Virologic Response in Children Treated With Abacavir- compared With Stavudine-based Antiretroviral Treatment

A South African Multi-Cohort Analysis

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Background: Initiation criteria and pediatric antiretroviral treatment regimens have changed over the past few years in South Africa. We reported worse early virological outcomes associated with the use of abacavir (ABC)-based regimens at 1 large site: here, we expand this analysis to multiple sites in the IeDEA-Southern Africa collaboration.

Methods: Data for 9543 antiretroviral treatment-naïve children <16 years at treatment initiation started on either stavudine/lamivudine (d4T/3TC) or ABC/3TC with efavirenz (EFV) or ritonavir-boosted lopinavir (LPV/r) treated at 6 clinics in Johannesburg and Cape Town, South Africa, were analyzed with χ^2 tests and logistic regression to evaluate viral suppression at 6 and 12 months.

Results: Prevalence of viral suppression at 6 months in 2174 children started on a d4T-based LPV/r regimen was greater (70%) than among 438 children started on an ABC-based LPV/r regimen (54%, $P < 0.0001$). Among 3189 children started on a d4T-based EFV regimen, a higher proportion (86%) achieved suppression at 6 months compared with 391 children started on ABC-containing EFV regimens (78%, $P < 0.0001$). Relative benefit of d4T versus ABC on 6-month suppression remained in multivariate analysis after adjustment for pretreatment characteristics, cohort and year of program [LPV/r: odds ratio = 0.57 (confidence interval: 0.46–0.72); EFV: odds ratio = 0.46 (confidence interval: 0.32–0.65)].

Conclusions: This expanded analysis is consistent with our previous report of worse virological outcomes after ABC was introduced as part of first-line antiretroviral treatment in South Africa. Whether due to the drug itself or coincident with other changes over time, continued monitoring and analyses must clarify causes and prevent suboptimal long-term outcomes.

Key Words: HIV, children, abacavir, first-line ART

(*Pediatr Infect Dis J* 2014;33:617–622)

South African pediatric antiretroviral treatment (ART) guidelines have been adapted in terms of initiation criteria and recommended regimens in response to changes adopted by the World Health Organization.[1–3] Abacavir (ABC) was incorporated into pediatric ART first-line regimens in April 2010 largely due to concerns around stavudine (d4T) toxicity.[4,5] Under current guidelines, ABC is combined with lamivudine (3TC) as a preferred nucleoside reverse transcriptase inhibitor (NRTI) backbone option.[3,6] Concurrent with the introduction of ABC, the South African prevention of mother to child transmission (PMTCT) guidelines included a longer duration of antenatal zidovudine administration and extended postnatal nevirapine prophylaxis for HIV-exposed infants.[7]

We recently reported poor early virological efficacy and durability of the ABC-based regimens compared with d4T-based regimens from a large pediatric HIV clinic in Johannesburg, South Africa.[8] Here, we investigate whether this phenomenon is more widespread by including multiple sites in the International epidemiologic Databases to Evaluate AIDS in Southern Africa (IeDEA-SA) collaboration and whether poor virological performance in recent years may be attributed to the national programmatic switch to ABC-containing first-line regimens.

MATERIALS AND METHODS

Characteristics of the IeDEA-SA collaboration (www.iedea-sa.org) participating sites have been previously described.[9] Each site collects and enters prospective data into electronic databases which are centrally collated at annual intervals extracting a standard set of routine data for analysis. Eight South African sites affiliated to this collaboration contributed data including the Rahima Moosa Mother and Child Hospital (RMMCH) which previously reported poor performance of ABC-based regimens.[8]

Data of ART-naïve children (<16 years at ART start) initiating d4T/3TC or ABC/3TC with efavirenz (EFV) or ritonavir-boosted lopinavir (LPV/r) who commenced ART 3 months before the last visit recorded for that cohort were included. Two sites with fewer than 10 children on any one ABC arm were excluded (Fig. 1). Data

Accepted for publication November 11, 2013.

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This study was supported by the National Institutes of Health (National Institute of Allergy and Infectious Diseases and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, grant number U01AI069924, PI: Egger and Davies). M.D. was also supported by a CDC grant (U2GGH000371) to strengthen pharmacovigilance in South Africa. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript. The authors have no funding or conflict of interest to disclose.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).

ISSN: 0891-3668/14/3306-0617
DOI: 10.1097/INF.0000000000000222

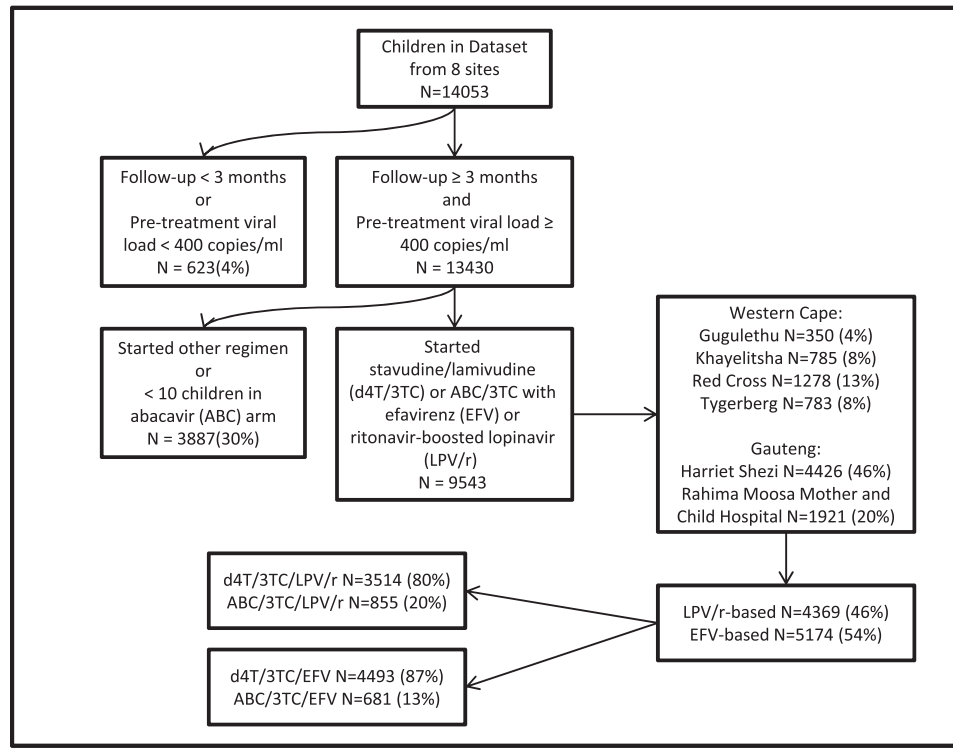

FIGURE 1. Study population.

from 2 Johannesburg and 4 Cape Town sites were included with a data window from August 17, 1998, to April 5, 2013. All sites were related to academic centers and situated within these 2 large metropolitan areas. Children with a pretreatment viral load (VL) of 0–400 copies/mL were excluded and assumed not to have been ART-naïve. Available pretreatment characteristics included age at ART initiation, year of ART initiation, weight-for-age z-score (WAZ), height-for-age z-score (HAZ), CD4 percentage and absolute count and VL ($\log_{10}$ copies/mL) value. Pretreatment WAZ and HAZ included measurements from 1 month before to 2 weeks after, while pretreatment CD4 and VL values were from 6 months before to 1 week after ART initiation, in cases with multiple measurements, the value closest to ART initiation was used.

Virological outcomes were evaluated at 6 and 12 months using results of samples collected within a window between 3–9 and 9–15 months after treatment initiation, respectively. Virological outcomes included time since treatment initiation at VL measurement, actual VL $\log_{10}$ value and suppression to <400 copies/mL and <50 copies/mL at these 2 time windows compared for children on ABC versus d4T. If more than 1 result was available, the 1 nearest to the middle of the window was chosen. χ^2 tests were used to compare proportions suppressed, while VL $\log_{10}$ values were compared across groups using t-tests if normally distributed or Wilcoxon tests if not normally distributed. Year of program was defined as the calendar year ART was initiated and was plotted against suppression rates stratified by regimens for all children and assessed using the Cochran-Armitage test for trend. Associations between first-line regimen (ABC/d4T) and not attaining VL<400 copies/mL at 6 and 12 months were examined using logistic regression adjusted *a priori* for gender, age at initiation, pretreatment WAZ, CD4 percentage, pretreatment VL (greater or lower than 100,000 copies/mL), year of ART initiation and cohort. Missing data for WAZ, VL $\log_{10}$, CD4 and 6- and 12-month suppression were imputed using multiple imputation.[10] Results were combined with Rubin's rules and are presented as odds ratios (OR) with 95% confidence intervals (CI).[11] A sensitivity analysis was performed using a restricted 2-year time window around ABC introduction (April 1, 2009, to March 31, 2011) and the interaction between cohort and d4T/ABC was investigated.

Each site has institutional ethical approval to contribute data to IeDEA analyses. Data were analyzed using Microsoft Excel, SAS (Version 9.3, SAS Institute Inc., Cary, NC) and STATA 12.0 (College Station, TX) software.

RESULTS

Figure 1 shows the total of 9543 ART-naïve children <16 years included in the analyses. Two-thirds of the final dataset was from the 2 Johannesburg sites, contributing 59% of the data for children on LPV/r regimens but 73% of data for children on EFV regimens.

Table 1 outlines pretreatment characteristics grouped by ABC/3TC versus d4T/3TC for children on LPV/r and EFV separately. Differences are noted between the groups, particularly age at initiation; children on ABC/LPV/r were slightly younger than children having started d4T. In contrast, those on EFV were more recently initiated (on ABC) and older. Children started on ABC/3TC, with either EFV and LPV/r had not only higher pretreatment WAZ, HAZ, CD4 absolute and percentage values but also marginally higher VL. Sites differed in proportions of children initiated on d4T compared with ABC for those initiating LPV/r (ranging from 78% on d4T at Harriet Shezi Clinic and Red Cross Children's Hospital to 90% at Gugulethu—$P = 0.0002$), while the distribution between d4T and ABC for children on EFV was more constant ranging from 84% to 90% on d4T. Overall, 20% initiated LPV/r with ABC, while only 13% of children initiated EFV with ABC ($P < 0.0001$).

Table 2 shows the virological outcomes in the 6- and 12-month window for all children and then excluding data from RMMCH. A smaller proportion of children in the ABC groups

TABLE 1. Pretreatment Characteristics and Originating Site of the Study Population Stratified by Starting Regimen

		LPV/r Based			EFV Based		
		ABC/3TC	d4T/3TC	*P*	ABC/3TC	d4T/3TC	*P*
Pretreatment Characteristics	N	855	3514		681	4493	
Age at ART initiation in months	N	855	3514	0.043	681	4493	<0.0001
	Median (IQR)	7 (4;18)	10 (5;21)		96 (63;129)	81 (55;112)	
Male gender	N (column %)	427 (50)	1741 (50)	0.84	337 (49)	2298 (51)	0.42*
Pretreatment CD4 cells/mm^3	N	574	2488	0.0006	517	3195	0.44
	Median (IQR)	766 (315–1349)	662 (319–1158)		294 (115–529)	294 (131–522)	
Pretreatment CD4 %	N	564	2478	<0.0001	496	3087	<0.0001
	Median (IQR)	18.8 (12.2–27.1)	16 (10.2–23.0)		13.8 (6.9–20.2)	11.5 (6.3–16.3)	
WAZ	N	641	2683	0.030	397	2889	0.019
	Median (IQR)	−2.4 (−3.6 to −1.0)	−2.5 (−3.9 to −1.3)		−1.3 (−2.1 to −0.5)	−1.5 (−2.4 to −0.7)	
HAZ	N	508	2330	0.0005	478	3179	0.039
	Median (IQR)	−2.3 (−3.5 to −1.2)	−2.7 (−3.9 to −1.5)		−2.1 (−2.8; −1.3)	−2.2 (−3.0 to −1.4)	
Pretreatment VL $\log_{10}$	N	522	2249	0.0004	447	2878	0.062
	Median (IQR)	6.0 (5.3–6.5)	5.8 (5.1–6.3)		5.1 (4.5–5.5)	5.0 (4.4–5.5)	
<100,000 copies/mL	N (column %)	96 (18)	468 (21)	0.22	202 (45)	1501 (52)	0.0061*
Site							
Gugulethu	N (row %)	12 (10)	109 (90)	0.0002	36 (16)	193 (84)	0.32*
Harriet Shezi	N (row %)	375 (22)	1360 (78)		345 (13)	2346 (87)	
Khayelitsha	N (row %)	55 (15)	317 (85)		55 (13)	358 (87)	
RMMCH	N (row %)	141 (17)	704 (83)		157 (15)	919 (85)	
red cross	N (row %)	175 (22)	627 (78)		58 (12)	418 (88)	
Tygerberg	N (row %)	97 (20)	397 (80)		30 (10)	259 (90)	

d4T, stavudine; 3TC, lamivudine; IQR, interquartile range.
*χ^2 tests used to compare proportions. All continuous variable comparisons were done using t-tests if normally distributed or Wilcoxon tests if not normally distributed.

TABLE 2. Virological Outcomes in Children at 6 and 12 Months After Treatment Initiation in Children on LPV/r and EFV Comparing Stavudine-based to ABC-based Treatment for All Children and Children Not From RMMCH

		LPV/r Based			EFV Based		
		ABC/3TC	d4T/3TC	*P*	ABC/3TC	d4T/3TC	*P*
All Children with available data	N	855	3514		681	4493	
Follow-up duration		9 (4–14)	31 (12–51)	<0.0001	9 (5–14)	40 (23–64)	<0.0001
3- to 9-month window							
Reached window*	N (%)	676 (79)	3018 (86)	<0.0001	586 (84)	4254 (94)	<0.0001
VL done if reached window†	N (%)	438 (65)	2174 (72)	0.0002	391 (67)	3189 (75)	<0.0001
VL $\log_{10}$ value	Median (IQR)	2.6 (1.6–3.8)	2.1 (1.4–2.9)	<0.0001	1.7 (1.4–2.6)	1.4 (1.4–2.1)	<0.0001
VL<400 in 6-month window	N (%)	235 (54)	1528 (70)	<0.0001	304 (78)	2741 (86)	<0.0001
VL<50 in 6-month window	N (%)	136 (31)	956 (44)	<0.0001	208 (53)	2110 (66)	<0.0001
9- to 15-month window							
Reached window*	N (%)	405 (47)	2725 (78)	<0.0001	327 (48)	4057 (90)	<0.0001
VL done if reached window†	N (%)	256 (63)	1909 (70)	0.0056	202 (62)	3002 (74)	<0.0001
VL $\log_{10}$ value	Median (IQR)	2.6 (1.6–3.8)	1.7 (1.4–2.6)	<0.0001	1.7 (1.4–2.6)	1.4 (1.4–2.1)	0.0002
VL<400 in 12-month window	N (%)	158 (62)	1437 (75)	<0.0001	155 (77)	2535 (84)	0.0038
VL<50 in 12-month window	N (%)	104 (41)	985 (52)	0.0010	115 (57)	1996 (66)	0.0055
All Children excluding RMMCH	N	714	2810		524	3574	
3- to 9-month window							
VL $\log_{10}$ value	Median (IQR)	2.5 (1.6–3.7)	2.1 (1.4–2.9)	<0.0001	1.7 (1.6–2.3)	1.4 (1.4–2.1)	0.0051
VL<400 in 6-month window	N (% of VL done)	199 (56)	1196 (70)	<0.0001	254 (82)	2161 (85)	0.25
VL<50 in 6-month window	N (% of VL done)	126 (35)	726 (42)	0.016	180 (58)	1654 (65)	0.022
9- to 15-month window							
VL $\log_{10}$ value	median (IQR)	2.3 (1.4–3.4)	1.8 (1.4–2.6)	0.0026	1.7 (1.4–2.6)	1.4 (1.4– 2.2)	0.0016
VL<400 in 12-month window	N (% of VL done)	144 (65)	1118 (75)	0.0014	126 (77)	1990 (83)	0.046
VL<50 in 12-month window	N (% of VL done)	96 (43)	728 (49)	0.11	92 (56)	1536 (64)	0.042

*Children who did not reach the window were transferred out, lost to follow up or had died before the start of the window.
†Measure of uptake of VL testing in each window. VL cut-off values of 400 and 50 are in copies/mL.
3TC, Lamivudine.

reached the windows and if they reached the windows, fewer had VLs done compared with children on d4T. Within the group of children on ABC, uptake (ie, reached window and had VL done) of testing at 6 and 12 months was similar [65% at 6 and 63% at 12 months, $P = 0.60$ (LPV/r) and 67% and 52%, $P = 0.13$ (EFV)]; similarly, uptake in children on d4T remained the same for 6- and 12-month testing [72% at 6 and 70% 12 months, $P = 0.10$ (LPV/r); 75% at 6 and 74% at 12 months, $P = 0.31$ (EFV)]. A comparison in children reaching the 6- and 12-month follow-up windows was done comparing those who had VLs compared with those who

did not have VLs. In both the LPV/r and EFV groups, among children who reached the VL windows, there were no clinically significant differences between children who had or did not have VL measurements.

The VL $\log_{10}$ values (Table 2) were significantly lower in children on d4T at both the 6- and 12-month window in both LPV/r and EFV regimens. The proportions suppressed (400 and 50 copies/mL thresholds) were significantly lower in the ABC groups for the 6- and 12-month windows for both LPV/r and EFV regimens. When data excluding RMMCH were analyzed, the VL values were still significantly lower in children on d4T. The proportions suppressed to <400 copies/mL were lower with ABC except for suppression to <400 copies/mL at the 6-month window for children on EFV-based treatment. Supplemental digital content 1 (http://links.lww.com/INF/B757) shows the virological outcomes for each individual site at 6 and 12 months stratified by regimen. This shows that the differences in 6- and 12-month virological outcomes between d4T and ABC regimens were strongest at RMMCH. The trend is present at all other sites but significant values are seen in 3 of the 6 sites.

The effect of advancing program year is demonstrated in Figure 2. The LPV/r data (panel A) show that there is a decline in the 6- and 12-month suppression rates of children on d4T which seems to be continued as the graph continues into the ABC era from 2010 onwards. The decline of suppression over program year is significant for both the 6- and 12-month rates ($P < 0.0001$). When examining the 6- and 12-month rates for all children on EFV (Fig. 2, panel B), the trend was not significant.

Table 3 shows the results of the adjusted logistic regression which indicates in both crude and adjusted analyses that there was a higher risk of failing to suppress associated with ABC- compared with d4T-containing regimens in both the LPV/r and EFV groups at 6 and 12 months but this is not significant at 12 months in the LPV/r group. Analyses included adjustment for cohort. ART initiation at <6 months of age had an independent beneficial effect on suppression by 6 months in the LPV/r group [OR = 0.70 (CI: 0.57–0.87), $P = 0.002$]. Another significant effect on both 6 and 12 months suppression in both the LPV/r and EFV groups was a lower VL (<100,000 copies/mL) at ART initiation. The sensitivity analysis restricted to 2009–2011 shows similar effects; after adjustment, the negative effect of ABC on suppression was significant at 6 months [LPV/r group: OR = 0.50 (CI: 0.34–0.73), $P < 0.0001$; EFV group: OR = 0.38 (CI: 0.23–0.65), $P = 0.001$] and 12 months [LPV/r group: OR = 0.48 (CI: 0.28–0.83), $P = 0.012$; EFV group: OR = 0.48 (CI: 0.25–0.92), $P = 0.03$]. When examining for interaction between cohort and d4T/ABC effect, no interaction was found

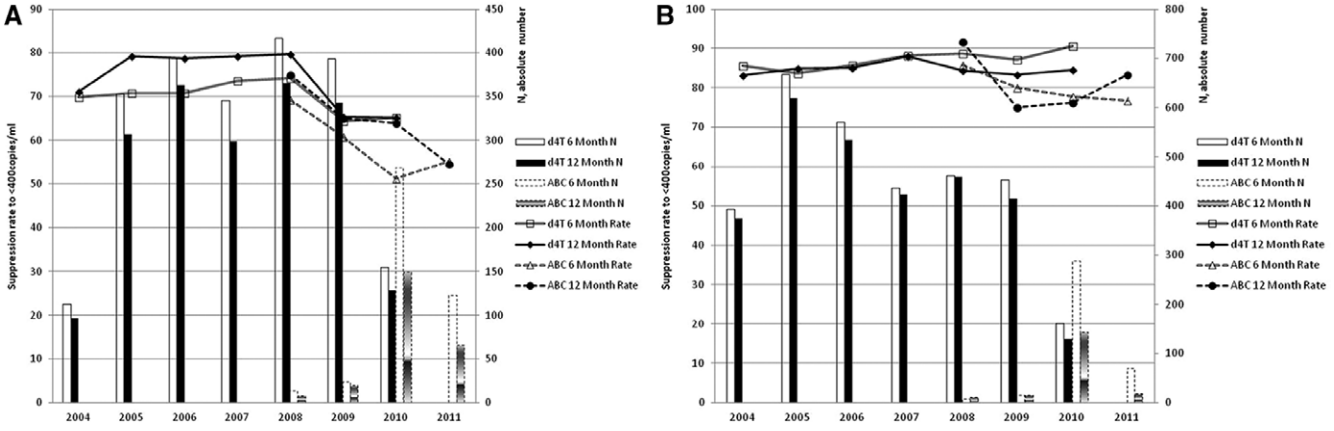

FIGURE 2. Program year effect on 6- and 12-month viral suppression rates stratified by ABC and stavudine (d4T) for children on LPV/r (A) and EFV (B), respectively.

TABLE 3. OR With 95% CI for Adjusted Logistic Regression of Failure to Reach a VL < 400 Copies/mL at 6 and 12 Months of Treatment in Children Initiating LPV/r- or EFV-based Antiretroviral Treatment (ART)

	LPV/r-based (N = 4369)				*EFV-based (N = 5174)*			
	6 Months	*P*	12 Months	*P*	6 Months	*P*	12 Months	*P*
Unadjusted OR (95% CI)								
d4T-based vs. ABC-based	0.49 (0.40–0.60)	<0.0001	0.52 (0.39–0.69)	0.001	0.56 (0.43–0.72)	<0.0001	0.55 (0.36–0.85)	0.013
Adjusted OR (95% CI)								
d4T-based vs. ABC-based	0.57 (0.46–0.72)	<0.0001	0.69 (0.46–1.02)	0.061	0.46 (0.32–0.65)	<0.0001	0.56 (0.36–0.86)	0.012
Male	0.99 (0.86–1.15)	0.942	1.05 (0.85–1.29)	0.62	1.07 (0.90–1.27)	0.415	1.05 (0.83–1.33)	0.648
Age at initiation*	0.70 (0.57–0.87)	0.002	0.86 (0.57–1.30)	0.411	0.99 (0.99–1.00)	0.001	1.00 (0.99–1.00)	0.631
Pretreatment WAZ	0.89 (0.83–0.96)	0.007	0.93 (0.89–0.98)	0.006	0.91 (0.85–0.98)	0.009	0.93 (0.86–1.01)	0.085
Pretreatment CD4%	0.98 (0.96–1.00)	0.043	0.98 (0.97–0.99)	0.003	0.98 (0.97–1.00)	0.032	0.98 (0.96–0.99)	0.002
Pretreatment VL < 100,000 copies/mL	0.65 (0.52–0.82)	<0.0001	0.69 (0.49–0.96)	0.032	0.72 (0.58–0.88)	0.002	0.79 (0.64–0.99)	0.04
Year of ART initiation	1.06 (1.01–1.12)	0.026	1.12 (1.04–1.20)	0.004	0.97 (0.92–1.03)	0.358	1.02 (0.95–1.10)	0.555

Adjusted for cohort (individual cohort results not shown). OR < 1 indicate factors improving viral suppression rate at 6 months.
*Age at initiation categorized as < 6 months (reference) and > 6 months of age for LPV/r group and as continuous variable (months) for EFV group.
d4T, stavudine; ABC, abacavir.

in the LPV/r group (at 6 months $P = 0.46$ and 12 months $P = 0.73$) while in the EFV group there was a possible interaction between effect of d4T/ABC by cohort (at 6 months, $P = 0.046$ but not at 12 months, $P = 0.33$).

DISCUSSION

Our study showed reduced virological suppression at both 6 and 12 months in children treated with ABC-based compared with d4T-based regimens with either LPV/r or EFV as the third drug in the regimen. As the change to ABC-based regimens was concurrent with a number of PMTCT and pediatric treatment protocol and program changes, it is difficult to ascribe the lower suppression rates to ABC. Nevertheless, the effect remains despite adjustment for pretreatment characteristics, calendar time and cohort.

Both the RMMCH and this analysis were based on routinely collected observational data.[8] Careful consideration needs to be given before attributing causality of these trends and associations. Routine data provide useful sentinel surveillance monitoring to inform policymakers and program managers and alert clinical researchers to potential problems. Although these data do not provide definitive evidence for the superiority of either of the 2 specific NRTI backbones, urgent attention is warranted to ensure that early pediatric virological outcomes are improved in South Africa. Randomized control trial evidence for the superiority of ABC/3TC as an NRTI backbone is drawn from the Pediatric European Network for the Treatment of AIDS trial.[6] Children enrolled were older (median 5.4 years) than children on LPV/r in our data, the trial included asymptomatic children on dual therapy and use of nelfinavir rather than LPV/r or EFV as starting regimen. The mean VL at starting ART (5.1 log10 copies/mL) was lower than that reported in our LPV/r group and similar to that reported in our EFV group.

Pretreatment characteristics have changed since inception of the South African ART program reflecting a trend towards earlier initiation of healthier children. These changes in pretreatment characteristics are likely to be related to changing initiation guidelines. More favorable pretreatment characteristics would lead one to expect better treatment outcomes in the ABC groups.

The low and declining uptake (65–75%) of VL testing at 6 and 12 months is a further concerning finding for the South African program. The proportion of children who had VL testing done differs between those on d4T and those on ABC. This may be related to the more recent introduction of ABC and therefore fewer data for children started on ABC. It may also be a selection bias if testing was done in children who appeared to be doing well although this would have been inconsistent with the VL testing guidelines in place. Nevertheless, there were no clinically significant differences in pretreatment characteristics between children with and without VL tests done. This analysis demonstrates poorer early virological outcomes, but it is too early to assess the effect of this decline on mortality, clinical events, regimen switches and long-term outcomes.

In both children treated with LPV/r and EFV, viral suppression rates were greater with d4T than with ABC. Adult data suggest that higher pretreatment VL levels may predispose to poor performance of ABC-based therapy.[12–15] Achieving suppression was more likely in children with lower pretreatment VL levels in our cohort. The youngest children (<6 months old) starting LPV/r based therapy had better outcomes than those starting >6 months. This may indicate the benefits of early treatment.[16] Better growth recovery has also been observed amongst children starting ART before compared with after 6 months of life.[17]

The majority of reported data was from Johannesburg where isolated incidents of ABC stock-outs were reported during 2011. In some cases tablet formulations ran out, for example, ABC tablets were not available and had to be substituted by syrup. Caregivers may have had to return more frequently than usual as only limited stock could be issued. The available data do not contain details of formulation changes or pharmacy only visits and the continuity of ABC or particular formulation supply can therefore not be included in the analysis but may have contributed to poorer performance or durability of ABC-containing regimens.

While PMTCT coverage has increased with lower overall numbers of vertically infected infants, there may be a reversal of the in utero versus intrapartum ratio of infection emerging in HIV-infected infants who were exposed to perinatal antiretroviral prophylaxis.[18] A larger proportion of intrauterine-acquired infection may contribute to worse clinical outcomes due to infection occurring in the fetus when the immune system is very immature,[19] but the effect on virological suppression is not clear. Improved coverage of PMTCT and ART for adults combined with expanding use of a wider range of antiretrovirals for PMTCT may have led to a larger proportion of infected children with primary antiretroviral drug resistance both selected and transmitted.[20] With transmission of M184V there may be reduced activity of ABC.[21] This could also contribute to treatment outcomes, but requires further study.

Data suggesting ABC levels are reduced by 32% in the presence of LPV/r are further cause for concern when interpreting our results.[22] Children, especially infants, who receive LPV/r-based treatment tend to have higher pretreatment VL values. The change to ABC was a clear switch of protocol but switches to generic versions of d4T, 3TC or EFV cannot be accounted for and cannot be excluded as a cause for the problem if drug quality was inferior. Similarly, quality of LPV/r formulations was assumed to have remained constant. Such assumptions may be problematic given the size of the South African epidemic and the quantities of medications that have to be ordered, shipped, redistributed, checked and dispensed on a regular basis and in correct conditions (especially with need for cold-chain for LPV/r syrup). The data available for analysis does not include exact dosing or formulation, neither was there a consistent adherence measure across sites. These potential confounders were not controlled for. Further pharmacological studies investigating these factors in the large South African program are appropriate.

Limitations of this analysis include shorter follow-up time for children on ABC-based regimens. Some sites still have too few children who started ABC-based regimens for meaningful analysis. Significantly fewer children have results available at both the 6-and 12-month windows in the ABC group compared with the d4T groups. Details of exact formulations issued and month-to-month drug supply are not available which would have been useful to quantify whether ABC supply issues were a factor.

This analysis (which includes the site originally reporting a concern about ABC performance) is consistent with the prior observation of worse outcomes in children treated with ABC-containing regimens as recommended in the more recent guidelines. Whether this is due to the ABC-based regimen per se or other factors in more recent time cannot be distinguished with these data. Continued evaluation of the South African program and early pediatric outcomes is required as thousands of children still initiate ART annually. There is enough evidence of possible poorer virologic efficacy of ABC to warrant ongoing careful monitoring, analyses in other settings and pharmacological studies; a randomized control trial in infants and young children in Africa to determine best NRTI options may be required. There are few NRTI options for children in resource limited settings, especially with moves away from d4T and didanosine. Zidovudine may be one option but may complicate matters in malaria endemic areas. Another alternative may be to consider d4T or AZT initially and then switch to ABC

after suppression is reached but switch protocols add significant complexity to national protocols. While more recent data are scrutinized, VL monitoring should continue, quality control of drugs should be ensured, strong adherence messaging should continue and if trends persist, guideline review may be required.

ACKNOWLEDGMENTS

All the children whose data were used in this analysis, as well as their caregivers are gratefully acknowledged. We appreciate the efforts of all site and data centre staff who contribute to the improvement of cohort data quality in the collaboration as well as to the South African Department of Health that strives to improve the lives of children affected by HIV.

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