the highest burden of tuberculosis in the world, accounting for one-third of the world's cases [13].We have shown in our study that pulmonary tuberculosis is an important risk factor for mortality in AIDS patients.

A study from Chennai, South India showed that the most common AIDS –defining illness was Pulmonary Tuberculosis seen in 49% of the patients with a median duration of survival of 45 months [14].

In another study from Bangalore in South India, Rajagopalan et al.[15] observed that pulmonary tuberculosis (TB) at first admission (OR = 4.86) was a significant risk factor for mortality while TB in general also negatively impacted survival (p = 0.002). In a study from Uganda, Africa, the overall relative hazard for death associated with tuberculosis was 1.81 (95% CI, 1.24± 2.65). [16]. This shows TB/HIV co-infection still remains a big challenge for survival of AIDS patients.

There was a median increase of 184.5 cells per cubic millimetre in the CD4 counts after six months of HAART. Other studies from the developing world have also shown good increase in the CD4 counts after HAART initiation[5,7].

The one-year survival after HAART initiation in our study was 88.46%. Severe et al [7], reported an identical one-year survival rate of 87 percent. Good one-year survival rates have also been reported by other studies from the developing world [5,9,14]. In contrast, the mean duration of survival without antiretroviral therapy for adults in India was about 33 percent [14]. This shows the beneficial effects of HAART on survival even in resource-limited settings.

The hazard ratio for EFV-based regimens as calculated by Cox-regression model was 1.104 times that for NVP-based regimens for survival. However, as the significance value was >0.1, any difference between the two regimens is due to chance. This shows that both the generic HAART regimens are equally efficacious in improving survival.

The small size of our study group and the short duration of the study period were the major limitations of our study.

More studies will be required in the area of ART in resource-limited

Factors	No. of survivors	No. of non-survivors	p-value	Adjusted odds-ratio
Pulmonary Tuberculosis	**19**	**5**	**0.050**	**4.768**
Tubercular lymphadenitis	5		0.999	
Abdominal Tuberculosis	3	1	0.174	6.340
Tuberculous meningitis	1		1.000	
Tuberculous pleural effusion	5		0.999	
Pneumocystis jiroveci pneumonia	1		1.000	
Oral Candidiasis	13		0.648	1.524
Cryptococcal meningitis	1		1.000	
Herpes Zoster	7	1	0.943	0.921
Herpes genitalis	1		1.000	

Table 2: Opportunistic infections at first admission and mortality multivariate regression.

settings, particularly in identifying easier ways of detecting resistance to anti-retrovirals, reducing the pill burden on the patients to improve compliance and to identify other optimal regimens which have better cost-effectiveness ratios.

This study has shown the short-term effectiveness of generic HAART regimens in resource-limited settings and established a strong case for further scale-up of HAART in the entire developing world.

References

1. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, et al. (1998) Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med 338: 853-860.

2. Hammer SM, Katzenstein DA, Hughes MD, Gundacker H, Schooley RT, et al. (1996) A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500 per cubic millimeter. N Engl J Med 335: 1081-1090.

3. Hammer SM, Squires KE, Hughes MD, Grimes JM, Demeter LM, et al. (1997) A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. N Engl J Med 337: 725-733.

4. Mouton Y, Alfandari S, Valette M, Cartier F, Dellamonica P, et al. (1997) Impact of protease inhibitors on AIDS-defining events and hospitalizations in 10 French AIDS reference centres. AIDS 11: 101-105.

5. Corey DM, Kim HW, Salazar R, Illescas R, Villena J, et al. (2007) Brief report: effectiveness of combination antiretroviral therapy on survival and opportunistic infections in a developing world setting: an observational cohort study. J Acquir Immune Defic Syndr 44: 451-455.

6. Djomand G, Roels T, Ellerbrock T, Hanson D, Diomande F, et al. (2003) Virologic and immunologic outcomes and programmatic challenges of an antiretroviral treatment pilot project in Abidjan, Cote d'Ivoire. AIDS Suppl 3: 5-15.

7. Severe P, Leger P, Charles M, Noel F, Bonhomme G, et al. (2005) Antiretroviral therapy in a thousand patients with AIDS in Haiti. N Engl J Med 353: 2325-2334.

8. Madec Y, Laureillard D, Pinoges L, Fernandez M, Prak N, et al (2007) Response to highly active antiretroviral therapy among severely immuno-compromised HIV-infected patients in Cambodia. AIDS 21: 351-359.

9. Kumarasamy N, Solomon S, Chaguturu SK, Cecelia AJ, Vallabhaneni S, et al. (2005) The changing natural history of HIV disease: before and after the introduction of generic antiretroviral therapy in southern India. Clin Infect Dis 41: 1525-1528.

10. Pattanapanyasat K, Thakar MR (2005) CD4+ T cell count as a tool to monitor HIV progression & anti-retroviral therapy. Indian J Med Res 121: 539-549.

11. National AIDS Control Organization (2001) HIV testing manual: Laboratory diagnosis, Biosafety and Quality Control. New Delhi: National AIDS Control Organization 162p.

12. World Health Organization (2006) Antiretroviral therapy for HIV infection in adults and adolescents: Recommendations for a public health approach. Available: www.who.co.in. Accessed 4 March 2010.

13. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC (1999) Consensus statement Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. JAMA 282: 677-686.

14. Kumarasamy N, Solomon S, Flanigan TP, Hemalatha R, Thyagarajan SP, et al.(2003) Natural history of human immunodeficiency virus disease in southern India. Clin Infect Dis 36: 79-85.

15. Rajagopalan N, Suchitra JB, Shet A, Khan ZK, Martin-Garcia J, et al. (2009) Mortality among HIV-Infected Patients in Resource Limited Settings: A Case Controlled Analysis of Inpatients at a Community Care Center. Am J Infect Dis 5: 219-224.

16. Whalen CC, Nsubuga P, Okwera A, Johnson JL, Hom DL, et al. (2000) Impact of pulmonary tuberculosis on survival of HIV-infected adults: a prospective epidemiologic study in Uganda. AIDS 14: 1219-1228.