

Research article

Community adherence support improves programme retention in children on antiretroviral treatment: a multicentre cohort study in South Africa

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Abstract

Background: HIV-positive children in low-income settings face many challenges to adherence to antiretroviral treatment (ART) and have increased mortality on treatment compared to children in developed countries. Adult ART programmes have demonstrated benefit from community support to improve treatment outcomes; however, there are no empirical data on the effectiveness of this intervention in children. This study compared clinical, virological and immunological outcomes between children who received and who did not receive community-based adherence support from patient advocates (PAs) in four South African provinces.

Methods: A multicentre cohort study of ART-naïve children was conducted at 47 public ART facilities. Outcome measures were mortality, patient retention, virological suppression and CD4 percentage changes on ART. PAs are lay community health workers who provide adherence and psychosocial support for children's caregivers, and they undertake home visits to ascertain household challenges potentially impacting on adherence in the child. Corrected mortality estimates were calculated, correcting for deaths amongst those lost to follow-up (LTFU) using probability-weighted Kaplan-Meier and Cox functions.

Results: Three thousand five hundred and sixty three children were included with a median baseline age of 6.3 years and a median baseline CD4 cell percentage of 12.0%. PA-supported children numbered 323 (9.1%). Baseline clinical status variables were equivalent between the two groups. Amongst children LTFU, 38.7% were known to have died. Patient retention after 3 years of ART was 91.5% (95% CI: 86.8% to 94.7%) vs. 85.6% (95% CI: 83.3% to 87.6%) amongst children with and without PAs, respectively ($p = 0.027$). Amongst children aged below 2 years at baseline, retention after 3 years was 92.2% (95% CI: 76.7% to 97.6%) vs. 74.2% (95% CI: 65.4% to 81.0%) in children with and without PAs, respectively ($p = 0.053$). Corrected mortality after 3 years of ART was 3.7% (95% CI: 1.9% to 7.4%) vs. 8.0% (95% CI: 6.5% to 9.8%) amongst children with and without PAs, respectively ($p = 0.060$). In multivariable analyses, children with PAs had reduced probabilities of both attrition and mortality, adjusted hazard ratio (AHR) 0.57 (95% CI: 0.35 to 0.94) and 0.39 (95% CI: 0.15 to 1.04), respectively.

Conclusion: Community-based adherence support is an effective way to improve patient retention amongst children on ART. Expanded implementation of this intervention should be considered in order to reach ART programmatic goals in low-income settings as more children access treatment.

Keywords: antiretroviral treatment; children; community-based adherence support; outcomes; HIV; South Africa; low-income settings.

Received 17 September 2011; Revised 6 February 2012; Accepted 30 March 2012; Published 31 May 2012

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Introduction

Adherence to treatment is a challenge for patients with chronic disease (with average adherence being 50% in patients in developed countries) [1], and particularly for adults on antiretroviral treatment (ART) in low- and middle-income countries (LMIC), with patient retention being as low as 60% after 2 years of treatment [2,3]. These challenges are amplified in children in LMIC as parents are often no longer alive and children need to depend on relatives or others to access care and receive medication, with the potential for poor adherence to prescribed regimens. In addition, many paediatric ART formulations have complex and strict dosage schedules needing constant

review as weight may increase over short periods of time. Poor childhood cognitive skills, emotional distress, poverty, food and shelter insecurity, non-disclosure, domestic violence, substance abuse along with geographic and community isolation all increase the difficulty of treatment adherence [4]. Reviews have, nevertheless, indicated equal or increased adherence amongst children in LMIC compared to developed countries [5,6]. In contrast, children in LMIC start ART with significantly more advanced disease progression and have increased mortality on ART than children in developed countries [5,7], and LMIC programme attrition, particularly due to loss to follow-up (LTFU), is substantial (17% after 2 years of ART) [8].

The South African Government expanded treatment access in 2010 by including all HIV-positive children aged <1 year as eligible for ART and by increasingly devolving paediatric ART delivery to the primary healthcare (PHC) level and to nursing staff [9]. This places a greater burden on PHC services as skills, capacity, infrastructure, as well as new strategies are required to address the large treatment need [10]. In addition, PHC personnel are often not confident about caring for young HIV-positive infants [11]. In these circumstances, psychosocial support and adherence counselling tend to be neglected; hence, a need exists for lay community adherence support programmes. Recently, there have been calls to strengthen community-based support initiatives for patients on ART [12,13]. Lay healthcare workers in primary and community care have produced improved tuberculosis (TB) treatment outcomes and reductions in morbidity and mortality from childhood illnesses in non-ART settings [14–16]. Amongst adults receiving ART, social and community support have been associated with improved adherence and treatment outcomes [17–20]. There is, however, little or no data assessing the effectiveness of community-based adherence-support programmes for children receiving ART.

Kheth'Impilo (KI) is a non-governmental organization (NGO) in South Africa that has developed a community adherence-support programme employing patient advocates (PAs), who are lay community health workers providing adherence and psychosocial support for patients on ART [18]. PAs provide education and support for children's caregivers during treatment preparation and initiation at the clinic, and they undertake home visits to ascertain household challenges potentially impacting on adherence in the child. These are addressed at clinic multidisciplinary team (MDT) meetings where solutions are presented and implemented. Regular home visits continue after treatment initiation during which caregivers are supported to ensure any ongoing challenges to adherence are addressed.

The aim of this study was to evaluate the effectiveness of an NGO-managed community-based support programme amongst a multicentre cohort of children receiving ART in South Africa, by comparing clinical, virological and immunological outcomes between children who received and who did not receive community-based adherence support from PAs.

Methods

Study design and setting

A multicentre cohort study (with prospective data collection and a retrospective definition of the study question) of children enrolling for ART was conducted at 47 routine public healthcare facilities supported by KI. All sites that had electronic data collection systems were included in the study. Facilities were distributed across four provinces (Western Cape, KwaZulu-Natal, Eastern Cape and Mpumalanga), with 15 facilities being secondary level hospitals and 32 being PHC clinics. Seventeen sites had operational community-based adherence-support programmes. All sites treated both adults and children. All ART-naïve children starting ART at these sites were eligible for this study.

Inclusion criteria

All ART-naïve children (<16 years of age) who enrolled for triple combination ART between 1 January 2004 and 30 September 2009, who had their date of birth, gender and date of starting ART documented, who were initiated on ART at least 6 months before site database closure and who had at least 1 day of follow-up time, and for whom it was ascertained whether they received support from a PA or not, were included in analyses.

Children were selected to start ART according to the National Department of Health guidelines [21]. Briefly, children with modified World Health Organization (WHO) clinical Stage III or Stage IV disease, or a low CD4 cell percentage irrespective of disease stage (<20% in children under 18 months of age, or <15% if over 18 months old), or recurrent or prolonged hospitalization were eligible for ART. In addition, children were required to have an identifiable adult caregiver who could administer the medication. First-line ART consisted of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) for those aged older than 3 years or a protease inhibitor (PI) for those younger than 3 years.

Community-based support intervention

Patient advocates are community workers, chosen through a transparent process as possible with community representatives, clinic staff and NGO line managers involved in the choice of appropriate candidates. They had completed high school, were numerate and literate in English, were able to speak the local language and had good community standing. They were trained (for a 3 week intensive) on aspects of adult and paediatric HIV and TB infection and treatment, including psychosocial issues that impact on adherence and how best to address these. PAs were remunerated by sub-contracted NGOs prior to 2009, but have since been remunerated directly by KI. The company cost per PA (January 2012) is USD 225 to 275 per PA per month. Each PA is assigned approximately 80 to 120 ART patients (adults and children), with an approximate cost of USD 1.88 to 3.43 per patient per month. The PA programme is funded by the Global Fund to Fight AIDS, Tuberculosis and Malaria, US Presidents Emergency Plan for AIDS Relief and the Western Cape Department of Health. KI has a memorandum of understanding with each respective provincial health department.

During the treatment initiation phase, carers of children were linked to a PA from the geographical area in which they lived. As the community support programme for paediatric ART patients was reasonably new, a relatively small proportion of children at each site received PA support. Children were eligible to be linked to a PA if a PA was active in the area of the child's home, PA capacity was available and if consent was obtained from the carers. Clinical or socio-economic criteria were not used to influence eligibility status.

During the initial home assessment, family and other household members were evaluated together with the patient. Issues assessed (using a standardized form) included TB and HIV testing status of the household, nutrition insecurity, substance abuse, domestic violence, non-disclosure, social income grant access and documentation,

including birth and death certification. An assistant to the home child-carer, such as a Treatment Buddy, was potentially identified from the household or a close neighbour to further support adherence. All psychosocial issues were discussed at clinic MDT meetings (comprising doctors, nurses, clinic adherence counsellors, PAs and social workers), and planned interventions agreed by the MDT were implemented by the PA, auxiliary social worker or social worker, depending on the complexity of the issue.

Carers were also offered educational sessions, with topics including HIV/TB information, the need for adherence to medication, useful tips on nutrition, immunization schedules and information about minor childhood illnesses and home management of these, for example, preparation of oral hydration solution for diarrhoeal disease.

Following the psychosocial screening visit, home visits occurred weekly for a month. PAs supervised the taking of medication and advised on problems that may have arisen. The appropriate storage and hygiene of medicine utensils was stressed. The frequency of subsequent visits remained high, being at least monthly, as children were considered to be very important patients, 'VIP'. If clinic visits were delayed, home visit frequency increased.

Patient assignment and outcome measures

Patients were assigned to the PA-supported group if supported by a named KI patient advocate; else they were assigned to the non-PA-supported group. An intention-to-treat analysis was performed ignoring changes in assignment status after treatment commenced. Outcome measures were death, attrition, virological suppression and changes in CD4 cell percentage on ART. Attrition was defined as a combined endpoint of children dying or LTFU. LTFU was defined as no clinic visit by a patient for 3 months or more after the last scheduled appointment was missed. This definition was used by clinic staff at the time and was chosen to facilitate reasonably early tracing of non-attendees. Children generally attended clinics monthly; visits were spaced up to alternate monthly for certain older children who were stable on treatment. Non-PA-supported children who missed appointments would initially be traced by telephone or, where available, a district tracing team would visit the child's house. Time was measured from the start of ART and ended at the earliest of the date of last clinic follow-up visit (for patients dying, transferring out or LTFU), 36 months after starting ART, NGO exit from a site or 31 March 2010. The NGO exited from 10 sites during the study period, which facilitated staff (including PAs, as applicable) to be absorbed by the department of health. Follow-up data were censored where the NGO exited from a site.

To ascertain deaths amongst patients LTFU, the vital status of patients LTFU who had valid civil identification numbers were cross-checked by comparing with national death records. Data were compared anonymously. Cause of death data were not available.

CD4 cell count and percentage were measured at ART initiation and at 6-monthly intervals, and viral load was monitored 6-monthly on treatment. The proportion of children achieving virological suppression was measured

amongst children remaining in care and having available viral load test results and was defined as a viral load <400 copies/ml. Severe immunodeficiency was defined according to age-specific WHO criteria [22]. Laboratory monitoring was performed by the National Health Laboratory Services using the Panleucogating method (CD4 cell count) [23] and the Nuclisens HIV1 QT assay (bioMerieux, Marcy-Etoile, France) (viral load).

Data collection and statistical analyses

Individual-level patient data were collected prospectively for routine monitoring purposes by designated site-based data capturers at each patient visit using custom-designed databases, which were pooled on a quarterly basis to a central data warehouse using standard operating procedures. Continual data cleaning and quality control routines were implemented to enhance data validity. Missing data values were attempted to be retrieved by hand searching paper-based patient records at facilities.

Baseline characteristics between groups were compared using the Pearson's χ^2 and Wilcoxon rank-sum tests, as appropriate. Kaplan-Meier estimates of time to death and attrition after starting ART were calculated. To correct for patients who were LTFU but had died, corrected mortality estimates were derived using probability-weighted Kaplan-Meier functions [24]. In this approach, the updated vital status amongst patients who were LTFU at facility level for whom a definitive outcome could be established from the national death registry was used to represent outcomes among all those LTFU. A probability weight (the ratio of all patients LTFU to those LTFU with updated vital status) was assigned to lost patients with sampling-updated vital status, and other lost patients were dropped from the analysis. The logrank test was used to compare groups.

Multivariable Cox proportional hazards regression was used to assess group effect associated with death (based on the weighted data) and attrition after starting ART, adjusting for baseline patient variables (age, gender, WHO clinical stage, immunological status, weight-for-age z (WAZ)-score, year of starting ART, tuberculosis treatment, initial regimen) and site-related variables (health system level, province, rural/urban nature of site) as well as accounting for unmeasured heterogeneity between site cohorts. Missing baseline values were considered as separate categories within variables [8], to retain observations in multivariable models. All adjusted models included all baseline variables.

Three sets of multivariable sensitivity analyses of mortality and attrition were performed: I – ignoring death registry information and assigning vital status based on site-level ascertainment only; II – restricting outcome analyses to children enrolled at facilities at which the community-based adherence programme was operational; and III – restricting analyses to children enrolled at PHC facilities only (excluding hospital-based clinics). Statistical analyses were performed using Stata versions 9.1 and 11.1 (Stata Corporation, College Station, TX, USA). The study was approved by the University of Cape Town Research Ethics committee.

Results

Database records for a total of 6442 children younger than 16 years of age were screened for eligibility for the study. Children excluded were 1134 who commenced ART within 6 months of closure of the site database, 1381 who were documented as being ART experienced, 269 who had 0 days of follow-up time and 95 for whom it could not be definitively ascertained as to whether they received support from a PA or not. Thus, 3563 ART-naïve children were included in analyses.

There were 323 (9.1%) and 3240 (90.9%) children who received and did not receive support from a PA, respectively (Table 1). At the start of treatment, PA-supported children

had a higher proportion aged below 1 year, a higher proportion treated at PHC facilities, a lower proportion who were treated at rural facilities, lower proportions from Mpumalanga and Eastern Cape provinces and a lower proportion having Zidovudine (ZDV) instead of Stavudine included in the initial regimen. Baseline clinical status variables were equivalent between the groups. Patients supported by PAs had significantly fewer missing baseline TB treatment values (2 [0.6%] vs. 276 [8.5%]; $p < 0.0005$), as well as fewer missing baseline immunological values (44 [13.6%] vs. 766 [23.6%]; $p < 0.0005$).

The total observation time was 4848 person-years, with median observation times of 18.5 months per child (IQR: 8.4

Table 1. Baseline characteristics of ART-naïve children beginning antiretroviral therapy

	All	Children with PAs	Children without PAs	<i>p</i>
No. of children <i>n</i> (%)	3563	323 (9.1)	3240 (90.9)	
Median age, <i>y</i> (IQR)	6.3 (3.3 to 9.5)	6.8 (3.2 to 9.8)	6.2 (3.3 to 9.5)	0.488
Age group categories, <i>n</i> (%)				0.043
< 1 year	184 (5.2)	26 (8.1)	158 (4.9)	
1 to 2 years	323 (9.1)	26 (8.1)	297 (9.1)	
> 2 years	3056 (85.8)	271 (83.9)	2785 (86.0)	
Female, <i>n</i> (%)	1757 (49.3)	161 (49.9)	1596 (49.3)	0.841
WHO clinical stage, <i>n</i> (%) ^a , (<i>n</i> = 2350)				0.175
I/II	939 (40.0)	77 (35.7)	862 (40.4)	
III/IV	1411 (60.0)	139 (64.4)	1272 (59.6)	
WAZ-score, median (IQR), (<i>n</i> = 2259)	-1.43 (-2.46 to -0.55)	-1.28 (-2.51 to -0.37)	-1.44 (-2.46 to -0.56)	0.106
WAZ-score < -3, <i>n</i> (%) ^a	361 (15.6)	22 (11.7)	339 (16.4)	0.209
CD4 cell percentage; median (IQR), (<i>n</i> = 1734)	12.0 (7.0 to 17.9)	11.0 (7.0 to 15.0)	12.0 (7.1 to 18.0)	0.178
Absolute CD4 cell count (cells/μl); median (IQR), (<i>n</i> = 2256)	239 (66 to 547)	218 (81 to 457)	240 (64 to 565)	0.214
Severe immunodeficiency ^a , <i>n</i> (%) ^a , (<i>n</i> = 2753)	1914 (69.5)	201 (72.0)	1713 (69.2)	0.335
Tuberculosis, <i>n</i> (%) ^b (<i>n</i> = 3285)	124 (3.8%)	16 (5.0%)	108 (3.6%)	0.231
Initial ART regimen, <i>n</i> (%) ^b , (<i>n</i> = 3390)				
NNRTI based	2633 (77.7) ^c	262 (81.1)	2371 (77.3)	0.118
PI-based	665 (19.6) ^c	55 (17.0)	610 (19.9)	0.218
Including d4t	3266 (96.3) ^c	321 (99.4)	2945 (96.0)	0.002
Including ZDV	216 (6.3) ^c	8 (2.5)	208 (6.8)	0.003
PHC based care, <i>n</i> (%)	1507 (42.3)	306 (94.7)	1201 (37.1)	<0.0005
Year of starting ART, <i>n</i> (%)				0.072
2004/2005	204 (5.7)	26 (8.1)	178 (5.5)	
2006/2007	1399 (39.3)	113 (35.0)	1286 (39.7)	
2008/2009	1960 (55.0)	184 (57.0)	1776 (54.8)	
Rural ART facility, <i>n</i> (%)	334 (9.4)	9 (2.8)	325 (10.0)	<0.0005
Province, <i>n</i> (%)				<0.0005
Western Cape	486 (23.7)	57 (17.6)	429 (13.3)	
Eastern Cape	410 (11.5)	16 (5.0)	394 (12.2)	
Kwazulu-Natal	2472 (69.4)	158 (48.9)	2314 (71.4)	
Mpumalanga	195 (5.5)	92 (28.5)	103 (3.2)	

PA, patient advocates; WHO, World Health Organization; IQR, interquartile range; WAZ, weight for age z-score; ART, antiretroviral treatment; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; d4t, stavudine; ZDV, zidovudine; PHC, primary healthcare.

^aSevere immunodeficiency was defined according to World Health Organization's age-specific CD4 cell count and percentage criteria; ^bProportion of children with available results; ^c92 children received d4t and ZDV and did not receive an NNRTI or a PI.

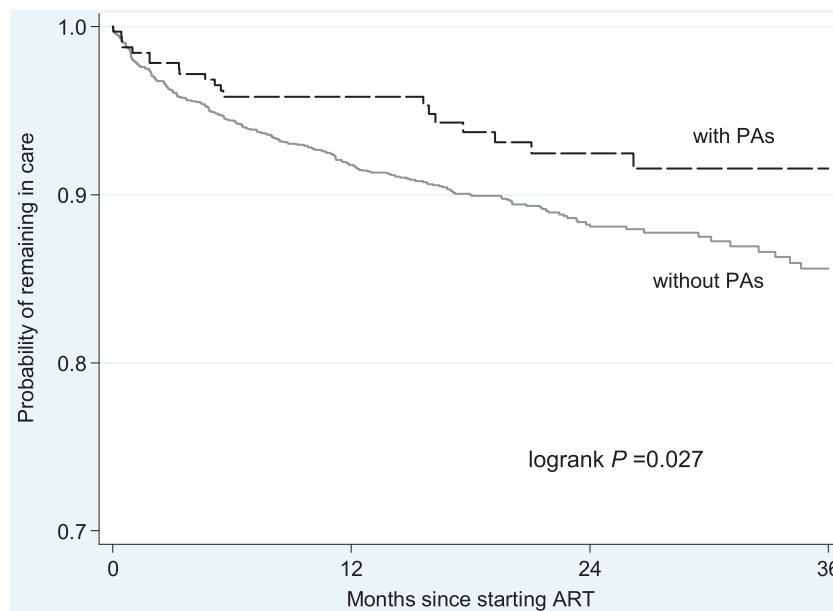
to 30.2) amongst children with PAs and 15.2 months per child (IQR: 8.2 to 22.4) amongst children without PAs. Using facility-level data, amongst children with and without PAs, 4 (1.2%) and 106 (3.3%) children were ascertained as having died during the study period, respectively, and 16 (5.0%) and 195 (6.0%) were LTFU, respectively. Patient retention (1 – attrition) after 3 years of ART in children with PAs was 91.5% (95% CI: 86.8% to 94.7%) vs. 85.6% (95% CI: 83.3% to 87.6%) amongst children without PAs (logrank $p = 0.027$) (Fig. 1). Amongst children aged below 2 years when starting ART, retention after 3 years was 92.2% (95% CI: 76.7% to 97.6%) vs. 74.2% (95% CI: 65.4% to 81.0%) in children with and without PAs, respectively ($p = 0.053$; $n = 507$; 52 [10.3%] PA-supported).

Cumulative mortality based on facility-held data after three years of ART was 1.5% (95% CI: 0.5% to 4.1%) in children with PAs vs. 4.7% (95% CI: 3.6% to 6.2%) amongst children without PAs (logrank $p = 0.032$). Amongst all children LTFU, 93 (44.0%) had valid civil identification numbers, of whom 36 (38.7%) were registered as having died in the national registry by November 2010. The estimates of corrected mortality based on the weighted dataset after 3 years of ART were 3.7% (95% CI: 1.9% to 7.4%) amongst children with PAs vs. 8.0% (95% CI: 6.5% to 9.8%) amongst children without PAs (logrank $p = 0.060$) (Fig. 2). Corrected mortality rates on ART were 1.6 deaths per 100 child-years (95% CI: 0.7 to 4.9) vs. 4.2 deaths per 100 child-years (95% CI: 3.5 to 5.1) in children with and without PAs, respectively ($p = 0.060$). Amongst children aged below 2 years when

starting ART, corrected mortality rates were 1.5 deaths per 100 child-years (95% CI: 0.5 to 10.5) vs. 7.7 deaths per 100 child-years (95% CI: 5.3 to 11.7) in children with and without PAs, respectively ($p = 0.12$).

In multivariable analyses adjusting for all available baseline variables (Table 2), children with PAs had an independently reduced probability of attrition, adjusted hazard ratio (AHR) 0.57 (95% CI: 0.35 to 0.94; $p = 0.026$) and a reduced probability of mortality (based on the weighted data), AHR 0.39 (95% CI: 0.15 to 1.04; $p = 0.060$). Other baseline factors independently associated with mortality were age under 2 years (AHR 1.70 [95% CI: 1.01 to 2.85]), WAZ-scores below -3 (AHR 3.95 [95% CI: 2.38 to 6.56]), severe immunodeficiency (AHR 2.36 [95% CI: 1.27 to 4.64]) and receiving treatment for TB (AHR 2.37 [95% CI: 1.21 to 4.64]). Mortality was higher in KwaZulu-Natal and Mpumalanga provinces compared with that of the Western Cape. Mortality and attrition were equivalent between PHC and hospital facilities.

The improved outcomes in PA-supported children remained apparent when sensitivity analyses were performed. When death registry information was ignored and vital status based on site-level ascertainment only, PA-supported children had an independently reduced probability of death, AHR 0.26 (95% CI: 0.09 to 0.75; $p = 0.013$, $n = 3563$). Analyses limited to the sites at which PAs were active included 1577 (83.0%) patients who did not receive PA support. In multivariable models, attrition and corrected mortality were both independently reduced in PA-supported children at these sites; AHR 0.49 (95% CI: 0.28 to 0.87, $p = 0.015$, $n = 1900$)



No. patients (events)						
Children with PAs	323	(13)	212	(6)	122	(1)
Children without PAs	3240	(241)	1953	(51)	678	(9)
Retention as % (95% CI)						
Children with PAs			95.8 (92.9–97.6)		92.5 (88.2–85.2)	91.5 (86.8–94.7)
Children without PAs			91.8 (90.7–92.7)		88.1 (86.6–89.5)	85.6 (83.3–87.6)

Figure 1. Kaplan-Meier estimates of retention in care for children with and without patient advocates. ART, antiretroviral therapy, PAs, patient advocates; CI, confidence interval.

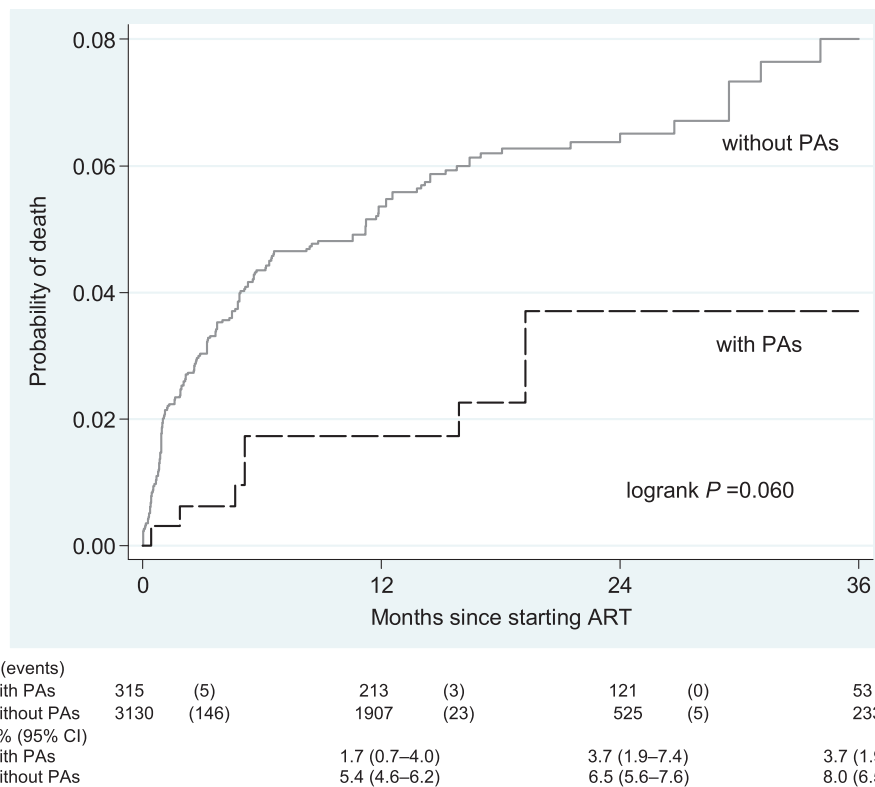


Figure 2. Weighted Kaplan-Meier estimates of corrected mortality for children with and without patient advocates. For patients who were lost to follow-up with available civil identification numbers, vital status was ascertained from the national death registry. These patients were weighted in the analysis to represent all patients lost to follow-up. ART, antiretroviral therapy, PAs, patient advocates; CI, confidence interval.

and AHR 0.24 (95% CI: 0.07 to 0.76, $p = 0.015$, $n = 1848$), respectively.

Analyses limited to the 32 PHC clinics included 1507 children, with 306 (20.3%) receiving PA support. After 36 months of ART, retention in care was 90.1% (95% CI: 85.9% to 94.3%) in patients with PAs vs. 80.0% (95% CI: 73.0% to 85.3%) in patients without PAs, respectively (logrank $p = 0.036$). In multivariable models, attrition and corrected mortality were independently reduced in PA-supported children, AHR 0.57 (95% CI: 0.34 to 0.97; $p = 0.039$) and AHR 0.37 (95% CI: 0.13 to 1.06; $p = 0.065$), respectively.

The proportion of patients achieving virological suppression was equivalent between children with and without PA support. Virological suppression was 78.8% (95% CI: 71.7% to 85.9%; $n = 132$) and 82.4% (95% CI: 80.4% to 84.4%; $n = 1409$) ($p = 0.30$) in children with and without PAs, respectively, after 6 months of ART; and after 12 months it was 80.6% (95% CI: 73.0% to 88.1%; $n = 108$) vs. 78.5% (95% CI: 75.9% to 81.1%; $n = 959$) ($p = 0.62$) in children with and without PAs, respectively. Virological suppression was also equivalent between PHC and hospital facilities ($p = 0.10$ after 6 months; $p = 0.85$ after 12 months).

Median CD4 percentage increases were equivalent between children with and without PA support; overall increases were 8.0% (IQR: 4.0% to 12.7%; $p = 0.57$; $n = 972$) after six months and 11.1% (IQR: 6.8% to 17.1%; $p = 0.43$; $n = 652$) after 12 months of ART. Median CD4 percentage increases

were also equivalent between PHC and hospital facilities ($p = 0.86$ after 6 months; $p = 0.87$ after 12 months).

Discussion

This study is amongst the first to evaluate the impact of a multicentre community-based adherence-support programme for children receiving ART in sub-Saharan Africa and has demonstrated an approximately 40% reduction in patient attrition over 3 years of treatment. Mortality rates of children with PAs were comparable with those of children on ART in developed countries [7]. Community health workers form a significant workforce in HIV programmes in South Africa [25] and this data provides empirical evidence of their benefit for children receiving ART, as has previously been demonstrated for adults [18,20]. It contributes to possible solutions to the poor paediatric survival on ART in LMIC [7], as well as augments the existing body of data from non-ART settings demonstrating the positive impact of community health workers in improving child survival [14]. These results also concur with previous studies showing that paediatric ART can be successfully provided in a decentralized manner at PHC facilities located within the community being served [26,27].

Infants are a particularly vulnerable group with increased risk of death on ART due to immune system immaturity [5,28]. PA-supported children had a higher proportion of infants aged below one year when starting ART; nevertheless, PA-supported children demonstrated lower overall mortality on ART. In addition, although the sample was small, retention

Table 2. Characteristics at the start of ART associated with mortality and attrition in multivariable Cox regression models^a.

	Mortality (corrected) ^b			Attrition ^c		
	Adjusted hazard ratio	95% confidence interval	p value	Adjusted hazard ratio	95% confidence interval	p value
Children with PAs	0.39	0.15 to 1.04	0.060	0.57	0.35 to 0.94	0.026
Male gender	0.96	0.68 to 1.34	0.94	0.92	0.76 to 1.12	0.46
Age category						
≥ 2 years ^d	1	–		1	–	
< 2 years	1.70	1.01 to 2.85	0.048	1.64	1.17 to 2.29	0.007
WHO stage						
I–II ^d	1	–		1	–	
III–IV	1.28	0.79 to 2.07	0.48	0.89	0.67 to 1.16	0.32
WAZ-score						
> –2 ^d	1	–		1	–	
–3 to –2	1.23	0.59 to 2.56	0.38	1.04	0.71 to 1.51	0.42
< –3	3.95	2.38 to 6.56	<0.0005	2.74	1.95 to 3.84	<0.0005
Severe Immunodeficiency	2.36	1.27 to 4.39	0.001	1.20	0.89 to 1.62	0.34
Tuberculosis	2.37	1.21 to 4.64	0.006	1.40	0.79 to 2.49	0.21
Initial ART regimen						
PI-based	0.88	0.53 to 1.47	0.78	1.07	0.80 to 1.44	0.67
d4t-based	0.59	0.20 to 1.72	0.45	0.91	0.55 to 1.51	0.60
PHC-based care	0.83	0.51 to 1.37	0.48	0.85	0.63 to 1.16	0.25
Rural ART facility	0.76	0.45 to 1.29	0.31			
Province						
Western Cape ^d	1	–				
Eastern Cape	2.44	0.80 to 7.51	0.112	1.20	0.64 to 2.25	0.57
Kwazulu-Natal	3.53	1.43 to 8.70	0.006	1.40	0.83 to 2.32	0.20
Mpumalanga	3.85	1.20 to 12.32	0.023	1.63	0.81 to 3.23	0.17

ART, antiretroviral therapy; CI, confidence interval; PHC, primary healthcare; WAZ, weight for age z-score; WHO, World Health Organization; d4T, stavudine.

^aEstimates are adjusted for all variables in the table as well as year of starting ART. Children with missing baseline values were included in analyses by adding a missing category to variables; ^bWeighted analyses with corrected mortality, weighted $n = 3445$; ^c $n = 3563$; ^dReference category.

amongst children aged below 2 years was particularly improved in PA-supported children.

In addition to healthcare, PAs assist with access to vital documentation and social income grants, as fewer than 70% of eligible carers access child or foster care grants in South Africa [29]. This is expected to improve the households' economic status and reduce food insecurity, both of which are associated with improved child survival [30,31]. PA-supported children also had more recorded data on TB, which may indicate an earlier awareness of potential health problems and referral for appropriate interventions, leading to improved survival.

The large numbers of missing viral loads amongst all children is, however, of concern. This problem applies to both adults and children at government facilities, is common to ART programmes in sub-Saharan Africa and other LMIC [27,32] and is due to a combination of testing being omitted, misplacing of blood specimens, laboratory technical problems, non-retrieval of laboratory results and failure to enter results in site databases timeously due to human resource

constraints. Attempts are currently underway to improve the availability of viral load test results.

Community-based adherence-support expands the nexus of interdependent factors needed to sustain adherence and patient retention on ART [4,20]. Scaling-up community interventions may significantly impact children's treatment outcomes and need to be considered as part of the implementation and not as a substitute for the formal health sector [25] of large-scale treatment initiatives as the country ramps up to meet the United Nations vision of zero AIDS-related deaths and zero new infections, in a climate of zero discrimination by 2015 [33]. This strategy should form part of clinical services provided at the PHC level if South Africa is to achieve this goal. Formal cost-effectiveness studies of this intervention should also be conducted.

Strengths and limitations

The strengths of this study are that pooled data from a large number of patients and sites in different settings

were used, and prospective individual-level data were collected enabling adjustment of patient factors associated with outcomes. In addition, the vital status of patients LTFU who had identification numbers was determined from the national death registry, allowing corrected mortality estimates to be derived.

This study analyzed routine data with its inherent limitations; however, it is likely to be indicative of the situation at the operational level. As PAs worked in the geographic areas of the local clinics, children who did not receive PAs at sites with the community-based programme may have lived at greater distances from the clinic than children who received PAs. This may have increased the risk of LTFU in non-PA-supported children, which was not able to be accounted for in the analysis as travel distance does not form part of the routine data collected on public sector ART patients. Adherence determination data were not analyzed as there are no national standard government protocols or tools to measure patient-level adherence. Baseline socio-economic factors may be associated with mortality, but this variable could not be included in analyzes as it was not possible to collect socio-economic data for the whole cohort. However, previous analyzes in adults showed that patients from lower socio-economic strata at baseline were more likely to be attached to a PA [18]; therefore, this factor is unlikely to have confounded effect measures in favour of PA support. All the sites were supported by an NGO, and it is possible that the outcomes may not be well generalizable to non-NGO-supported government health facilities. Data on maternal characteristics, which may be a potential confounder of outcomes, were not available for analysis.

Conclusion

This study indicates that community-based adherence support is an effective way to improve patient retention amongst children receiving ART in a low-income setting. As more children start accessing ART as South Africa scales-up programmes to meet its treatment needs, support for the carers of these children is critical to maintain patient retention. Future randomized studies should be undertaken which include larger samples of children receiving community-based support that include measurement of adherence, psychosocial barriers to adherence and clinic travel distance. In the absence of these, however, large-scale implementation of this low-cost, useful intervention should be considered as part of collective practical interventions by health authorities [12,34] embarking on the ambitious programme to see every HIV-positive child under 1 year of age access ART and almost all PHC facilities initiate paediatric treatment across South Africa. The provision of ward-based community healthcare workers is one of the three critical interventions envisaged by the National Department of Health's Re-engineering of PHC strategy for improving health outcomes [35]. The PA programme has much valuable learning that could further inform and refine this strategy.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AG, GF, EM, MM designed the study. GF analyzed the data. All authors interpreted the data. All authors contributed to the writing of the manuscript, and all authors approved the manuscript for publication.

Abbreviations

AHR, adjusted hazard ratio; ART, antiretroviral treatment; LMIC, low and middle-income countries; LTFU, lost to follow-up; MDT, multidisciplinary team; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTIs, nucleoside reverse transcriptase inhibitors; Pas, patient advocates; PHC, primary health-care; PI, protease inhibitor; WAZ, weight for age z-score.

Acknowledgements

Results from this study were presented at the 6th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention in Rome, Italy, 17 to 20 July 2011. The authors wish to acknowledge Anita Jason, Helen Schneider, Kheth'Impilo colleagues, PEPFAR, the Global Fund to Fight AIDS, Tuberculosis and Malaria, Absolute Return for Kids, and the Departments of Health from the Western Cape, Eastern Cape, KwaZulu-Natal and Mpumalanga. No sources of funding to declare.

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