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Improved virological suppression in children on antiretroviral treatment receiving community-based adherence support: A multicentre cohort study from South Africa

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Adherence to antiretroviral treatment (ART) is a challenge in childhood, and children on ART have reduced virological suppression compared to adults. This study evaluated the effect of community-based adherence support (CBAS) on virological outcomes amongst children receiving ART in four South African provinces. Patient Advocates are lay CBAS workers who provide adherence and psychosocial support for patients, undertaking home visits to address household challenges affecting adherence. Patient Advocates provide counselling for children’s carers regarding adherence and psychosocial problems. A multicentre cohort study using routinely collected data was conducted at 57 public ART sites including ART-naive children (<16 years) starting ART. Virological suppression until four years of ART was compared between children who received and did not receive CBAS. Analyses were by intention-to-treat, controlling for confounding using multivariable generalised estimating equations. A total of 4853 children were included, of whom 982 (20.2%) received CBAS. The median baseline age was 6.3 years and the baseline CD4 cell percentage was 12.0%; both were equivalent between the two groups. CBAS children had more advanced baseline clinical disease (62.1% vs. 52.6% World Health Organisation stages III or IV; P < 0.0001). A total of 5908 viral load results were analysed. Virological suppression was 65.6% (95% confidence interval [CI]: 62.7–68.4%) vs. 55.5% (95% CI: 54.1–57.0%) in CBAS and non-CBAS children, respectively, at any time-point on treatment (P < 0.0001). In analyses controlling for baseline clinical, demographic, site-related variables and time on ART, children receiving CBAS were more likely to achieve virological suppression, adjusted odds ratio (aOR) 1.60 (95% CI: 1.35–1.89; P < 0.0001). The effect of CBAS increased in magnitude with increasing durations of ART, and CBAS particularly improved virological suppression in a higher-risk subgroup (children younger than two years, aOR 2.47 [95% CI: 1.59–3.84]). CBAS was associated with improved virological suppression in children receiving ART. Expanded implementation of this low-cost intervention should be considered in resource-poor settings.

Keywords: community-based adherence support; antiretroviral treatment; children; virological suppression; South Africa; HIV

Introduction

Long-term adherence to antiretroviral treatment (ART) is a challenge in children, and children have lower virological suppression rates on ART compared to adults (Davies et al., 2011; Kamya et al., 2007). Adherence decreases over time, and may be linked to caregiver “treatment fatigue” and depression (Byakika-Tusiime et al., 2009; Nachega et al., 2011). Paediatric ART formulations may have complex dosage schedules which increase the difficulty with adherence. In addition, poor childhood cognitive skills, poverty, food and shelter insecurity, non-disclosure, domestic violence and substance abuse in the family complicate treatment adherence. Children also depend on others to receive medication and clinic follow-ups. Treatment durability is, however, more crucial in children than in adults, and young children failing to achieve virological suppression is an important concern (Calmy & Ford, 2011).

Community-based adherence support (CBAS) programmes have been shown to improve virological outcomes and programme retention amongst adults receiving ART (Fatti, Meintjes, She, Eley, & Grimwood, 2012; Igumbor, Scheepers, Ebrahim, Jason, & Grimwood, 2011), and improves retention in children receiving ART (Grimwood et al., 2012). However, little data on the effectiveness of community adherence support on virological outcomes in children on ART is available. This study evaluated the effect of CBAS on virological outcomes amongst children receiving ART in four South African provinces.

Methods

Patient Advocates are lay CBAS workers who provide regular adherence and psychosocial support for patients and undertake home visits to address household challenges affecting adherence. Family and household
members are assessed together with children. During a patient’s initial home assessment by a Patient Advocate, issues assessed include tuberculosis (TB) and household HIV-testing status, nutrition security, substance abuse, domestic violence, non-disclosure, social assistance grant eligibility and vital documentation including birth certification. Issues affecting adherence are discussed at clinic multidisciplinary team meetings, and interventions agreed by the team are implemented by the Patient Advocate or social worker. Patient Advocates also offer group educational sessions to carers at the clinic about HIV/TB, the importance of adherence, and nutrition. After the initial home assessment, home visits occur weekly for a month, then at monthly intervals. Patient Advocates provide one-on-one counselling for carers regarding adherence and psychosocial problems, supervise taking of medication and do adherence checks. Once the child is stable (regular clinic attendance and virologically suppressed), visits continue at least quarterly for long-term treatment.

Patient Advocate requirements include completion of high school, English literacy and numeracy, fluency in the local language and good community standing. They are trained regarding HIV and TB infection and treatment, including psychosocial issues impacting adherence and how to address these.

A multicentre cohort study using routinely collected clinical data was conducted at 57 public ART sites supported by Kheth’Impilo (KI), a non-governmental organisation that supports South African Department of Health ART facilities. KI employs medical and pharmacy staff, provides a CBAS programme, and provides quality improvement initiatives. Facilities are located in the Western Cape Province, Eastern Cape, KwaZulu-Natal and Mpumalanga. ART-naive children (<16 years) starting ART at KI-supported sites at which the CBAS programme was operational between January 2004 and September 2010, who had at least one follow-up visit after starting ART were included. Site database closure was end-March 2011.

Patients were allocated to receive CBAS during the pre-treatment preparation period by the community area coordinator if a Patient Advocate was active in the area of the child’s home, Patient Advocate capacity was available and carer consent was obtained. As the development of the CBAS programme at sites was progressive, few children were initially allocated to Patient Advocates but this increased as the programme expanded. Individual-level patient data were collected prospectively for routine monitoring purposes by designated site-based data capturers using standardised custom-designed databases, which were pooled quarterly to a central data warehouse.

The primary outcome was the proportion of children achieving virological suppression (viral load <400 copies/ml) until four years after starting ART by intention-to-treat (ITT) (Hollis & Campbell, 1999). All patients were included in the denominator for each group as allocated but observations were censored for patients in care with missing viral load results. Virological suppression at six-monthly intervals after starting ART by ITT was also analysed. In addition, an on-treatment (OT) analysis was performed, including only patients in the denominator who had an available viral load result at each particular time interval. A patient was defined as lost to follow-up (LTFU) if no visits to the clinic occurred for 180 days or more.

Baseline characteristics between groups were compared using Pearson’s χ² and Wilcoxon’s rank-sum tests. Multivariable generalised estimating equations were used to model the effect of CBAS on virological suppression by ITT controlling for baseline demographic, clinical, site-related potential confounders and time of ART. Age and gender were included as covariates in adjusted models as well as variables that were associated with the outcome with a p-value < 0.10 on bivariate analysis. Logistic regression was used to analyse the effect of CBAS after annual intervals of ART, similarly controlled for confounding. Analyses were performed with Stata 11.1 (Texas, USA). This study was approved by the University of Cape Town Research Ethics Committee.

Results

Database records of 6595 ART-naive children were screened for inclusion in the study. The following were excluded: 670 children from sites without a CBAS programme, 953 who started ART after 30 September 2010 and 119 who had no follow-up visits. Thus, 4853 children were included, of whom 982 (20.2%) received CBAS and 3871 (79.8%) did not (Table 1). The median baseline age was 6.3 years (interquartile range, IQR: 3.2–9.7 years) and the median baseline CD4 cell percentage was 12.0% (IQR: 7–17.1%); both were equivalent between the two groups. CBAS children had more advanced baseline clinical stage disease (62.1 vs. 52.6% WHO stages III or IV; P < 0.0005). CBAS children had a higher proportion receiving TB treatment at baseline (7.5 vs. 5.0%; P = 0.002). CBAS children were more likely to receive treatment at primary healthcare and rural facilities.

After starting ART, 22 (2.2%) CBAS children and 116 (3.0%) non-CBAS died (P = 0.188). Thirty-two (3.3%) CBAS children and 192 (5.0%) non-CBAS children were LTFU after starting ART (P = 0.020).

A total of 5908 viral load results were available; a mean of 1.2 viral loads per child. In crude analyses, at any time-point on treatment, virological suppression was 65.6% (95% confidence interval [CI]: 62.7–68.4%) in CBAS children vs. 55.5% (95% CI: 54.1–57.0%) in
non-CBAS children ($P < 0.0005$). In adjusted analyses, CBAS children were more likely to achieve virological suppression, adjusted odds ratio (AOR) 1.60 (95% CI: 1.35–1.89; $P < 0.0005$) (Table 2). Children younger than two years of age had substantially reduced virological suppression (54–67% reduction) compared to those older than two years. However, when limiting analyses to children aged under two years, CBAS was particularly effective to improve virological suppression; AOR 2.47 (95% CI: 1.59–3.84; $P < 0.0005$).

Figure 1a indicates virological suppression by ITT according to duration of ART in children with and without CBAS in crude analyses. Children with CBAS had comparatively improved virological suppression, the magnitude of which increased with increasing duration of ART. Table 3 indicates adjusted effect measures of CBAS on virological suppression at annual time-points after starting ART. The adjusted effect of CBAS also improved progressively in magnitude for increasing durations of ART (AOR 1.23 [95% CI: 0.84–1.81] at 12 months and 15.9 [95% CI: 1.91–130] at 4 years).

Figure 1b indicates OT virological suppression after starting ART. Virological suppression was equivalent between the groups in this analysis (AOR 0.92 [95% CI: 0.78–1.10; $P = 0.39$] at any time-point on ART).

**Discussion**

CBAS was associated with improved virological suppression in children receiving ART in ITT analyses. This was despite finding that CBAS children had more advanced baseline clinical stage disease and a greater proportion were managed in rural areas (with associated poorer outcomes) (Fatti, Bock, Grimwood, & Eley, 2010). The magnitude of improvement increased with increasing duration of ART. CBAS also particularly improved virological suppression in a subgroup at risk for virological failure (children younger than two years).

Although virological suppression was not improved in OT analyses, the ITT approach is the preferable
analytic method for the pragmatic assessment of the effect of an intervention (Hernan et al., 2008; Hollis & Campbell, 1999). CBAS likely retains a larger pool of patients at increased risk of having unsuppressed viral loads by reducing mortality and LTFU amongst higher-risk children (Fatti et al., 2012; Grimwood et al., 2012). OT analyses are thus likely biased in the estimation of the true effect of CBAS on virological outcomes.

CBAS may help to combat “treatment fatigue” associated with long-term ART (Nachega et al., 2011). CBAS likely assists carers in overcoming denial, enhances understanding of adherence and helps to improve psychosocial problems thereby promoting adherence-related behaviour skills (Fisher, Fisher, Amico, & Harman, 2006). CBAS likely reduces stigmatisation, leads to greater social capital (Ware et al., 2009),

Figure 1. Virological suppression amongst children receiving and not receiving community-based adherence support (CBAS). (a) Intention-to-treat (ITT) analysis. (b) On-treatment (OT) analysis.
widens the “community safety net” (Foster, 2007) and heightens social responsibility, which all positively impact adherence, as ART adherence in Africa is a community effort (Binagwaho & Ratnayake, 2009).

The company cost per Patient Advocate per month (in January 2012) was USD 225–275, with an approximate cost of USD 1.88–3.43 per patient per month (Fatti et al., 2012). This CBAS programme is thus a low-cost intervention which can be introduced in low-income settings.

The limitations of this study include the use of routine data, missing viral load data and the non-randomised allocation of patients to groups. However, randomised studies of this intervention are logistically difficult to implement and observational studies may be of greater value in this context (Thomas, Curtis, & Smith, 2011). In addition, viral load data amongst children in routine sub-Saharan African settings is commonly unavailable (Keiser et al., 2008). As mortality was not the main outcome of interest in this study we did not ascertain or correct mortality estimates for mortality amongst those LTFU. Corrected mortality has, however, previously been found to be reduced amongst children with CBAS (Grimwood et al., 2012).

In conclusion, CBAS appears to improve long-term virological suppression amongst children receiving ART. Expanded implementation of this low-cost intervention should be considered in resource-poor settings.

Acknowledgements

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References


Table 3. Logistic regression results of virological suppression (by intention-to-treat) at annual intervals on ART amongst children who received community-based adherence support (CBAS) compared to those without CBAS.

<table>
<thead>
<tr>
<th>Time on ART (years)</th>
<th>Children with CBAS</th>
<th>Children without CBAS</th>
<th>Adjusted odds ratio</th>
<th>95% confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>161/238</td>
<td>704/1105</td>
<td>1.23</td>
<td>0.84–1.81</td>
<td>0.325</td>
</tr>
<tr>
<td>2</td>
<td>64/107</td>
<td>222/479</td>
<td>3.00</td>
<td>1.45–6.54</td>
<td>0.004</td>
</tr>
<tr>
<td>3</td>
<td>35/62</td>
<td>47/215</td>
<td>4.02</td>
<td>1.52–10.63</td>
<td>0.005</td>
</tr>
<tr>
<td>4</td>
<td>18/30</td>
<td>7/107</td>
<td>15.93</td>
<td>1.91–130</td>
<td>0.010</td>
</tr>
</tbody>
</table>

Note: ART, antiretroviral treatment.


