RESEARCH PAPER

Survival of Children Living with Human Immunodeficiency Virus on Antiretroviral Therapy in Andhra Pradesh, India

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ABSTRACT

Objectives: To assess the survival probability and associated factors among children living with human immunodeficiency virus (CLHIV) receiving antiretroviral therapy (ART) in India.

Methods: The data on 5874 children (55% boys) from one of the high HIV burden states of India from the cohort were analyzed. Data were extracted from the computerized management information system of the National AIDS Control Organization (NACO). Children were eligible for inclusion if they had started ART during 2007-2013, and had at least one potential follow-up. Kaplan Meier survival and Cox proportional hazards models were used to measure survival probability.

Results: The baseline median (IQR) CD4 count at the start of antiretroviral therapy was 244 (153, 398). Overall, the mortality was 30 per 1000 child years; 39 in the <5 year age group and 25 in 5-9 year age group. Mortality was highest among infants (86 per 1000 child years). Those with CD4 count $\leq$ 200 were six times more likely to die (adjusted HR: 6.3, 95% CI 3.5, 11.4) as compared to those with a CD4 count of $\geq 350/mm^3$.

Conclusion: Mortality rates among CLHIV is significantly higher among children less than five years when the CD4 count at the start of ART is above 200. Additionally, lower CD4 count, HIV clinical staging IV, and lack of functional status seems to be associated with high mortality in children who are on ART.

Keywords: HIV, *Mortality, Outcome, Treatment.*

INTRODUCTION

India has witnessed a decline in mortality among people (including children) living with human immunodeficiency virus (HIV) who are on antiretroviral therapy (ART), during 2007-2011 [1]. This decline in mortality is argued to be attributed to the scale-up of ART in the country [2]. Globally, half the Children living with HIV (CLHIV) die of acquired immune deficiency syndrome (AIDS) before their second birth day, and one-third during infancy in the absence of ART [3]. On the other hand, ART coverage for CLHIV had been scaled up from 4127 to 46515 children, and number of ART centers providing treatment to children from 107 to 400 across the country during 2007 to 2013 [2]. Studies that examine the mortality/survival status of children who are on ART are scarce in India.

The National AIDS Control Organisation (NACO) revealed an overall decline in people dying of AIDS related causes during 2007-2013, however, not much improvement was noted for children. This absence of improvement in survival among CLHIV might have been related to patient factors like parents' survival, CD4 levels etc. This study was conducted to assess the mortality among CLHIV receiving ART during 2007-2013 and the factors influencing the same.

METHODS

We analysed records of 5874 CLHIV under 15 years of age, who had been initiated on ART between January 2007 and December 2013. Data were obtained from 45 ART centres across 23 districts in high HIV prevalence settings (combined Andhra Pradesh and Telangana) in India. These ART centres were set up at different points of time during 2007 to 2013. The patients' ART identification numbers were used to extract information from the patients' records entered in electronic Computerized Management Information System Software (CMIS). The information on socio-demographic characteristics, baseline clinical and laboratory measurement, and treatment outcomes were extracted from the database, and the primary outcome measure of patient mortality (time death) was noted.

Data were analyzed using the Kaplan Meier survival and Cox proportional hazard model to measure survival and identify independent predictors of mortality of CLHIVs on ART. Cox proportional hazard ratios (HR) and adjusted hazard ratios (AHR) with 95% confidence intervals were used to assess the effect of baseline predictors on the survival of children on ART. Key variables used in the analysis included: gender, educational status (no schooling, attended school, information missing), CD4 count at ART initiation (<= 200, 201-250, 251-350, >=350), age at registration, age at start of ART (0-4 years, 5-9 years, 10-14 years), follow-up at most recent visit, CD4 count at ART initiation, WHO clinical stage (I, II, III, IV) and functional status (ambulatory, bed ridden and functional).

This study follows Cox regression model fulfilling the assumption of "non-informative censoring". The incidence rates of mortality, the primary end point of interest, were calculated by dividing the number of deaths by the total number of person-years. For each member of the cohort, person-years at risk were measured from the start date of ART until the date of the most recent clinic visit. Kaplan-Meier methods were used to assess the cumulative probability of survival after the start of ART. For analysis and compilation of data SPSS 20.0, STATA 12.0 and MS-Excel were used.

RESULTS

Of the 5874 children who were included in the analyses, 4461 (76%) children were alive, 336 (6%) died, 760 (13%) were transferred out of the facility, and 317 (5%) were lost to follow up over the study period (*Fig*. **1**). *Table* **I** depicts the characteristics of children included in the study. The median (IQR) age at the start of ART was 8 (5, 11) years. [Inter Quartile Range (IQR): 5-11 years]. The median (IQR) CD4 count at the start of ART was 244 (153, 398)/mm^3.

The age-specific mortality rate among children on ART was highest among children aged < 5 years (39 per 1000 child-years), followed by 10-14 years age group (32 per 1000 child-years) and 5-9 year age group (25 per 1000 child-years). (*Table* **II**).

Children with CD4 count ≤ 200 were six times more likely to die (Adjusted Hazard Risk Ratio (AHR): 6.3, 95% CI: 3.5-11.4) and those with a CD4 count of 251-350 were three times more likely to die (AHR: 3.2, 95% CI: 1.7-6.3) as compared to those with a higher CD4 count (>=350) (*Table* **III**). Similarly, children who are in the HIV clinical stage IV were three times more likely to die (AHR: 3.2, 95% CI: 1.9-5.3) and those in HIV clinical stage III were more than one times more likely to die with (AHR: 1.4; 95% CI: 3.3-6.6) as compared to those in the clinical stage I and II . Bedridden children were 4.5 times more likely to die (AHR: 4.5; 95% CI: 2.2-9.4) and ambulatory (but not functional) children were more than twice likely to die (AHR: 2.3; 95% CI: 1.4-3.6) as compared to the children who were functional [*Table* **III**]. There is no interaction effect between the child's age and CD4 count. Baseline CD4 count had independent risk and the incidence is around 90, which is 3 times higher than the overall incidence density of 30. In the category with CD4 count 201-250, age (under 5 years) is a significant predictor, with mortality of 100 per 1000 person years, which is more than 3 times higher than the overall mortality of 30 per 1000 person years and also two and half times that (HR: 2.621, 95% CI: 1.05-6.52) observed in the age-group 10-14 years age-group (*P*<0.05).

Out of those children who died 37% of them died within a month of starting ART, and by six months 74% died. The overall estimated cumulative survival probability was 0.948 (95% CI: 0.94-0.95) after 12 months, and 0.911 (95% CI: 0.89-0.92) after 60 months. In the younger (<5 years) age group, cumulative survival probability at 12 months was 0.929 (95% CI: 0.91-0.94) and 0.897 (95% CI: 0.86-0.92) after 60 months. In the older age group (10 years and above), the cumulative survival probability after 12 months was 0.949 (95% CI: 0.93-0.95) and after 60 months was 0.889 (95% CI: 0.85-0.91) (*Fig*. **2).**

DISCUSSION

Our findings indicate high levels of mortality among CLHIV. The incidence mortality rates are marginally higher amongst the youngest children (less than five years) than those among the older

children. Post-hoc analyses, however, suggested that the incidence mortality rates are significantly higher among children less than one year of age. The corresponding probability of survival among children living with HIV is 95% after 12 months follow-up and 91% after 60-month from the start of their ART initiation. Results further suggest that CD4 count at ART initiation, WHO clinical staging and functional status of children at the time of baseline seems to independently determine the subsequent survival status of the children. Analyses of CLHIV deaths indicates that out of those children who died, 37% of them died within one month of the start of the ART and cumulative 74% of the them died within six months.

These results are comparable with earlier research from Gujarat (India) that suggested similar (but lower) survival probability of 86% after 36 months from the start of ART among children. This suggests an improvement in child survival over time in India. The child mortality (30 per 1000 child years) in the current study found to be lower when compared to two different cohort studies conducted in Kenya which reported an overall mortality as 47 and 84 deaths per 1000 child years) [6,7]. The timing of deaths after start of ARI in this study is consistent with study results from northwest Ethiopia which showed that majority (90%) of the deaths occurred within the first year of treatment, and almost 50% within the first month [3,4,8].

The present study findings are important given the paucity of literature documenting the survival status of children who are on ART in India. However, the results must be considered in light of certain limitations. First and foremost, this is a secondary data analyses and is limited in terms of the number of variables or information available in the data base leading to several unexplained variations in the results. For example, the lack of key clinical data around weight, height, hemoglobin and body mass index (BMI) of children, and demographic information such as parental survival status, economic status limits our ability to interpret the data. Due to the retrospective nature of this study several critical variable were missing for several children whose data could not be included. Since, the analyses was carried out taking a cohort of CLHIV who had been initiated on ART over a period six years there may have been variations in survival status of children with the maturity of ART era. Future research could examine the survival status of children who are on ART at various time points during the ART era and also understand the reasons behind high mortality among specific sub-groups of children.

Despite these limitations, the present results document the mortality rates among huge number of children who have initiated ART during the early stage of ART introduction in India. The findings show that children less than five years, those with CD4 count less than $250/mm^3$ at the start of ART, and those in the clinical stage III or IV are more vulnerable to mortality. Thus, greater emphasis is needed to improve early HIV diagnosis and treatment in the young age group. Also, large-scale and long-term

research is needed to confirm some of the current findings and also to ascertain the reasons for high mortality among children less than five years.

WHAT IS ALREADY KNOWN?

Previous research has documented a survival probability of children living with HIV at 12 months as 90%.

Almost 50% of the child HIV deaths happen within first month of start of ART.

WHAT THIS STUDY ADDS?

There seems to be an improvement in survival status of CLHIV with the current study indicating a survival probability of children living with HIV at 12 months as 95%.

Lower CD4 count, worse clinical staging and functional status independently determine the mortality among children with HIV.

The mortality is highest among children less than five years when their CD4 levels are above 200.

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TABLE I CHARACTERISTICS OF CHILDREN (N=5874) ON INTIRECTROVIRAL THERAPY IN PRESENT STUDY

Variables	Number (%)
Male gender	3245 (55.2)
Age group	
0 - 4 y	967 (16.5)
5 - 9 y	2558 (43.5)
10 - 14 y	2349 (40)
CD4 count at start of ART (n=4843)	
≤ 200	1814 (37.5)
201-250	680 (14)
251 – 350	970 (20)
351+	1379 (28.5)
HIV clinical stage (n=4981)	
I+II	3354 (57.1)
III	1398 (23.8)
IV	229 (3.9)
Functional status (n=4991)	
Ambulatory	316 (6.3)
Bedridden	65 (1.3)
Functional	4610 (92.4)
Treatment outcomes	
Alive	4461 (75.9)
Died	336 (5.7)
Transfer out	760 (12.9)
Lost to follow-up	317 (5.4)

TABLE II AGE-SPECIFIC MORTALITY RATES AMONG CHILDREN ON IN PRESENT STUDY
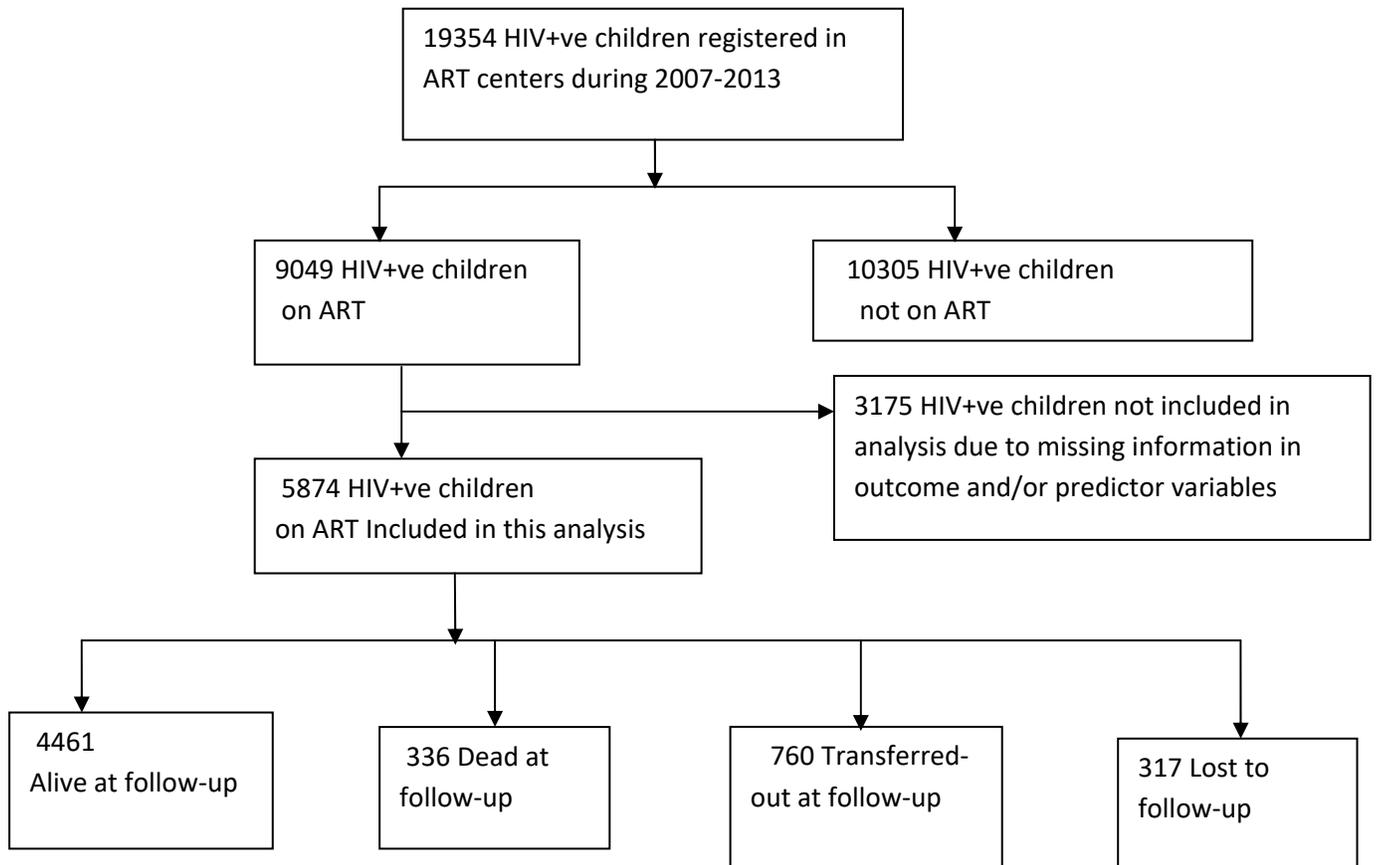
Age group	Number at the start of ART	Number of LFU	Number of deaths	Total child-years	Incidence mortality rates (per 1000 person years)	CD4 count (per mm³) Meduab (IQR)
0 – 4 y	967	65	73	1884	39	341 (195,766)
5 – 9 y	2558	108	132	5357	25	240 (155,383)
10 – 14 y	2349	144	131	4107	32	227 (139, 336)
Total	5874	317	336	11348	30	244 (153, 398)

Note: ART: anti-retroviral therapy; IQR: inter quartile range; LFU: Lost to follow-up.
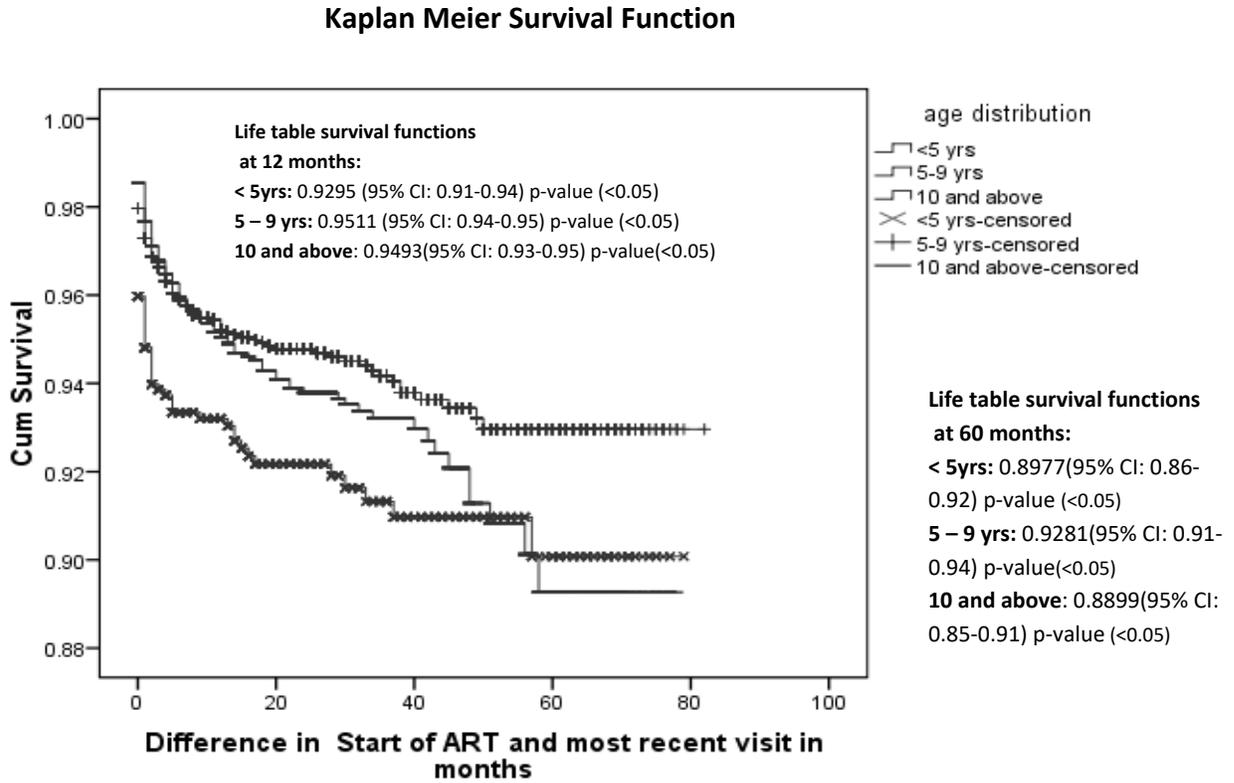
TABLE III   FACTORS ASSOCIATED WITH MORTALITY AMONG CHILDREN ON ART

Characteristics	Censored	Dead	Unadjusted Hazard ratio (95% CI)	Adjusted Hazard ratio (95% CI)
Age at ART initiation				
0 – 4 years	894	73	1.34 (1.01, 1.78)**	0.48 (0.22, 1.08)
5 – 9 years	2426	132	0.88 (0.68, 1.12)	0.84 (0.62, 1.14)
10 – 14 years	2218	131	Ref	Ref
Gender				
Male	3050	195	1.12 (.90-1.39)	1.20 (0.90,1.62)
Female	2488	141	Ref	Ref
CD4 count at ART initiation				
≤ 200	1656	158	4.45 (2.29, 6.62)***	6.27 (3.46, 11.36)***
201-250	647	33	2.48 (1.51, 4.09) ***	2.97 (1.45, 6.09)***
251 – 350	927	43	2.32 (1.45, 3.72) ***	3.241 (1.66, 6.32***
351+	1350	29	Ref	Ref
WHO clinical stage				
I/II	3218	136	Ref	Ref
III	1293	105	1.82 (1.41, 2.34)***	1.38 (1.01, 1.91)**
IV	188	41	4.89 (3.45, 6.95)***	3.18 (1.92, 5.28
Functional status				
Ambulatory	272	44	3.13 (2.27, 4.34)***	2.263 (1.44, 3.55)***
Bed ridden	41	24	10.06 (6.60, 15-36)***	4.51 (2.17, 9.36)***
Functional	4385	225	Ref	Ref

*P<0.10; ** P<0.05; *** P<0.001

19354 HIV+ve children registered in
ART centers during 2007-2013

9049 HIV+ve children
on ART

10305 HIV+ve children
not on ART

3175 HIV+ve children not included in
analysis due to missing information in
outcome and/or predictor variables

5874 HIV+ve children
on ART Included in this analysis

4461
Alive at follow-up

336 Dead at
follow-up

760 Transferred-
out at follow-up

317 Lost to
follow-up

Fig. 1: *Flow diagram of distribution of HIV +ve children included in the study*

Fig. 2: *Survival curves of HIV-positive children by age*