Impact of orphan status on HIV treatment outcomes and retention in care of children and adolescents in Asia

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Abstract

An analysis of the impact of orphanhood at antiretroviral therapy (ART) initiation on HIV outcomes in Asia included 4300 children, 51% were male. At ART initiation, 1805 (42%) were non-orphans (median age: 3 years), 1437 (33%) were single orphans (6 years) and 1058 (25%) were double orphans (7 years). Ten-year post-ART survival was 93.4–95.2% across orphan categories. Clinic transfers were higher among single and double orphans than non-orphans (41% vs 11%, P < 0.001).

Introduction

An estimated 17.8 million children have lost one or both parents to the global HIV epidemic. [1] Orphaned children infected with HIV have been reported in multiple contexts to be at greater risk of delayed access to care, poor adherence and mental health issues [2–6]. As children age, they experience additional psychosocial stressors, including the need for HIV disclosure, fear of stigma and discrimination, managing antiretroviral therapy (ART) in the context of adolescent development, and impending transition to adult HIV care [7,8]. Orphanhood also puts social and financial strain on the remaining parent or non-parental caregivers [9–11].

We conducted an analysis of a regional paediatric HIV cohort in Asia to determine the impact of orphanhood on treatment outcomes and retention in care of children and adolescents.

Methods

Data were extracted from the TREAT Asia Pediatric HIV Observational Database (TApHOD), which is a member cohort of the International Epidemiology Databases to Evaluate AIDS (ieDEA) [12]. Data were collected from 16 participating clinical programmes in six countries comprising Cambodia, India, Indonesia, Malaysia, Thailand and Vietnam. Prospective data collection in TApHOD commenced in 2008 and retrospective clinical data were provided from the date of first entry into the clinic where available. For this analysis, the study population was restricted to children enrolled in TApHOD through September 2014, who initiated this analysis, the study population was restricted to children from the date of first entry into the clinic where available. For Thailand and Vietnam. Prospective data collection in TApHOD in six countries comprising Cambodia, India, Indonesia, Malaysia, Thailand and Vietnam. Prospective data collection in TApHOD in six countries comprising Cambodia, India, Indonesia, Malaysia, Thailand and Vietnam.

Definitions and statistical analysis

The primary endpoint for this analysis was the proportion of children who stayed in care after ART initiation and the study factor of interest was orphan status. We used the following classification for orphan status of a child at the time of ART initiation: non-orphan (both parents were alive or were recorded as the primary caregivers); single orphan (one parent died or a child had only one parent involved in their care); and double orphan (both parents died or a child lived in an orphanage, group home or was homeless). If the vital status of both parents was unknown and there was no evidence of their involvement in care, the child was categorised as a double orphan. Children with insufficient data to make a determination on orphan status using these criteria were excluded from the analysis.

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parental vital status. Institutional Review Board approvals were obtained at participating sites, the data management and analysis centre (Kirby Institute, UNSW Australia) and the coordinating centre (TREAT Asia/amfAR, Bangkok, Thailand).

Demographic and clinical characteristics for different orphan groups were presented as proportions or median and interquartile ranges.
The Chi-squared test was used for comparison of categorical variables and the Kruskal–Wallis test for comparison of continuous variables. The incidence rates of mortality 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 date of starting ART until the date of death or the date of the most recent clinic visit.

The Kaplan–Meier method was used to assess the cumulative probability of retention after starting ART. We used Cox regression to assess factors associated with LTFU of children and adjusted by country. Covariates included sex, baseline age, orphan status, weight- and height-for-age z score, first regimen (lasting $\geq 7$ days), CD4 cell count and viral load. Analyses were primarily based on data at the time of ART initiation and not updated over the course of follow-up. Variables with a $P$-value of $<0.10$ in the univariate analysis were included in the multivariate models. Statistical significance for the final model was identified using a two-sided $P$-value of 0.05.

Table 1. Characteristics of patients by orphan group at antiretroviral therapy initiation

| Characteristics, n (%) | Total $n=4300$ | Non-orphan $n=1805$ | Single orphan $n=1437$ | Double orphan $n=1058$ | $P$ |
|------------------------|---------------|----------------------|------------------------|------------------------|-----|
| Male                   | 2179 (51)     | 958 (53)             | 718 (50)               | 503 (48)               | 0.014 |
| Median (IQR) age, years| 5 (2–8)       | 3 (2–6)              | 6 (3–9)                | 7 (5–10)               | $<0.001$ |
| Country                |               |                      |                        |                        |     |
| Thailand               | 1764 (41)     | 473 (26)             | 636 (44)               | 655 (62)               |     |
| Vietnam                | 1331 (31)     | 748 (41)             | 412 (30)               | 171 (16)               |     |
| Cambodia               | 491 (11)      | 234 (13)             | 149 (10)               | 108 (10)               |     |
| Malaysia               | 303 (7)       | 121 (7)              | 106 (7)                | 76 (7)                 |     |
| Indonesia              | 256 (6)       | 129 (7)              | 87 (6)                 | 40 (4)                 |     |
| India                  | 155 (4)       | 100 (6)              | 47 (3)                 | 8 (1)                  |     |
| Primary caregiver category |            |                      |                        |                        | $<0.001$ |
| Parent                 | 2445 (56)     | 1570 (86)            | 875 (61)               | 0 (0)                  |     |
| Grandparent            | 776 (18)      | 86 (5)               | 288 (20)               | 402 (38)               |     |
| Other relative         | 416 (10)      | 65 (4)               | 135 (9)                | 216 (20)               |     |
| Non-Family member      | 358 (8)       | 15 (1)               | 71 (5)                 | 272 (26)               |     |
| Foster family          | 152 (4)       | 2 (0)                | 24 (2)                 | 126 (12)               |     |
| Unknown                | 153 (4)       | 67 (4)               | 44 (3)                 | 42 (4)                 |     |
| Residential status     |               |                      |                        |                        | $<0.001$ |
| Living with family     | 3658 (85)     | 1669 (92)            | 1287 (90)              | 702 (67)               |     |
| Group home             | 354 (8)       | 87 (5)               | 116 (8)                | 151 (14)               |     |
| Orphanage/Homeless     | 169 (4)       | 0 (0)                | 0 (0)                  | 169 (16)               |     |
| Unknown                | 119 (3)       | 49 (3)               | 34 (2)                 | 36 (3)                 |     |
| WHO stage              |               |                      |                        |                        | 0.052 |
| WHO stage 3 and 4      | 1953 (45)     | 843 (47)             | 656 (46)               | 454 (43)               |     |
| WHO stage 1 and 2      | 1387 (32)     | 595 (33)             | 452 (31)               | 340 (32)               |     |
| Unknown                | 960 (23)      | 367 (20)             | 329 (23)               | 264 (25)               |     |
| Median (IQR) CD4%      | 10 (3–17)     | 13 (5–19)            | 9 (3–16)               | 8 (2–15)               | $<0.001$ |
| n (%)**                | 3333 (78)     | 1436 (80)            | 1120 (78)              | 777 (73)               | 1    |
| Median (IQR) CD4 count cells/mm$^3$ | 258 (60–618) | 355 (9–839)         | 227 (54–516)          | 156 (37–416)          | $<0.001$ |
| n (%)*                 | 3413 (79)     | 1479 (82)            | 1165 (81)              | 769 (73)               |     |
| Weight and Height, n (%)** | 2932 (68) | 1305 (73)           | 953 (66)               | 674 (64)               |     |
| Median (IQR) weight-for-age z score | $-2 (-2.74 to -0.99)$ | $-2 (-2.72 to -0.83)$ | $-2 (-2.73 to -0.99)$ | $-2 (-2.8 to -1.19)$ | 0.001 |
| Median (IQR) height-for-age z score | $-2 (-3.07 to -1.00)$ | $-2 (-2.83 to -0.78)$ | $-2 (-3.07 to -1.06)$ | $-2 (-3.34 to -1.35)$ | $<0.001$ |

* n (%) reflects patients for whom data were available for the variable.

** WHO 1977 Standards were used for weight-for-age Z score [13] and WHO 2006/2007 Child Growth Standards were used for height-for-age Z score [14].

Results

Baseline characteristics

A total of 4679 HIV-infected children were enrolled into TApHOD and received ART by September 2014. We excluded 44 with incomplete information on orphan status, 22 with incomplete ART information, and 313 who had been on ART for less than 6 months, leaving 4300 in the analysis (Table 1). Approximately half were male (51%). At ART initiation, 1805 (42%) were non-orphans (median age: 3 years); 1437 (33%) were single orphans (median age: 6 years) and 1058 (25%) were double orphans (median age: 7 years). The median age was significantly different between orphan groups ($P<0.001$).

Statistical analyses were performed using SAS software version 9.1.3 (SAS Institute Inc, Cary, NC, USA) and Stata version 12 (StataCorp, College Station, Texas, USA).
Overall, 56% were cared for by one or both parents, and grandparents were the main caregiver for 38% of double orphans. At ART initiation, the median CD4 percentage was 10%, and the median CD4 cell count 258 cells/mm$^3$. Both median CD4% and CD4 cell count were significantly higher for the non-orphan group at 355 cells/mm$^3$, compared to single orphans (227 cells/mm$^3$) and double orphans (156 cells/mm$^3$; $P = 0.001$ for the overall comparison). At the start of ART, 45% of children were in WHO stage 3 or 4. Most children were initiated on triple non-nucleoside reverse transcriptase-based regimens (85%), with 10% starting with other regimens such as mono-, dual- or triple-nucleoside reverse transcriptase inhibitors (NRTI), and 5% with protease inhibitor-based regimens.

Programme and treatment outcomes

The median duration of follow-up was 6 (IQR: 3–9) years overall (5 (IQR: 3–8) years for non-orphans, 6 (IQR: 3–9) years for single orphans and 7 (IQR: 5–10) years for double orphans, which was significantly different by orphan status ($P = 0.001$).

At the last visit, 82% (n=2000 of 2437 with testing) of children with available data had HIV-RNA $<400$ copies/mL (non-orphan 84%; single orphan 81%; double orphan 81%; $P=0.10$), the median CD4 cell count (cells/mm$^3$) was 759 (IQR: 512–1048; n=4019 of 4300 with testing; non-orphan 864 [IQR: 578–1181]; single orphan 706 [IQR: 487–977]; double orphan 681 [IQR: 457–926]) and CD4% was 27% (IQR: 22–32%; n=3723 of 4300 with testing; non-orphan 28% [IQR: 23–33%]; single orphan 27% [IQR: 21–32%]; double orphan 27% [IQR: 21–32%]). The trends in CD4 values showed statistically significant differences ($P=0.001$) between the three orphan groups. Seven-hundred (16%) children were transferred (transfer rate: 2.58 per 100 person-years, 95% CI 2.39–2.77). Transfers were higher among single and double orphans than in non-orphans (41% vs 11%, $P<0.001$).

There were 170 post-ART deaths, representing a crude rate of 0.63 (95% CI 0.54–0.73) per 100 person-years with no significant differences by orphan status; 60 deaths happened in non-orphans (0.59, 95% CI 0.46–0.76), 57 in single orphans (0.61, 95% CI 0.47–0.79) and 53 in double orphans (0.69, 95% CI 0.52–0.90). Ten-year post-ART survival was 93.4% in non-orphans (95% CI 91.2–95.1%), 95.2% in single orphans (95% CI 93.4–96.5%) and 94.8% in double orphans (95% CI 92.8–96.3%).

A total of 148 children were LTFU, including 61 (3.4%) non-orphans (P=0.85) and 87 (3.5%) single and double orphans, at an overall rate of 0.54 (95% CI 0.46–0.64) per 100 person-years. The Kaplan–Meier estimate of 3-year retention in care after ART initiation was 98.5% overall (95% CI 98.1–98.9%), and 97.6% at 3 years (95% CI 97.0–98.0%), with no differences (log rank $\chi^2=1.38$, $P=0.50$) between non-orphans (97.6, 95% CI 96.7–98.3%), single orphans (97.7%, 95% CI 96.7–98.4%) and double orphans (97.3%, 95% CI 96.1–98.2%). The multivariate model adjusted by country indicated that children aged ≥3 years at ART initiation (HR 1.58 vs <3 years, 95% CI 1.11–2.24) were more likely to be LTFU. Orphan status, weight and height for age, CD4 ≥25%, HIV RNA ≥5 log$_{10}$ copies/mL, and WHO stage at ART initiation and first ART regimen did not predict LTFU. A total of 148 children were LTFU, including 61 (3.4%) non-orphans (P=0.85) and 87 (3.5%) single and double orphans, at an overall rate of 0.54 (95% CI 0.46–0.64) per 100 person-years (Table 2).

**Discussion**

In this regional cohort of 4300 children in Asia, with a median duration of follow-up of 6 years, we observed that although most

| Characteristics                  | $n$ (%) | LTFU | LTFU rate | Univariate | Multivariate |
|---------------------------------|---------|------|-----------|------------|--------------|
|                                |         | Events | Per 100 person-years (95% CI) | HR (95% CI) | $P$  |
| Sex                             |         |        |           |            |              |
| Male                            | 2179 (51) | 81     | 0.60 (0.48–0.75) | 1.22 (0.88–1.69) | 0.23         |
| Female                          | 2121 (49) | 67     | 0.49 (0.39–0.62) | ref         |              |
| Age at ART initiation            |         |        |           |            |              |
| <3 years                        | 1281 (30) | 67     | 0.81 (0.64–1.03) | 1.58 (1.11–2.24) | 0.01         |
| ≥3 years                        | 1167 (27) | 81     | 0.43 (0.34–0.53) | ref         |              |
| Orphan status                   |         |        |           |            |              |
| Non-orphan                      | 1805 (42) | 61     | 0.60 (0.47–0.78) | ref         | 0.58         |
| Single orphan                   | 1437 (33) | 46     | 0.49 (0.37–0.66) | 0.82 (0.55–1.2) |              |
| Double orphan                   | 1058 (25) | 41     | 0.53 (0.39–0.72) | 0.93 (0.61–1.41) |              |
| Pre-ART weight-for-age z score  |         |        |           |            |              |
| <−1.5                           | 1835 (63) | 58     | 0.53 (0.41–0.69) | ref         | 0.57         |
| ≥−1.5                           | 1097 (37) | 29     | 0.47 (0.33–0.68) | 0.89 (0.57–1.4) |              |
| Pre-ART height-for-age z score  |         |        |           |            |              |
| <−1.5                           | 1857 (63) | 49     | 0.44 (0.34–0.59) | ref         | 0.31         |
| ≥−1.5                           | 1075 (37) | 38     | 0.63 (0.46–0.86) | 1.4 (0.91–2.15) |              |
| First ART regimen               |         |        |           |            |              |
| NNRTI-based                     | 3674 (85) | 119    | 0.55 (0.46–0.66) | 1.44 (0.86–2.4) | 0.24         |
| PI-based                        | 190 (5)  | 8      | 0.80 (0.40–1.61) | 1.88 (0.79–4.44) |              |
| Others                          | 436 (10)  | 21     | 0.46 (0.30–0.71) | ref         |              |
| WHO stage at ART initiation     |         |        |           |            |              |
| Stage 1, 2                      | 1387 (42) | 37     | 0.46 (0.33–0.63) | ref         | 0.62         |
| Stage 3, 4                      | 1953 (58) | 71     | 0.58 (0.46–0.73) | 1.07 (0.71–1.61) |              |
| Pre-ART CD4%                    |         |        |           |            |              |
| <25%                            | 3033 (91) | 103    | 0.55 (0.46–0.67) | 1.77 (0.72–4.36) | 0.29         |
| ≥25%                            | 300 (9)  | 5      | 0.31 (0.13–0.74) | ref         |              |
| Pre-ART HIV-RNA                 |         |        |           |            |              |
| <5 log$_{10}$ copies/mL         | 400 (34)  | 11     | 0.42 (0.23–0.75) | ref         |              |
| ≥5 log$_{10}$ copies/mL         | 775 (66)  | 32     | 0.61 (0.43–0.86) | 1.14 (0.57–2.28) | 0.57         |

LTFU: lost to follow-up; HR: hazard ratio; ART: antiretroviral therapy; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor.
Recent CD4 cell count values were high across all groups, they were still significantly lower among those who were orphans. There were no other significant differences in post-ART HIV outcomes related to growth, virological status, being LTfu, or mortality related to orphan status at ART initiation. However, there were multiple differences in terms of orphaned children being older at the time of starting ART, and having more advanced immunosuppression by CD4 values and poorer growth parameters. They were also more frequently transferred out of the cohort sites, which is likely to reflect increased geographical movement due to more frequent changes in caregivers over time.[15,16]

Data on the impact of orphanhood on HIV treatment and programme retention outcomes have varied between and within regions. An earlier study in Cambodia showed that orphans had poorer outcomes [2], while another study in India showed that this was not a factor, citing extended family support as a key factor for supporting treatment adherence [17]. There have been similar differences between data from Kenya and Rwanda [3,18,19]. In some settings, paternal orphans with HIV-infected mothers as their primary caregivers face greater challenges to stay in school and in paediatric care due to the added household burden of maternal illness and greater financial stresses, compared to double orphans being raised by relatives [4,20].

More recent research has focused on the complex interaction of issues surrounding parental deaths and the subsequent shifts to non-parental caregivers, economic insecurity, psychological consequences and weakened social protections that form the socio-economic background within which a child or adolescent receives medical care [4,21–24]. Family and household resources are increasingly being viewed as key factors that influence vulnerability, emphasising the potential value that direct (e.g. cash transfers) and indirect (e.g. nutritional supplements) financial support may have in addition to societal interventions to address stigma and fear of discrimination [9,25].

Our study was limited by the categorical determination of orphan status only at the time of ART initiation, which does not capture those who became orphans during follow-up and the impact of time as an orphan on outcomes. The lack of patient tracing after being lost to follow-up meant that we were unable to ascertain whether children remained in care elsewhere or died out of care [26]. Cohort data are unable to fully characterise the potentially broad and complex effects of orphanhood on clinical outcomes. Because of the challenges in collecting detailed data on social and economic variables in large cohorts, orphan status is a surrogate for identifying those who may be in greater need of social support and adherence and retention interventions. However, it does not fully define the social risk profile of an individual patient. In addition, study cohort sites were primarily better-resourced tertiary care centres providing paediatric HIV care within urban or provincial referral centres. This limits the extrapolation of our results to rural or primary care settings, where orphan status and associated familial financial insecurity may play a larger role in health outcomes.

Within this primarily perinatally infected regional cohort, although post-ART mortality and retention did not differ by orphan status at the time of ART initiation, orphans were at greater risk of starting ART at older ages, at which point they were experiencing more severe immunosuppression and poorer growth. Outcomes research, taking orphan status into account, should be conducted into adulthood to monitor the longer-term impact of having had more severe immunosuppression at the time of starting ART. While data through middle childhood demonstrate substantial immune recovery, it is less clear whether there could be more rapid immunosuppression should treatment failure develop around adolescence. In general, research into immediate and long-term paediatric HIV outcomes should include a greater emphasis on social and economic risk factor data collection.

Acknowledgements

Sources of support

The TREAT Asia Pediatric HIV Observational Database is an initiative of TREAT Asia, a program of amfAR, The Foundation for AIDS Research, with support from the U.S. National Institutes of Health’s National Institute of Allergy and Infectious Diseases, Eunice Kennedy Shriver National Institute of Child Health and Human Development, and National Cancer Institute as part of the International Epidemiology Databases to Evaluate AIDS (IeDEA; U01AI069907), and the AIDS LIFE Association and ViIV Healthcare. The Kirby Institute is funded by the Australian Government Department of Health and Ageing, and is affiliated with the Faculty of Medicine, UNSW Australia. The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of any of the governments or institutions mentioned above.

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