

## Original Research Article

# Risk factors for mortality among Human Immuno Virus infected children on antiretroviral therapy

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### ABSTRACT

**Background:** Children infected with HIV often reach the health care well after progression to severe immunosuppression which results in higher morbidity and mortality as compared to adults. They are vulnerable to faster disease progression compounded by susceptibility infections and social factors like attrition of caretakers. The present study delineates the factors for poor outcomes among HIV infected children.

**Methods:** The records of HIV infected children from 1 to 15 years of age, started on HAART, registered at ART Centre at a tertiary hospital were reviewed in the Retrospective descriptive study. The demographic details, growth parameters, clinical features, WHO staging and investigations were assessed to study the risk factors for mortality in these children.

**Results:** Amongst the 205 HIV infected children, enrolled in the study, the incidence of mortality was 27/205 (13.7%). The mean age of HIV infected children on ART in the no mortality and mortality group was 8.19 years and 8.25 years. The mean WHO stage of HIV infected children on ART in no mortality and mortality groups at the start of the study was 2.75 (SD=0.89) and 3.66 (SD=0.48), respectively. The mean CD4 count at start in the mortality group ( $195.85 \pm 105.57$  cells/mm<sup>3</sup>) is significantly lower as compared to the no mortality group ( $306.2 \pm 355.66$  cells/mm<sup>3</sup>). The mean grade of malnutrition in the no mortality and mortality groups was 1.84 and 2.88, respectively. Tuberculosis was present in 48.78% at start.

**Conclusions:** Presence of advanced clinical stage, immunosuppression, poor nutritional state, and shorter duration of therapy are important factors deciding outcome of the children on HAART. The intense monitoring in period post starting of HAART will ensure better outcomes.

**Keywords:** Antiretroviral therapy, Children, HIV, Mortality, Risk factors

### INTRODUCTION

HIV epidemic in Asia is ongoing with large number of infected patients in pediatric age group. Children have far more severe manifestation and initiation of HAART early, in children infected with HIV still remains a challenging issue in this part of the world. Expanded access to antiretroviral therapy (ART) and a declining incidence of HIV infections have led to a steep fall globally in the number of adults and children dying from HIV-related causes but HIV related deaths are still

unacceptably high.<sup>1</sup> Out of 1.7 million [1.3 million-2.2 million] children aged 0-14 living with HIV globally, only 54 [37-73] per cent were receiving life-saving antiretroviral therapy (ART) in 2018.<sup>2</sup> Only 51% of HIV-exposed infants were tested for HIV by the age of 2 months as recommended by the World Health Organization (WHO) guidelines.<sup>2</sup> With current interventions the risk of mother-to-child HIV transmission can be reduced to less than 1%.<sup>3</sup> However, such interventions are still not widely accessible in most resource-limited countries where the burden of HIV is

highest.<sup>4</sup> Globally, children under age 15 account for about 5% of all people living with HIV, 9% of new HIV infections and 13 per cent of all AIDS-related deaths.<sup>1</sup>

Continued focus on identifying, prioritising, and providing access to optimal antiretroviral formulations suitable, tolerable for infants, children, and adolescents is key to ensuring that global HIV treatment targets can be met.<sup>5</sup> The number of children receiving Anti-Retroviral therapy in 2016, in India was 55,606 which is 68% of estimated children living with HIV, while globally 54% [37-73%] of children aged 0–14 years have access to therapy.<sup>6,7</sup> Various factors like late detection, care givers constraints and compliance related issues affect the outcome of the children infected with HIV. Identifying individuals who are at risk of deaths and risk factors associated with it will be helpful for targeting potential interventions to prevent mortality in children placed on ART. Present study, centres around identifying the risk factors for mortality in HIV infected children who were started on ART. Number of factors like stage of HIV, CD4 count, nutrition, duration of ART, opportunistic infection were evaluated. The study is aimed to determine the cumulative proportion of death that occurred after starting ART in pediatric population at Tertiary care Hospital.

## METHODS

This study is a retrospective descriptive study carried out on HIV infected children registered in ART centre of a tertiary care hospital between January 2005 to December 2012. The study was approved by Committee for Academic Research Ethics (CARE), the Institutional Ethics Committee. As it was retrospective study waiver for consent form was obtained from ethics committee. Case records of HIV infected children over 8 year period from January 2005 to December 2012 was used to collect the data. There was a formal sample size as it was time bound study.

The aim of the study was to determine the cumulative proportion of death that occurred after starting ART in pediatric population at tertiary care hospital and to identify the various risk factors that may be associated with mortality. The inclusion criteria was, HIV infected children up to 15 years of age on Antiretroviral Therapy registered in ART Centre of Hospital. Children lost to follow up and those transferred out were excluded from the study. To protect the confidentiality of the patients, name and address was recorded in coded form.

ART registration number was used as code in Case Record Form. The data was collected from case records of ART centre. The demographic details, duration of Antiretroviral Therapy, WHO clinical stage of disease, baseline CD4 count, weight, height, body mass index (BMI), grade of malnutrition, opportunistic infections and number of deaths were noted.

## Statistical analysis

Cumulative proportion of death after initiating ART was determined. Risk factors assessed using logistic regression and death as scalar variable and risk factors as explanatory variable. For categorical data chi square test was used. The statistical tool SPSS version 20 was used for analysis.

## RESULTS

A total of 631 HIV infected children were registered from January 2005 to December 2012 at outpatient facility at ART centre of the tertiary care hospital. Of these children, 231 were started on ART. Amongst them, 26 patients were excluded based on enrolment criteria. A total of 205 HIV infected children who were started on antiretroviral therapy and satisfying inclusion criteria were enrolled in the study. The results of our study are presented under the headings of demographic details of study population at start antiretroviral therapy and comparison between mortality and no mortality group.

Among the study population, of the total 205 HIV infected children on antiretroviral therapy, 116 (56.59%) patients were male and 89(43.41%) were females. The male to female ratio was 1.3. The demographic characteristics of the study cohort are presented in (Table 1). The maximum number of HIV infected children on ART, 87(43%) were between 6 years to 10 years, followed by children between 11 years to 15 years of age were 67(33%) and then less than 5 years of age were 51(24%).

**Table 1: Demography of the study cases.**

Age (years)	No. of children on HAART	Percentage
1-5	51	24.8
6 -10	87	42.5
11-15	67	32.7
Total	205	100
Gender		
Male	116	56.6
Female	89	43.4
Outcome of patients in study		
Mortality	27	13.2
No mortality	178	86.8
Total	205	100

Of the 205 HIV infected children on HAART, 27 (13.17%) children died while on antiretroviral therapy. The proportion of mortality in HIV infected children started on ART in the study was 13.17%. In our study, HIV infected children ranged in age from 1 year to 15 years (Table 2). The mean age of HIV infected children on antiretroviral therapy in the study was 8.2 years (SD=3.35). The mean age of HIV infected children on ART in the no mortality and mortality group was

comparable, 8.19 years (SD=3.25) and 8.25 years (SD=4.03) respectively.

**Table 2: Age Distribution of HIV infected children on HAART.**

Age in years	No mortality	Mortality	Total
1 to 5	44 (86.3)	7 (13.7%)	51
6 to 10	77 (88.5)	10 (11.5%)	87
11 to 15	57 (85.1)	10 (14.9%)	67
Total	178 (86.8)	27 (13.2%)	205

The figures in parentheses indicates percentages.

The risk factors were studied in these two groups of children to find out association between different variables and the outcome.

The mortality in the study group was associated with WHO Staging of HIV, duration of ART received, CD4

counts and nutritional status of the children. Table 3 provides a comparison of these risk factors between the group with children on HAART with mortality and those without mortality. While age and gender were not significantly associated with mortality in our study. On evaluating, it was found that the WHO staging at start of HAART, in the mortality group was significantly higher as compared to the no mortality group. The mean WHO stage of HIV infected children on ART in no mortality and mortality groups at the start of the study was 2.75 (SD=0.89) and 3.66 (SD=0.48), respectively.

It was found that the CD4 count at start in the mortality group is significantly lower as compared to the no mortality group. The study displayed that the mean grade of malnutrition in the no mortality and mortality groups at the start of the study was 1.84 (SD=1.301) and 2.88 (SD=1.15), respectively. Thus, the grade of malnutrition, at start in the mortality group was significantly higher as compared to the no mortality group (p value 0.0002).

**Table 3: Risk Factors for Mortality in HIV infected children at the start of HAART.**

Characteristics at the baseline	No mortality (178)		Mortality (27)		p value
	Mean	SD	Mean	SD	
Age	8.19	3.25	8.25	4.03	0.82
Gender	M: 99 F: 79	55.7% 44.3%	M:17 F: 10	62.96% 37.03%	0.53*
Duration of ART	43.80	13.94	23.44	20.44	<0.0001
WHO staging at start	2.75	0.89	3.66	0.48	<0.0001
CD4 counts	278.22	355.7	195.85	105.57	0.0024
PEM Grade	1.84	1.30	2.88	1.15	0.0002
Tuberculosis at start of ART	76	42.69%	24	88.89%	<0.0001*
PJP Infection	11	6.18%	6	22.22%	0.01*

p value by Mann Whitney test, \*p value by Fisher's exact test

The mean duration of antiretroviral therapy in HIV infected children on ART in the study was 41.12 months (SD=6.41). Maximum duration of antiretroviral therapy was 72 months and minimum was 4 months in the study group. Mortality was higher in HIV infected children receiving ART <12 months. On comparing the two groups, for duration for retroviral therapy it was found that the duration of the anti-retroviral therapy in HIV infected children on ART in the mortality group was significantly lower as compared to the no mortality group (p value <0.0001).

The frequency of opportunistic infections like Tuberculosis, Pneumocystis Jiroveci pneumonia (PJP), and bacterial pneumonia was higher in mortality group as against no mortality group (Table 3). The study displayed that occurrence of Tuberculosis was common amongst both the groups of mortality as well as no mortality (Figure 1). Amongst the children on HAART, the

commonest type of Tuberculosis was seen in the form of Pulmonary involvement, followed by Abdominal Koch and then tuberculous meningitis. The maximum deaths were noted children with Pulmonary Tuberculosis. Toxoplasmosis was diagnosed in 2 children and 1 each with chronic diarrhoea and Hepatitis C. Of the 205 children on HAART, 3(1.46%), children were diagnosed with Cardiomyopathy, 1(0.5%) with Nephropathy and 6(2.92%) had Encephalopathy. Amongst these, 2 children with Encephalopathy expired. Also seen was occurrence of Malignancy, 1 each of Non-Hodgkin's Lymphoma and Burkitt's Lymphoma, both of these expired.

## DISCUSSION

In the present study we determined mortality in a cohort of HIV infected children enrolled in ART centre of hospital. The Study reported risk factors for death among these HIV-infected children in whom HAART was

initiated. The mean age of the HIV infected children in our study was 8.2 years which was higher than that in the studies by Mofenson LM et al, 3.41 years.<sup>8</sup> Padmapriyadarsini et al. conducted in South India, the average age of the children in study was approximately 5.9 years with 17% under 3 years of age.<sup>9</sup> This difference in age could be due the delay in diagnosis of HIV infection in our study population. The proportion of males in the no mortality and mortality groups in our study was 55.62% and 62.96% respectively while that of females was 44.38% and 37.03% respectively. The sex distribution in both the groups was comparable which was similar to the findings in the other studies.<sup>9</sup> The mean CD4 count of study population in our study was 267 cells/mm<sup>3</sup> at start of the study. This was similar to the findings in the study by Zanoni BC et al, 226 cells/cu mm.<sup>10</sup>

In the present study, we observed that mortality rate in HIV infected children after initiation of ART was 13.17%. The proportion of mortality in the HIV infected children on ART in study by Mofenson LM et al, was 36.2.8. The mortality in the study by Mofenson LM et al, was comparatively higher as the study was conducted in era when the HAART was in the initial phase and single drug Zidovudine was given to children in study. Compared to the study by Puthanakit et al, wherein the mortality was 5.7%, the mortality in our study was higher.<sup>11</sup> Multiple factors like age at initiation of HAART, duration of ART, WHO stage of disease, CD4 count, nutritional state, opportunistic infection may be responsible for the increased mortality in the study. Age was not significantly associated with mortality in our study, this could be due to poor implementation of early infant diagnosis. The study from Zambia by Muthunga et al found that the hazards of mortality were highest among infants and children aged less than 12 months of age and is consistent with predictive models that have been done in both developed and developing countries and in fact motivated the universal ART policy by WHO to test and treat all HIV-exposed infants and children.<sup>12</sup>

In our study it was noted that the WHO clinical stage at time beginning of HAART, in the mortality group (Mean: 3.66), was higher than the no mortality group (Mean: 2.75). Our findings were consistent with previous studies by reports by Reddi et al, and Fenner et al, which suggests that, WHO clinical staging of HIV, affects the survival of the subject.<sup>13,14</sup>

We observed that the CD4 count at start of the study in the mortality group was lower than the no mortality group. Kabua et al, studied the outcomes of HAART in HIV infected children from Swaziland, did not detect any difference in CD4 counts or percentage at ART initiation in children who were alive and on treatment at 2 years compared to those who were either not alive or not in care at that time ( $p=0.6$ ), but their study had high rates of missing data.<sup>15</sup> Another study by Kiboneka A et al (2008) in Pediatric patients in Uganda, also observed similar association of mortality with lower CD4 cell percentage at initiation.<sup>16</sup> According to study by Walker AS et al (2012) in HIV infected children on ART in Uganda and Zimbabwe it was found that one-year mortality after initiating ART with 0-49, 50-99 or  $\geq 100$  CD4 cells/ $\mu$ L was 10.1%, 4.4%, and 1.3%, respectively, in children aged 4-15 years.<sup>17</sup> Thus the cohort, with lower CD4 count at the start of HAART demonstrated highest mortality.

We found a trend of association between low weight-for-height and mortality. Thus, severe grade of malnutrition was associated with poor outcome in our study which is consistent with observation of many previous studies. These findings are similar to a retrospective study from KwalaZulu in South Africa by Zanoni et al, where univariate associations between demographic and clinical characteristics and mortality were examined.<sup>10</sup> The Weight-for age Z-score ( $p=0.0001$ ), chronic diarrhea ( $p=0.0002$ ), lower hemoglobin ( $p=0.002$ ), age, 3 years ( $p=0.003$ ), and CD4%, 10% ( $p=0.005$ ) were noted to be strongly associated with mortality. In study by Taye B et al severe wasting strong independent risk factor for survival.<sup>18</sup> Growth failure (measured as low weight-for-height or low weight-for-age) has been found to independently predict mortality in several studies.<sup>19</sup> According to Bong CN et al, in children on ART in Malawi it was found that the incidence in children in WHO clinical stage 4 having severe wasting and severe immunodeficiency were factors significantly associated with 3-month mortality and 6-month mortality, respectively.<sup>20</sup> The effect of severe protein energy malnutrition on both humoral and cell-mediated immunity has been previously described.<sup>9,18</sup> It is conceivable that children with both conditions, advanced HIV-1 disease and severe protein energy malnutrition will have limited capacity for immune recovery and are especially prone to life-threatening microbial infections. In the current study, we also evaluated the change in various parameters post six months of HAART (Table 4).

**Table 4: Changes in various parameter in HIV infected children after 6 months of HAART.**

Change in Parameter over 6 months	No mortality (178)	Mortality (27)	p value and its association
CD4 count	350.94 (SD=378.40)	137.58 (SD= 212.72)	<0.0001 Significant
WHO staging	0.28 (SD=0.5)	-0.07 (SD=0.27)	0.0072 Significant
Weight	1.26 (SD=1.03)	0.12 (SD=1.13)	< 0.0001 Significant
BMI	0.94 (SD= 1.06)	0.11 (SD=1.17)	0.00006 Significant

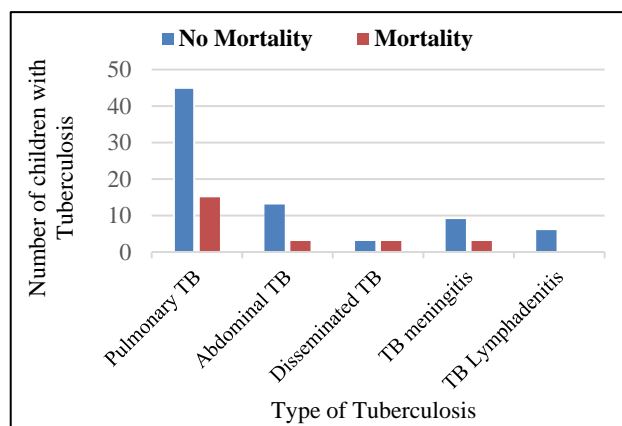
Statistical test applied Mann Whitney test

The improvement in the height for age, BMI as well as weight for age after 6 months of ART were positively associated with survival in our study. We noted that, the mean weight of HIV infected children on ART in the no mortality and mortality groups at start of the antiretroviral therapy was 17.06 kg (SD=6.30) and 14.73 kg (SD=5.64), respectively, which was comparable between the two groups. The mean change in weight over 6 months in HIV infected children on ART in the no mortality and mortality groups was 1.26 kg (SD=1.03) and 0.12 kg (SD=1.13), respectively. It was noted that the change in weight over 6 months in the mortality group is significantly lower as compared to the no mortality group. The Sinikithemba cohort studied by Reddi et al, demonstrated an immediate and significant response to therapy: 65 out of 88 children (73.8%) reported a significant increase in WAZ score after the first month following HAART.<sup>13</sup>

Response to HAART, was evaluated by the degree of changes in WHO clinical staging post six months of HAART. The mortality group exhibited significantly poor response wherein change in staging deteriorated to -0.7 compared to 0.26 in no mortality group. The mean CD4 count of the no mortality and mortality groups at the 6 months of the study was 628.16±300.68 and 324.13±225.14 cells/mm<sup>3</sup>, respectively. In this cohort of HIV infected children who initiated highly active antiretroviral therapy at advanced immunosuppression we documented high mortality. These trend concurs with the earlier observations of Kedir and Abaya et al.<sup>21,22</sup>

The mean duration of antiretroviral therapy in the no mortality group was 43.8 months (SD=13.94) and in the mortality group was 23.44 months (SD=20.44). Mortality was higher in HIV infected children receiving ART <12 months. Finding of our study reaffirms that, the duration of the anti-retroviral therapy in HIV infected children on ART in the mortality group significantly affected the survival. Thus, children who survived initial period post ART initiation were less likely to die in subsequent period. This finding of a high mortality rate in the first 12 months after HAART is similar to that reported from another developing country, Thailand, where Putnanakit et al (2007), suggested that longer duration of HAART was associated with better outcomes.<sup>11</sup> In that study, the mortality rate during the first 24 weeks after HAART initiation was 5.7%. The 24-week mortality rate decreased to a mean of 0.24% in the following five 24-week intervals. They also noted that among Fifty-nine hospital admissions (54.6%) occurred during the first 24 weeks of HAART. Causes of hospitalization were pneumonia and other bacterial infections (61.7%), immune reconstitution syndrome (23.4%), noninfectious illness (6.5%), opportunistic infection (5.6%), and drug-related events (2.8%). The authors suggested that the higher mortality rates in low-income countries during the first few months of treatment, compared with those in Europe and North America, could be explained by the low CD4 cell counts, the more advanced clinical stage,

and the prevalence of coexisting infection at the time of HAART initiation, as well as the occurrence of IRS in these patients with late-stage HIV infection.



**Figure 1: Tuberculosis in HIV infected children on ART.**

The overall prevalence of tuberculosis in our study was 48.78%. In a study by Gebremedhin A et al the proportion of children with presence of tuberculosis at start of study in the no mortality and mortality group was 28.3% and 75% respectively.<sup>23</sup> The incidence of tuberculosis at start was higher in the mortality group (88.89%) compared to the no mortality group (42.69%) as shown in (Figure 1). This validates the findings of the studies proving association of coinfection with tuberculosis with mortality in the HIV infected children. In a study conducted by Rajasekaran et al, has similarly high prevalence (63%) of tuberculosis coinfection in paediatric children with HIV in their study.<sup>24</sup> While it was recorded as 42.5% by Zaroni BC et al.<sup>10</sup> The study by Shubangu et al validates the findings of the studies proving association of tuberculosis with mortality in the HIV infected children wherein children diagnosed with tuberculosis at baseline, all other variables constant were estimated to have 3.81(95%CI 2.36-6.13) times higher hazard of death than those without it.<sup>25</sup> High frequency of tuberculosis amongst children with HIV at baseline as well as statistically significant association of tuberculosis in mortality suggests that factors like poor nutritional status, immune reconstitution syndrome may have important role in outcomes.

The incidence Pneumocystis carinii pneumonia was 7.3% children in the study by Reddi A et al, which was similar to that as the noted in our study 8.29%.<sup>13</sup> The occurrence of Pneumocystis carinii pneumonia in our cohort of HIV infected children at the time of starting of HAART in the mortality group (22.22%) was significantly higher than the no mortality group (6.18%). In our study, pneumonia at start of the study in the mortality group was 29.63% compared to 12.36% in the no mortality group. These findings were similar to those in the study by Walker AS et al.<sup>17</sup> Presence of PJP and bacterial pneumonia is one of important risk factor and may be the immediate reason

for death in HIV infected children. We observed that presence of other infections or conditions like Hepatitis C, Burkitt's Lymphoma, NHL in the mortality group was significantly higher than that in the no mortality group. Thus, presence of other comorbid conditions increases the risk of mortality in the HIV infected children. Simard et al. investigated the long-term cancer risks in young adults diagnosed with AIDS during childhood.<sup>26</sup> The study showed that KS (caused by an infection with Human Herpes Virus 8 (HHV-8), is a frequent cancer in sub-Saharan Africa (SSA) and in SSA migrants in Europe, but cases are rare in children outside of this regions. Comparing cancer incidence in the pre-combined ART with the cART era the risk of developing KS was reduced by almost 90% (relative risk (RR) 0.13, 95%CI 0.20-0.74) and the NHL risk by 60% (RR 0.40, 95%CI 0.21-0.75).<sup>27</sup>

The strength of our study is that along with risk factors at the baseline, we observed changes post 6 months of HAART in parameters like anthropometrical measures, WHO clinical stage and CD4 levels. Limitations of the study were that, being a retrospective cohort study design limited our ability to gather data about factors that may influence the risk of mortality. The details of lost to follow up patients were not included. The findings of our study suggests that early initiation of HAART along with monitoring for the simple parameters of growth and being watchful for signs of IRIS will significantly improve the outcomes of the patients on treatment. It is also important to further investigate targeted interventions that intensify support for children during the first 4-6 months following HAART initiation with particular attention given to those presenting with coinfections and low weight-for-height as suggested by Wamalwa et al.<sup>28</sup>

Advanced WHO clinical stage of HIV, severe immune suppression, low weight and height for age, opportunistic infections like tuberculosis, pneumonia, Pneumocystis carinii pneumonia are risk factors for mortality in HIV infected children on ART. We conclude that, the outcome of children started on HAART can be improved by interventions which will address the risk factors like malnutrition, inadequate CD4 rise after ART, frequent CD4 counts monitoring in first 12 months post initiation of HAART, more aggressive treatment of bacterial infections and actively looking out for features of immune reconstitution syndrome. Targeted intervention should be undertaken especially for children with risk factors. This information would be useful for public health authorities for training programs targeted at these specific causes of morbidity and mortality would enable health care workers to make diagnosis and give treatment in a timely manner.

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