Outcomes of the South African National Antiretroviral Treatment Programme for children: The IeDEA Southern Africa collaboration

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Objectives. To assess paediatric antiretroviral treatment (ART) outcomes and their associations from a collaborative cohort representing 20% of the South African national treatment programme.

Design and setting. Multi-cohort study of 7 public sector paediatric ART programmes in Gauteng, Western Cape and KwaZulu-Natal provinces.

Subjects. ART-naïve children (≤16 years) who commenced treatment with ≥3 antiretroviral drugs before March 2008.

Outcome measures. Time to death or loss to follow-up were assessed using the Kaplan-Meier method. Associations between baseline characteristics and mortality were assessed with Cox proportional hazards models stratified by site. Immune status, virological suppression and growth were described in relation to duration of ART.

Results. The median (interquartile range) age of 6 078 children with 9 368 child-years of follow-up was 43 (15 - 83) months, with 29% being <18 months. Most were severely ill at ART initiation. More than 75% of children were appropriately monitored at 6-monthly intervals with viral load suppression (<400 copies/ml) being 80% or above throughout 36 months of treatment. Mortality and retention in care at 3 years were 7.7% (95% confidence interval 7.0 - 8.6%) and 81.4% (80.1 - 82.6%), respectively. Together with young age, all markers of disease severity (low weight-for-age z-score, high viral load, severe immune suppression, stage 3/4 disease and anaemia) were independently associated with mortality.

Conclusions. Dramatic clinical benefit for children accessing the national ART programme is demonstrated. Higher mortality in infants and those with advanced disease highlights the need for early diagnosis of HIV infection and commencement of ART.

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South Africa's paediatric antiretroviral treatment (ART) programme is the largest in the world, with an estimated 32 000 children <15 years of age on treatment at the end of 2007.[1] Nevertheless the programme reaches less than half of the children estimated to need ART according to national guidelines,[2] and an even lower proportion if need is defined using revised 2008 World Health Organization (WHO) guidelines for early treatment of HIV-infected infants.[3]

Despite the size of the national programme, few individual cohorts have published treatment outcomes, with follow-up limited to 1 year.[4-6] Similar to other African countries, these cohorts have demonstrated good short-term outcomes.[7,8] However, the small size of any individual South African cohort has limited statistical power to robustly describe associations with mortality for all markers of disease severity.[9-14] Furthermore, the lack of routinely collected national monitoring data means that South Africa has lagged behind other southern African countries in publishing programme outcomes, and more importantly, has no mechanism to assess the effectiveness of this enormous health service intervention.[9,15] South Africa could potentially generate valuable paediatric ART data, not only because of the size of the programme but also due to the uniform approach to treatment shaped by national guidelines, as well as good access to laboratory testing facilities, particularly viral load.

The International epidemiologic Databases to Evaluate AIDS (IeDEA) Southern Africa Collaboration includes 8 sites in South Africa providing paediatric ART at different levels of care in 3 provinces. More than 6 000 children had commenced ART at these sites by the end of 2007, representing >20% of children in the national programme at that time. This collaboration therefore provides a unique opportunity to examine the effectiveness of the South African paediatric ART programme and the extent to which national guidelines are being followed.

Our objectives were to describe for this combined cohort the outcomes of children receiving ART, factors associated with these outcomes, and the extent to which national programme guidelines are being followed.

Methods

Study, design, setting and population

Data for this cohort analysis were collected prospectively at sites and transferred anonymously to the IeDEA data centre in a standard format between May 2007 and February 2008. Each site has institutional ethical approval for contribution of data to IeDEA collaborative analyses.

HIV-infected, ART-naïve children with known gender and date of birth who initiated treatment with at least 3 antiretroviral drugs at age ≤16 years on a documented date between 1 June 1999 and 29 February 2008 were included. Sites where less than 25 children met these criteria were excluded.

Key variables

Information describing ART programmes was provided on standardised questionnaires by site representatives. Child characteristics included measures of disease severity (WHO stage, weight, height, haemoglobin (Hb), CD4 percentage or count, viral load) at ART initiation and at 6-monthly follow-up intervals, together with initiating regimen. CD4 percentage and absolute counts are reported, with the worst of these being used to determine whether the child was severely immunosuppressed according to WHO criteria.[16] Primary caregiver and exposure to prevention of mother-to-child transmission (PMTCT) regimens were recorded.

As sites changed from the WHO 3-stage to WHO 4-stage classification of disease severity during the latter half of 2004, all children with stage 3 or 4 disease under either system were considered to have clinically advanced disease.[17] Viral loads and CD4 counts were performed by local laboratories using standard methods. A viral load <400 copies/ml was considered undetectable. Sex- and age-standardised z-scores for weight and height were calculated for children ≤10 years at time of measurement using WHO 2007 growth reference standards.[18]

Sites provided data on known deaths and transfers out (TFO). Children were deemed lost to follow-up (LFU) if the last visit date was more than 6 months before date of closure of the site database, with the last visit date used as date of LFU.

Analysis

Kaplan-Meier estimates of mortality, LFU and TFO were determined. Cox proportional hazards models stratified by site were used to assess associations between baseline characteristics and mortality. Multivariate models were built by sequentially adding the next most significant predictor variable from univariate analysis, and variables with a p-value <0.1 after adjustment for those already in the model, or that changed the hazard ratio (HR) for variables in the model by more than 10%, were retained. Separate models were generated excluding the weight-for-age z-score (WAZs) as this could only be calculated for children ≤10 years of age, and viral load, as this is not routinely available in most resource-limited settings. Since Hb at ART initiation was only available for a third of children, this was excluded from the main model, but a separate model was generated to assess the effect of anaemia on mortality. Age was categorised as <12 months, 12 - 35 months and ≥36 months. WAZs were categorised as <–3, –3 to –2 and ≥–2, according to United Nations Children's Fund (UNICEF) definitions.[19] Viral load was categorised as ≤100 000, 100 000 to 1 million and >1 million copies/ml, and year of starting ART as ≤2005 and ≥2006 as these thresholds explained the largest amount of variability in mortality. Anaemia was defined as Hb <8 g/dl.

As these data include a substantial proportion of children who received ART through donor-funded programmes before commencement of National Department of Health provision on 1 April 2004, a sensitivity analysis was performed on descriptions of baseline characteristics and survival models with data limited to those children who started ART after 31 March 2004. All statistical analyses were performed using Stata version 10 (STATA Corporation, College Station, TX).

Results

Exclusions

Of the 8 South African IeDEA sites, 1 was excluded because the cohort comprised <25 children. The remaining data included 6 266 children on ART. Of these, 85 did not meet inclusion criteria due to missing or inconsistent baseline data. Non-naïve patients (N=39) and those commenced on <3 drugs (N=64) were excluded. The final data-set therefore comprised 6 078 children (49.1% female) from 7 sites with 9 368 child-years of follow-up, and median (interquartile range (IQR)) follow-up duration of 16 (6 - 29) months.

Contributing sites

Site characteristics are shown in Table I. Of note, sites are all urban and represent major centres in 3 provinces (Western Cape, Gauteng and KwaZulu-Natal); however, all levels of care

Table I. Characteristics of facilities providing ART

Cohort name and location	Main level of care provided	Type of clinic and payment	Target population	First year of ART provision	No. of children on ART	Median (IQR) age (mo.) of children at ART initiation	Number of children (%) <1 yr of age at ART initiation
Harriet Shezi Clinic, Soweto	All levels	Public and research, free ART	Children only	2001	2 183	55.9 (21.9 - 90.3)	328 (15.0)
Rahima Moosa, Mother and Child Hospital Johannesburg	All levels	Public, free ART	Children and pregnant women	1999	1 023	44.0 (15.9 - 84.4)	202 (19.8)
Red Cross Children's Hospital, Cape Town	Tertiary	Public and research, free ART	Children only	2001	839	16.1 (6.3 - 50.2)	351 (41.8)
Tygerberg Hospital, Cape Town	Tertiary	Public and, research free ART	Adults and children, separate clinics	2000	690	21.6 (8.5 - 59.0)	240 (34.8)
Khayelitsha Community Health Centre, Cape Town	Primary	Public, free ART	Adults and children, separate clinics	2001	650	41.7 (20.3 - 74.2)	94 (14.5)
Gugulethu Community Health Centre, Cape Town	Primary	Public and, research free ART	Adults and chil dren, separate clinics	2001	262	47.1 (18.3 - 82.4)	42 (16.0)
McCord Hospital, Durban	Secondary	Government-subsidised mission hospital, small co-payment	Adults and children, separate clinics	2003	431	72.4 (33.0 - 109.2)	33 (7.7)
Total					6 078		

are represented. There is a wide variation in the number of children being treated with ART at different sites, from >2 000 at a site providing all levels of care in Gauteng to <300 at a smaller primary care clinic in Cape Town. The median age of children from tertiary care sites is less than that of children from sites providing other levels of care (18.4 v. 51.9 months; $p<0.0001$).

Characteristics at ART start

Most children were severely ill with advanced clinical disease, immunosuppression, high viral load and impaired growth at the start of ART (Table II). The median (IQR) age of children commencing ART was 42.7 (14.7 - 82.5) months, with nearly 30% of children less than 18 months of age. The starting regimen included stavudine (d4T) and lamivudine (3TC) with either efavirenz or lopinavir/ritonavir (Kaletra) as the third drug for 81% of children.

Data were incomplete for many key variables. In particular, WHO stage was unknown for nearly a third of children, while caregiver and PMTCT exposure information was provided by only a few sites at which exposure status was still unknown for nearly 50%. Characteristics at start of ART were not substantially different when the data were limited to those initiating treatment after formal commencement of the national programme (N=5 601, results not shown).

Survival and retention in care

Mortality at 3 years was 7.7% (95% confidence interval (CI) 7.0 - 8.6%), and 81.4% (95% CI 80.1 - 82.6%) of children were alive and in care at 3 years (Fig. 1, a, b). There was rapid transfer from sites providing exclusively tertiary care to lower levels after the first 6 months of ART, with the tertiary cohort reduced by nearly 50% at 2 years (Fig. 1, c). LFU at 1 year increased from 2.2% (95% CI 1.1 - 4.7%) in those who commenced ART before 2004 to 8.2% (95% CI 7.1 - 9.4%) in those who commenced during or after 2006.

Mortality was higher for younger children, those with more advanced disease and those who were more severely immunosuppressed (Fig. 1). All markers of disease severity were independent predictors of mortality in multivariate analysis (Table III). Use of a protease inhibitor versus a non-nucleoside reverse transcriptase inhibitor as the third drug had no effect on mortality (p=0.572). Similarly, Hb <8 g/dl independently predicts mortality after adjustment for disease severity, age and programme year (adjusted hazard ratio 1.65; 95% CI 1.07 - 2.55%; p=0.024). Models excluding WAZ and viral load as predictors yielded similar results to the full model, as did models limited to those children treated after commencement of the national programme (results not shown).

Table II. Characteristics of children at ART initiation (*N*=6 078)

Year of ART start (%)	
≤2003	321 (5.3)
2004	1 076 (17.7)
2005	1 809 (29.8)
2006	1 707 (28.1)
≥2007	1 165 (19.2)
Female (%)	2 981 (49.1)
Age	
Median (IQR) age (mo.)	42.7 (14.7 - 82.5)
Less than 18 mo. (%)	1 758 (28.9)
WHO stage (%)	
1	263 (4.3)
2	745 (12.3)
3/4	3 073 (50.1)
WHO stage unknown	1 997 (32.9)
PMTCT exposure (%) (*N*=4 695)*	
Known exposed	596 (12.7)
Known unexposed	1 764 (37.6)
Exposure status unknown	2 335 (49.7)
Primary caregiver (%) (*N*=4 045)†	
Mother	2 449 (60.5)
Father	141 (3.5)
Grandmother	204 (5.0)
Other family	712 (17.6)
Other	123 (3.0)
Institution	225 (5.6)
Unknown	191 (4.7)
Laboratory measurements	
Median (IQR) CD4% by age group (*N*=4 592)	
≤11 mo. (*N*=1 045)	16.4 (10.0 - 23.6)
12 - 35 mo. (*N*=1 089)	13.0 (9.0 - 18.1)
36 - 59 mo. (*N*=712)	12.0 (7.2 - 16.5)
≥5 yrs (*N*=1 746)	10.0 (4.7 - 15.0)
Median (IQR) CD4 absolute count (cells/µl) by age group (*N*=4 852)	
≤11 mo. (*N*=1 062)	642 (280 - 1 132)
12 - 35 mo. (*N*=1 145)	636 (345 - 1 014)
36 - 59 mo. (*N*=750)	437 (251 - 691)
≥5 yrs (*N*=1 895)	435 (81 - 241)
Severely immunosuppressed (%) (*N*=4 934)‡	4 024 (81.6)
Median (IQR) log viral load (*N*=4 063)	5.36 (4.74 - 5.89)
Viral load >1million copies/ml (%) (*N*=4 063)	850 (20.9)
Haemoglobin <8 g/dl (%) (*N*=1 803)	220 (12.2)
Anthropometry§	
z-scores	
Median (IQR) weight-for-age z-score (*N*=3 892)	–1.89 (–3.20 - –0.93)
Median (IQR) height-for-age z-score (*N*= 3 690)	–2.39 (–3.37 - –1.44)
Median (IQR) weight-for-height z-score (*N*=3 186)	–0.46 (–1.73 - 0.55)
Weight-for-age z-scores (*N*=3 892)	
–3 - –2 (%)	747 (19.1)
<–3 (%)	1 096 (28.2)
Height-for-age z-score (*N*=3 690)	
–3 - –2 (%)	1 011 (27.4)
<–3 (%)	1 242 (33.7)
Weight-for-height z-score (*N*=3 186)	
–3 - –2 (%)	312 (9.8)
<–3 (%)	365 (11.5)
Regimen (%) (*N*=5 484)	
Most common regimens	
d4T+3TC+efavirenz	2 839 (51.8)
d4T+3TC+lopinavir/ritonavir¶	1 603 (29.2)
First NRTI	
d4T-based regimen	4 856 (88.5)
Third drug	
Lopinavir/ritonavir-based regimen‖	1 808 (33.0)
Ritonavir-based regimen	191 (3.5)
Regimen not recorded	594

*Data only available for Rahima Moosa, Harriet Shezi, Khayelitsha and Red Cross.

†Data only available for Rahima Moosa, Harriet Shezi and Red Cross; for Harriet Shezi caregiver information was collected at first visit – may be different from caregiver at ART start.

‡WHO criteria for severe immune suppression (CD4% <25 or CD4 count <1 500/µl if age ≤11months; CD4% <20 or CD4 count <750/µl if age between 12 and 35 months; CD4% <15 or CD4 count <350/µl if age between 36 and 59 months; CD4% <15 or CD4 count <200/µl if age ≥60 months.

§Only calculated for children ≤120 months (*N*=5 535).

¶Includes 201 children with additional ritonavir boosting.

‖Includes 214 children with additional ritonavir boosting.

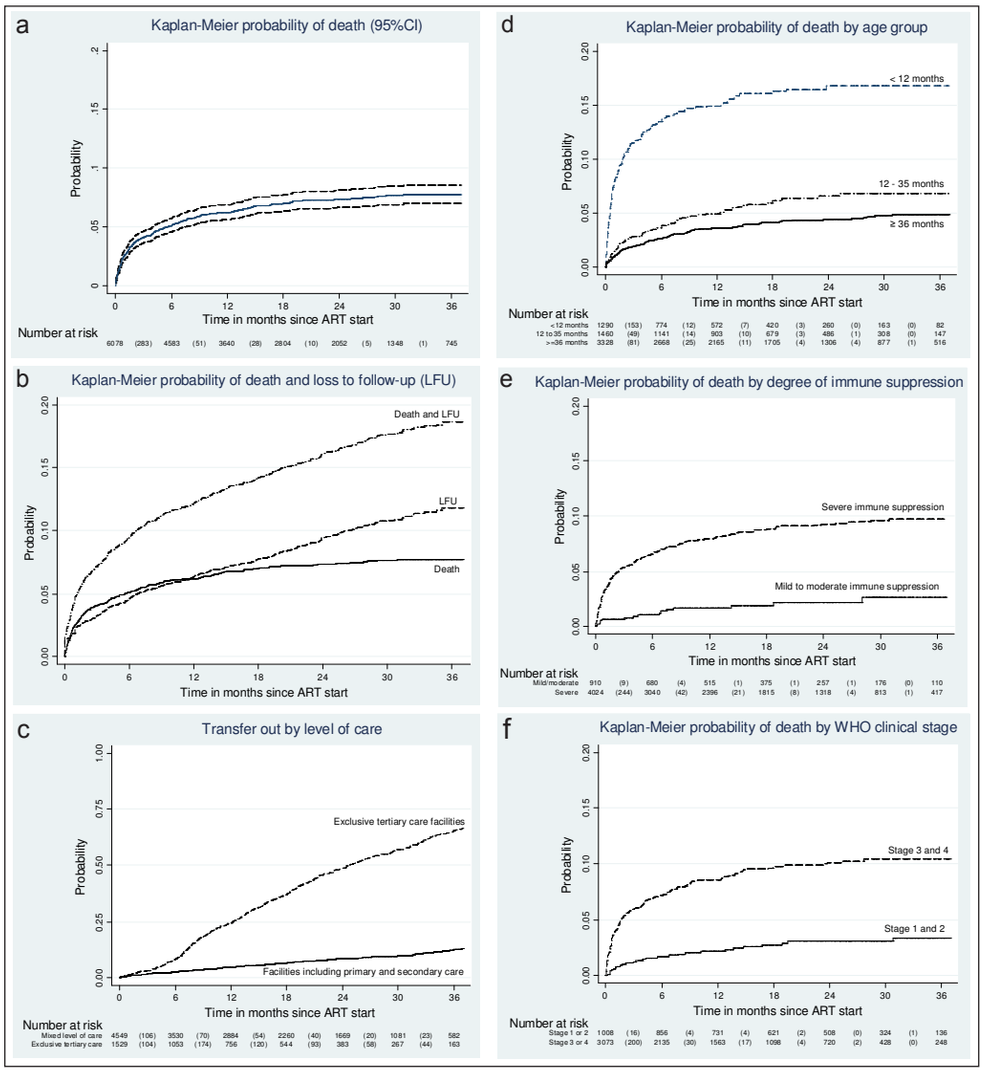


Fig. 1. Kaplan-Meier estimates for outcomes of (a) death, (b) death and loss to follow-up, and (c) transfer out. Kaplan-Meier estimates of mortality by (d) age group, (e) degree of immunosuppression and (f) WHO clinical stage.

Monitoring of viral and immune response to treatment

Follow-up measurements of CD4 and viral load are shown in Fig. 2. Notably, measurements of CD4 and viral load at 6-monthly intervals were available for over 80% and 75% of children respectively through to 36 months, with ≥80% of children virologically suppressed throughout (82.4% at 3 years; 95% CI 79.4 - 85.5%). The percentage (95% CI) of children severely immunosuppressed at 1 and 3 years dropped to 16.9% (15.4 - 18.3%) and 6.4% (4.2 - 8.6%), respectively.

Growth response to treatment

There was initial rapid weight gain from a median WAZ of –1.80 to –0.75 by 12 months, remaining relatively constant thereafter (Fig. 3). Height increased more slowly but was still increasing at 36 months, when a quarter of children still had a height-for-age z-score <–2.

Discussion

Main findings of the study

Outcomes of this cohort of ART-treated children in South Africa, the largest from a single country in Africa to date, were good with mortality of 7.7% and 81.1% of children alive and in care at 3 years. As expected, young age together with all markers of disease severity were independent predictors of mortality. These findings are strikingly similar to those of a similar combined cohort analysis of sub-Saharan paediatric ART programmes, the Kids' Antiretroviral Treatment in Lower-Incomes Countries (KIDS-ART-LINC) Collaboration.[8] Furthermore, follow-up monitoring of laboratory parameters was excellent, with more than 75% of children tested 6-monthly according to national guidelines. Although comparisons with rich countries are difficult owing to the older age of ART commencement in the South African children and inherent survival bias, the high level of virological suppression is encouraging and compares favourably with cohorts from Europe[20] and North America[21] and other African studies.[7,14] Similarly, children remaining in care experienced dramatic improvements in growth and immune status. While the proportion and absolute number of nearly 2 000 very young children accessing ART are much greater than in most other African studies, across the country older children are still preferentially accessing treatment with more than 70% of the cohort being over 18 months of age.[7,8,22]

Strengths and generalisablity of findings

This study is valuable because of the large number of children and length of follow-up, but particularly because of the high

Table III. Predictors of mortality using Cox-proportional hazards model stratified by site (adjusted for year of ART start)

Characteristic at ART start	Crude HR	95% CI	*p*-value	Adjusted HR Full model (*N*=2 449)	95% CI	*p*-value
WAZ			<0.001*			<0.001*
>–2	1			1		
–3 - –2	1.93	1.29 - 2.89		1.13	0.69 - 1.87	
< –3	5.23	3.84 - 7.12		2.44	1.65 - 3.59	
Viral load (copies/ml)			<0.001*			0.010*
<100 000	1			1		
100 000 to 1 million	1.75	1.24 - 2.45		1.68	1.02 - 2.76	
>1 million	3.30	2.32 - 4.70		2.22	1.31 - 3.77	
Severe immunosuppression (WHO definition)	4.23	2.55 - 7.00	<0.001	3.83	1.68 - 8.72	0.001
WHO stage 3 or 4 (v. 1 or 2)	3.01	2.00 - 4.54	<0.001	2.16	1.28 - 3.62	0.004
Age			<0.001*			0.002*
>3 yrs	1			1		
1 - 3 yrs	1.31	0.98 - 1.74		1.17	0.76 - 1.84	
<1 yr	3.38	2.65 - 4.31		2.00	1.30 - 3.07	
ART commenced before 2006	1.28	1.02 - 1.60	0.036	1.68	1.18 - 2.39	0.004

p-values derived from likelihood ratio tests.

absolute number of those under 18 months of age. With new WHO guidelines encouraging early ART initiation in infants, a better understanding of clinical outcomes in this age group is required.[3] In addition, the availability of regular viral load information is unusual in the African context. Inclusion of children from a number of different sites in 3 provinces and at different levels of care enhances representivity, while uniformity of treatment protocols lends itself to collation into a single analysis.

Limitations

Although the study includes some of the busiest routine public sector clinics, it should be acknowledged that IeDEA collaboration sites must have capacity for electronic collection of routine data, which is not the norm. Some high-burden provinces are not included in the study, and there is disproportionate representation of sites with tertiary care capacity. The thorough monitoring and high number of infants on ART therefore probably represent best-practice examples in well-resourced clinics.

While LFU in this study is relatively low compared with adult publications of routine cohort data,[23] there is variation in LFU at different sites. This is of concern as many of those who are LFU are likely to have died, resulting in under-ascertainment of mortality. Indeed, while there are various plausible explanations for the apparent protective effect on mortality of starting ART after 2005 (including that children starting earlier are 'sicker' in ways not captured by markers of disease severity available for this analysis), the contribution of increasing LFU in later years as programmes expand should not be underestimated. In this respect, the effect of choice of first drug (zidovudine v. stavudine) on mortality could not be definitively assessed owing to changes in prescribing patterns after the introduction of national treatment guidelines in 2004 and increasing LFU over time. The high transfer rate from tertiary sites to lower levels of care limits duration of follow-up for these patients. Systems of data collection integrated across sites are needed to ascertain outcomes for transferred patients.

Poor integration of health information systems is also reflected in the paucity of PMTCT exposure data. This reflects poor integration of antenatal, routine child care and HIV services themselves within the health system, a major barrier to timeous HIV diagnosis and referral for care of those infants infected despite PMTCT exposure.[7,22,24] Completeness and accuracy of other exposure variables is also limited, while historical changes in the WHO staging system limit its value as a measure of disease advancement.

Reflections on the South African national paediatric ART programme

This study indicates that the programme is successful *for those children who access it*. The latter caveat is important, as the fact that 20% of all children are treated at a handful of sites, all in large urban centres, suggests that considerable inequities in access are likely. Nevertheless the fastidious monitoring, utilisation of first-line regimens recommended in national guidelines, good survival, high proportions of children with viral suppression and favourable immune and growth responses – at least at these sites – are encouraging. The Western Cape has the specific aim of treating children at their nearest health centre whenever possible, with only those warranting specialist care remaining at tertiary facilities.[24]

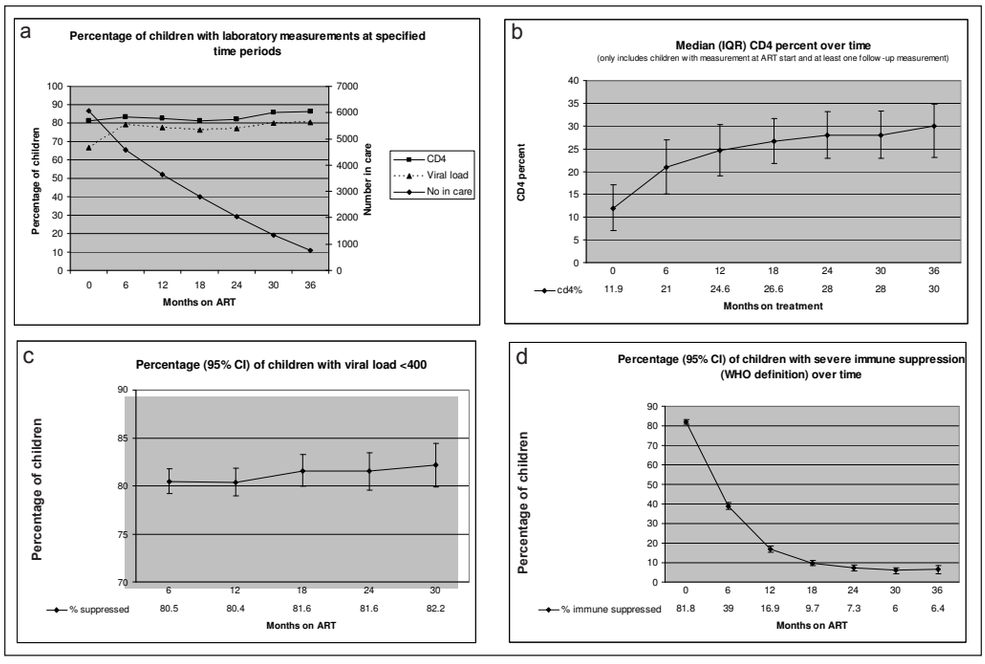
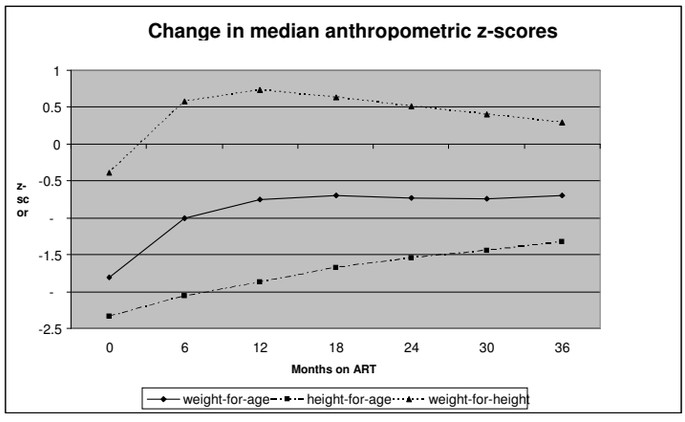


Fig. 2. Immune and virological response to ART.



Change in anthropometric z-scores during ART

Months on ART	0	6	12	18	24	30	36
No. in care <10 years of age*	5 535	4 009	3 063	2 357	1 739	1 185	653
Median weight-for-age	−1.81	−1.00	−0.75	−0.70	−0.73	−0.74	−0.69
IQR	−2.97 to −0.87	−1.75 to −0.20	−1.48 to 0.00	−1.43 to 0.00 1	−1.42 to −0.07	−1.39 to −0.10	−1.30 to −0.09
N†	2 966	2 893	2 105	543	1 095	725	350
Median height-for-age	−2.34	−2.06	−1.87	−1.66	−1.54	−1.44	−1.32
IQR	−3.28 to −1.43	−2.89 to −1.20	−2.64 to −1.08	−2.42 to −0.92	−2.27 to −0.82	−2.13 to −0.76	−2.02 to −0.60
N†	2 732	2 639	1 925	1 382	970	637	281

*z-scores only calculated for children <10 years at time of measurement.
†Only includes children with measurement at ART start and at least one follow-up measurement.

Fig. 3. Growth response to ART (only includes children with measurement at ART start and at least one subsequent measurement).

In this respect, the rapid transfer of children from exclusive tertiary to primary care sites, together with the difference in ages of children starting ART at different levels of care, indicate that children are indeed receiving care at the appropriate level.

Although the cohort includes several infants, the number is negligible compared with the estimated 64 000 new infections that occur perinatally and through breastfeeding every year.[25] Together with lack of integration of antenatal PMTCT and paediatric HIV services, perceived and actual lack of expertise in the care of young HIV-infected infants pose significant barriers to access for infants, who are still largely cared for at tertiary sites. These problems need to be addressed urgently if South Africa seeks to implement revised WHO guidelines recommending early ART for infants irrespective of disease severity.[3]

In this respect it should be noted that the relatively poor outcomes for infants in this study would not necessarily be the scenario should infant ART initiation be prioritised. Disease progression is rapid in HIV-infected infants, and in this study children commencing ART at a young age are those whose disease progressed rapidly enough to meet previous WHO disease severity criteria while they were still young *and* who were able to access treatment before otherwise inevitable early death.[26] Better outcomes for older children represent a survivor effect, with older age at ART initiation being a proxy for slower disease progression. In contrast, other South African studies have shown excellent outcomes for infants commencing ART before disease progression.[27,28]

Conclusion

This study of a substantial proportion of the South African national ART programme for children demonstrates the dramatic

clinical benefit for those accessing the programme. The higher mortality in infants and young children and those with advanced disease highlights the need to identify HIV-infected infants and commence ART before disease progression.

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IeDEA Southern Africa Steering Group

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