Mortality and loss to follow up before initiation of antiretroviral therapy among HIV-infected children eligible for HIV treatment

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Abstract

Data on attrition due to mortality or loss to follow-up (LTFU) from antiretroviral therapy (ART) eligibility to ART initiation of HIV-infected children are scarce. The aim of this study is to describe attrition before ART initiation of 247 children who were eligible for ART in a cohort study in India. Multivariable analysis was performed using competing risk regression. The cumulative incidence of attrition was 12.6% (95% confidence interval, 8.7-17.3) after five years of follow-up, and the attrition rate was higher during the first months after ART eligibility. Older children (>9 years) had a lower mortality risk before ART initiation than those aged <2 years. Female children had a lower risk of LTFU before ART initiation than males. Children who belonged to scheduled tribes had a higher risk of delayed ART initiation and LTFU. Orphan children had a higher risk of delayed ART initiation and mortality. Children who were >3 months in care before ART eligibility were less likely to be LTFU. The 12-month risk of AIDS, which was calculated using the absolute CD4 cell count and age, was strongly associated with mortality. A substantial proportion of ART-eligible children died or were LTFU before the initiation of ART. These findings can be used in HIV programmes to design actions aimed at reducing the attrition of ART-eligible children in India.

Introduction

In the absence of any intervention, over half of children infected with human immune-deficiency virus (HIV) die by the second year of life.[1] Antiretroviral therapy (ART) reduces the mortality risk by 75%,[2] but only 28% of children who are eligible for ART are receiving it.[3] Consequently, there is an urgent need to increase the uptake of ART among children living with HIV, especially in low or middle-income countries.[3] Typically, the preparation of HIV infected children eligible for ART requires several counselling sessions on the part of the caregivers, before ART is started.[4] During this period, children may drop out. Studies from low and middle-income countries have shown that 25% of adults in need of HIV treatment die or are lost to follow up (LTFU) before starting ART.[5,6] However, data on the attrition of ART-eligible children, especially outside sub-Saharan Africa, is scarce.[7]

India has the highest burden of paediatric HIV in Asia.[8] Of the 112,385 children registered in ART centres by December 2012, only 34,367 (30.6%) had started ART.[8] A better understanding of the attrition process before ART initiation is essential to design effective strategies to increase the uptake of ART among HIV-infected children in India. The objective of this study is to describe the proportion of ART-eligible children who started ART in a cohort study in India. In particular, we aimed to find predictors of mortality and LTFU before ART initiation, which could help HIV programmes to design actions intended to reduce the attrition from care of HIV-infected children in India.

Materials and Methods

Setting and design

The study was performed in Anantapur, a district situated in the south border of Andhra Pradesh, India. Anantapur has a population of approximately four million people of which 72% live in rural areas.[9] The HIV epidemic in Anantapur is largely driven by heterosexual transmission and is characterized by poor socio-economic conditions and high levels of illiteracy.[10] Rural Development Trust (RDT) is a non-governmental organization that provides free-of-charge medical care to HIV-infected people, including medicines, consultations, and hospital admission charges.

The Vicente Ferrer HIV Cohort Study (VFHCS) is an open cohort study of all HIV infected patients who have attended RDT hospitals. The characteristics of the cohort have been described in detail elsewhere.[10,11] For this study, we selected HIV infected children (<15 years old) from the VFHCS who became eligible for ART between January 1st 2007 and July 15th 2013. ART eligibility was defined by immunological criteria (CD4 count <1500 cells/μL or <25% in children aged <12 months, CD4 count <750 cells/μL or <20% in children aged 12-35 months, CD4 count <350 cells/μL or <15% in children aged 36-59 months, and CD4 count <350 cells/μL in children aged >59 months) according to the Indian National Guidelines.[4]

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Definitions

The designation of the patients' community was self-reported. The scheduled caste community is marginalised in the traditional Hindu caste hierarchy and, therefore, suffers from social and economic exclusion and disadvantage. In general the scheduled tribe (ST) community is geographically isolated with limited economic and social contact with the rest of the population. Backward castes form a series of *intermediate* castes that were considered low in the traditional caste hierarchy, but above scheduled castes.[12] Patients were considered as living near a town when they lived in a mandal (administrative subdivision of districts in Andhra Pradesh; *e.g.,* Anantapur District has 64 mandals) including a town with a population >100,000 people. For children with both parents alive, parents were asked whether they lived in a rented house or in an owned house, as a marker of the economical conditions for the caregivers.

In HIV infected children <5 years, the CD4 lymphocyte percentage has been generally preferred for monitoring the immune status because of the variability of the CD4 cell count during the first years of life.[13] However, an analysis of the HIV Paediatric Prognostic Markers Collaborative Study (HPPMCS) demonstrated that the CD4 percentage provides little or no additional prognostic value

compared with the CD4 cell count in children.[14] Therefore, the immune status of children was calculated using the 12-month risk of AIDS adopted in the HPPMCS, which is based on the CD4 cell count and the age of children to calculate the level of immunodeficiency.[15] Because of the small number of older children included in the HPPMCS, children >12 years were recorded as if they were 12 years old to calculate the 12-month AIDS risk.[16]

Statistical analysis

Statistical analysis was performed with Stata Statistical Software (Stata Corporation. Release 11. College Station, Texas, USA). To investigate predictors of ART initiation, mortality and LTFU, time-to-event methods were used. Time was measured from the date of ART eligibility to ART initiation or death, whichever occured first.[17] Children who did not die nor started ART were recorded at the last visit date. Children who did not come to the clinics for at least 180 days after their last visit date were considered LTFU.[18] Cox regression models assume that the distribution of censoring times and the time-to-event distribution are independent of each other.[19] When studying the cumulative incidence of ART initiation, a group of children will be censored at death or at the last visit date. However, dead children will not be able to start ART and LTFU children have a higher probability of not starting ART than those who come regularly to the clinics.[20] The inclusion of these children in standard survival models may lead to an overestimation of the proportion of children who start ART. Thus, multivariable analysis and estimation of the cumulative incidence of ART initiation, mortality and LTFU were performed using competing risk proportional hazard models taking the other events of interest as competing events.[21] These models estimate sub-distribution hazard ratios (SHRs), which can be interpreted similarly to hazard ratios estimated by Cox proportional models, but they take into account the hazard of the competing events.[19] The cumulative incidence of ART initiation, mortality and LTFU were estimated using the *stcompet* command in Stata.[22,23] The study was approved by the Ethical Committee of the RDT Institutional Review Board.

Results

We identified 247 children from the VFHCS who met the inclusion criteria. The study included 1452 child-months and, during the study, 195 started ART, 10 children died and 20 were LTFU. Among children who were LTFU, the median time of follow-up was 2.8 months [interquartile range (IQR), 0.4-12.5; mean 8.4 months] and, the median time from ART eligibility to ART initiation was 0.95 months (IQR, 0.16-3.2). Among children who died, the median time from ART eligibility to death was 1.2 months (IQR, 0.07-9.2).

Baseline characteristics at time of ART eligibility and the multivariable analysis of factors associated with ART initiation, mortality and LTFU are described in Table 1. The median age was 6.74 years (IQR, 3-10.14), over half were female, over half belonged to BC communities, 60% were living far from a town and 27% lived near the hospital. Near half of the children had lost one or both of their parents, and the majority of those with parents alive were living in a rented house. Three quarters of children became ART eligible within three months from entry into care. Taking into account the age and the CD4 lymphocyte count, the median estimated 12-month risk of AIDS was 6.77% (IQR 4-17.34, range 2.75-75.2). Older children (>9 years) had a lower risk of mortality than those aged <2 years. Female children had a lower risk of LTFU than males. Children who belonged to ST communities had a higher risk of delayed ART initiation and LTFU. Children who lived near a town had a higher risk of LTFU. Compared to orphan children, children who lost only their mother had a lower risk of delayed ART initiation and mortality. Children who lost only their father had also a lower risk of death than orphan children. Children who were >3 months in the programme before ART eligibility were less likely to be LTFU. The 12-month risk of AIDS was strongly associated with mortality, since a 1% increase of the 12-month risk of AIDS was associated with a 4% increase in the risk of mortality. Raw and adjusted SHRs for these variables are presented in Table 1.

A stacked graph of the status of HIV-infected children since ART eligibility is presented in Figure 1. The cumulative incidence of children who started ART was 59.1% (95% CI, 52.6-64.9) at 3 months, 64.5% (95% CI, 58.1-70.1) at 6 months, 72.9% (95% CI, 66.8-78.1) at 1 year, 78.3% (95% CI, 72.4-83.1) at 2 years, and 82.2% (95% CI, 76.3-86.8) at 3 years. The cumulative incidence of attrition (mortality or LTFU) before ART initiation was 7.3% (95% CI, 4.5-11) at 3 months, 7.7% (95% CI, 4.8-11.5) at 6 months, 9.5% (95% CI, 6.2-13.6) at 1 year, 10.4% (95% CI, 7-14.7) at 2 years, and 12.6% (95% CI, 8.7-17.3) at 3 years. At 3 years, the cumulative incidence of mortality and LTFU was 3.8% (95% CI, 1.9-6.7) and 8.9% (95% CI, 5.6-13.1), respectively.

Discussion

The results of this study show that approximately 13% of ART eligible children die or are LTFU before starting ART. This proportion is substantially smaller than the proportion of ART eligible adults who are lost-to-programme before ART initiation described in a meta-analysis study in sub-Saharan Africa,[5] which was 24.6% (95% CI, 18.8-30.3). The median time from ART eligibility to ART initiation was less than one month, which is considerably shorter than in studies from sub-Saharan Africa and Cambodia.[24-26] The proportion of children who started ART was similar in Ivory Coast, Lesotho and Zambia (70-86%),[27-29] but higher than the ones reported in studies from

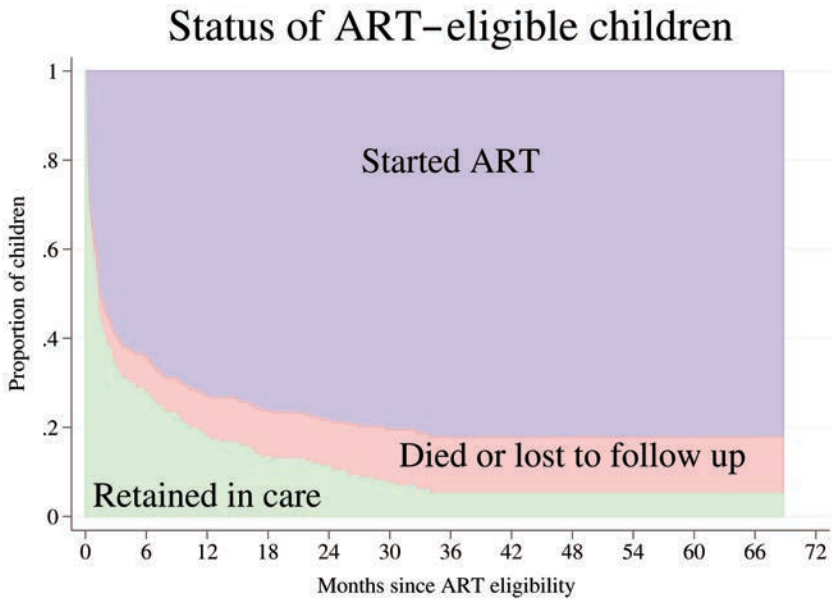

Figure 1. Stacked graph describing the cumulative incidence of antiretroviral therapy (ART) initiation and attrition in 247 ART-eligible children in Anantapur, India.

Gambia and South-Africa (33-40%).[24,30]

To our knowledge, this is the first study that describes the risk factors of attrition among ART eligible children in India. In accordance with previous studies,[1,24,29] children aged <2 years have a higher risk of mortality than older children. In line with studies from sub-Saharan Africa,[31,32] orphan children have a higher risk of mortality suggesting that they are more vulnerable than children who have at least one of their parents. In contrast with studies from sub-Saharan Africa,[24,28] we found significant gender differences. While there is a trend towards higher mortality in female children, male children are more likely to become LTFU. Children who belonged to ST communities have a higher risk of delayed ART initiation and LTFU, indicating that these children should be followed up until ART is started, and their caregivers may need extra-support and counselling. The risk of LTFU is significantly higher in children who have become ART eligible within three months of inclusion in the program, indicating that paediatric ART programmes should put more emphasis on the follow-up of children who become ART eligible soon after entering into care.

Children with higher levels of immunodeficiency are more likely to die before initiating ART and the mortality is concentrated in the first months after ART eligibility. These findings are in accordance with the studies conducted in the Ivory Coast and Gambia,[24,28] suggesting that strategies to ensure earlier diagnosis, prompt inclusion and timely initiation of ART could be effective in reducing the mortality of HIV-infected children living in the developing countries.[33]

The study has some limitations. Children who are LTFU might not be lost forever, since they may be included again at a later time or in other HIV centres. Children who lived near a town might have been more likely to attend other ART centres near their homes after their caregivers knew they needed to start ART. However, studies performed in adults have demonstrated a high mortality in LTFU patients,[34] as was observed also in a study on children conducted in Western Kenya.[35]

Conclusions

In our setting, 13% of ART eligible children are lost-to-program before ART initiation. Children who are orphans or belong to ST communities need extra support, because they are at higher risk of attrition. Male children and children who become ART eligible soon after

Table 1. Baseline characteristics and raw and multivariable analysis of factors associated with antiretroviral therapy (ART) initiation, mortality and loss to follow up of 247 children eligible for ART in Anantapur, India.

	N (%)	ART initiation		Mortality		Loss to follow up	
		SHR	aSHR	SHR	aSHR	SHR	aSHR
Age (years)							
0-2	69 (27.94)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
3-4	38 (15.38)	0.78 (0.48-1.27)	0.75 (0.45-1.23)	0.74 (0.14-3.92)	0.92 (0.09-9.84)	1.03 (0.30-3.51)	0.76 (0.14-4.02)
5-9	70 (28.34)	1.13 (0.77-1.65)	1.07 (0.67-1.70)	0.56 (0.14-2.27)	1.29 (0.22-7.55)	0.67 (0.21-2.08)	0.85 (0.24-2.92)
>9	70 (28.34)	1.52* (1.04-2.21)	1.29 (0.81-2.04)	0.00* (0.00-0.00)	0.00* (0.00-0.00)	0.55 (0.16-1.88)	0.43 (0.07-2.42)
Gender							
Female	115 (46.56)	0.87 (0.66-1.15)	0.89 (0.66-1.19)	2.72 (0.71-10.41)	2.79 (0.62-12.53)	0.48 (0.19-1.25)	0.32* (0.13-0.80)
Male	132 (53.44)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Community							
OC	48 (19.43)	0.91 (0.66-1.25)	0.90 (0.63-1.28)	1.37 (0.15-12.41)	0.58 (0.02-19.43)	2.17 (0.49-9.57)	3.37 (0.72-15.70)
BC	139 (56.28)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
SC	47 (19.03)	0.94 (0.60-1.45)	0.82 (0.49-1.37)	4.24 (0.46-38.87)	4.02 (0.15-107.36)	1.56 (0.26-9.22)	1.00 (0.13-7.85)
ST	13 (5.26)	0.33* (0.12-0.87)	0.37* (0.14-0.97)	4.06 (0.25-66.77)	1.63 (0.09-30.44)	7.41* (1.25-43.80)	9.24* (1.02-83.46)
Living near a town							
No	149 (60.32)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	98 (39.68)	0.83 (0.63-1.11)	0.82 (0.60-1.13)	0.36 (0.08-1.66)	0.38 (0.07-2.08)	2.90* (1.16-7.24)	4.48* (1.11-18.02)
Time to ART centre							
<30 min	67 (27.13)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
>30 min	180 (72.87)	1.19 (0.86-1.63)	1.15 (0.79-1.68)	0.85 (0.22-3.28)	0.34 (0.10-1.10)	0.85 (0.33-2.21)	2.16 (0.58-8.09)
Year of ART eligibility							
<2009	62 (25.1)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
2009	43 (17.41)	0.99 (0.68-1.44)	0.95 (0.62-1.46)	0.49 (0.05-4.59)	1.09 (0.09-12.52)	1.10 (0.24-5.00)	1.63 (0.26-10.03)
2010	55 (22.27)	0.66 (0.43-1.03)	0.75 (0.48-1.18)	0.39 (0.04-3.72)	0.40 (0.02-9.79)	2.56 (0.80-8.22)	3.35* (1.12-10.05)
2011	43 (17.41)	0.92 (0.62-1.36)	0.88 (0.57-1.36)	0.50 (0.05-4.74)	0.62 (0.06-5.96)	1.12 (0.25-5.04)	1.47 (0.28-7.56)
2012	44 (17.81)	0.77 (0.51-1.18)	0.81 (0.51-1.28)	2.19 (0.53-8.97)	3.84 (0.41-36.32)	0.38 (0.04-3.39)	0.50 (0.07-3.81)
Status of parents							
Alive, rented house	71 (28.74)	0.49* (0.32-0.75)	0.65 (0.40-1.06)	1.17 (0.23-5.91)	0.41 (0.05-3.65)	3.18 (0.73-13.91)	3.92 (0.69-22.30)
Alive, owned house	55 (22.27)	0.70 (0.44-1.09)	0.88 (0.55-1.41)	1.16 (0.21-6.46)	0.32 (0.06-1.81)	0.36 (0.03-3.96)	0.39 (0.03-4.32)
Father died	64 (25.91)	0.90 (0.59-1.37)	1.17 (0.73-1.87)	0.32 (0.03-3.37)	0.08* (0.01-0.44)	1.65 (0.33-8.34)	2.23 (0.37-13.44)
Mother died	18 (7.29)	1.43 (0.81-2.53)	1.81* (1.06-3.10)	0.00* (0.00-0.00)	0.00* (0.00-0.00)	1.14 (0.10-12.96)	2.91 (0.16-53.07)
Both died	39 (15.79)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Pre-ART care							
<3 months	185 (74.9)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
>3 months	62 (25.1)	0.68* (0.50-0.93)	0.74 (0.53-1.02)	1.34 (0.35-5.13)	1.00 (0.25-4.01)	0.33 (0.08-1.40)	0.19* (0.05-0.78)
12-month AIDS risk (%)	6.8 (4-17.3)°	1.00 (0.99-1.01)	1.00 (0.99-1.01)	1.04* (1.02-1.07)	1.04* (1.01-1.07)	1.01 (0.98-1.03)	1.01 (0.97-1.05)

*P <0.05; °median (interquartile range). aSHR, adjusted sub-distribution hazard ratio; ART, antiretroviral, therapy; BC, backward castes; CI, confidence interval; N, number; OC, other castes; SHR, sub-distribution hazard ratio; SC, scheduled castes; ST, scheduled tribes.

inclusion in the program are more likely to be LTFU and, therefore, they should be followed-up with utmost attention. The results of this study can be used in HIV program to design actions aimed at reducing the attrition of HIV-infected children before the initiation of ART in India.

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