Research Article

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Estimation of life-time survival and predictors of mortality among the people living with HIV/AIDS: a case study in Andhra Pradesh, India

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ABSTRACT

Background: Antiretroviral treatment (ART) consistently improved survival of people living with HIV and contributes to prevent new infections. In this study, we estimated the life-time survival and examined the associated correlates of mortality amongst HIV-patients registered during 2007-11 in Andhra Pradesh, India.

Methods: A total 63,882 adult HIV/AIDS cases (≥15 years) with complete follow-up information were extracted from ART database and included in the analysis. The Kaplan-Meier method was used to estimate the survival and Cox PH model was used to determine the relative hazard of mortality.

Results: Nearly twelve percent (11.9%) of the total cases them (n=7,621) died during the follow-up period. Overall life-time survival was estimated to 12.2 (95% C.I. 12.0-12.3) years. Multivariable Cox proportional hazard model indicated the mortality was significantly associated with age, CD4 count, gender, clinical stage and functional status.

Conclusions: The scale-up of ART has resulted in substantial reductions in mortality and increased survival. Such information is useful for institution of intervention measures to reduce risk of death.

Keywords: HIV/AIDS, ART, Survival, Kaplan-Meier, Andhra Pradesh, India

INTRODUCTION

HIV/AIDS illness remains global public health challenge and main cause of morbidity and mortality worldwide since the first case was reported in the early 1980's. After 30 years, roughly 34 million people (31.6-35.2 million) were living with HIV (PLHIV) worldwide in 2010 that increased 17% from 2001. Demographically, India is the second largest country in the world has also the third largest number of people living with HIV/AIDS. The national adult HIV prevalence was estimated as 0.31% (C.I. 0.25-0.39%) in 2009 with persons living with HIV/AIDS were 2.40 million (C.I. 1.93-3.04 million).² Andhra Pradesh has second highest HIV prevalence (0.90%) after Manipur among six high prevalent states with more than 1, 00,000 PLHIV at one point of time.³

The early initiation of antiretroviral therapy (ART) improved survival of HIV infected individuals worldwide since its inception as in the absence of cure for HIV.^{4,5} The main purpose of ART is to prolong lives, making HIV/AIDS as a chronic disease rather than death sentence.6 The low- and middle-income countries expended the access to ART in early 2000, particularly with the World Health Organisations' "3 by 5" initiative, which aimed to have three million people on ART by 2005.7 In 2004, the ART program in India was initiated under national AIDS control programme (NACP) with the aim to provide free services and across the country more than 350 ART centers serving the nation at present.⁸ As of January 2014 in Andhra Pradesh, 55 ART centers are functional. The scale-up of ART access took place in 2007 with new criteria for ART

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initiation that results more than seven million PLHIVs had access to ART in 2012. 10

The AIDS-related mortality decreases due to introduction of highly active antiretroviral therapy in developed countries and the life-time survival after infection was estimated in the range from 12-25 years. 11 However, in developing and low-income countries the lower survival was reported after HIV-infection. 12-14 The survival of PLHIV individuals and underlying associated factors with mortality depend on demographic characteristics, laboratory variables and clinical indicators. 15-19 nationwide large scale household survey suggested that only 17% and 25% currently married women have heard about STIs and HIV, respectively.²⁰ Moreover, empirical research in India have reported conflicting trends in mortality rates; few studies reported increasing mortality trends among HIV infected individuals while another set of studies reported a decline in mortality rates over the years. 18,19,21 This has prompted researchers and policy makers to questions on contributions of ART on survival status of HIV infected individuals.

There is a little evidence regarding life-time survival and correlates of mortality in HIV-infected individuals in Andhra Pradesh and India by large due to the lack of prospective studies. This analysis aimed to investigate the survival and associated determinants of survival probability in HIV/AIDS-patients registered at various ART centers in Andhra Pradesh, India.

METHODS

Study settings and participants

The records of HIV-positive individuals who registered at different ART centers (around 55) across the Andhra Pradesh state, India during Jan 2007 to Dec 2011 with the follow-up till Dec 2013 was extracted from ART surveillance database. A retrospective cohort of 3, 13, 175 HIV-positive patients were registered at different ART centers during 2007-11. Out of this, 2,93,560 were adult (age ≥15 years; 1,51,878 male, 1,81,514 female and 451 were TS/TG) and remaining 19,615 were registered as paediatric cases. Out of these, 63,882 records were found with complete follow-up information (Figure 1).

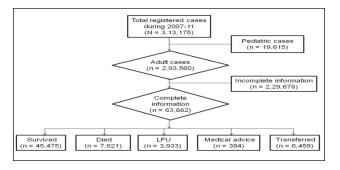


Figure 1: Description of sample data with corresponding follow-up status.

All adult male and female were included in the present study. The baseline information on different demographic covariate includes: age, education, gender, marital status, occupation. It also includes important programme variables: year of HIV detection, year of ART registration, ART status, mode of transmission and the follow up status at the end of the study. Out of 33, 060 males 22,270 were alive, 5,024 died, 3,301 were transferred out, 162 on medical advice and 2,303 were lost to follow up. Similarly among 30,822 females 23,205 were alive, 2,597 were died, 3,158 were transferred out, 232 on medical advice and 1,630 were lost to follow up during the period. Death of a HIV patient was taken as the primary end point.

Permission to use ART programme data for this analysis has been obtained from National AIDS Control Organization (NACO), Ministry of Health and Family Welfare, Government of India, New Delhi.

Data description and analysis

Demographic information on age, education, gender, marital status, occupation, mode of HIV transmission and initial clinical indicators: clinical stage, CD4 count and functional status of patients was categorized to assess any association with the survival probability. Age was categorized into four groups as 15-30, 31-49 and \geq 50 years. Education was categorized into illiterate, primary, secondary and college or above. Occupation was categorized as unemployed and employed. Marital status was categorized as single (unmarried, widow/widower, divorced/separate) and married/live-in. The mode of transmission was categorized as sexual (heterosexual+MSM) and others (injecting drug users/blood transfusion/mother to child). HIV clinical stage was categorized as I, II, III and IV. CD4 count was labeled into <200, 200-349, 350-499 and ≥500. The functional status of patients was assessed whether the patient was ambulatory, bedridden or working at the time of registration. At the end, individual case in the database can be classified into the following four categories: alive, death, LFU/transferred and don't know based on the status as on 31st Dec 2013.

The life-time survival was measured as a duration between date of HIV confirmation (as the date of infection is unknown) to date of death for patients who died or the date of the last recorded visit for patients who were censored (e.g. either alive till the end of the study period or lost to follow-up). For the comparison of unadjusted survival rates, Kaplan-Meier (K-M) methods were used and patients were stratified by different population sub-groups and it was plotted among different categories of demographic variables. We used the Wilcoxon log rank tests to assess statistical differences between the groups. To visually present the product limit estimates of the cumulative survival rate, Kaplan-Meier curves were generated to show the life time survival of the patients. Student's't' test was used for statistical

difference between mean ages of male and female and Spearman's rank correlation was applied for correlation between age and median survival.

The widely accepted Cox proportional hazard regression model was applied to identify the associated factors. ^{11,18,19} The proportional hazards assumption was tested using Schoenfeld residuals. Unadjusted hazard ratios (HR) and adjusted hazard ratios were estimated with 95% confidence intervals (95% C.I.). The data were analyzed using IBM SPSS statistics for windows version 21.0

(Armonk, NY, USA). The two tailed 'p' value less than 0.05 was considered as statistical significance.

RESULTS

A total of 63,882 adult HIV-positive cases were retrospectively extracted with complete follow-up information from ART surveillance database. The demographic and initial clinical profile of the PLHIV's presented in Table 1.

Table 1: Background profile of HIV-positive individuals registered at different ART centres in Andhra Pradesh, India during 2007-11.

B 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	Male (N=33060)		Female N=30822)		Total (N=63882)	
Background variables	n	%	n	%	n	%
Age at registration (years)						
15-30	9597	29	16314	52.9	25911	40.6
31-49	20165	61	12861	41.7	33026	51.7
>=50	3298	10	1647	5.3	4945	7.7
Educational status						
Illiterate	14758	44.6	19032	61.7	33790	52.9
Primary	7526	22.8	6102	19.8	13628	21.3
Secondary	7288	22	4282	13.9	11570	18.1
College & above	3488	10.6	1406	4.6	4894	7.7
Employment status						
Unemployed	792	2.4	848	2.8	1640	2.6
Employed	32268	97.6	29974	97.2	62242	97.4
Marital status						
Married	27019	81.7	16697	54.2	43716	68.4
Single	6041	18.3	14125	45.8	20166	31.6
Mode of HIV transmission						
Sexual (Hetro+MSM)	30860	93.3	29096	94.4	59956	93.9
Others	2200	6.7	1726	5.6	3926	6.1
HIV clinical stage						
I	6135	18.6	7351	23.8	13486	21.1
II	12516	37.9	12391	40.2	24907	39
III	13356	40.4	10415	33.8	23771	37.2
IV	1053	3.2	665	2.2	1718	2.7
CD4 count						
<200	19308	58.4	14628	47.5	33936	53.1
200-349	8913	27	9242	30	18155	28.4
350-499	2851	8.6	3611	11.7	6462	10.1
>=500	1988	6	3341	10.8	5329	8.3
Functional status						
Ambulatory	4995	15.1	3885	12.6	8880	13.9
Bedridden	458	1.4	284	0.9	742	1.2
Working	27607	83.5	26653	86.5	54260	84.9
Follow-up status						
Surviving	22270	67.4	23205	75.3	45475	71.2
Died	5024	15.2	2597	8.4	7621	11.9
Transfer out	3301	10	3158	10.2	6459	10.1
On medical advice	162	0.5	232	0.8	394	0.6
Lost to follow-up	2303	7	1630	5.3	3933	6.2

Table 2: Estimation of life-time survival (95% C.I.) and mortality distribution according to subgroups of different variables.

Background characteristics	Number (n)	No. of deaths (%)	Average life-time survival (year)	S.E.	95% C.I. of survival	Kaplan-Meier survival analysis: comparison of groups using log rank test
Age group (years)						
15-30	25911	2530 (9.8)	12.6	0.13	12.4-12.9	p < 0.01
31-49	33026	4274 (12.9)	11.9	0.11	11.7-12.2	p < 0.01
>=50	4945	817 (16.5)	10.9	0.35	10.2-11.6	p < 0.01
Gender						
Male	33060	5024 (15.5)	11.3	0.12	11.1-11.6	p < 0.001
Female	30822	2597 (8.4)	13	0.12	12.8-13.2	p < 0.001
HIV clinical stage						
I+II	38393	4383 (11.4)	12.3	0.11	12.0-12.5	p > 0.05
III	23771	2901 (12.2)	12.1	0.13	11.9-12.4	p < 0.01
IV	1718	337 (19.6)	8.2	0.22	7.8-8.6	p < 0.001
CD4 counts						
<200	33936	5501 (16.2)	11.1	0.14	10.9-11.4	p < 0.05
200-349	18155	1698 (9.4)	11.9	0.1	11.7-12.1	p < 0.001
350-499	6462	271 (4.2)	14.1	0.09	13.9-14.2	p < 0.001
>=500	5329	151 (2.8)	14.2	0.14	13.9-14.5	p > 0.05
Functional status						
Working	54260	6099 (11.2)	12.1	0.11	11.9-12.3	p > 0.05
Ambulatory	8880	1329 (15.0)	12.2	0.12	12.0-12.5	p < 0.001
Bedridden	742	193 (26.0)	8.6	0.47	7.6-9.5	p < 0.001
Total	63882	7621 (11.9)	12.2	0.09	12.0-12.3	

The average age (\pm SD) at registration of PLHIV was recorded as 36.5 ± 9.1 years among male and 32.1 ± 8.8 years among female (t = 62.1; p <0.001). More than 90% of HIV patients were acquired infection at their younger age (below 50 years), 52.9% were illiterate, 97.4% employed, 68.8% reported as married/Live-in, 93.9% of them were acquired HIV through sexual (hetero+MSM) mode of transmission. Around 40% of them were belong to clinical stage III and IV, 53.1% had CD4 count \leq 200, 84.9% were functionally well at the time of registration and 71.2% were alive at the end of the follow-up.

The mortality distribution within the subgroup of predictors during the study period, life-time survival estimation (with 95% C.I.) and their comparison were presented in Table 2.

Around 11.9% PLHIV (n = 7,621) died during the follow-up period. 27.9% (n = 2,128) of them were died within one year of their registration with similar distribution over male (28.0%) and female (29.6%). Lifetime survival was estimated to 12.2 (95% C.I. 12.0-12.3) years that was significantly higher among women 13.0 (95% C.I. 12.8-13.2) years than men 11.3 (95% C.I. 11.1-11.6) years. Further, the stratified Kaplan-Meier survival plots illustrated the survival probabilities in different

subgroups of in dependent variables (Figure 2) and the log-rank test were used for statistical significance (Table 2).

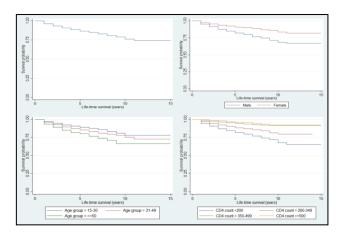


Figure 2: Kaplan-Meier survival probability plots according to different sub-groups of the predictors.

The mean survival after ART registration was estimated to 5.3 (95% C.I. 4.9-5.7) years and it was also negatively correlated with age at registration (r = -0.13; p < 0.001).

Univariate and multivariate Cox proportional hazard models were used to examine the association between different predictor variables and hazard of death showed in Table 3.

The univariable regression analysis demonstrated age, gender, clinical stage CD4 count and functional status were associated with the survival of a patient. Further, all these variables were used in multivariable regression analysis to estimate the adjusted hazard of death. Adjusted hazard ratio (HR) was significantly higher in older age groups (1.2 for 31-49 years and 1.5 for \geq 50 vears) with reference to the <30 years. Males were higher at risk (1.6 times) then female. Multivariate HR was also higher in the higher clinical stage groups (1.2 for stage III, 1.5 for stage IV) as compared with the combination of stage I+II. The risk of death was significantly increase as CD4 decreases (6.3 for <200, 3.6 for 200-349 and 1.4 for 350-499) with respect to CD4 count ≥500. The PHIV's with bedridden functional status at the time of ART registration was significantly associated with risk of death (1.8 times) with reference to well (or working).

Table 3: Univariate and multivariate Cox PH model with 95% C.I. to predict risk of mortality.

Predictors	Univariate analysis		Multivariate analysis				
of mortality	HR	95% C.I.	AHR	95% C.I.			
Age group (years)							
15-30	1 (Ref.)		1 (Ref.)				
31-49	1.4*	1.3-1.6	1.2*	1.1-1.3			
>=50	2.0**	1.8-2.2	1.5**	1.4-1.7			
Gender							
Female	1 (Ref.)		1 (Ref.)				
Male	1.9**	1.8-2.0	1.6**	1.5-1.7			
HIV clinical stage							
I+II	1 (Ref.)		1 (Ref.)				
III	1.4*	1.1-1.7	1.2*	1.1-1.8			
IV	1.7**	1.6-2.0	1.5**	1.3-1.8			
CD4 count							
<200	6.8***	5.7-8.0	6.3***	5.4-7.5			
200-349	3.7**	3.1-4.4	3.6**	3.0-4.3			
350-499	1.5*	1.2-1.9	1.4*	1.2-1.8			
>=500	1 (Ref.)		1 (Ref.)				
Functional status							
Working	1 (Ref.)		1 (Ref.)				
Ambulatory	1.3*	1.2-1.5	1.1	0.9-1.3			
Bedridden	2.5**	2.1-2.9	1.8*	1.6-2.1			

*P<0.05; **P<0.01; ***P<0.0001

DISCUSSION

The present analysis is based on a retrospective cohort of HIV/AIDS patients registered at different ART centers during 2007-11 in Andhra Pradesh, India. The median CD4 count at the time of ART registration remained low,

at 190 (IQR: 110-295). These data clearly indicate that people are typically being early diagnosed with HIV in India. At the end of follow-up, 71.2% of them were alive, 11.9% were dead, 10.1% were transferred out and 6.2% were LFU. Sexual root (heterosexual+MSM) (93.9%) remains highest vulnerable mode of HIV transmission. 27.9% deaths occurred within one year of HIV registration. The higher mortality in the first year estimated by this analysis corroborates the findings from several other studies.^{8,12,18,19,22} The higher mortality within the first year of HIV registration could be due to some other reasons like poor adherence to ART regimen combined with other co-morbid infections and low CD4 cell count.¹⁸ Furthermore, we found that the overall lifetime mean survival time was around 12.2 years from the date of HIV detection and around 5.3 years from the date of ART registration with higher average survival among women as reported by others. 12,19 The analysis showed a strong association between survival probability and demographic variables and clinical indicators. The increasing risk of death in HIV-patients has significantly been high in higher age groups as previously reported. 12,15,17-19,23-25 This empirical analysis clearly revealed that higher mortality in older age. Therefore, survival of HIV-positive individuals was inversely correlated with age. This analysis also recorded the higher proportion of deaths among males (15.2%) as compared with females (8.4%). Around 7.0% in male and 5.3% in female were recorded as lost to follow up, however such differences were minimal in this study. The hazard of death among men was significantly higher than among women, as previously reported by others. 12,26 Higher mortality among male may be due to high reporting by males or biological differences or drug response to ART. However, in some studies it was not found statistically significant. ²³⁻²⁵ The clinical parameters like CD4 count, clinical stage and functional status play vital role in survival of an individual as reported by multivariate regression model. The findings are in agreement with other several studies. 12,26 Though the plenty of research is available worldwide regarding survival of HIV/AIDS patients, however it still required further research in Indian context.

The findings of the present study should be examined in light of certain limitations. The first limitation of this study was related with its study design. We analyzed a retrospective cohort with demographic characteristics and some of clinical variables as CD4 cell count, HIV staging and functional status. Hence we could not take into account all the potential confounders such as, viral load, co-morbid condition that could have influenced the survival of individuals due to non-availability in the data. Another limitation was associated with the cause of death. We considered all-cause mortality in the analysis. There is a possibility that a few of the deaths may have occurred due to causes not related to HIV/AIDS. The third limitation was related to the missing information in different covariates as well as date of death.

CONCLUSION

Despite these study limitations, the study findings have important policy implications for ART programme in India. ART services in India are freely available to all HIV infected persons. The estimates of the survival rate among ART individuals suggests that country's ART program has been successful in increasing longevity of life of HIV infected individuals. However, there are certain concerns regarding missing information in the database. Efforts are required at the management as well as at implementation level for constant and regular follow-up with all patients. In addition, the program should expand to cover more remote areas to provide services to some of the underserved population groups like women. Our study also demonstrated higher mortality among individuals within one year of registration. This argues for the need to identify and treat eligible HIV infected individuals at an early stage. In addition, late appearance to ART centers is one of the main reasons for higher mortality in the first year after registration. Therefore, attention is needed to ensure early diagnosis and enrollment into ART for PLHIV's.

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Institutional Ethics Committee

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