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Geoffrey Fatti, MBChB, MPH,* † Peter Bock, MBChB, MRCP, MRCGP, MPH,* † Brian Eley, MBChB,‡ Eula Mothibi, MBChB, FCP,* and Ashraf Grimwood, MBChB, MPH*

Background: Few studies describe temporal trends in pediatric antiretroviral treatment (ART) programs in sub-Saharan Africa. Adult studies show deteriorating patient retention in recent years. We describe temporal trends in baseline characteristics and treatment outcomes amongst ART-naive children between 2004 and 2009 at 30 facilities in 4 South African provinces.

Methods: Linear trend in baseline parameters between annual enrolment cohorts was assessed. Corrected mortality estimates were calculated, correcting for deaths amongst those lost to follow-up using probability-weighted Kaplan–Meier functions. On-treatment immunologic changes were modelled using generalized estimating equations.

Results: Three thousand seven children (median age 6.4 years) were included. Monthly enrollment increased from 1.9 children in 2004 to 106 in 2009. Proportions with severe baseline immunodeficiency decreased from 85.5% to 64.5% between 2004/2005 and 2009, \( P < 0.0005 \). Proportions with baseline World Health Organization clinical stages III and IV reduced from 72.9% to 49.0% between 2006 and 2009, \( P < 0.0005 \). Later calendar cohorts had independently and progressively reduced on-treatment probabilities of severe immunodeficiency despite adjusting for baseline immunologic status, adjusted odds ratio: 0.38 [confidence interval (CI): 0.26 to 0.55; \( P < 0.0005 \); 2008/2009 compared with 2004/2005]. After 24 months, corrected mortality was 6.1% (CI: 5.1% to 7.3%) and lost to follow-up was 6.8% (CI: 5.7% to 8.2%), with no deterioration amongst more recently enrolled cohorts (\( P = 0.50 \) and \( P = 0.55 \), respectively). After 4 years, program retention was 84.1% (CI: 80.9% to 86.7%).

Conclusions: Children’s baseline condition when starting ART has improved considerably. Improving immunological treatment outcomes, the high medium-term patient retention with lack of temporal deterioration despite rapid patient number increases, provide evidence that pediatric ART programs are increasingly effective for those accessing them. However, children must start treatment when younger, following current international guidelines.

Key Words: antiretroviral therapy, baseline characteristics, children, program outcomes, South Africa, temporal trends

INTRODUCTION

South Africa has the largest pediatric antiretroviral treatment (ART) program in the world, with 86 000 children <15 years of age receiving treatment by October 2009; at least 3-fold more children than in any other country. South African guidelines have recently extended ART eligibility to include HIV-positive infants younger than 1 year of age irrespective of CD4 cell count or clinical stage. Despite this progress, 46% of ART eligible children are still not receiving treatment, and there are considerable inequities in ART provision and treatment outcomes between different areas of the country. Due to a lack of routinely collected monitoring data, South Africa has not been able to report national pediatric treatment outcomes, and there are few large cohorts that have published ART program outcomes. The absolute number and proportion of infants starting ART have also been low, particularly in light of the 43,000 estimated new infections acquired perinatally or through breast milk, annually. Although pediatric ART programs have demonstrated favorable results in low-income countries with excellent patient adherence, loss to follow-up (LTFU) and early mortality have been shown to be substantial. Reports of significant numbers of children experiencing virologic failure have also recently emerged. Adult cohorts of patients on ART have also shown deterioration in patient retention in more recent years in South Africa due to increasing levels of LTFU as the number of patients on ART has increased. Few reports have yet described temporal trends in ART program patient characteristics and outcomes in southern Africa because the ART roll-out commenced. However, this information is valuable to be able to evaluate progress and identify areas for improvement in ART program effectiveness.

This study describes temporal trends in baseline characteristics and programmatic outcomes amongst children starting ART at 30 government ART facilities in 4 provinces, more than the first 5 years of the South African ART program roll-out.
out between 2004 and 2009. Specifically, it was assessed whether pediatric ART program outcomes have worsened over time as the number of children on treatment has increased.

METHODS

Study Design, Setting, and Participants

A retrospective cohort study of ART-naive children starting ART was conducted at routine government health care facilities supported by Kheth’Impilo (previously Absolute Return for Kids), a nongovernmental organization (NGO) that supports the South African department of health in the scale-up of ART programs. The NGO provides clinical staff, infrastructure, capacity development, a community-based adherence–support program, and electronic data collection systems at these sites. Facilities were distributed across 4 provinces (Western Cape, KwaZulu-Natal, Eastern Cape, and Mpumalanga) were situated in both urban and rural areas, with 12 facilities being secondary-level hospitals and 18 being primary health care (PHC) clinics. All facilities offered free health care for patients and treated both adults and children. The vast majority of patients accessing care at all levels of the health care system are impoverished, with unemployment rates ranging from 21%–28% in these provinces in 2010.21

All ART-naive children (<16 years of age) enrolled on ART between January 1, 2004, and September 30, 2009, with documented date of birth, gender, and date of starting ART, who had initiated triple combination ART, had at least 1 day of follow-up time, who were enrolled at least 6 months before site database closure and in whom follow-up data were available, were included in the analyses. Facilities that enrolled <20 children were excluded from the analysis.4 Time was measured from the date of starting ART until the earliest of date of last clinic appointment (for patients dying, LTFU, or transferring to other facilities), NGO exit from a site, March 31, 2010 or 48 months of ART.

Children were selected to start ART according to the South African national department of health guidelines.22 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 more than 18 months old), or recurrent or prolonged hospitalization were eligible for ART. Additionally, children were required to have an identifiable adult caregiver who could administer the medication.

First-line ART consisted of 2 nucleoside reverse transcriptase inhibitors plus a nonnucleoside reverse transcriptase inhibitor for those aged older than 3 years or a protease inhibitor (PI) for those younger than 3 years. PI-containing regimes were used for children who were exposed to perinatal nevirapine. Children requiring ART and tuberculosis (TB) medication where treated according to national guidelines.22 For young children (<3 years) treated with PI-containing regimens, ritonavir at standard doses was the preferred PI between 2005 and 2007. After 2007, coformulated lopinavir/ritonavir boosted with additional ritonavir became the standard approach for overcoming the metabolic effect of rifampicin.23

Outcome Measures and Definitions

Outcome measures were death, LTFU, virological suppression, CD4 cell percentage, and proportions of children with severe immunodeficiency. LTFU was defined as no clinic visit by a patient for 3 months after the last scheduled appointment was missed. Children who missed appointments would initially be traced by telephone and in certain cases, dependent on community health worker availability, and if prior consent was obtained, a community health worker or district tracing team would visit the client’s house.

To ascertain deaths amongst patients classified as 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. Severe immunodeficiency was defined by age-specific CD4 percentage and CD4 cell count according to the 2006 WHO guidelines.24 Virologic suppression was defined as a viral load <400 copies per milliliter. Laboratory monitoring was performed by the National Health Laboratory Services using the Panleucogating method (CD4 cell count)25 and the Nuclisens HIV1 QT assay (bioMerieux, Marcy-Etiole, Rhone, France) (viral load).

Data Collection

Individual-level patient data were collected prospectively for routine monitoring purposes by designated site-based datacapturers at each patient visit using custom-designed electronic databases. Data were merged 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. The study was approved by the University of Cape Town Research Ethics committee.

Statistical Analyses

Linear trends in baseline characteristics between annual enrollment cohorts were assessed using the Cochrane-Armitage and Cuzick nonparametric tests for proportions and medians, respectively. Kaplan–Meier estimates of time till death and LTFU were calculated. Corrected mortality estimates were derived using probability-weighted Kaplan–Meier functions, to correct for patients who were LTFU but had died, by weighting those patients who were LTFU at facility level for whom a definitive outcome could be established from the national death registry, to represent all patients who were LTFU.26 The log-rank test was used to compare groups. As the 2004 enrollment cohort was small, this cohort was combined with the 2005 cohort for analyses.
Multivariable Cox proportional hazards regression was used to analyze the association between annual enrolment cohorts and death (based on the weighted data) and LTFU after starting ART, adjusting for baseline variables (age, gender, WHO clinical stage, weight for age Z score (WAZ), immunological status, baseline tuberculosis treatment, initial regimen, province, hospital/PHC site, rural/urban nature of site), and accounting for heterogeneity between individual site cohorts. The covariates selected were a priori specified potential confounders that formed part of routine data collection. Virological suppression was analyzed using proportions of children achieving viral suppression at 6-monthly intervals on ART using the Cochrane-Armitage and Pearson χ² tests.

Multivariable generalized estimating equation repeated-measures analyses accounting for intraindividual correlation through an exchangeable correlation matrix were used to analyze the association between annual enrolment cohorts and proportions of children with severe immunodeficiency until 24 months of ART, adjusting for the same set of covariates as for the Cox models. Robust standard errors and a logit link function were employed. For multivariable analyses, missing baseline WHO stage and WAZ variables were considered as separate categories within these variables. Statistical analyses were performed using Stata 11.1 (Stata Corporation, College Station, TX).

RESULTS

Database records for a total of 6442 children <16 years of age were screened for eligibility for the study. Children excluded were 1134 children who commenced ART within 6 months of closure of the site database, 1381 who were documented as being ART experienced, 570 from 2 sites that had incomplete follow-up data, 269 who had zero days of follow-up time, and 81 children at 23 sites that enrolled <20 children. Thus, 3007 ART-naive children from 30 facilities were included in analyses. PHC clinics enrolled 1436 (47.8%) children, with the remainder enrolled at hospital-based facilities.

Between 2004 and 2009, the number of NGO-supported facilities that enrolled children increased 12-fold, and the mean number of children enrolled per month increased substantially from 1.9 to 106.1 (Fig. 1). The median age when starting treatment increased slightly from 5.8 years (IQR: 3.0–8.4) to 6.7 years (IQR: 3.4–9.9) between 2004/2005 and 2009 (P = 0.032), as the proportion of children aged 10 years and over increased from 15.3% [95% confidence interval (CI): 10.2% to 21.6%] to 24.8% (95% CI: 22.1% to 27.6%) during this time, P = 0.0035 (Table 1). However, the proportion of children aged under 18 months starting treatment increased between 2006 and 2009 from 6.8% (95% CI: 4.5% to 9.7%) to 10.8% (95% CI: 8.9% to 12.9%), P = 0.040.

The proportion of children with advanced clinical stage disease (WHO stages III and IV) decreased from 72.9% to 49.0% between 2006 and 2009, P < 0.0005. (In the 2004/2005 cohort, 50.9% of children had advanced clinical stage disease, being a deviation from the trend apparent between 2006 and 2009). The median CD4 cell percentage increased from 10.8 (IQR: 7.0–14.2) to 13.0 (IQR: 8.0–18.0) between 2004/2005 and 2009 (P = 0.007), and the proportion of children with severe immunodeficiency decreased substantially from 85.5% to 64.5% (P < 0.0005) over this period (Fig. 1).

The proportion of children recorded as taking TB treatment when starting ART increased from 0.6% to 5.2% between 2004/2005 and 2009 (P = 0.0014). The proportion of children starting PI-based regimens decreased from 20.6% in 2006 to 16.9% in 2009 (P = 0.040), reflecting the increase in median age and the South African guideline recommendation to start PI-based therapy in younger children. The proportion of children starting regimens containing zidovudine decreased from 10.7% to 6.9% between 2004/2005 and 2009 (P = 0.0056), as children taking stavudine-based regimens increased from 89.4% to 93.1% over the corresponding period.

The total observation time was 4209 person-years. Using facility level data, 99 (3.3%) children died and 146 (4.9%) became LTFU during the study period. Amongst those children LTFU, 68 (46.5%) had a valid civil identification number, of whom 23 (33.8%) were registered as deceased in the national registry by November 2010. After 2 years of ART, mortality using facility-level data was 3.9% (95% CI: 3.1% to 4.8%), corrected mortality based on the weighted dataset was 6.1% (95% CI: 5.1% to 7.3%), LTFU was 6.8% (95% CI: 5.7% to 8.2%), and program retention was 89.6% (95% CI: 88.1% to 91.0%), with no differences between annual enrollment cohorts for any of the outcomes (P = 0.75; P = 0.50; P = 0.55; P = 0.75, respectively) (Table 2). After 4 years of ART, corrected mortality was 10.7% (95% CI: 8.3% to 13.7%), and retention in care was 84.1% (95% CI: 80.9% to 86.7%; 125 children remaining in care).

Multivariable analyses adjusted for baseline variables confirmed that corrected mortality and LTFU were equivalent between annual enrolment cohorts (adjusted hazard ratio: 0.91 (95% CI: 0.77 to 1.08, P = 0.23; and adjusted hazard...
TABLE 1. Characteristics of Children Starting ART by Calendar Year of Initiation

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>2004/2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of children, n (%)‡</td>
<td>3007</td>
<td>170 (5.7%)</td>
<td>385 (12.8%)</td>
<td>501 (16.7%)</td>
<td>996 (33.1%)</td>
<td>955 (31.7%)</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>1466 (48.8%)</td>
<td>82 (48.2%)</td>
<td>174 (45.2%)</td>
<td>249 (49.7%)</td>
<td>491 (49.3%)</td>
<td>470 (49.2%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>6.4 (3.5–9.6)</td>
<td>5.8 (3.0–8.4)</td>
<td>6.2 (3.7–9.1)</td>
<td>6.5 (3.7–9.7)</td>
<td>6.5 (3.4–9.7)</td>
<td>6.7 (3.4–9.9)</td>
<td>0.032</td>
</tr>
<tr>
<td>WHO clinical stages III &amp; IV, n (%) (n = 1945)</td>
<td>1105 (56.8%)</td>
<td>82 (50.9%)</td>
<td>231 (72.9%)</td>
<td>225 (59.8%)</td>
<td>328 (54.4%)</td>
<td>239 (49.0%)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>WHO clinical stages III &amp; IV, n (%) (n = 1957)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>WAZ score, mean (95% CI) (n = 1957)</td>
<td>–1.5 (–1.59 to –1.46)</td>
<td>–1.67 (–1.90 to –1.43)</td>
<td>–1.47 (–1.64 to –1.31)</td>
<td>–1.53 (–1.67 to –1.39)</td>
<td>–1.45 (–1.57 to –1.39)</td>
<td>–1.61 (–1.74 to –1.49)</td>
<td>0.83</td>
</tr>
<tr>
<td>WAZ score &lt; –3, n (%) (n = 1957)</td>
<td>318 (16.3%)</td>
<td>29 (19.6%)</td>
<td>41 (14.5%)</td>
<td>59 (15.5%)</td>
<td>109 (16.7%)</td>
<td>80 (16.3%)</td>
<td>0.92</td>
</tr>
<tr>
<td>CD4 cell %, median (IQR) (n = 1505)</td>
<td>12 (7–17)</td>
<td>10.8 (7.0–14.2)</td>
<td>11.5 (6.9–18)</td>
<td>11.9 (6.6–15.5)</td>
<td>12 (7.0–17.7)</td>
<td>13.0 (8.0–18.0)</td>
<td>0.007</td>
</tr>
<tr>
<td>Severe immunodeficiency, n (%) (n = 2427)</td>
<td>1681 (69.3%)</td>
<td>136 (85.5%)</td>
<td>229 (72.7%)</td>
<td>312 (76.1%)</td>
<td>540 (65.5%)</td>
<td>464 (64.5%)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Proportion on TB treatment at ART start, n (%) (n = 2681)</td>
<td>105 (3.9%)</td>
<td>1 (0.6%)</td>
<td>10 (2.7%)</td>
<td>14 (3.1%)</td>
<td>38 (4.3%)</td>
<td>42 (5.2%)</td>
<td>0.0014</td>
</tr>
<tr>
<td>PI-based initial regimen, n (%) (n = 2798)</td>
<td>509 (18.2%)</td>
<td>32 (18.9%)</td>
<td>76 (20.6%)</td>
<td>100 (22.2%)</td>
<td>151 (16.4%)</td>
<td>150 (16.9%)</td>
<td>0.040</td>
</tr>
<tr>
<td>d4t-based regimen, n (%) (n = 2798)</td>
<td>2622 (93.7%)</td>
<td>151 (89.4%)</td>
<td>326 (88.3%)</td>
<td>436 (96.7%)</td>
<td>883 (95.8%)</td>
<td>826 (93.1%)</td>
<td>0.0056</td>
</tr>
<tr>
<td>ZDV included in initial regimen, n (%) (n = 2798)</td>
<td>176 (6.3%)</td>
<td>18 (10.7%)</td>
<td>43 (11.7%)</td>
<td>15 (3.3%)</td>
<td>39 (4.2%)</td>
<td>61 (6.9%)</td>
<td>0.0056</td>
</tr>
</tbody>
</table>

*The Cochran-Armitage and Cuzick nonparametric tests of trend were used to compare proportions and medians, respectively.
†Proportion of total children included.
‡Proportion of children with available values.
ZDV, zidovudine; d4t, stavudine.

The proportion of children achieving virological suppression after 6 and 12 months of ART were 83.0% (95% CI: 80.8% to 85.1%; n = 1203) and 79.7% (95% CI: 76.6% to 82.6%; n = 725) respectively, with no differences between annual enrollment cohorts (P = 0.52 and P = 0.35, respectively) (Table 2). Children aged more than 2 years of age at the start of treatment had significantly better virological suppression, being 81.8% (95% CI: 80.2% to 83.3%; n = 2504) at 12 months.

TABLE 2. ART Programmatic Outcomes by Calendar Year Cohort of Children Starting ART

<table>
<thead>
<tr>
<th></th>
<th>2004/2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-Month corrected mortality, % (95% CI)‡</td>
<td>3.0 (1.3 to 7.1)</td>
<td>2.7 (1.5 to 5.0)</td>
<td>4.0 (2.6 to 6.2)</td>
<td>5.1 (3.9 to 6.7)</td>
<td>3.7 (2.4 to 5.6)</td>
<td>0.50</td>
</tr>
<tr>
<td>24-Month corrected mortality, % (95% CI)‡</td>
<td>5.7 (3.0 to 10.7)</td>
<td>4.5 (2.7 to 7.3)</td>
<td>6.5 (4.5 to 9.4)</td>
<td>6.1 (4.7 to 7.9)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>12-Month facility based LTFU, % (95% CI)‡</td>
<td>2.5 (1.0 to 6.4)</td>
<td>5.1 (3.3 to 7.9)</td>
<td>4.2 (2.7 to 6.4)</td>
<td>3.5 (2.5 to 5.0)</td>
<td>3.4 (2.1 to 5.5)</td>
<td>0.55</td>
</tr>
<tr>
<td>24-Month facility based LTFU, % (95% CI)‡</td>
<td>6.4 (3.5 to 11.5)</td>
<td>7.9 (5.4 to 11.2)</td>
<td>7.2 (5.1 to 10.1)</td>
<td>6.2 (4.3 to 8.9)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>12-Month retention, % (95% CI)‡</td>
<td>94.6 (90.0 to 97.2)</td>
<td>92.6 (89.5 to 94.9)</td>
<td>93.6 (91.1 to 95.5)</td>
<td>92.8 (90.1 to 94.3)</td>
<td>93.8 (91.5 to 95.6)</td>
<td>0.75</td>
</tr>
<tr>
<td>24-Month retention, % (95% CI)‡</td>
<td>89.7 (83.9 to 93.5)</td>
<td>89.3 (85.6 to 92.1)</td>
<td>90.1 (86.7 to 92.6)</td>
<td>89.7 (86.9 to 91.9)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>6-Month viral load suppression, % (95% CI)‡</td>
<td>85.4 (77.1 to 91.6)</td>
<td>83.0 (77.6 to 87.5)</td>
<td>80.6 (74.8 to 85.7)</td>
<td>85.2 (81.1 to 88.6)</td>
<td>81.1 (75.9 to 85.6)</td>
<td>0.52</td>
</tr>
<tr>
<td>12-Month viral load suppression, % (95% CI) (n = 1203)‡</td>
<td>74.7 (64.7 to 83.1)</td>
<td>82.3 (76.1 to 87.1)</td>
<td>80.3 (72.6 to 86.6)</td>
<td>80.5 (75.3 to 85.1)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>CD4 Percentage increase (0–6 months), median (IQR) (n = 805)</td>
<td>9.5 (4.8 to 13.8)</td>
<td>8.0 (4.0 to 12.4)</td>
<td>7.6 (4.1 to 11.2)</td>
<td>8.0 (3.3 to 13.3)</td>
<td>8.0 (4.0 to 13.0)</td>
<td>0.72</td>
</tr>
<tr>
<td>CD4 Percentage increase (6–12 months), median (IQR) (n = 481)</td>
<td>4.0 (0.0 to 7.5)</td>
<td>3.1 (–0.2 to 7.0)</td>
<td>2.7 (–0.4 to 5.1)</td>
<td>4.0 (–1.0 to 7.9)</td>
<td>3.0 (–3.0 to 8.0)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

*The log-rank test was used to compare cohorts for mortality, LTFU, and retention. Pearson χ² test was used to compare viral load suppression. The Kruskal–Wallis test was used to compare CD4 percentage increases.
†Greenwood point-wise confidence intervals.
‡Binomial exact confidence intervals.
TABLE 3. Generalized Estimating-Equation Model of Factors Associated With On-Treatment Severe Immunodeficiency Between Months 6–24 After Starting ART*

<table>
<thead>
<tr>
<th>Patient Factor</th>
<th>Adjusted Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>1.30</td>
<td>1.04–1.61</td>
<td>0.017</td>
</tr>
<tr>
<td>Year of enrollment</td>
<td>2004/2005</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2006/2007</td>
<td>0.56 (0.40–0.79)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>2008/2009</td>
<td>0.38 (0.26–0.55)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Baseline age</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>2 years and over</td>
<td>1.64 (1.11–2.41)</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>&lt;2 years</td>
<td></td>
<td></td>
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<tr>
<td>Baseline WHO clinical stage</td>
<td>I/II</td>
<td>1</td>
<td></td>
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<tr>
<td></td>
<td>III/IV</td>
<td>1.11 (0.88–1.42)</td>
<td>0.44</td>
</tr>
<tr>
<td>Severe baseline immunodeficiency</td>
<td></td>
<td>6.43 (4.35–9.49)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Baseline WAZ score</td>
<td></td>
<td>&gt;−2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>−3 to −2</td>
<td>1.14 (0.84–1.56)</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>−3</td>
<td>1.45 (1.03–2.03)</td>
<td>0.030</td>
</tr>
<tr>
<td>Tuberculosis (baseline)</td>
<td></td>
<td>1.05 (0.70–1.59)</td>
<td>0.79</td>
</tr>
<tr>
<td>PT-based initial regimen</td>
<td></td>
<td>0.99 (0.69–1.41)</td>
<td>0.97</td>
</tr>
<tr>
<td>ZDV-based initial regimen</td>
<td></td>
<td>0.82 (0.58–1.16)</td>
<td>0.27</td>
</tr>
<tr>
<td>Duration of ART</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>1.61 (0.39–6.43)</td>
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<tr>
<td></td>
<td>12 months</td>
<td>0.49 (0.39–0.60)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td></td>
<td>24 months</td>
<td>0.23 (0.17–0.30)</td>
<td>&lt;0.0005</td>
</tr>
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*(n = 2680 children having 3245 immunological values). Odds ratios are adjusted for all variables displayed. Severe immunodeficiency was defined by age-specific CD4 percentage and CD4 cell count according to WHO guidelines.

ZDV, zidovudine.

The median increase in CD4 percentage after 6 months of treatment was 8.0% (IQR: 4.0% to 13.0%), with increases being equivalent between annual cohorts (P = 0.72). Compared with the 2004/2005 cohort, however, the proportions of children with severe immunodeficiency on treatment were significantly lower for more recently enrolled cohorts (Fig. 2). Severe immunodeficiency at 6 months of ART reduced from 38.0% to 20.8% between 2004/2005 and 2009 (P trend = 0.0001) and after 12 months of ART from 31.0% to 0.55; P = 0.0053. In multivariable analyses of associations with severe on-treatment immunodeficiency (between months 6 and 24 of ART), adjusted for baseline immunological, clinical, demographic variables and duration of ART, children enrolled in later years had independently and progressively reduced probabilities of severe immunodeficiency compared with the 2004/2005 cohort; adjusted odds ratio 0.38 (95% CI: 0.26 to 0.55; P < 0.0005 for the 2008/2009 cohort); Table 3. Children with severe immunodeficiency at baseline had a 6-fold higher probability of having severe immunodeficiency on treatment. Males, children under 2 years of age, and children with baseline WAZ scores below −3 also had independently raised probabilities of severe immunodeficiency on treatment. The proportion with severe immunodeficiency reduced dramatically during the first 6–12 months of treatment and continued to decrease more gradually thereafter. No association with initial ART regimen was apparent.

When stratifying patient outcomes between hospitals and PHC clinics, hospitals had higher corrected mortality; 7.1% (95% CI: 5.7% to 8.7%) versus 4.7% (3.4% to 6.4%) at PHC clinics, after 2 years of ART, P = 0.036. LTFU was, in contrast, reduced at hospitals, being 5.4% (95% CI: 4.1% to 7.1%) versus 8.3% (95% CI: 6.5% to 10.6%) at PHC clinics, P = 0.012. Overall patient retention was similar between facilities; 90.4% (95% CI: 88.4% to 92.1%) at hospitals versus 88.7% (95% CI: 86.2% to 90.7%) at PHC clinics, after 2 years of ART, P = 0.38. Virological suppression was equivalent between hospitals (80.6%) and clinics (79.2%) after 12 months of ART (P = 0.65). CD4 percentage increases were also equivalent, being 11.5% (IQR: 6.0%–18.0%) at hospitals and 11.0% (IQR: 6.8%–17.0%) at PHC clinics, P = 0.53, after 12 months of ART.

**FIGURE 2.** Proportion of children with severe immunodeficiency in calendar cohorts by duration of treatment with ART. *Error bars are 95% confidence intervals.

**DISCUSSION**

This study is among the first to describe temporal trends in baseline characteristics and program outcomes in a large multisite pediatric cohort in Southern Africa, over the first 5 years of the South African government roll-out of ART. The baseline clinical and immunological condition of children enrolling for ART have shown considerable improvement over time as the ART program has expanded in the country. After starting treatment, children enrolled in more recent years had greater improvement in immunological status compared with children enrolled near the start of the ART program. The high patient retention, with 84% of children remaining in care after 48 months of ART compares very favorably with other cohorts from the region, and the lack of temporal deterioration despite rapid increases in the number of children enrolled contrasts with adult cohorts in
specifically, LTfu has not increased amongst children in more recent years as was found at 2 rural Zambian clinics and in a large pediatric cohort from 7 South African facilities between 2003 and 2007. Facilities in the latter study had higher patient loads (median 690 children/site), were all situated in large cities and at comparatively higher levels of the health care system, compared with facilities in our study that had lower patient loads (median 53 children/site) and which were generally more peripherally located and at lower levels of the health care system. LTfu is known to increase at larger facilities with large patient loads amongst adults on ART.

Similar to these results, children in Zambia and adults in South African cohorts have displayed temporal improvements in baseline immunological status and clinical stage as the most ill patients commence ART first. Progress is thus being made in starting children on treatment at earlier stages of the disease; however, in 2009, the majority of children still had severe immunodeficiency and half the children were clinically severely ill before starting treatment.

Increasing proportions of children have been receiving TB treatment when starting ART as has similarly been found in adults. This is probably as a result of increasing awareness of and reduced underdiagnosis of TB and increased HIV testing in children presenting with TB.

The proportion of young children starting ART in this cohort has increased in recent years, but remains low. Young HIV-infected children are a vulnerable group with high mortality; however, initiation of ART in young infants markedly reduces mortality. The WHO recommended ART initiation in HIV-infected children younger than 12 months of age irrespective of clinical or immunological stage in April 2008, but South African revised treatment guidelines adopting this position were published almost 2 years later in March 2010 (which was after the enrolment period of this study). In 2010, the WHO extended their recommendation to treat all HIV-infected children under 2 years of age. Most pediatric ART programs in sub-Saharan Africa have included low proportions of young children starting ART. The Thailand national pediatric ART program also had a high median age at ART initiation of 7.3 years (IQR: 5.0–9.4), which increased in a similar way to our data as the program expanded. Tertiary hospitals and research sites in Southern Africa have in contrast been able to recruit from 18% to 53% of children being younger than 18 months of age at baseline. The finding that children under 2 years of age at baseline had poorer virological outcome than older children is consistent with other data.

Early infant diagnosis of HIV is generally poor in South Africa, with national estimates of HIV-exposed infants receiving an early HIV DNA polymerase chain reaction (PCR) test being 31% in 2008 rising to 55% in 2010. Early infant diagnosis of HIV infection in South Africa: 2008–2010, South African National Health Laboratory Service; 2011, unpublished report). Uptake of HIV testing in older children is also poor in routine settings. Inadequate integration of maternal and child health services, delays in retrieval of test results, delays in follow-up and referral to ART centres of HIV-infected infants, a lack of pediatric ART care at PHC facilities, and actual or perceived lack of expertise in the care of young infants all post-pone implementation of ART in HIV-infected children.

A multilayered approach to resolving these issues is required as follows: closer integration of maternal, child, and HIV/ART services at all sites is critical. PHC facilities need to have efficient systems to promote early infant PCR testing, utilizing strategies such as routine testing during immunization visits and ensure rapid retrieval of PCR results. HIV-negative infants should have their HIV status checked by 18 months of age. Guidelines should be developed, and medical and nursing staff trained regarding the practical implications of fast-tracking HIV-infected infants onto ART. A clear understanding of the flow of children eligible for ART in health districts is critical for successful scale-up of high quality services. Treatment regimens and formulations appropriate for younger children, which simplify treatment and promote adherence, need to be developed and implemented. Scale-up of community adherence support for young children initiating ART is also imperative.

Although LTfu was higher at PHC clinics compared with hospitals in this dataset, mortality was found to be lower, with virological and immunological outcomes being equivalent between the health system levels. These findings concur with previously published data supporting the provision of pediatric ART at PHC clinics.

**STRENGTHS AND LIMITATIONS**

The strengths of this study are that pooled data from a large number of children and sites in different settings were used with prospective collection of electronic individual-level data enabling adjustment of patient factors associated with outcomes. In addition, the vital status of patients LTfu who had valid identification numbers was determined from the national death registry, allowing corrected mortality estimates to be derived.

This study is a retrospective analysis using routine data with its inherent limitations; however, it is likely to be indicative of the situation at an operational level. Missing viral load results were prevalent; however, pediatric viral load results are unusual in many routine sub-Saharan treatment programs, and all important outcomes in this study pointed in the same direction. The sites included were all supported by an NGO, and it is possible that the outcomes may not be well generalizable to non-NGO-supported government health facilities. Patient tracing systems were not necessarily standardized between sites and over time as provincial health department strategies were not of necessity consistent or static. Multivariable analyses did, however, control for site and provincial related heterogeneity.

As few children were enrolled near the start of the ACT program in South Africa, the 2004/2005 group is small, forming 5.7% of the sample. Greater variation in point estimates with wide associated confidence intervals is thus expected in this group. Accordingly, point estimates in baseline characteristics for this group that do not fit a trend apparent amongst the other 4 cohorts will not of necessity negate the validity of a linear trend across the whole sample.
Adherence determination data (such as medication volume checks and pill counts) were not collected as they do not form part of the routine data captured for public sector ART patients in South Africa. Socioeconomic factors may be associated with mortality, but it was not possible to collect socioeconomic data for the whole cohort; therefore, this variable was not included in analyses.

In conclusion, this study demonstrates that pediatric ART can be successfully provided in a decentralized manner in a low-income setting, and that program outcomes were maintained or improved as the number of children on treatment increased, during the first 5 years of the South African national ART program. There remains, however, an urgent need for improved co-ordination of maternal and child health programs to improve early infant diagnosis of HIV and to initiate ART at earlier stages of HIV infection and in younger children.

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