Poor Early Virologic Performance and Durability of Abacavir-based First-line Regimens for HIV-infected Children


**Background:** Concerns about stavudine (d4T) toxicity have led to increased use of abacavir (ABC) in first-line pediatric antiretroviral treatment (ART) regimens. Field experience with ABC in ART-naïve children is limited.

**Methods:** Deidentified demographic, clinical and laboratory data on HIV-infected children initiating ART between 2004 and 2011 in a large pediatric HIV treatment program in Johannesburg, South Africa, were used to compare viral suppression at 6 and 12 months by initial treatment regimen, time to suppression (<400 copies/mL) and rebound (>1000 copies/mL after initial suppression). Adjusted logistic regression was used to investigate confounders and calendar effects.

**Results:** Two thousand thirty-six children initiated either d4T/3TC- or ABC/3TC-based first-line regimens in combination with either boosted lopinavir (LPV/r) or efavirenz (EFV). 1634 received d4T regimens (LPV/r n = 672; EFV n = 962) and 402 ABC regimens (LPV/r n = 192; EFV n = 210). At 6 and 12 months on ART, viral suppression rate was poorer in ABC versus d4T groups within both the LPV/r and EFV groups (P < 0.0001 for all points). In ABC groups, time to suppression was significantly slower (log-rank P < 0.0001 and P = 0.0092 for LPV/r- and EFV-based, respectively) and time to rebound after suppression significantly faster (log-rank P = 0.014 and P = 0.0001 for LPV/r- and EFV-based, respectively). Logistic regression confirmed the worse outcomes in the ABC groups even after adjustment for confounders.

**Conclusion:** Data from this urban pediatric ART service program show significantly poorer virological performance of ABC compared with d4T-based regimens, a signal that urgently warrants further investigation.

**Key Words:** HIV, children, abacavir, first-line antiretroviral therapy

*Pediatric Infect Dis J 2013;32: 851–855*

**Improved availability of antiretroviral therapy (ART) has transformed pediatric HIV infection in sub-Saharan Africa from a rapidly fatal to a treatable disease, saving tens of thousands of lives.**

Clinical trials have been conducted to determine optimal ART regimens with careful attention being given to evaluating the efficacy of protease inhibitors versus non-nucleoside reverse transcriptase inhibitors for pediatric first-line regimens. Relatively little attention has been given to the nucleoside reverse transcriptase inhibitor (NRTI) “backbone” of the regimens. South African guidelines recommend treatment with ritonavir-boosted lopinavir (LPV/r)-based regimens for children under 3 years of age and efavirenz (EFV)-based regimens for children older than 3 years of age. Lamivudine (3TC) and stavudine (d4T) were initially used as standard first-line NRTI backbone. In 2010, following World Health Organization recommendations, South African guidelines replaced d4T with abacavir (ABC) due to concerns around toxicity. We were unable to find evidence comparing ABC-containing to other NRTI-containing regimens in similar pediatric populations. The closest comparison comes from the Paediatric European Network for the Treatment of AIDS (PENTA-5) trial demonstrating better virological suppression on a nevirapine-based regimen for ABC relative to zidovudine (AZT) in older children. This analysis was undertaken in response to clinicians raising concerns about viral suppression after the introduction of ABC for first-line ART. We investigated virological outcomes among children receiving different starting regimens using routinely collected program data.

**METHODS**

Empilweni clinic at Rahima Moosa Mother and Child Hospital (RMMCH) is a large pediatric HIV treatment centre in Johannesburg, South Africa, and has provided HIV services since 1995: over 1600 HIV-infected children are in active care. National guidelines are followed, which require HIV viral load (VL) monitoring at 6 months and 12 months after ART initiation. VL monitoring was recommended 6 monthly during therapy but since 2010 only annual monitoring after the first year of treatment is recommended. No fixed dose combinations have been used at RMMCH. The formulations available during the period of observation included: d4T syrup and capsules; 3TC syrup and...
and had initiated d4T/3TC+LPV/r (n = 672), ABC/3TC+LPV/r (n = 192), d4T/3TC+EFV (n = 962) or ABC/3TC+EFV (n = 210). The children excluded had initiated other regimens (n = 387, including nevirapine, ritonavir, didanosine, zidovudine and “super-boosted” LPV/r for concurrent rifampicin usage).

Pretreatment characteristics of the children stratified by starting regimen are tabulated in Table, Supplemental Digital Content 1, http://links.lww.com/INF/B507. The data reflect the ABC-containing regimens being the more recent regimens. There were no differences in gender distribution but age at initiation was different in the EFV-based group with children initiating ABC-containing regimens being a median of 8 months older than those initiating d4T-containing regimens (P = 0.005). Children who initiated ABC-containing regimens had marginally higher pretreatment WAZ and HAZ scores (P = 0.02 and 0.93, respectively) in the EFV-based group but significantly higher scores in the LPV/r group (P < 0.0001). CD4 percentages were higher in children commenced on ABC-containing regimens, but a difference in absolute CD4 counts was only evident in the EFV group (P = 0.04). Pretreatment VL was slightly higher in the d4T/LPV/r group (P = 0.03) but not significantly different within the EFV and LPV/r groups in terms of proportion above 100,000 copies/mL. Children on EFV had lower VLs than those on LPV/r-based regimens (50% versus 81% above 100,000 copies/mL; P < 0.0001). Mortality, loss to follow-up and transfer-out rates were similar between children given ABC and d4T stratified by LPV/r or EFV-based treatment (Supplemental Digital Content 1, http://links.lww.com/INF/B507, Table of pretreatment characteristics stratified by starting regimen).

At both 6 and 12 months, fewer children reached virological suppression, and median VL logs were higher in children receiving ABC compared with d4T, in both the EFV- and LPV/r-treated children (Table 1). In children treated with LPV/r-based regimens, 71% receiving d4T versus 40% receiving ABC had VL<400 copies/mL at 6 months (P < 0.0001). Similarly, in those on EFV, 91% versus 67% had VL<400 copies/mL at 6 months when receiving d4T versus ABC (P < 0.0001). No significant changes to these findings were noted when using only data from 2008 onwards.

Sixty percent of all children who were eligible for VL measurement at 6 months had a VL done and 81% at 12 months. There were no significant differences in compliance with testing guidelines for the 6-month window between those receiving ABC or d4T. More ABC-treated children had yet to reach the 12-month testing window, but among those on ABC who had reached the 12-month window, proportionately more underwent the 12-month test (P = 0.02 in EFV-based group, P = 0.13 in LPV/r group; Table 1), suggesting a trend toward increased testing at 12 months in ABC-based, that is, more recent regimens.

Time to viral suppression was significantly longer and time to viral rebound (>1000 copies/mL) after suppression shorter in the ABC-treated children for both LPV/r- and EFV-based regimens (Fig. 1). A stronger association was seen in the LPV/r-based regimens, where children on ABC had an almost 2-fold increased risk of failure to suppress (41% versus 21%, log-rank P < 0.0001) by 12 months. Children receiving EFV had an almost 2-fold higher risk of rebound by 12 months after first suppression (35% versus 18%, log-rank P = 0.0001) if they were on ABC compared with d4T (Fig. 1). Adjusted multiple logistic regression analysis (Table 2) was performed using all data and then only data from 2008 onwards in order to limit the calendar effect, but this did not significantly affect the results and therefore the complete model is shown. The strongest predictor of viral suppression at 12 months remained receiving d4T instead of ABC. Missed visits, a proxy for poorer adherence, showed a significant independent effect toward not suppressing at 12 months (stronger within LPV/r group P = 0.0021 than within EFV group P = 0.057).

RESULTS

Among 2423 children who initiated ART at RMMCH from April 2004 until December 28, 2011, 2036 (84%) were included and had initiated d4T/3TC+LPV/r (n = 672), ABC/3TC+LPV/r (n = 192), d4T/3TC+EFV (n = 962) or ABC/3TC+EFV (n = 210). The children excluded had initiated other regimens (n = 387, including nevirapine, ritonavir, didanosine, zidovudine and “super-boosted” LPV/r for concurrent rifampicin usage).

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RESULTS

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TABLE 1. Virological Outcomes for 2036 HIV-infected Children Stratified by Starting ART Regimen

<table>
<thead>
<tr>
<th></th>
<th>LPV/r-based ART</th>
<th>EFV-based ART</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>ABC/3TC</td>
<td>d4T/3TC</td>
</tr>
<tr>
<td>Months followed-up since ART initiation, median (IQR)*</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Reached follow-up window, N (%)</td>
<td>138 (72)</td>
<td>547 (81)</td>
</tr>
<tr>
<td>Median months at VL (IQR)</td>
<td>5.7 (5.1–6.4)</td>
<td>5.8 (5.3–6.7)</td>
</tr>
<tr>
<td>VL &lt;400 cps/mL, N (%)</td>
<td>35 (40)</td>
<td>249 (71)</td>
</tr>
<tr>
<td>Median log VL (IQR)</td>
<td>2.9 (2.2–4.8)</td>
<td>1.9 (1.4–2.9)</td>
</tr>
</tbody>
</table>

6-month virological outcomes*:

- Reached follow-up window, N (%): 138 (72) vs. 547 (81)
- Median months at VL (IQR): 5.7 (5.1–6.4) vs. 5.8 (5.3–6.7)
- VL <400 cps/mL, N (%): 35 (40) vs. 249 (71)
- Median log VL (IQR): 2.9 (2.2–4.8) vs. 1.9 (1.4–2.9)

12-month virological outcomes*:

- Reached follow-up window, N (%): 96 (50) vs. 514 (76)
- Median months at VL (IQR): 11.0 (9.7–12.2) vs. 11.4 (10.1–12.5)
- VL <400 cps/mL, N (%): 41 (51) vs. 308 (77)
- Median log VL (IQR): 2.6 (1.9–4.0) vs. 1.4 (1.4–2.6)

IQR, interquartile range.

*In each of the 6- and 12-month outcomes, the first denominator is the total group of children initiated on the regimen and the subsequent denominators are the numerators from the row above. “Median Months at VL” indicates the median time since ART when the VLs were performed in those children who had VLs done. Suppression at 6 and 12 months for all children (combining data for those on ritonavir-boosted LPV/r and EFV) shows poorer suppression (P < 0.0001 at all points) on abacavir/lamivudine (ABC/3TC) (106/194 [55%] at 6 and 121/198 [61%] at 12 months) than on stavudine/lamivudine (d4T/3TC) (686/831 [83%] at 6 months and 891/1057 [84%] at 12 months).


**TABLE 2.** Odds Ratios With 95% Wald Confidence Intervals for Adjusted Logistic Regression of Failure to Reach VL <400 copies/mL at 12 Months of Antiretroviral Treatment in HIV-infected Children Initiating Ritonavir-boosted LPV/r- or EFV-based Regimens

<table>
<thead>
<tr>
<th></th>
<th>LPV/r-based (N = 479)</th>
<th>P</th>
<th>EFV-based (N = 776)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted OR (95% confidence interval)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stavudine vs. abacavir-based</td>
<td>0.30 (0.18–0.49)</td>
<td>&lt;0.0001</td>
<td>0.28 (0.18–0.44)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adjusted OR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stavudine vs. abacavir-based</td>
<td>0.36 (0.18–0.72)</td>
<td>0.0035</td>
<td>0.31 (0.16–0.60)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Male</td>
<td>1.18 (0.77–1.80)</td>
<td>0.44</td>
<td>1.13 (0.75–1.71)</td>
<td>0.56</td>
</tr>
<tr>
<td>Year of initiation</td>
<td>1.51 (0.98–1.36)</td>
<td>0.095</td>
<td>1.12 (0.96–1.30)</td>
<td>0.14</td>
</tr>
<tr>
<td>Age at initiation</td>
<td>1.00 (0.99–1.02)</td>
<td>0.72</td>
<td>1.00 (0.99–1.01)</td>
<td>0.38</td>
</tr>
<tr>
<td>Pretreatment WAZ</td>
<td>0.97 (0.83–1.13)</td>
<td>0.68</td>
<td>0.88 (0.75–1.08)</td>
<td>0.22</td>
</tr>
<tr>
<td>Pretreatment CD4 percentage</td>
<td>0.99 (0.97–1.02)</td>
<td>0.80</td>
<td>0.97 (0.94–0.99)</td>
<td>0.041</td>
</tr>
<tr>
<td>Pretreatment VL &lt;100,000 copies/mL</td>
<td>0.75 (0.37–1.51)</td>
<td>0.42</td>
<td>0.97 (0.57–1.64)</td>
<td>0.91</td>
</tr>
<tr>
<td>Missed visits</td>
<td>2.15 (1.32–3.50)</td>
<td>0.0021</td>
<td>1.64 (0.98–2.74)</td>
<td>0.057</td>
</tr>
</tbody>
</table>

OR indicates odds ratio.

**DISCUSSION**

These data demonstrate that children treated with ABC/3TC had a lower probability of viral suppression at 6 and 12 months and a higher probability of virological rebound than those treated with d4T/3TC in both LPV/r- and EFV-based regimens, even after adjustment for calendar time and other potential confounders. These results raise concern that the shift to ABC regimens may not be as virologically efficacious as d4T regimens in this pediatric HIV service.

The poorer virological outcomes in children on ABC/3TC were seen despite higher pretreatment WAZ, HAZ and CD4 percentages. The differences were found with LPV/r- and EFV-based regimens. Within the LPV/r group of mostly younger children, the probable explanation for the improvement in pretreatment characteristics is earlier diagnosis within an expanding and improving prevention of mother-to-child transmission (PMTCT) service including early infant diagnosis in South Africa. This would lead us to expect better, not worse virological outcomes in the ABC group. However, earlier treatment may pose other challenges including those related to adherence.

It is difficult to determine the reasons for the poorer performance of ABC-containing regimens in our setting. Because the change in regimen is almost entirely related to calendar time, we cannot exclude secular trends in the population characteristics of children. In particular, guideline changes on when to initiate therapy have occurred. ART initiation for infants is recommended upon diagnosis and initiation of older children earlier, that is, at higher pretreatment CD4 counts and/or percentages than in earlier guidelines. Changes have also occurred in the recommended PMTCT regimens as well as improvements in coverage of these programs. In addition, programmatic changes over time such as increasing program size accompanied by less intensive follow-up and possibly less intensive adherence counseling cannot be excluded as reasons for poorer virological outcomes, yet the effect remains when limiting to data from 2008 onwards and adjusting for missed patient visits.

Intermittent brief interruptions of ABC supply occurred particularly toward the end of 2011 due to national procurement and supply problems. Drug stock-outs were managed on a case by case basis with drug or formulation substitutions, for example, ABC syrup was used to replace tablets when these went out of stock. These changes may have resulted in confusion for caregivers leading to treatment interruptions and adherence challenges. Stock-outs of d4T have not been recorded at RMMCH since program inception. In addition, administering LPV/r to young children can be challenging due to poor palatability. Because d4T has a comparatively higher genetic barrier to resistance than ABC, d4T is theoretically better able to “tolerate” suboptimal adherence than ABC. Although ABC and 3TC share the cross-resistant mutation, M184V, d4T and 3TC do not. In fact, d4T resistance may be delayed by 3TC resistance. For these reasons, children with treatment interruptions or suboptimal adherence on ABC/3TC may fare worse compared with those on d4T/3TC and potential M184V mutations selected for by PMTCT regimens may further compound this. This is especially of concern as a slightly stronger effect size was seen in the LPV/r-treated group, which represents the youngest children, possibly also exposed to the more recent multidrug PMTCT regimens. The greater effect seen with LPV/r seems contrary to the superiority of LPV/r over non-nucleoside reverse transcriptase inhibitor (nevirapine based) regimens reported recently in young children on AZT/3TC, although this trial compared the 2 regimens in younger children, whereas our data separate LPV/r in younger from EFV in older children. A possible explanation of the greater effect in LPV/r-based regimens may be a potential drug interaction between ABC and LPV/r of as yet uncertain clinical significance.

Given the short follow-up period presented in our analysis, it is not possible to determine whether the worse virological outcomes in the first year of treatment indicate lower absolute rates of suppression or simply slower time to suppression. Nevertheless, viral suppression is expected by 12 months on ART, even in infants. Failure to suppress within the first year of treatment in such a proportion of children is of concern and may influence longer term outcomes with reduced regimen options at later time points. More rapid evolution of resistance in a failing or nonsuppressed ABC/3TC regimen described in the PENTA-5 trial is a further concern. More rapid rebound in the EFV group (with lower genetic resistance threshold compared with LPV/r) may theoretically predispose children to higher rates of regimen failure and increased need for regimen switches.

Our analysis does not directly corroborate or refute findings from recently published data showing poorer virological performance of ABC/3TC versus tenofovir/emtricitabine regimens among adults with higher pretreatment VL (>100,000 copies/mL). It is important to note that 82% of children on LPV/r had pretreatment VL ≥100,000 copies/mL. Other adult studies have found suboptimal performance of an ABC-containing triple NRTI regimen at higher pretreatment VL levels when compared with AZT/3TC and a protease inhibitor.

A limitation and important concerning finding was the low rate of VL testing in all treatment groups during the 6-month window, although rates improved by the 12-month window. With suboptimal rates of VL testing, we cannot rule out selection bias as a potential explanation for the findings. Other limitations include...
that these findings are from a single center with limited follow-up time related to the relatively recent introduction of ABC as well as an almost concurrent change in the technology used to determine VL. Nevertheless the consistency of the association in children treated with both EFV and LPV/r within a large public sector pediatric treatment centre in South Africa is notable. Formulations and exact doses issued were not captured and therefore the impact of formulation changes cannot be further assessed. Data on PMTCt exposure is incomplete, and stratification by presence/absence of PMTCT and details of drug exposure is important but not possible in this study. Previous analyses in our setting have shown that 30–50% of infants starting ART did not have any previous PMTCT ART exposure.22

This study is a retrospective analysis of data from a nontrial setting with inherent limitations, and it cannot be taken as a definitive comparison between ABC and d4T-containing NRTI backbones. Children initiating ART in the same clinic at 2 different time periods are compared, and we are unable to control for other ecological factors and unanticipated confounders. Electronic data capture has been ongoing since 2006 and data cleaning and verification systems are in place, but data quality is not that of a clinical trial given the resource constraints of the public health sector.

These results highlight the importance of routine VL measurements and close monitoring of children initiating ART. We recommend a return to 6 monthly monitoring after the first year of treatment particularly for children on ABC/3TC. We strongly recommend urgent review of data from other pediatric treatment sites to establish whether the lower virological effectiveness seen in our cohort exists elsewhere. We advise close monitoring of outcomes at clinical sites following any guideline changes. Furthermore, a central surveillance system that tracks trends in virological suppression rates across multiple sites should be considered.

ACKNOWLEDGMENTS

We would like to acknowledge all the children and their caregivers, whose data were used in this analysis. We acknowledge the work of Mr. Vincent Kgakgadi and his administrative team.

REFERENCES


