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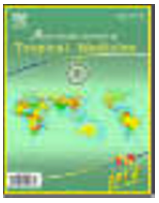

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Predictors of mortality among HIV-infected patients initiating anti retroviral therapy at a tertiary care hospital in Eastern India

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ABSTRACT

Objective: To assess early mortality and identify its predictors among the ART naive HIV-infected patients initiating anti retroviral therapy (ART) available free of cost at the ART Centres. **Methods:** A retrospective cohort analysis of routinely collected programme data was done for assessing mortality of all ART naive adult patients who received first-line ART at a government tertiary care hospital in eastern India during 1st March 2009 and 28th February 2010. Bivariate and multiple regression analyses of the baseline demographic, clinical and laboratory records using SPSS 15.0 were done to identify independent predictors of mortality. **Results:** The mortality rate at one year was estimated to be 7.66 (95% *CI* 5.84-9.83) deaths/100 patient-years and more than 50% of the deaths occurred during first three months of ART initiation with a median time interval of 73 days. Tuberculosis was the major cause of death. ART naive patients with baseline serum albumin <3.5 mg/dL were eight (*OR* 7.9; 95% *CI*: 3.8-16.5) at risk of death than those with higher serum albumin levels and patients with CD4 count <100 cells/μL were two times (*OR* 2.2; 95% *CI*: 1.1-4.4) at risk of death compared to higher CD4 counts. **Conclusions:** Risk of mortality is increased when ART is initiated at advanced stages of immunosuppression denoted by low serum albumin levels and CD4 cell counts. This highlights the importance of early detection of HIV infection, early management of opportunistic infections including tuberculosis and timely initiation of the antiretroviral drugs in the resource-limited countries, now available free in the Indian national ART programme.

1. Introduction

One of the targets of the ´Millennium Development Goal´ was to "achieve, by 2010, universal access to treatment for HIV/AIDS for all those who need it"[1]. In the year 2009, UNAIDS estimated 33.3 million people living with HIV worldwide, with more than 90% from the low and middle-income countries, and the total deaths due to AIDS to be 1.8 million[2]. Sub Saharan Africa is affected the most followed by South East Asia, thereby mostly affecting the poor socio-economies of the world[1]. Even though 5 million people in these low- and middle-income countries have access to antiretroviral therapy (ART), it represents only one third of the people who are in need of ART[3]. Access to antiretroviral treatment still remains a major barrier in these parts of the world.

The Indian National ART programme was launched in April, 2004 with a target of providing free ART to all people living with HIV (PLHIV) through ART centres and Link ART centres in the country, and in 2007, National AIDS Control Organisation (NACO) issued guidelines for scaling up ART in the country[4,5]. Although steady progress is being made towards achieving universal access to HIV prevention, treatment, care and support, yet ART initiation is often delayed. Significant proportions of patients still continue to be enrolled in the programme with advanced immunosuppression leading to higher mortality. Current antiretroviral therapeutic guidelines reflect the growing consensus that the early initiation of treatment for HIV is beneficial in terms of virological, immunological, and clinical outcome. The Indian National ART guideline was revised in 2009 raising the threshold of CD4 count to 250 cells/μL for initiation of antiretroviral therapy irrespective of the clinical stage[5,6]. Early detection of asymptomatic HIV-1 infection increases the scope to control the transmission of infection and interventions in

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the form of timely initiation of antiretroviral treatment to increase patients´ life expectancy, with a faster resolution of opportunistic infections and a decreased risk of recurrence[6]. Delayed diagnosis and late entry, as indicated by low CD4 counts, into HIV care on the contrary results in early death among HIV-infected patients[6,7]. Malnutrition is another common hallmark of advanced HIV infection which plays a synergistic role in immune suppression initiated by HIV and is considered to be an independent risk factor for HIV disease progression[8]. The non pharmacological factors related to the PLHIV vary across the populations based on the socio-economic context[6]. Very few studies have examined the effects of pre-ART baseline characteristics on early mortality after initiation of ART among Indian population, and reports from the developed world are not necessarily applicable to such resource limited settings. Nevertheless, mortality has been found to be high in these parts of the world, particularly the initial months after starting ART[7-11]. A better knowledge of the pre ART factors contributing to this high mortality can help implement targeted interventions among the high risk patients, thereby helping to reduce excess mortality. The aim of this study was to assess mortality and to identify the predictors of mortality among the ART naive HIV-infected patients initiating ART from the ART Centres in Kolkata city.

2. Materials and methods

2.1. Programme description

In the national ART programme, treatment is offered free of cost to all clinically eligible PLHIV. Patients diagnosed to be HIV positive at the integrated counselling and testing centre are further evaluated by a counsellor and a physician. They are subjected to baseline laboratory investigations including a CD4 test as per national treatment protocols[5]. If they are in WHO stage Ⅳ irrespective of CD4 cell count, WHO stage Ⅲ with CD4 + 350 cells/μL, or have CD4 + 250 cells/μL regardless of clinical stage, then they are considered eligible for ART[5]. Any opportunistic infection is firstly treated to stabilise the patient and cotrimoxazole prophylaxis is started. After two weeks or when the patient is stabilised, whichever is later, and if they agree to adhere to treatment, then these ART naive patients are prescribed the first-line ART regimen consisting of either zidovudine or stavudine plus lamivudine plus a non-nucleoside reverse transcriptase inhibitor (nevirapine or efavirenz) depending upon the patient profile[5].

For each patient registered for HIV care and treatment, a separate individual patient treatment record is filled in to record the sociodemographic characteristics, baseline clinical status, laboratory results and the prescribed ART regimen. These standardized patient cards are maintained at ART centres for tracking the progress of every patient.

2.2. Study design

A retrospective cohort analysis was done for records of all patients enrolled for first-line ART at the selected government run tertiary care hospital between 1st March 2009 and 28th February 2010. All ART naive adult patients ⩾15 years of age excluding pregnant women, who were enrolled consecutively and registered to receive ART during this period were included in the study. Those lost to follow up or transferred out to other ART centres were also excluded.

2.3. Study setting

Calcutta School of Tropical Medicine is a government run tertiary care hospital in Kolkata, the largest metropolis of eastern India, where an Antiretroviral Therapy Centre was started since March, 2005. Out of the four ART centres of the city, this ART Center is situated centrally and caters to maximum number of PLHIV in the state, maintaining good patient records and is also designated by NACO as the Centre of Excellence in HIV.

2.4. Data abstraction

Data sources included the ART patient register, patient treatment cards and additional records, if any, kept at the ART centre. Uniform data abstraction was conducted using a structured format. Key baseline demographic, clinical and laboratory data including age, sex, education, marital status, monthly family income, history of smoking, history of alcohol, WHO clinical stage, weight, height, haemoglobin (Hb), serum albumin, CD4 count, active tuberculosis infection and particulars of ART regimen started were collected. No personal identification information was collected from the patient records during data abstraction. Body mass index (BMI) was calculated by standard procedure and patients were regarded as malnourished if BMI was <18.5 kg/m^2. Each patient card was followed for one year from the date of start of ART to record any death reported within this period. The causes of death for all these cases were noted from in-patient records, by telephonic contact with their family members or relatives and with the help of home visits by outreach workers.

2.5. Data entry, storage and statistical analysis

All data abstracted were converted to an electronic format by entering them into Microsoft Office 2007 Excel spreadsheets and were cleaned for any error or outliers. This data was then imported into SPSS (version 15.0) for statistical analysis. Frequencies (with percentages) were calculated for all the variables.

The data of the dead and alive patients were statistically compared. *Chi*-square tests and Fisher´s exact tests were used to examine any statistically significant associations. Odds ratios (with 95% confidence intervals, *CI*) were calculated. A *P*-value of less than 0.05 was considered to be statistically significant for all analyses. Multiple regression analysis was done including age, sex, current tuberculosis infection, WHO clinical stage, nutritional status (BMI kg/m^2), serum albumin, Hb and CD4 count in the model using dead

status as the reference category.

3. Results

Of the 1 182 patients enrolled into HIV care during the study period, 759 ART naive adults initiating ART were included in the study. The median age of these PLHIV (66% male) was 35 years (range 15-75 years). The median BMI was18.22 kg/m^2 (range 9.18-40.63 kg/m), median Hb was 10.4 g/dL (range 4.4-16.6 g/dL); median serum albumin was 3.9 mg/dL (range 1.2-9.2 mg/dL) and median CD4 count was 140 cells/μL (range 3-735 cells/μL). The baseline characteristics are given in Table 1.

Among the study subjects, 56 patients died within one year of ART initiation and more than 50% of these deaths occurred during the first three months of ART initiation. The median time interval between ART initiation and time of death was 73 days. The mortality rate at one year was estimated to be 7.66 (95% *CI* 5.84-9.83) deaths/100 patient-years. The causes of death are given in Table 2. Tuberculosis (extra-pulmonary, 39% and pulmonary, 9%) emerged out to be the major cause of death.

The factors that emerged to be significant during bivariate analysis were BMI<18.5 kg/m^2, Hb <9 g/dL, serum albumin <3.5 mg/dL, CD4 count <100 cells/μL, presence of active tuberculosis and WHO clinical stages Ⅲ and Ⅳ as risk for mortality. The results of bivariate analysis are represented in Table 3. During multiple regression analysis, baseline serum albumin <3.5 mg/dL had eight times the risk (*OR* 7.9; 95% *CI*: 3.8-16.5) and CD4 count <100 cells/μL had two times the risk (*OR* 2.2; 95% *CI*: 1.1-4.4) of mortality among these Indian PLHIV. The results of multiple regression analysis are given in Table 4.

4. Discussion

Mortality rate of this cohort was found to be 7.66 deaths/100 patient-years at one year of starting ART with more than 50% of these deaths occurring within three months of ART initiation. Studies have suggested that PLHIV initiating ART in the developing world have higher rates of mortality during the initial months of therapy, compared to those in developed countries[8,11-14]. Under similar limited-resource settings, a study from Senegal has reported higher mortality rate although studies from South Africa and Zambia have shown lower mortality rates at one year[7,10,15,16]. A study conducted in western India during the period when free ART roll out programme was not started in the country have reported mortality rate nearly double the rate observed in the present study from eastern India[17]. Provision of ART, free of cost, to these PLHIV through the current national programme could have been the major factor behind such lowering of mortality rate[11]. Early treatment deaths are due to advanced immunodeficient status at enrollment and independent of the responses of ART that defines the late deaths. Furthermore

Table 1
Baseline characteristics [*n*(%)].

Variable		Dead	Alive	Total
Age	⩽ 35years	28 (50.0)	397 (56.7)	425 (56.2)
	> 35years	28 (50.0)	303 (43.3)	331 (43.8)
Gender	Male	43 (76.8)	459 (65.6)	502 (66.4)
	Female	13 (23.2)	241 (34.4)	254 (33.6)
Presence of spouse	yes	39 (69.6)	486 (69.1)	525 (69.2)
	no	17 (30.4)	217 (30.9)	234 (80.8)
Educational status	illiterate	14 (25.0)	223 (31.8)	237 (31.3)
	literate	42 (75.0)	478 (68.2)	520 (68.7)
Family income in Rupees	⩽ 2000	35 (64.8)	359 (56.3)	394 (56.9)
	>2000	19 (35.2)	279 (43.7)	298 (43.1)
History of smoking	never smoked	26 (46.4)	352 (50.3)	378 (50.0)
	ever smoked	30 (53.6)	348 (49.7)	378 (50.0)
History of alcohol	never consumed	27 (48.2)	327 (46.8)	354 (46.9)
	ever consumed	29 (51.8)	372 (53.2)	401 (53.1)
Active tuberculosis	present	27 (9.5)	258 (90.5)	285 (38.4)
	absent	25 (5.5)	433 (94.5)	458 (61.6)
WHO clinical stage	Stages Ⅲ & Ⅳ	24 (43.6)	196 (28.1)	220 (29.2)
	Stage Ⅰ & Ⅱ	31 (56.3)	502 (71.9)	533 (70.8)

Source: Primary survey, 2009-11 Kolkata.

Table 2
The causes of death.

Cause of death	*n* (%)
Extra -pulmonary tuberculosis	22 (39.3)
Pulmonary tuberculosis	5 (8.9)
Cryptococcal meningitis	5 (8.9)
Pneumocystis jiroveci pneumonia	3 (5.4)
Diarrhea	2 (3.6)
Septicemia	2 (3.6)
Toxoplasmosis	2 (3.6)
Encephalopathy	2 (3.6)
Nevirapine induced severe rash	1 (1.8)
Drug induced hepatitis	1 (1.8)
Cerebro-vascular accident	3 (5.4)
Acute myocardial infarction	2 (3.6)
Cause of death could not be ascertained	6 (10.7)

Table 3

Predictors of mortality: results of bi-variate analyses.

Variable		Dead [*n* (%)]	*OR* (95% *CI*) of death	*P* value
Nutritional status	BMI <18.5 kg/m^2	40 (12.3)	2.4 (1.3-4.4)	0.003
	BMI >18.5 kg/m^2 r	16 (5.5)		
Hb level	<9 g/dL	20 (11.8)	2.2 (1.2-4.1)	0.006
	≥9 g/dL r	31 (5.6)		
Serum albumin	<3.5 mg/dL	45 (30.4)	11.2 (5.6-22.5)	0.000
	≥3.5 mg/dL r	11 (3.8)		
CD4 count	<100 cells/μL	36 (12.9)	3.5 (1.9-6.2)	0.000
	≥100 cells/μL r	19 (4.1)		
Active tuberculosis	present	27 (9.5)	1.8 (1.0-3.2)	0.037
	absent r	25 (5.5)		
WHO clinical stage	Stages Ⅲ & Ⅳ	24 (10.9)	1.9 (1.1-3.5)	0.015
	Stage Ⅰ & Ⅱ r	31 (5.8)		

OR: Odds ratio; *CI*: Confidence interval; r: Reference category;
Dependent variable: Death, other variable(s) considered and not found to be significant includes age, gender, presence of spouse, educational status, family income, history of smoking and alcohol consumption.

Table 4

Predictors of mortality: results of multiple regression analyses.

Variables:		Adjusted *OR* for death	95% *CI* for adjusted *OR*		Significance(*P*-value)
			Lower	Upper	
Serum albumin	<3.5 mg/dL	7. 9	3.8	16.5	0.000
	≥3.5 mg/dL r				
CD4 count	<100 cells/μL	2.2	1.1	4.4	0.029
	≥100 cells/μL r				

OR: Odds ratio; *CI*: Confidence interval; r: Reference category; Dependent variable: Death, other variable(s) considered in this model and not found to be significant includes the current tuberculosis infection, nutritional status (BMI<18.5 kg/m^2), Hb <9 g/dL and WHO clinical stage Ⅳ.

the most important cause of these deaths was found to be due to tuberculosis, both extra-pulmonary and pulmonary together, causing 48% of the total deaths in our study, almost equal to that reported by Ghate *et al*[17]. This could be attributed to the high prevalence of tuberculosis in India and its coexistence with HIV. Tuberculosis is still the commonest opportunistic infection among the PLHIV as reported from other parts of India[17-19].

Serum albumin levels of the ART naive PLHIV prior to start of their ART was a strong predictor of mortality in our study. A serum albumin level <3.5 mg/dL carried eight times the risk for mortality compared to higher levels. A study from the US has shown that serum albumin level <3.5 mg/dL had 3 times higher risk of death among HIV positive American women[18] HIV infection is known to be associated with systemic inflammation and elevations in the levels of pro-inflammatory cytokines leading to vascular endothelial dysfunctions. Serum albumin has direct protective effect on this by the virtue of its vaso-dilating, anti-haemostatic and platelet-lowering properties coupled with its antioxidant and antiviral activities[19,20]. During advanced immunosuppressed stages there is widespread inflammation and HIV-1 disrupts the barrier function of the endothelium, resulting in increased transcapillary escape of albumin with dissemination of HIV-infected cells into tissue, thereby enhancing disease progression[21]. HIV infection also induces a hypermetabolic state in the host and HIV-related anorexia further depresses albumin synthesis creating a vicious cycle of malnutrition[18]. Diminished serum albumin levels, the marker of poor nutritional status induced by the stress of illness, appear long before any change in body weight or other clinical markers become evident[22]. Associated active tuberculosis also induces a lowering effect on serum albumin level[23]. Serum albumin remained as a powerful predictor of mortality not only in severely immunosuppressed states (CD4 cell count <100 cells/μL) but even in patients not acutely ill with normal hepatic and renal functions as measured by levels of blood urea nitrogen, serum creatinine and transaminases[18]. A simple prognostic model based on albumin level could therefore be a useful tool for initial risk assessment in resource-limited settings. Future research to find out any role of albumin supplementation during initiation of ART in reducing mortality in the current setting can be undertaken.

Baseline CD4 cell count <100 cells/μL was another strong predictor of mortality in our study. PLHIV initiating ART with plasma CD4 count <100 cells/μL were two times at risk of death compared to higher CD4 cell counts. Studies from Africa have demonstrated CD4 count <50 cells/μL as a strong predictor of mortality whereas earlier studies from India have reported CD4 count <200 cells/μL to be a strong predictor[24-26]. Yet, a recent study from western India has demonstrated baseline CD4 cell count <100 cells/μL as a risk of mortality[17]. Although low serum albumin levels and low CD4 cell count at baseline were independent risk of mortality in our study, it is important to note that diminished CD4 T cell function is associated with falling serum albumin levels and rising serum immunoglobulin levels reversing the albumin: globulin ratio in immune compromised persons. Studies have substantiated the fact that low CD4 cell count, a marker of advanced immunodeficiency, was associated with opportunistic infection thereby increasing the likelihood of death[17,24-27]. Early detection of HIV-infected individuals and timely initiation of ART could therefore prevent deaths

in the Indian setting.

Conflict of interest statement

We declare that we have no conflict of interest.

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