ANTIRETROVIRAL THERAPY OUTCOMES IN RURAL AND URBAN CHILDREN ATTENDING PUBLIC HEALTH FACILITIES IN SOUTH AFRICA

MOPEB 077

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INTRODUCTION

South Africa has the largest paediatric HIV epidemic and the largest paediatric anti-retroviral treatment (ART) programme in the world. At the end of 2007, more than 300 000 South African children were living with HIV infection, of whom more than 30 000 were receiving ART. Despite the rapid scale-up of ART programs however, marked inequities remain in access to ART between and within provinces in the country.

Previous South African studies describing the outcome of paediatric ART have demonstrated favourable short-term responses. These studies have concentrated on urban-based programmes. A significant proportion of South African children who require ART however live in rural areas, and there is currently limited information on the outcomes of children managed in rural ART programmes.

Absolute Return for Kids South Africa (ARK) is a non-governmental organisation established in November 2003 which supports the scale-up of ART in public sector clinics in South Africa. Since 2004, it has facilitated the initiation of ART in > 2500 children in four provinces. In this study, paediatric data generated in ARK-supported clinics were used to compare the outcomes of children treated with ART in rural and urban operational settings.

METHODS

A retrospective analysis of routine cohort data of children (<16 years), enrolled for ART between November 2003 and March 2008 in three settings, namely urban residence and ART facility attended (Group 1), rural residence and rural facility attended (Group 2) and rural resident attending urban facilities (Group 3). Children were categorised according to the Global Rural-Urban Mapping Project definitions. Children were followed until August 2008 or until ARK exited from a site.

Outcome measures were: death, loss to follow-up (LTFU), virological suppression, changes in CD4%, absolute CD4 cell count and weight-for-age-Z-scores (WAZ). LTFU was defined as no patient visit for three months after the last scheduled appointment was missed and viral load suppression as a viral load < 400 copies/ml.

Baseline characteristics between groups were compared using the ANOVA, Kruskal-Wallis, Pearson's χ^2 and Bonferroni tests as appropriate. Kaplan-Meier curves were fitted to estimate mortality and LTFU from the program. The logrank test was used to compare groups. Multivariable Cox regression was used to assess group effect associated with death and LTFU, adjusting for baseline demographic and clinical variables. When comparing groups, the group with the lowest Kaplan-Meier estimates of each outcome was selected as the comparative group. For regression analyses, severe immunodeficiency was defined according to World Health Organisation (WHO) criteria, and severe clinical status was defined as a WAZ score <-3 or WHO clinical stage ≥ 3.

A multivariate generalized estimating equation population-averaged model of WAZ scores up to 24 months of treatment was used to compare group effect adjusted for baseline variables.

RESULTS

2,332 ART-naïve children from 7 rural and 37 urban sites in four provinces were included, 50.3% of whom were female. There were 1727 (74.1%), 228 (9.8%) and 377 (16.2%) children in groups 1, 2 and 3 respectively (table 1). At ART initiation, children accessing care at rural sites (group 2) were older, had a lower mean WAZ score but less advanced WHO clinical stage disease than other children. The median (IQR) baseline CD4 cell % was 12.3% (7.0–18.3%); there were no differences between groups. The majority (74%) of children commenced NNRTI-based regimens; urban-based children however had a higher proportion that started PI-based regimens or regimens that contained Zidovudine ($P < 0.0001$). There were significantly higher proportions of missing baseline clinical variables in children living in rural areas compared to urban children.

Over the observation period, 44 (2.6%), 14 (6.1%) and 11 (2.9%) children died in groups 1–3 respectively ($P = 0.011$). After 18 months of ART, mortality was significantly higher in children accessing care in rural areas, being 7.7% (CI: 4.5–13.0%; $P = 0.0137$) compared to 3.0% (CI: 2.2–4.1%) and 3.1% (CI: 1.7–5.6%) in groups 1 and 3 respectively, figure 1. Mortality rates during the first six months of treatment were also highest in these children, being 11.4 (CI: 6.3–20.6) compared to 5.4 (CI: 3.9–7.4) and 7.1 (CI: 3.9–12.8) deaths/100 person-years in groups 1 and 3 respectively.

Overall, 125 (7.2%), 10 (4.4%) and 44 (11.7%) children become LTFU in groups 1–3 respectively ($P = 0.002$). After 18 months of ART, LTFU was three-fold higher in rural children who travelled to urban treatment sites compared to those who accessed care in rural areas, the probability of LTFU being 9.9% (CI: 8.3–11.8%), 5.8% (CI: 2.7–12.2%) and 15.0% (CI: 11.2–20.0%) in groups 1-3 respectively (P =0.0028), figure 2.

There were no differences between groups in the rates of CD4 cell % increase (figure 3) or proportions with virological suppression (figure 4) after starting ART. There were however high proportions of patients with unavailable viral load results, especially in rural children, being 66.5%, 95.4%, and 71.8% in groups 1–3 respectively after six months of treatment, $P < 0.0001$.

In comparison to other groups, children accessing care in rural areas had significantly lower baseline WAZ scores that persisted during treatment (figure 5); a generalized estimating equation population-averaged model of WAZ scores up to 24 months of ART further indicated that this group had significantly lower on-treatment WAZ scores than children living in urban areas after adjusting for baseline variables ($P = 0.001$).

Table 2 shows the results of crude and adjusted regression models of baseline factors associated with death and LTFU over 36 months of ART. Children accessing care in rural areas had an independently increased probability of mortality, HR 2.41 (CI: 1.18–4.92; $P = 0.015$) in comparison with children living in urban areas. Severe clinical status, and unavailable clinical status variables were both independently associated with increased probabilities of mortality; HR 2.28 (CI: 1.12–4.64) and HR 3.98 (CI: 1.80–8.81) respectively. Severe immunodeficiency was independently associated with a four-fold increased probability of mortality, HR 4.39 (CI: 1.57–12.28).

Rural children traveling to urban facilities had an independently increased probability of LTFU, HR 2.68 (CI: 1.31–5.49; $P = 0.007$) compared to children accessing care in rural areas. Children with missing baseline clinical variables had a modest independently increased risk of becoming LTFU on treatment, HR 1.55 (CI: 1.01-2.40, $P = 0.047$).

Table 1: Characteristics of ART-naïve children beginning antiretroviral therapy at ARK-supported sites

	All	Group 1	Group 2	Group 3	P-value
	(n=2332)	(n=1727)	(n=228)	(n=377)	
Median age, y (IQR)	5.8 (3.0-9.0)	5.6 (2.8-8.9)	6.7 (4.3-10.0)	5.8 (3.2-9.3)	0.0001
Age group categories, n (%)					0.001
< 1 year	129 (5.5)	112 (6.5)	3 (1.3)	14 (3.7)	
1-2 yrs	246 (10.6)	188 (10.9)	17 (7.5)	41 (10.9)	
2-5 yrs	834 (35.8)	628 (36.4)	72 (31.6)	134 (35.5)	
6-10 yrs	814 (34.8)	573 (33.2)	94 (41.2)	145 (38.5)	
≥ 11 yrs	311 (13.3)	226 (13.1)	42 (18.4)	43 (11.4)	
Female, n (%)	1174 (50.3)	887 (51.3)	98 (42.0)	189 (50.1)	0.0590
CD4 cell count percentage; median (IQR)	12.3 (7.0-18.3)	12.3 (7.0-19.0)	12.0 (8.0-16.0)	11.6 (4.6-14.5)	0.1073
Absolute CD4 cell count (cells/µl); median (IQR)	247 (38-602)	277 (41-656)	201 (76-395)	114 (14-361)	0.0001
Weight-for-age Z-score, mean (95% CI)	-1.5 (-1.5; -1.37)	-1.4 (-1.5; -1.3)	-1.9 (-2.2; -1.6)	-1.2 (-1.5; -1.0)	0.0050
World Health Organisation clinical stage, n (%)					<0.0001
I	116 (6.8)	91 (6.7)	17 (14.3)	8 (3.5)	
II	473 (27.7)	358 (26.4)	49 (38.7)	69 (29.7)	
III/IV	1118 (65.5)	907 (66.9)	56 (47.1)	155 (66.8)	
Initial ART regimen					
NNRTI based	1682 (73.8)	1182 (70.2)	208 (93.3)	292 (78.9)	<0.0001
PI-based	540 (23.7)	452 (26.8)	13 (5.8)	75 (23.7)	
Including d4t	2089 (91.7)	1504 (89.3)	221 (99.1)	364 (98.4)	<0.0001
Including ZDV	133 (5.8)	130 (7.7)	0 (0)	3 (0.8)	

Figure 1: Kaplan-Meier estimates of cumulative mortality between groups

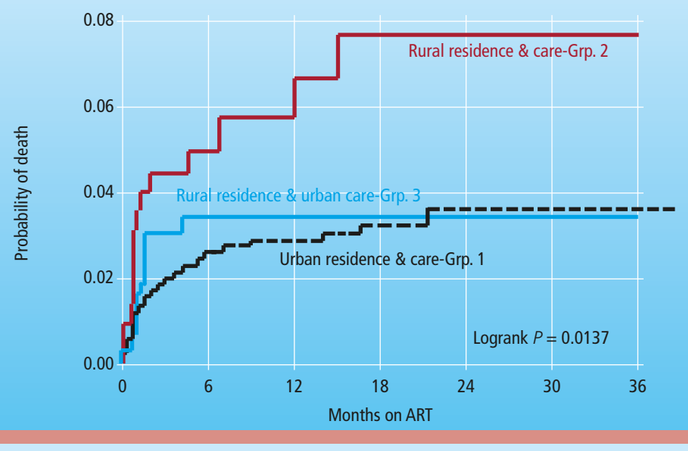

Figure 2: Kaplan-Meier estimates of cumulative loss to follow-up between groups

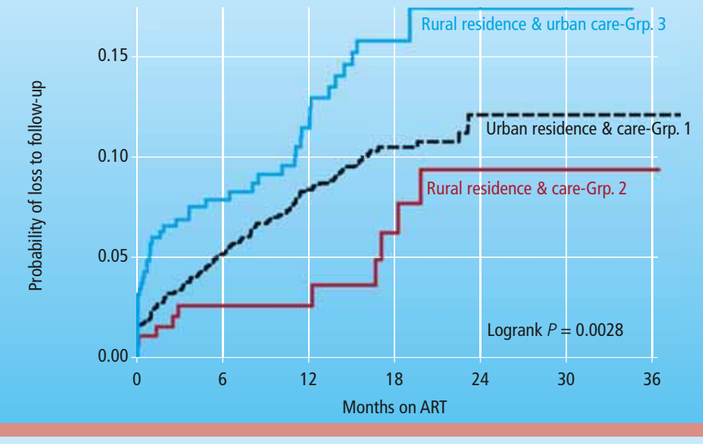

Figure 3: Changes in CD4 cell percentage after initiating ART in rural and urban children.

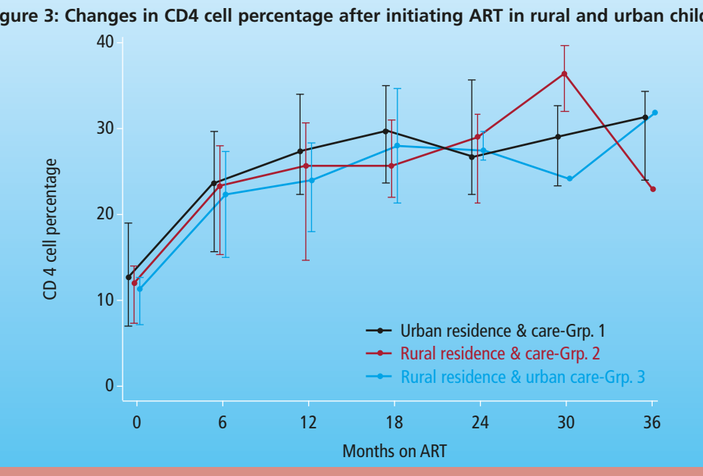

Figure 4: Proportions of children with virological suppression (<400 copies/ml) after initiating ART in rural and urban children.

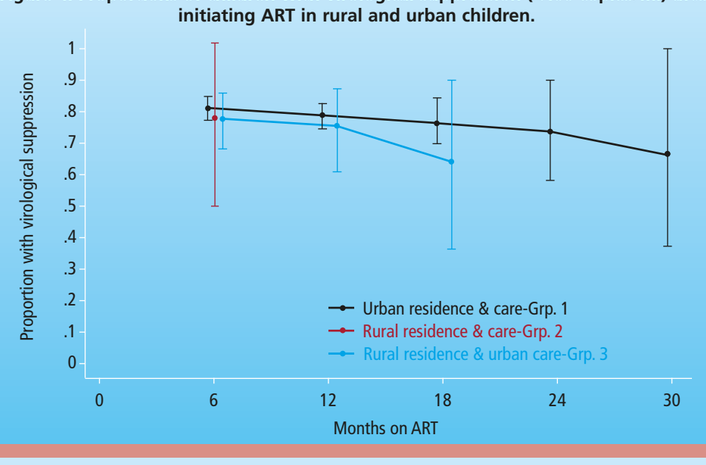

Figure 5: Changes in weight-for-age Z-score after initiating ART in rural and urban children

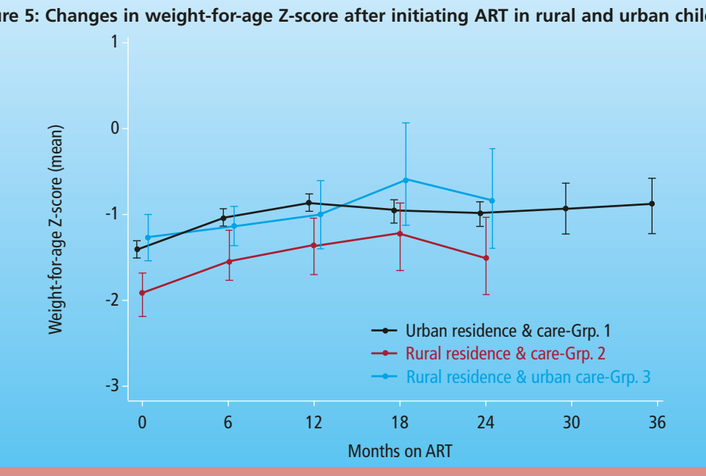

Table 2: Factors associated with death and loss to follow-up (LTFU) over the first three years after starting ART. (n=2332)

	HR (95% CI) of death		HR (95% CI) of LTFU	
	Crude	Adjusted	Crude	Adjusted
Gender				
Female	1	1	1	1
Male	0.86 (0.54-1.38)	0.89 (0.54-1.45)	1.06 (0.79-1.42)	1.1 (0.82-3.12)
Age (years)	0.99 (0.92-1.07)	0.99 (0.54-1.45)	0.98 (0.94-1.02)	1.00 (0.82-1.49)
Severe clinical status				
No	1	1	1	1
Yes	2.32 (1.14-4.38)	2.28 (1.12-4.64)	1.65 (1.17-2.32)	1.54 (1.08-2.20)
Not available	4.08 (1.97-8.47)	3.98 (1.80-8.81)	1.87 (1.28-2.72)	1.55 (1.01-2.40)
Immunodeficiency				
Not severe	1	1	1	1
Severe	3.69 (1.46-9.30)	4.39 (1.57-12.28)	0.87 (0.58-1.33)	0.84 (0.56-1.29)
Not available	2.46 (0.92-6.54)	2.56 (0.83-7.87)	1.32 (0.87-2.0)	0.90 (0.57-1.41)
Initial ART regimen				
PI-based	1.37 (0.80-2.37)	1.45 (0.72-2.96)	1.42 (1.02-1.98)	1.34 (0.88-2.04)
Non PI-based	1	1	1	1
d4T-based	0.91 (0.33-2.52)	0.87 (0.32-2.54)	0.80 (0.46-1.42)	0.79 (0.44-1.44)
Non d4t-based	1	1	1	1
Urban/Rural Classification				
Group 1	1	1	1.67 (0.89-3.19)	1.60 (0.82-3.12)
Group 2	2.38 (1.31-4.36)	2.41 (1.18-4.92)	1	1
Group 3	1.17 (0.60-2.26)	1.19 (0.85-2.45)	2.71 (1.36-5.39)	2.68 (1.31-5.49)

CONCLUSIONS

These results show that HIV-infected children on ART in rural settings constitute a vulnerable patient group. At baseline their nutritional status was more impaired than urban children, and differences persisted throughout the study. Although a lower percentage of children at rural clinics had advanced HIV infection at baseline, they experienced significantly higher mortality throughout the study period. LTFU was significantly increased in rural children managed at urban clinics. When children were successfully established on ART at rural clinics they experienced similar rates of virological suppression and immune restoration as their urban counterparts.

These findings suggest that the quality of ambulatory ART care is similar in rural and urban clinics, and the increased vulnerability of rural-based HIV-infected children is due in part to nutritional, socio-economic and other health system factors. Future research should explore the mechanisms underpinning the observed vulnerability, and determine whether HIV-infected children and their families in rural settings require increased social support.

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