Treatment outcomes among HIV-positive orphaned and non-orphaned children on antiretroviral therapy in Johannesburg, South Africa

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Background. Limited research investigating treatment outcomes for HIV-positive orphans compared with non-orphans has shown mixed results, with several studies indicating that HIV-positive orphans are at greater risk of delayed access to HIV care and poor antiretroviral therapy (ART) adherence, while other data suggest that ART outcomes of orphans can be similar to those of non-orphans. Understanding the impact of orphan status on short-term ART outcomes could improve targeted intervention strategies, and subsequent long-term treatment and developmental outcomes, for HIV-positive infants, children and adolescents.
Objectives. To evaluate the relationship between orphan status and ART outcomes among HIV-positive infants, children and adolescents initiating ART at two large public sector HIV clinics in Johannesburg, South Africa.
Methods. This was a retrospective cohort study of HIV-positive children aged <18 years initiating standard first-line ART between June 2004 and May 2013. Using propensity scores, orphans and non-orphans were matched for age, sex, World Health Organization stage and ART regimen. The effect of orphanhood on attrition from care (all-cause mortality and loss to follow-up) was evaluated using Cox proportional hazards regression analysis, and its effect on having a detectable viral load (≥400 copies/mL) at 12 months on ART using binomial regression analysis with modified Poisson distribution.
Results. A total of 251 (29.4%) orphans (maternal, paternal or both) and 603 (70.6%) non-orphans were included at ART initiation. Following multiple imputation for missing data and propensity score matching, 222 orphans and 222 non-orphans were included. Orphans had a median age of 8.0 years (interquartile range (IQR) 4.9 - 10.7) and non-orphans 7.4 years (IQR 4.2 - 10.2). A total of 12 (5.4%) orphans and 33 (14.9%) non-orphans experienced attrition from care during the first 12 months on ART (adjusted hazard ratio 0.32, 95% confidence interval (CI) 0.17 - 0.63). Among those alive and in care, with a viral load at 12 months on ART, 18.0% of orphans (33/183) and 14.8% of non-orphans (24/162) had a detectable viral load (adjusted risk ratio 1.15, 95% CI 1.04 - 1.28).
Conclusions. Orphans were less likely than non-orphans to experience attrition, but among those in care at 12 months, orphans were more likely to have detectable viral loads. Lower attrition among orphans may be due to their being in institutional or foster care, ensuring that they make their visits; however, their higher rates of non-suppression may result from lack of psychosocial support or stigma resulting in struggles to adhere. Additional research investigating age-specific outcomes will be important to elucidate these effects further.

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Worldwide, ~17.8 million children are estimated to have lost one or both parents due to HIV/AIDS.[1] In South Africa (SA) alone there are an estimated 3.9 million orphans, almost half of whom have lost one or both parents to AIDS-related diseases.[2] In 2012 the prevalence of orphanhood in SA was estimated at 16.9%, with orphans 3.5 times more likely to be HIV-positive compared with non-orphans.[3] With an estimated 320 000 children living with HIV in 2016, SA has the largest paediatric antiretroviral therapy (ART) programme in the world.[4]

Previous research indicates that social vulnerabilities including poverty, poor access to education, homelessness, neglect and abuse may result in orphans experiencing substantial barriers to accessing healthcare, leading to poorer treatment and developmental outcomes.[5-11] Furthermore, HIV-positive orphans have been shown to be at increased risk of delayed access to HIV care and poor ART adherence.[5,12-15] However, some limited data suggest that ART outcomes of orphans can be similar to those of non-orphans.[16-18] Given the high burden of combined HIV and orphanhood in SA, these are important problems to investigate but complicated ones to address, partly because orphans are such a vulnerable and difficult population to reach.

Objectives

To evaluate the association between orphan status (v. non-orphaned, matched on baseline characteristics) at ART initiation with attrition

from care and viral suppression at 12 months among a sample of HIV-positive infants, children and adolescents attending two large public sector HIV clinics in Johannesburg, SA.

Methods

We conducted a retrospective analysis of prospectively collected data from two paediatric primary healthcare clinics in Johannesburg. Both sites are public sector clinics that follow the national ART treatment guidelines.[19-21] All HIV-positive ART-naive infants, children and adolescents aged <18 years who initiated a standard first-line ART regimen between 1 June 2004 and 31 May 2013 were included. Demographic and clinical information was captured using an electronic patient management system (TherapyEdge-HIV; Advanced Biological Laboratories (ABL) S.A., Luxembourg), while laboratory data were uploaded directly into TherapyEdge-HIV from the South African National Health Laboratory Service on a daily basis. To supplement data from electronic medical records, hard copies of patient medical files were reviewed.

According to the United Nations Children's Fund (UNICEF) definition, an orphan is classified as a child aged <18 years who has lost one or both parents to any cause of death, while a double orphan is one who has lost both parents.[22] Baseline orphan status was defined as a child who had lost one or both parents prior to, or up to 6 months after, the date of ART initiation. A 6-month window after ART initiation was used to allow for passive follow-up and patient tracing or reporting of parent death. For the purpose of this analysis, the exposures of orphan v. non-orphan were considered. We used multiple imputation by chained equations to impute missing baseline values in our dataset. Baseline demographic and clinical characteristics of all patients were summarised and stratified by baseline orphan status, and we determined the association between these factors and being classified as an orphan using logistic regression analysis. Adjusted odds ratios with the corresponding 95% confidence intervals (CIs) are presented, and predictor variables (e.g. sex, age, nationality, year of ART initiation, baseline CD4+ count/percentage, World Health Organization (WHO) stage, tuberculosis, anaemia, weight, height, ART regimen and facility) were used to create a propensity score (Supplementary Table 1, available at http://www.samj.org.za/public/sup/13462_table.pdf). Researchers then matched each orphan with one potential non-orphan using propensity score matching, within facility, using a Mayo Clinic SAS macro.[23] As orphans and non-orphans were substantially different, particularly with regard to age at initiation (the median age for orphans and non-orphans was 8.5 years (interquartile range (IQR) 5.1 - 11.5) and 2.9 years (IQR 1.0 - 7.4), respectively), greedy matching with a difference of 0.2 was used. Baseline CD4+ count, CD4+ percentage, haemoglobin, WHO stage and weight were assigned as the measurement date closest to the date of ART initiation within 90 days before and 7 days after treatment start date. Table 1 defines the immunological, disease and growth categories at ART initiation.

Outcomes by 12 months on ART included: (*i*) attrition, a composite outcome of all-cause mortality and loss to follow-up (LTF); and (*ii*) failure to suppress viral load. Deaths were identified by the family or by medical record review, and/or linkage with the SA national vital registration system.[24] LTF was defined as at least 3 months late for the last scheduled visit. Person-time accrued from ART initiation until the earliest of: (*i*) outcome of interest; (*ii*) transfer; (*iii*) completion of 12 months of follow-up; or (*iv*) dataset closure on 31 May 2014, at which point person-time was censored. Cox proportional hazards models, clustered by facility, were used to evaluate the relationship between orphanhood and attrition.

Failure to suppress viral load at 12 months was defined as having a detectable viral load (>400 copies/mL) at 12 months after ART initiation.[25] To allow for variation in visit timing, for patients who were alive and in care at 12 months after ART initiation, the viral load closest to 12 months (±6 months) was used in the analysis. To evaluate the association between orphan status and a detectable viral load at 12 months on ART, researchers used binomial regression analysis with a modified Poisson distribution, clustered by facility. Proportions and relative rates (RRs) of virological suppression were calculated among those alive and in care, with a viral load at 12 months on ART,

Ethical approval was provided by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (ref.

Table 1. Adjusted WHO categorisations of immunosuppression, staging,* anaemia and growth standards

Immunosuppression†	**Not significant**	**Mild**	**Advanced**	**Severe**
Up to 12 months of age (CD4+ percentage)	>35	25 - 34	20 - 24	<20
≥12 - 59 months of age (CD4+ percentage)	>25	20 - 24	15 - 19	<15
≥5 years of age (CD4+ cells/μL)	>500	350 - 499	200 - 349	<200
Anaemia (haemoglobin, g/dL)‡	**No anaemia**	**Mild**	**Moderate**	**Severe**
0 - 6 months of age	No data	No data	No data	No data
6 - 59 months of age	≥11.0	10.0 - 10.9	7.0 - 9.9	<7.0
5 - 11 years of age	≥11.5	11.0 - 11.4	8.0 - 10.9	<8.0
12 - 14 years of age	≥12.0	11.0 - 11.9	8.0 - 10.9	<8.0
Females ≥15 years of age	≥12.0	11.0 - 11.9	8.0 - 10.9	<8.0
Males ≥15 years of age	≥13.0	11.0 - 12.9	8.0 - 10.9	<8.0
Weight for age§	**Normal**	**Undernourished**	**Severely undernourished**	
≤5 years of age (*z*-score)	≥2 SD	<–2 SD	<–3 SD	
BMI for age§	**Overweight**	**Obese**	**Thinness**	**Severe thinness**
5 - 19 years of age (*z*-score)	>+1 SD	>+2 SD	<–2 SD	<–3 SD

WHO = World Health Organization; BMI = body mass index; SD = standard deviation; ART = antiretroviral therapy.
*WHO clinical stage at ART initiation was determined either by physician classification or by conditions present at ART initiation.
†CD4+ percentage (%) and absolute (cells/μL) values as related to paediatric age and immunosuppression, adapted from the WHO's 'Interim WHO clinical staging of HIV/AIDS and HIV/AIDS case definitions for surveillance'.[30]
‡Haemoglobin levels to diagnose anaemia at sea level (g/dL), adapted from the WHO's 'Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity'.[31]
§Weight-for-age *z*-score was calculated using the WHO Child Growth Standards aged ≤5 years and BMI-for-age *z*-score for children and adolescents aged >5 - 19 years.[32] The severity of undernutrition was assessed by *z*-score according to the WHO classification of children,[33] with a *z*-score <–2 SD to ≤–3 SD for any anthropometric indices indicating undernourished and a *z*-score <–3 SD indicating severely undernourished.

no. M110140) and the Boston University Institutional Review Board (ref. no. H-29768).

Results

A total of 1 332 children and adolescents were enrolled on ART during the study period, of whom 269 did not fit the inclusion criteria and 209 had unknown baseline orphan status – these were excluded, resulting in a prematched dataset of 854 patients (603 non-orphans and 251 orphans, Fig. 1). Propensity score matching using predictor variables resulted in 222 orphans being matched with 222 non-orphans, with a similar age distribution between the two groups (Table 2 and Supplementary Fig. 1 – Supplementary Fig. 1 is available at http://www.samj.org.za/public/sup/13462_table.pdf). Patients contributed 421 years of person-time during the 12-month follow-up period (orphans 217, non-orphans 204, Table 3). The majority (94.6% of orphans, 85.1% of non-orphans) were still on ART after 12 months, but 12 orphans (5.4%) and 33 non-orphans (14.9%) were lost to care (died or LTF).

In crude Cox proportional hazard models (cHR), orphans had a reduced risk of attrition after 12 months on ART compared with non-orphans (cHR 0.32, 95% CI 0.17 - 0.63) (Table 4). The time period of ART initiation also appeared to have an effect on attrition, with those who initiated ART during the later years being at a reduced risk of 12-month attrition (cHR 0.09, 95% CI 0.01 - 0.79 for June 2012 - May 2013 compared with June 2004 - May 2006). In a model adjusted for period of ART initiation (>10% change in estimate), baseline CD4+ and anaemia (under-matching), orphans were still less likely to experience attrition (adjusted hazard ratio 0.32, 95% CI 0.17 - 0.63).

Among those alive and in care, with a viral load at 12 months on ART (77.7%, 345/444), 18.0% of orphans (33/183) and 14.8% of non-orphans (24/162) had a detectable viral load (>400 copies/mL). This did not differ by age group (p=0.7365). Crude analysis showed that orphans had an increased risk of a detectable viral load at 12 months after initiation of ART compared with non-orphans (crude risk ratio (cRR) 1.22, 95% CI 1.12 - 1.32, Table 4). Additionally, those with a high or moderate CD4+ count/percentage at baseline were 74% and 26% more likely to have a detectable viral load at 12 months, respectively, compared with those with a very low baseline CD4+. Those at WHO stage III/IV at ART initiation were less likely to have a detectable viral load compared with those at WHO stage I/II (cRR 0.74, 95% CI 0.64 - 0.87). Similarly, those with below-normal baseline anthropometric measurements had a lower risk of having a detectable viral load at 12 months than those with normal measurements (cRR 0.67, 95% CI 0.47 - 0.95). Compared with those who initiated ART on a non-stavudine-based regimen, those who initiated on a stavudine-based regimen were less likely to have a detectable viral load at 12 months after ART initiation (cRR 0.48, 95% CI 0.39 - 0.59). Similarly, patients who initiated ART in the later years of the study were less likely to have a detectable viral load compared with those who initiated ART in the first 2 years. Lastly, in crude analyses, patients were 45% less likely to have a detectable viral load at site B compared with site A. In a model adjusted for tuberculosis at ART initiation (>10% in effect estimate), baseline CD4+ and anaemia (under-matching), baseline WHO stage, anthropometric measurements and facility (significant in crude analyses), orphans were still more likely to have a detectable viral load at 12 months on ART (adjusted risk ratio (aRR) 1.15, 95% CI 1.04 - 1.28), with participants at site B less likely to do so than those at site A (aRR 0.75, 95% CI 0.61 - 0.94).

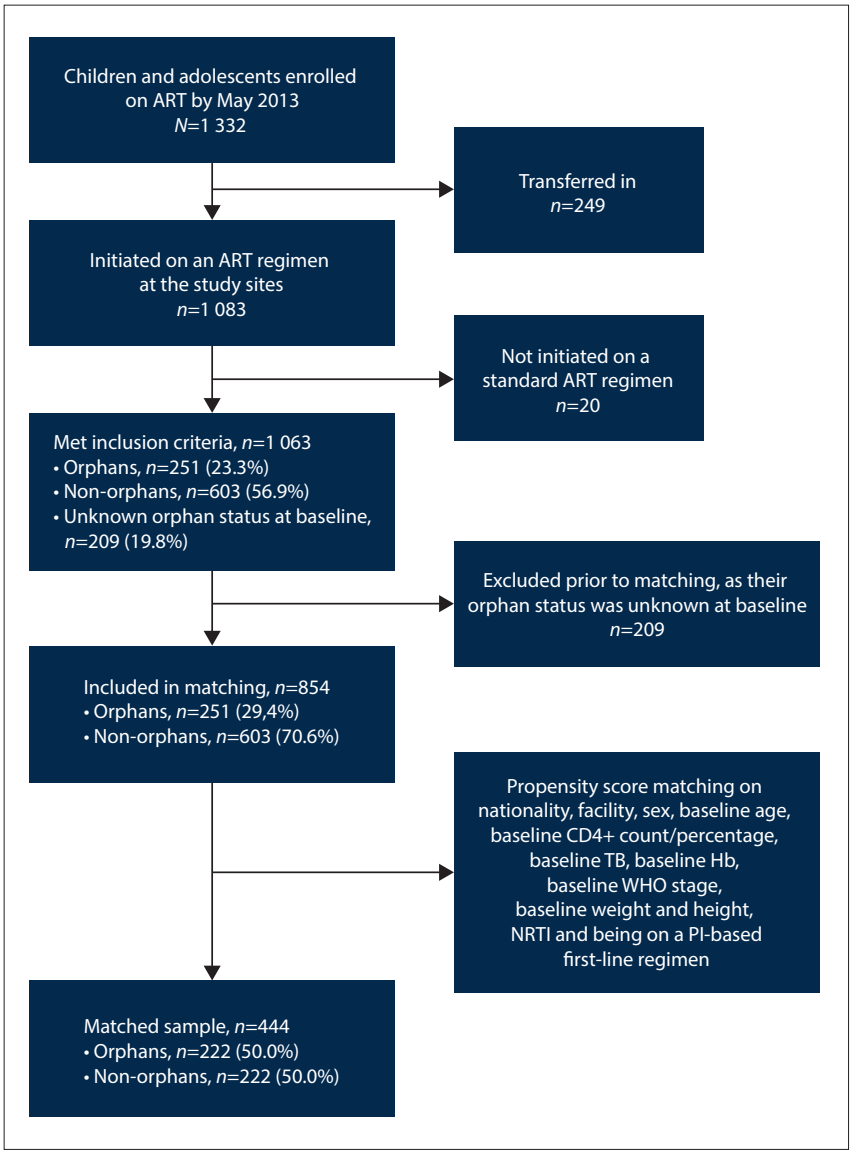

Fig. 1. Cohort profile of children and adolescents initiating ART at one of two study sites in Johannesburg, SA. (ART = antiretroviral therapy; SA = South Africa; TB = tuberculosis; Hb = haemoglobin; WHO = World Health Organization; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.)

Discussion

In this matched cohort of 444 infants, children and adolescents in SA, we observed that 5.4% of orphans and 14.9% of non-

Table 2. Clinical and demographic characteristics at ART initiation stratified by orphan status in HIV-positive children and adolescents initiating ART in Johannesburg, SA, after propensity score matching (*N*=444)

	Non-orphans (*N*=222)	Orphans (*N*=222)
Sex, *n* (%)		
Female	115 (51.8)	110 (49.6)
Male	107 (48.2)	112 (50.5)
Age at initiation (years), *n* (%)		
≤1	9 (4.1)	11 (5.0)
>1 - ≤5	58 (26.1)	50 (22.5)
>5 - ≤10	95 (42.8)	99 (44.6)
>10	60 (27.0)	62 (27.9)
Time period of ART initiation, *n* (%)		
June 2004 - May 2006	12 (5.4)	15 (6.8)
June 2006 - May 2008	48 (21.6)	45 (20.3)
June 2008 - May 2010	72 (32.4)	74 (33.3)
June 2010 - May 2012	60 (27.0)	65 (29.3)
June 2012 - May 2013	30 (13.5)	23 (10.4)
CD4+ measurement* at ART initiation, *n* (%)		
Severe	95 (42.8)	85 (38.3)
Advanced	51 (23.0)	56 (25.2)
Mild	28 (12.6)	35 (15.8)
Not significant	48 (21.6)	46 (20.7)
WHO clinical stage at ART initiation, *n* (%)		
I or II	138 (62.2)	145 (65.3)
III or IV	84 (37.8)	77 (34.7)
TB at ART initiation, *n* (%)		
Yes	45 (20.3)	44 (19.8)
No	177 (79.7)	178 (80.2)
Anaemia at ART initiation, *n* (%)		
None	79 (35.6)	95 (42.8)
Mild	47 (21.2)	45 (20.3)
Moderate/severe	96 (43.2)	82 (36.9)
Weight for age at ART initiation, *n* (%)		
Normal (WAZ ≥–2 SD)	51 (76.1)	48 (78.7)
Undernourished (WAZ <–2 to ≥–3 SD)	9 (13.4)	8 (13.1)
Severely undernourished (WAZ <–3 SD)	5 (7.5)	5 (8.2)
Missing	2 (3.0)	0 (00)
BMI for age at ART initiation, *n* (%)		
Overweight or obese (ZBA >1 SD)	7 (4.5)	8 (5.0)
Normal weight (ZBA –2 to 1 SD)	68 (43.9)	64 (39.8)
Thinness (ZBA <–2 SD)	14 (9.0)	18 (11.2)
Severe thinness (ZBA <–3 SD)	29 (18.7)	36 (22.4)
Missing	37 (23.9)	35 (21.7)
Baseline ART regimen, *n* (%)		
NRTI		
ABC	80 (36.0)	76 (34.2)
TDF	6 (2.7)	4 (1.8)
d4T	136 (61.3)	142 (64.0)
PI†		
No	201 (90.5)	195 (87.8)
Yes	21 (9.5)	27 (12.2)
Site, *n* (%)		
Site A	35 (15.8)	35 (15.8)
Site B	187 (84.2)	187 (84.2)

Continued ...

Table 2. (continued) Clinical and demographic characteristics at ART initiation stratified by orphan status in HIV-positive children and adolescents initiating ART in Johannesburg, SA, after propensity score matching (*N*=444)

	Non-orphans (*N*=222)	Orphans (*N*=222)
Age at ART initiation (years), median (IQR)	7.4 (4.2 - 10.2)	8.0 (4.9 - 10.7)
CD4+ absolute count‡ (cells/μL) at ART initiation, median (IQR)	258 (127 - 511)	274 (126 - 465)
CD4+ percentage‡ (%) at ART initiation , median (IQR)	16.8 (13.0 - 19.8)	15.5 (11.7 - 21.9)
Haemoglobin (g/dL) at ART initiation, median (IQR)	10.9 (9.9 - 11.8)	11.2 (10.3 - 12.0)
Weight for age§ at ART initiation (*z*-score), median (IQR)	−1.1 (−1.9 - −0.6)	−1.1 (−1.9 - −0.2)
BMI for age§ at ART initiation (*z*-score), median (IQR)	−1.3 (−2.9 - −0.5)	−1.6 (−3.2 - −0.3)

ART = antiretroviral therapy; SA = South Africa; WHO = World Health Organization; TB = tuberculosis; WAZ = weight-for-age *z*-score; BMI = body mass index; ZBA = BMI-for-age *z*-score; SD = standard deviation; NRTI = nucleoside reverse transcriptase inhibitor; ABC = abacavir; TDF = tenofovir; d4T = stavudine; PI = protease inhibitor; LPV/r = lopinavir/ritonavir; IQR = interquartile range.
*CD4+ classification as follows: (*i*) severe if children aged ≤12 months had a CD4+ percentage <20%, children aged 13 - 59 months had a CD4+ percentage <15%, or children and adolescents aged ≥5 years had a CD4+ count <200 cells/μL; (*ii*) advanced if children aged ≤12 months had a CD4+ percentage of 20 - 24%, children aged 13 - 59 months had a CD4+ percentage of 15 - 19%, or children and adolescents aged ≥5 years had a CD4+ count of 200 - 349 cells/μL; (*iii*) mild if children aged ≤12 months had a CD4 percentage of 25 - 34%, children aged 13 - 59 months had a CD4+ percentage of 20 - 24%, or children and adolescents aged ≥5 years had a CD4+ count of 350 - 499 cells/μL; and (*iv*) not significant if children aged ≤12 months had a CD4+ percentage >35%, children aged 13 - 59 months had a CD4+ percentage >25%, or children and adolescents aged ≥5 years had a CD4+ count >500 cells/μL.
†PI for all was LPV/r.
‡CD4+ percentage was calculated for children aged <5 years, and CD4+ absolute count for children and adolescents aged ≥5 years.
§Weight for age was calculated for children aged ≤5 years, and BMI for age for children and adolescents aged >5 years.

Table 3. Retention, attrition and immunological status at ART initiation stratified by orphan status in HIV-positive children and adolescents of all ages initiating ART in Johannesburg, SA, after propensity score matching (*N*=444)

	Total (*N*=444), *n*/*N* (%)	Orphans (*N*=222), *n*/*N* (%)	Non-orphans (*N*=222), *n*/*N* (%)
Person-time contributed (years)	421	217	204
Alive in care at 12 months on ART	399/444 (89.9)	210/222 (94.6)	189/222 (85.1)
Viral load suppressed*,†	288/345 (83.5)	150/183 (82.0)	138/162 (85.2)
Viral load not suppressed*,†	57/345 (16.5)	33/183 (18.0)	24/162 (14.8)
Died	6/444 (1.4)	1/222 (0.5)	5/222 (2.3)
LTF	39/444 (8.8)	11/222 (5.0)	28/222 (12.6)
Attrition	45/444 (10.1)	12/222 (5.4)	33/222 (14.9)

ART = antiretroviral therapy; SA = South Africa; LTF = lost to follow-up.
*The closest viral load to 12 months following ART initiation within a 6-month window either side of 12 months after initiation (i.e. 6 - 18 months post ART initiation).
†27 orphans and 27 non-orphans who were alive and in care at 12 months did not have a viral load result within the 12-month window and are excluded from the suppression analysis.

orphans had either died or been LTF, while 18.0% of orphans and 14.8% of non-orphans alive and in care after 12 months on ART had a detectable viral load. With regard to retention in care, orphans fared better than their non-orphan counterparts, with orphans having a 68% reduction in attrition. However, among those still in care at 12 months, orphans were 15% more likely than non-orphans to have a detectable viral load.

Data on outcomes of HIV-positive orphans v. non-orphans are sparse, with mixed results. Orphan status was not associated with death in a study in Kenya, while research in India concluded that orphans did not have worse outcomes than non-orphans.[16,17] Furthermore, a multicountry study in Asia found that post-ART mortality and retention did not differ by orphan status. However, orphans were at a greater risk of starting ART at older ages, and with more severe immunosuppression and poor growth.[18] Similar to our results, a Cambodian study reported that orphans had an increased risk of virological failure compared with non-orphans; the authors reflected that this worse outcome was likely to be due to poor adherence, which may well be the case in the present study.[26] As we did not measure adherence, we cannot state this with certainty; however, studies in Kenya and Rwanda have shown that double orphans are at higher risk of non-adherence to ART compared with single orphans and non-orphans.[12,16]

Prior to matching, and similar to other studies, orphans initiating ART were clinically different to non-orphans, with orphans presenting at an older age as well as being slightly healthier than non-orphans, probably because they were older.[14,16-18] Reasons for late presentation for clinical care may include parental illness delaying care-seeking for children, and that stigma around parental health and death could result in reluctance to access healthcare for the whole family. Parental death may also delay care owing to new caregivers not knowing the child's HIV status, or the general chaos of family transitions.[27] Survey data that looked at both orphanhood and co-residence with a chronically ill or HIV-positive adult offer insight into possible reasons for these results.[27,28] The researchers hypothesise that part of the explanation for orphans doing better than non-orphans lies in the possibility that some of the orphans are in residential or alternative care settings.[28] Orphans are more likely than non-orphans to be in formalised care and this may lead to better retention; however, it is difficult to hypothesise why retention might be improved, but viral suppression is worse. Further work should be done to investigate outcomes of orphans in formal care settings compared with those who are non-institutionalised.

Study limitations

Our study has several limitations. Firstly, the fact that baseline orphan status was collected retrospectively, while other clinical data were collected prospectively, may have resulted in some misclassification. Twenty percent of patients who did not have baseline orphan status were excluded, and it is possible that documentation of orphan status was better among orphans who were healthier or getting better care. This potential bias was mitigated by reviewing the entire medical record and corroborating orphans' status at baseline with caregiver records throughout the file. Our data also did not include detailed information on the primary caregivers of the children and adolescents (including their HIV status), children's nutritional status, height for age, ART adherence and indicators of socioemotional or cognitive development, which may have helped in

Table 4. Unadjusted and adjusted estimates of the relation between baseline orphan status and attrition (all-cause mortality and LTF) and viral suppression at 12 months on ART

	Attrition (*N*=444)		Failure to suppress viral load* (*N*=345)	
Characteristic	***n*/*N* (%)**	**aHR (95% CI)**	***n*/*N* (%)**	**aRR (95% CI)**
Orphan status at initiation				
Non-orphan	33/222 (14.9)	1.00	24/162 (14.8)	1.00
Orphan	12/222 (5.4)	0.32 (0.17 - 0.63)	33/183 (18.0)	1.15 (1.04 - 1.28)
Sex				
Female	23/225 (10.2)		29/173 (16.8)	
Male	22/219 (10.1)		28/172 (16.3)	
Age at initiation (years)				
≤1	1/20 (5.0)		4/18 (22.2)	
>1 - ≤5	18/108 (16.7)		9/77 (11.7)	
>5 - ≤10	15/194 (7.7)		20/161 (12.4)	
>10	11/122 (9.0)		24/89 (27.0)	
Time period of ART initiation				
June 2004 - May 2006	5/27 (18.5)	1.00	4/16 (25.0)	
June 2006 - May 2008	7/93 (7.5)	0.30 (0.10 - 1.00)	6/83 (7.2)	
June 2008 - May 2010	14/146 (9.6)	0.42 (0.15 - 1.19)	16/125 (12.8)	
June 2010 - May 2012	18/125 (14.4)	0.70 (0.26 - 1.89)	25/102 (24.5)	
June 2012 - May 2013	1/53 (1.9)	0.08 (0.01 - 0.69)	6/19 (31.6)	
Baseline CD4+ classification†				
Severe	25/180 (13.9)	1.00	19/138 (13.8)	1.00
Advanced	7/107 (6.5)	0.46 (0.20 - 1.08)	13/82 (15.9)	0.91 (0.53 - 1.57)
Mild	4/63 (6.4)	0.44 (0.15 - 1.27)	12/50 (24.0)	2.09 (1.73 - 2.52)
Not significant	9/94 (9.6)	0.71 (0.33 - 1.53)	13/75 (17.3)	1.05 (0.93 - 1.18)
Anaemia at ART initiation				
None	16/174 (9.2)	1.00	23/141 (16.3)	
Mild	11/92 (12.0)	1.34 (0.62 - 2.89)	11/65 (16.9)	1.05 (0.96 - 1.15)
Moderate/severe	18/178 (10.1)	0.96 (0.49 - 1.90)	23/139 (15.6)	1.05 (0.80 - 1.40)
TB at ART initiation				
No	35/355 (9.9)		46/269 (17.1)	1.00
Yes	10/89 (11.2)		11/76 (14.5)	0.91 (0.75 - 1.11)
WHO stage at initiation				
I/II	29/283 (103)		39/213 (18.3)	1.00
III/IV	16/161 (9.9)		18/132 (13.6)	1.00 (0.70 - 1.41)
Anthropometric measurements‡				
Normal/above normal	36/246 (14.6)		36/168 (21.4)	1.00
Below normal	5/59 (8.5)		7/49 (14.2)	0.70 (0.46 - 1.06)
Missing	4/139 (2.9)		14/128 (10.9)	
NRTI in first regimen				
Non-d4T based	16/166 (9.6)		29/114 (25.4)	
d4T	29/278 (10.4)		28/231 (12.1)	
PI in first regimen				
No	42/396 (10.6)		50/305 (16.4)	
Yes	3/48 (6.3)		7/40 (17.5)	
Site				
A	7/70 (10.0)		14/52 (26.9)	1.00
B	38/374 (10.2)		43/293 (14.7)	0.75 (0.61 - 0.94)

LTF = loss to follow-up; ART = antiretroviral therapy; aHR = adjusted hazard ratio; aRR = adjusted risk ratio; CI = confidence interval; TB = tuberculosis; WHO = World Health Organization; NRTI = nucleoside reverse transcriptase inhibitor; d4T = stavudine; PI = protease inhibitor; SD = standard deviation; BMI = body mass index.
*Among those with a viral load at 12 months.
†CD4+ classification as follows: (*i*) severe if children aged ≤12 months had a CD4+ percentage <20%, children aged 13 - 59 months had a CD4+ percentage <15%, or children and adolescents aged ≥5 years had a CD4+ count <200 cells/μL; (*ii*) advanced if children aged ≤12 months had a CD4+ percentage of 20 - 24%, children aged 13 - 59 months had a CD4+ percentage of 15 - 19%, or children and adolescents aged ≥5 years had a CD4+ count of 200 - 349 cells/μL; (*iii*) mild if children aged ≤12 months had a CD4 percentage of 25 - 34%, children aged 13 - 59 months had a CD4+ percentage of 20 - 24%, or children and adolescents aged ≥5 years had a CD4+ count of 350 - 499 cells/μL; and (*iv*) not significant if children aged ≤12 months had a CD4+ percentage >35%, children aged 13 - 59 months had a CD4+ percentage >25%, or children and adolescents aged ≥5 years had a CD4+ count >500 cells/μL.
‡Normal or above normal defined as weight-for-age *z*-score for children ≤5 years of age ≥–2 SD or BMI-for-age *z*-score for children and adolescents >5 years of age ≥–2 SD; below normal defined as weight-for-age *z*-score for children ≤5 years of age <–2 SD or BMI-for-age *z*-score for children and adolescents >5 years of age <–2 SD.
All baseline characteristics that resulted in a ≥±10% change in the effect of orphan status were included in the respective adjusted models. Additionally, potential confounders that had not balanced during the matching process were included in the adjusted models.

understanding the reasons for better attrition outcomes for orphans. This analysis only investigated short-term outcomes, resulting in small outcome numbers; longer follow-up may have elucidated additional information. Furthermore, the linkage in the national death register is poor for children, with only an estimated 42% of deaths that occurred under the age of 1 year recorded in 2007.[29] As such, it is likely that deaths are under-recorded, resulting in underestimation of mortality. Additionally, the researchers could not link the infant, child or adolescent file to parent files to verify parental vital status, resulting in inability to link parents to the death registry to verify orphan status. These data were only from two non-randomly selected urban sites, so results cannot be generalised to children accessing care in non-urban settings.

This study highlights the challenges in conducting outcomes research in clinical settings. There was probably patient self-selection, resulting in our data only comprising children with sufficient family or institutional support to get to care; it is possible that some HIV-positive orphans do not even make it into care before dying, and the ones who do may be healthier, resulting in skewed populations with regard to baseline differences. This possible selection bias may have led to uncontrolled confounding, making it difficult to say whether this bias would be different for orphans v. non-orphans in the general population, as the characteristics of those who did not initiate ART are not known. Despite this, the researchers believe that this clinic-based study still adds to the evidence base and can provide valuable insight for future programming, including highlighting possible predictors of poor treatment outcomes, allowing for targeted early engagement of children and caregivers at initial HIV care and treatment visits.

Conclusions

Our results show that, once on ART, orphans were less likely than non-orphans to be lost to care (die or be LTF). This result may be because orphans are more integrated into care owing to orphan-specific programming or foster care, or because the orphans in this study were systematically different to the non-orphans in a way that did not allow for the removal of all bias. Understanding the impact of orphan status on ART outcomes could improve targeted strategies, and subsequent treatment and developmental outcomes, for HIV-positive infants, children and adolescents. Additional research investigating age-specific outcomes as well as care-setting environments and the role of the caretaker will be important to elucidate these effects further.

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Conflicts of interest. None.

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