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%, $P<0.001$). On multivariate analysis, children ≥3 years at ART initiation (hazard ratio 1.58 *vs* <3 years, 95% confidence interval: 1.11–2.24) were more likely to be lost to follow-up. Although post-ART mortality and retention did not differ by orphan status, orphans were at greater risk of starting ART at older ages, and with more severe immunosuppression and poorer growth.

Key words: orphan, paediatric, HIV, Asia, antiretroviral, treatment

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 are 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 treatment at age <15 years for a duration >6 months, had at least one prospective follow-up visit after ART initiation (of any combination of antiretrovirals) and had recorded information on 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).

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.

The baseline CD4 cell count was the closest to the date of initiation of ART and within a window of 180 days before and 14 days after initiation of ART. Pre-ART HIV-RNA was the closest value to the initiation of ART, within a period of 365 days before or 14 days after ART initiation. For the most recent clinical data, we used the closest measurement within 12 months prior to the date of the last clinic visit. Patients were lost to follow-up (LTFU) if they did not have a recorded clinic visit or contact (e.g. lab test) for ≥6 months and were not documented to have been transferred or have died. Those LTFU were censored at the date of their last known clinic visit. Children who were transferred to other care services also were censored at their most recent clinic visit.

Demographic and clinical characteristics for different orphan groups were presented as proportions or median and interquartile ranges,

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

Characteristics, *n* (%)	Total	Non-orphan	Single orphan	Double orphan	*P*
	n=4300	*n*=1805	*n*=1437	*n*=1058	
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					<0.001
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].

as appropriate. 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 ≥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.

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).

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).

Table 2. Factors associated with being lost to follow-up after starting antiretroviral therapy

Characteristics		*n* (%)	LTFU	LTFU rate	Univariate		Multivariate	
			Events	Per 100 person-years (95% CI)	HR (95%CI)	*P*	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	1.58 (1.11–2.24)	0.01
	≥3 years	1167 (27)	81	0.43 (0.34–0.53)	ref		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.

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 difference ($P<0.001$) 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, 85% 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 five years (95% CI 97.0–98.0%), with no differences (log rank χ^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

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.

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References

1. UNICEF. Towards an AIDS-free generation, Children and AIDS, Sixth Stocktaking Report. Geneva: 2013. Available at: www.unicef.org/publications/index_70986.html (accessed September 2016).
2. Janssens B, Raleigh B, Soeung S *et al.* Effectiveness of highly active antiretroviral therapy in HIV-positive children: evaluation at 12 months in a routine program in Cambodia. *Pediatrics* 2007; **120**: e1134–1140.
3. Kikuchi K, Poudel KC, Muganda J *et al.* High risk of ART non-adherence and delay of ART initiation among HIV positive double orphans in Kigali, Rwanda. *PLoS One* 2012; **7**: e41998.
4. Kikuchi K, Poudel KC, Muganda J *et al.* What makes orphans in Kigali, Rwanda, non-adherent to antiretroviral therapy? Perspectives of their caregivers. *J Int AIDS Soc* 2014; **17**: 19310.
5. Kumar A. AIDS orphans and vulnerable children in India: problems, prospects, and concerns. *Soc Work Public Health* 2012; **27**: 205–212.
6. Ntanda H, Olupot-Olupot P, Mugyenyi P *et al.* Orphanhood predicts delayed access to care in Ugandan children. *Pediatr Infect Dis J* 2009; **28**: 153–155.
7. Sohn AH, Hazra R. The changing epidemiology of the global paediatric HIV epidemic: keeping track of perinatally HIV-infected adolescents. *J Int AIDS Soc* 2013; **16**: 18555.
8. Lowenthal ED, Bakeera-Kitaka S, Marukutira T *et al.* Perinatally acquired HIV infection in adolescents from sub-Saharan Africa: a review of emerging challenges. *Lancet Infect Dis* 2014.
9. Kasedde S, Doyle AM, Seeley JA, Ross DA. They are not always a burden: Older people and child fostering in Uganda during the HIV epidemic. *Soc Sci Med* 2014; **113**: 161–168.
10. Lee VC, Muriithi P, Gilbert-Nandra U *et al.* Orphans and vulnerable children in Kenya: results from a nationally representative population-based survey. *J Acquir Immune Defic Syndr* 2014; **66 Suppl 1**: S89–97.
11. Cluver L, Boyes M, Orkin M, Sherr L. Poverty, AIDS and child health: identifying highest-risk children in South Africa. *S Afr Med J* 2013; **103**: 910–915.
12. Kariminia A, Chokephaibulkit K, Pang J *et al.* Cohort profile: the TREAT Asia pediatric HIV observational database. *Int J Epidemiol* 2011; **40**: 15–24.
13. Kuczmarski RJ, Ogden CL, Guo SS *et al.* 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Stat* 2002; **11**:1–190.
14. World Health Organization. WHO growth chart 2006. Available at: www.who.int/growthref/en/. (accessed September 2012).
15. Shetty AK, Powell G. Children orphaned by AIDS: a global perspective. *Semin Pediatr Infect Dis* 2003; **14**: 25–31.
16. Young L, Ansell N. Young AIDS migrants in Southern Africa: policy implications for empowering children. *AIDS Care* 2003; **15**: 337–345.
17. Bhattacharya M, Saxena R. Outcome of anti-retroviral treatment in HIV-infected orphans and non-orphans at an ART centre in North India. *Paediatr Int Child Health* 2012; **32**: 228–232.
18. Nyandiko WM, Ayaya S, Nabakwe E *et al.* Outcomes of HIV-infected orphaned and non-orphaned children on antiretroviral therapy in western Kenya. *J Acquir Immune Defic Syndr* 2006; **43**: 418–425.
19. Vreeman RC, Wiehe SE, Ayaya SO *et al.* Association of antiretroviral and clinic adherence with orphan status among HIV-infected children in Western Kenya. *J Acquir Immune Defic Syndr* 2008; **49**: 163–170.
20. Mokgatle MM, Madiba S. The burden of disease on HIV-infected orphaned and non-orphaned children accessing primary health facilities in a rural district with poor resources in South Africa: a cross-sectional survey of primary caregivers of HIV-infected children aged 5–18 years. *Infect Dis Poverty* 2015; **4**: 18.
21. Govender K, Reardon C, Quinlan T, George G. Children's psychosocial wellbeing in the context of HIV/AIDS and poverty: a comparative investigation of orphaned and non-orphaned children living in South Africa. *BMC Public Health* 2014; **14**: 615.
22. Kuo C, Cluver L, Casale M, Lane T. Cumulative effects of HIV Illness and caring for children orphaned by AIDS on anxiety symptoms among adults caring for children in HIV-endemic South Africa. *AIDS Patient Care STDS* 2014; **28**: 318–326.
23. Mo PK, Lau JT, Yu X, Gu J. The role of social support on resilience, posttraumatic growth, hopelessness, and depression among children of HIV-infected parents in mainland China. *AIDS Care* 2014; **26**: 1526–1533.
24. Ssewamala FM, Nabunya P, Ilic V *et al.* Relationship between family economic resources, psychosocial well-being, and educational preferences of AIDS-orphaned children in Southern Uganda: baseline findings. *Glob Soc Welf* 2015; **2**: 75–86.
25. Crea TM, Reynolds AD, Sinha A *et al.* Effects of cash transfers on children's health and social protection in Sub-Saharan Africa: differences in outcomes based on orphan status and household assets. *BMC Public Health* 2015; **15**: 511.
26. Braitstein P, Songok J, Vreeman RC *et al.* 'Wamepotea' (they have become lost): outcomes of HIV-positive and HIV-exposed children lost to follow-up from a large HIV treatment program in western Kenya. *J Acquir Immune Defic Syndr* 2011; **57**: e40–46.