First-line antiretroviral drug discontinuations in children

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Abstract

Introduction

There are a limited number of paediatric antiretroviral drug options. Characterising the long term safety and durability of different antiretrovirals in children is important to optimise management of HIV infected children and to determine the estimated need for alternative drugs in paediatric regimens. We describe first-line antiretroviral therapy (ART) durability and reasons for discontinuations in children at two South African ART programmes, where lopinavir/ritonavir has been recommended for children <3 years old since 2004, and abacavir replaced stavudine as the preferred nucleoside reverse transcriptase inhibitor in 2010.

Methods

We included children (<16 years at ART initiation) who initiated ≥3 antiretrovirals between 2004–2014 with ≥1 follow-up visit on ART. We estimated the incidence of first antiretroviral discontinuation using Kaplan-Meier analysis. We determined the reasons for antiretroviral discontinuations using competing risks analysis. We used Cox regression to identify factors associated with treatment-limiting toxicity.

Results

We included 3579 children with median follow-up duration of 41 months (IQR 14–72). At ART initiation, median age was 44 months (IQR 13–89) and median CD4 percent was 15% (IQR 9–21%). At three and five years on ART, 72% and 26% of children respectively remained on their initial regimen. By five years on ART, the most common reasons for discontinuations were toxicity (32%), treatment failure (18%), treatment simplification (5%), drug interactions (3%), and other or unspecified reasons (18%). The incidences of treatment limiting toxicity were 50.6 (95% CI 46.2–55.4), 1.6 (0.5–4.8), 2.0 (1.2–3.3), and 1.3 (0.6–2.8) per 1000 patient years for stavudine, abacavir, efavirenz and lopinavir/ritonavir respectively.

Conclusions

While stavudine was associated with a high risk of treatment-limiting toxicity, abacavir, lopinavir/ritonavir and efavirenz were well-tolerated. This supports the World Health Organization recommendation to replace stavudine with abacavir or zidovudine in paediatric first-line ART regimens in order to improve paediatric first-line ART durability.

Introduction

World Health Organization (WHO) guidelines have progressively recommended earlier antiretroviral therapy (ART) initiation for children, with the most recent WHO recommendation being immediate ART irrespective of CD4 count for all adults and children [1–4]. Children are therefore increasingly initiating ART at younger ages. Since ART must be taken lifelong and there are a limited number of paediatric antiretroviral options, knowing the long term safety and durability of ART in children is important to optimise their management. In addition, accurately forecasting future need for different antiretrovirals in children is important considering the challenges of ensuring adequate supply of appropriate pediatric antiretroviral formulations given the small and diminishing size of the pediatric epidemic relative to the adult epidemic. Knowledge of durability of currently used regimens such as abacavir and lopinavir-ritonavir is therefore vital.

In 2010 the WHO advised against the use of stavudine due to its long term toxicity, and recommended the use of either abacavir or zidovudine instead [4]. In 2013 WHO recommended lopinavir/ritonavir for first-line ART in all children less than three years old due to its superior virologic suppression [5]. The limited data on ART modifications in children from resource-limited countries suggest that fewer treatment modifications for any reason tend to occur in resource-limited settings, where the number of alternative drugs is limited [6–8]. Notwithstanding, there are very few studies describing the durability of the currently recommended abacavir- or lopinavir/ritonavir-containing first-line paediatric ART regimens in routine care [9, 10].

In South Africa, lopinavir/ritonavir has been part of recommended first-line ART for all children less than three years old since 2004, and abacavir has been the preferred nucleoside reverse transcriptase inhibitor since 2010 [11, 12]. A study in South African adults showed that the incidence of antiretroviral substitutions decreased after stavudine was replaced with tenofovir as part of the preferred first-line regimen, [13] but it is unknown whether replacing stavudine with abacavir had a similar effect on first-line ART regimen durability in paediatric cohorts.

We describe ART regimen durability and reasons for discontinuation of first-line antiretrovirals in children at two South African ART programmes from 2004–2014 covering the periods both before and after the replacement of stavudine with abacavir in first-line paediatric ART.

Methods

Study setting and population

We included all eligible patients from the Khayelitsha HIV Treatment Programme, which comprises three primary care clinics in Cape Town, South Africa, and from the HIV clinics at Rahima Moosa Mother and Child Hospital (RMMCH) clinic, a tertiary hospital dedicated to mother and child clinical care in Johannesburg, South Africa. Both sites provide HIV

treatment services according to national guidelines and prospectively collect routine clinical data electronically. We included treatment-naïve children less than 16 years old who initiated ART with at least three antiretrovirals, between January 2004 and October 2013 (Khayelitsha) or March 2014 (RMMCH), and had at least one follow-up visit.

Guidelines for ART initiation and treatment

South African national guideline ART eligibility and first-line regimen recommendations changed over the study period (S1 and S2 Tables) [11, 12, 14, 15]. Briefly, in 2004, ART eligibility depended on CD4 percent/count values or WHO clinical stage [11]. By 2013, ART was recommended for all children less than five years old, regardless of CD4 percent/count [14]. Before 2007, the recommended first-line ART regimens comprised stavudine and lamivudine, with efavirenz in children older than three years; lopinavir/ritonavir in those aged six months to three years; or ritonavir in those younger than six months [11, 15]. In 2007, lopinavir/ritonavir was recommended instead of ritonavir in children less than six months old [15]. From 1 April 2010, abacavir was recommended instead of stavudine, and children were electively changed to abacavir to prevent stavudine toxicity [12].

Data management and statistical analysis

Data were captured electronically at the sites, and combined using a standard data transfer format. We looked for inconsistencies and possible errors, which were corrected by the sites to ensure completeness of ART prescription data. We used Stata 13.0 for data management and analysis.

We estimated the incidences of stavudine, abacavir, efavirenz and lopinavir/ritonavir discontinuations using Kaplan-Meier analyses. We determined the reasons for antiretroviral discontinuations using competing risks analysis. We explored associations with treatment-limiting toxicity using Cox regression. We included sex and weight-for-age z-score at ART initiation in the model *a priori*. We included age as a binary variable (<36 and ≥36 months) because of differing ART recommendations for those <36 months and ≥36 months old.

We censored patients at the first of: death, transfer out, loss to follow-up, database closure, or five years of follow-up. We considered patients lost to follow up if they had no visit for nine months before database closure and censored them at their last visit date. We did not consider treatment interruptions of less than two months to be a treatment discontinuation, unless the reason for the interruption was documented as toxicity. Treatment failure included virological, clinical, or immunological failure as defined by the treating physician using national guidelines. We defined treatment-limiting toxicity as the discontinuation of at least one antiretroviral with the reason for discontinuation documented as toxicity by the treating clinician.

Due to the 2010 guideline change that encouraged clinicians to change stavudine to abacavir to prevent toxicity, it is possible that a proportion of stavudine discontinuations after this date were actually pre-emptive to prevent toxicity rather than due to toxicity. We therefore performed a sensitivity analysis that censored patient follow-up on 01 April 2010 and excluded stavudine discontinuations that occurred after 01 April 2010.

Ethics

Data were anonymised to ensure patient confidentiality. The University of Cape Town and University of the Witwatersrand Human Research Ethics Committees approved data collection and analysis. The study protocol was also reviewed and cleared as human subjects' research by the U.S. Centers for Disease Control and Prevention (CDC).

Table 1. Characteristics of children initiated on antiretroviral treatment (N = 3579).

Characteristics at ART initiation		N[e]	All children N = 3579		Rahima Moosa N = 2464		Khayelitsha N = 1115	
			Median	(IQR)	Median	(IQR)	Median	(IQR)
Age (months)		3579	43.5	(13.4–89.2)	43.4	(12.4–91.0)	43.8	(15.2–86.1)
CD4 percent (%)		1993	15	(9–21)	14	(8–20)	17	(11–24)
CD4 count (cells/mm^3)		2192	468	(223–852)	436	(211–791)	536	(252–980)
Viral load (log$_{10}$ copies)		1840	5.3	(4.5–6.0)	5.4	(4.7–6.5)	4.9	(4.0–5.7)
Weight-for age z score		2379	-1.5	(-2.5 to -0.5)	-1.8	(-3.0 to -0.8)	-0.9	(-1.8 to -0.1)
			n	(%)	n	(%)	n	(%)
Male gender		3577	1787	(50%)	1257	(51%)	530	(48%)
WHO clinical stage 3 or 4		2315	1628	(70%)	865	(70%)	763	(71%)
Severe immunosuppression[a]		1845	1221	(66%)	947	(70%)	274	(55%)
Severe anaemia at ART initiation[b]		879	30	(3%)	30	(4%)	0	0
ART regimen[c]:		3579						
NRTI	Stavudine		2363	(66%)	1667	(68%)	696	(62%)
	Abacavir		1040	(29%)	740	(30%)	300	(27%)
	Zidovudine		161	(4%)	51	(2%)	110	(10%)
	Tenofovir		15	(0.4%)	6	(0.2%)	9	(0.8)%
PI or NNRTI[d]	Efavirenz		1849	(52%)	1356	(55%)	493	(44%)
	Nevirapine		153	(4%)	42	(2%)	111	(10%)
	Lopinavir/ritonavir		1522	(43%)	1034	(42%)	488	(44%)
	Ritonavir alone		54	(2%)	31	(1%)	23	(2%)

[a]. Severe immunosuppression defined according to WHO 2006 criteria.

[b]. Severe anaemia defined as a haemoglobin of <7g/dL.

[c]. Most of the regimens were in the form NRTI+lamivudine+NNRTI/PI. Two children received emtricitabine instead of lamivudine. Percentages might not add up to 100% due to rounding off.

[d]. Unspecified in one case.

[e]. Some variables were not measured in all children

ART: antiretroviral treatment. IQR: interquartile range. NRTI: nucleoside reverse transcriptase inhibitor. NNRTI: non-nucleoside reverse transcriptase inhibitor. PI: protease inhibitor. WHO: World Health Organization

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Results

Study cohort

We included 3 579 children with median follow-up of 41 months (IQR 14.1 to 71.8) (Table 1). Four percent (142/3 579) of included children died, 75% (107/142) in the first year of ART. Nineteen percent (662/3 579) of children were lost to follow up and 18% (648/3579) were transferred to another facility. Rates of loss to follow up were similar at both sites. The proportion of children who initiated ART before 12 months of age increased from 6% in 2004 to 29% (49/170) in 2013. The most common first-line regimen was lamivudine and stavudine with either efavirenz in children older than years (61%, 1199/1954)) or lopinavir/ritonavir in children younger than three years (52%, 842/1625)).

Antiretroviral discontinuations

Thirty percent (1 071/3 579) of children had an antiretroviral discontinuation. The reason for antiretroviral discontinuation was unknown in 58 (5%) children (13% at Khayelitsha and 2% at Rahima Moosa). The overall incidence of first antiretroviral discontinuation was 85.9 per 1000 patient years (py) (95% confidence interval (CI) 80.2 to 92.0). After one, three and five

Fig 1. Proportion of children remaining on initial first-line antiretroviral regimen and reasons for regimen change over 5 years of follow-up.

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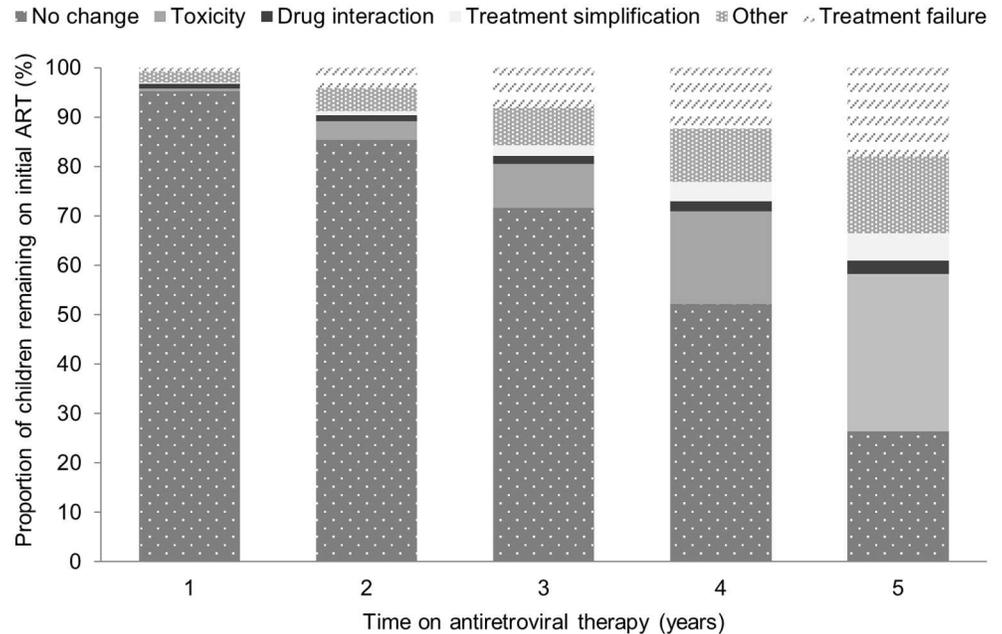
Years of follow-up	1	2	3	4	5
Number of children followed up (n)	2790	2368	1966	1566	1222
On initial regimen (%)	95	85	72	52	26
Toxicity[a] (%)	1	4	9	19	32
Drug interaction (%)	1	1	2	2	3
Treatment simplification[b] (%)	0	1	2	4	5
Treatment failure[c] (%)	1	4	8	12	18
Other[d] (%)	2	5	7	11	16

a. Toxicity: discontinuations due to lipodystrophy, lactic acidosis, hypersensitivity reaction, central nervous system, gastro-intestinal or haematological toxicities
b. Treatment simplification: discontinuations due to a more effective drug being available, protocol change or a drug not being available
c. Treatment failure: discontinuations due to virological, immunological or clinical failure
d. Other: discontinuations due to adverse event not specified, physician's decision, patient's wishes or an unknown reason

years 95%, 72% and 26% of children respectively remained on their initial first-line regimen (Fig 1). In the first two years on ART, the rates of discontinuations for treatment failure and for toxicity were similar, but toxicity was the most common reason for drug discontinuations from three years onwards, with a cumulative incidence of 7% and 23% at three and five years respectively. The drug most frequently discontinued was stavudine, with an incidence of 87 per 1 000 py (95% CI 81.1 to 92.8). In contrast, incidence of abacavir discontinuation was 30 per 1 000 patient years (95% CI 23.3 to 39.4). Drug-specific reasons for antiretroviral discontinuations are shown in S3 Table.

Treatment-limiting toxicity

The overall rate of treatment-limiting toxicity was 13.4 per 1 000 py (95% CI 11.3 to 16.0). The incidence of treatment limiting toxicity was 50.6 (95% CI 46.2 to 55.4) per 1 000 patient years

Table 2. Predictors of discontinuations due to toxicity using cox-proportional hazards regression among children followed up until 5 years (n = 3579).

Variable		Unadjusted HR (95% CI)	P value	Adjusted[a] HR (95% CI)	P value
Site	Khayelitsha (N = 1115)	1		1	
	Rahima Moosa (N = 2464)	2.5 (1.9 to 3.3)	<0.001	2.8 (2.0 to 3.8)	<0.001
Age (months)	<36 (N = 1625)	1		1	
	≥36 (N = 1954)	1.7 (1.4 to 2.2)	<0.001	1.80 (1.4 to 2.4)	<0.001
NRTI	Abacavir (N = 1043)	1		1	
	Stavudine (N = 2363)	17.0 (5.4 to 53.0)	<0.001	30.8 (4.3 to 220.2)	0.001
	Another NRTI (N = 1730)	0.8 (0.1 to 7.3)	0.8	4.7 (0.3 to 75.4)	0.279

[a]. Adjusted for sex and baseline weight-for-age z-score.

CI: confidence interval. HR: hazard ratio. NRTI: nucleoside reverse transcriptase inhibitor.

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for stavudine, and 1.6 (95% CI 0.5 to 4.8), 2.0 (95% CI 1.2 to 3.3), and 1.3 (95% CI 0.6 to 2.8) per 1 000 patient years for abacavir, efavirenz and lopinavir/ritonavir respectively. Lipodystrophy accounted for 95% (463/483) of treatment-limiting toxicities (450 due to stavudine and seven due to efavirenz). Other causes of treatment-limiting toxicity included: hyperlactataemia in five patients on stavudine; hypersensitivity reaction in two patients on abacavir; and neurological symptoms in one patient on efavirenz.

Results from adjusted cox-regression showed that children on stavudine were 30.8 times more likely to experience treatment-limiting toxicity compared with children on abacavir (95% CI: 4.3 to 220.2). Older age (≥36 months compared with <36 months) and site were also significant predictors of treatment-limiting toxicity (Table 2).

Sensitivity analysis

More than two-thirds (68%, 571/841) of stavudine discontinuations occurred after 01 April 2010. In the sensitivity analysis that excluded stavudine discontinuations and follow-up after 01 April 2010, durability of first-line therapy at five years on ART increased from 26% to 52%; and the adjusted hazard ratio for treatment-limiting toxicity for children on stavudine compared with children on abacavir decreased from 30.8 to 9.9 (95% CI 1.4 to 71.8, adjusted for age, site, sex and baseline weight-for-age z-score).

Discussion

In our cohort of 3 579 South African children, 28% and 74% of children had a first-line regimen discontinuation by three and five years on treatment respectively. The most common reason for discontinuation was toxicity (13%) followed by treatment failure (7%). Receiving stavudine and age over three years were associated with a higher risk of treatment-limiting toxicity.

Our study is one of the first to examine regimen durability and treatment-limiting toxicity after the replacement of stavudine with abacavir in first-line ART. In contrast to our findings, treatment failure was a more common reason for antiretroviral discontinuation than toxicity in other South African studies conducted before 2010. Reddi et al. [8] reported that 4.6% and 1.3% of discontinuations were due to treatment failure and toxicity respectively after a median follow up of eight months, and Kampiire et al [16] reported that 6.7% and 3.1% of discontinuations were due to treatment failure and toxicity respectively by three years on ART. This probably reflects the fact that without access to abacavir, clinicians were largely unable to switch patients off of stavudine, even if they experienced toxicity. Although our study may over-

estimate stavudine toxicity as some patients were probably switched off of stavudine to prevent toxicity, rather than because of toxicity itself, it is clear that introduction of abacavir-based first-line regimens significantly reduced treatment-limiting toxicity. Only two patients experienced abacavir hypersensitivity reaction in our study. The incidence of abacavir hypersensitivity reaction in children is lower than in adults [9, 17], and African descent reduces the risk further [10, 18].

Our study shows that lopinavir/ritonavir and efavirenz were relatively well-tolerated with incidences of treatment-limiting toxicity of 1.3 (95% CI 0.6 to 2.8) and 2.0 (95% CI 1.2 to 3.3) per 1 000 patient years respectively. In contrast, studies conducted in Rwanda, Uganda and India, where were most patients were on nevirapine-based ART, reported overall probabilities of treatment-limiting toxicities of 8.3% [19], 19% [20], and 25.4% [21] respectively.

In our study, in addition to ART regimen (being on stavudine versus abacavir) older age and site were independent predictors of treatment-limiting toxicity. It is unclear why older children are more likely to experience treatment-limiting toxicity. The majority of children ≥36 months receive efavirenz while children <36 months receive lopinavir/ritonavir and, due to these age-based regimens, we could not adjust for both age and efavirenz versus lopinavir/ritonavir in the models. Consequently, we cannot exclude the possibility that efavirenz and not older age is a risk factor for a treatment-limiting toxicity. Older children are more able to verbalize when they experience toxicity compared to younger children which may be important especially for neuropsychiatric toxicity. In addition, lipodystrophy, the most common toxicity, might be easier to diagnose in older children. Similarly, only three patients reported stavudine-related peripheral neuropathy. The low incidence of peripheral neuropathy relative to adult patients is consistent with previous studies, and might be due to both lower incidence and difficulty diagnosing peripheral neuropathy in children [20, 22].

After adjusting for age, concomitant antiretrovirals, sex, and weight-for-age z-score, children at Rahima Moosa Mother and Child Hospital were 2.8 times as likely as those at Khayelitsha clinic to experience a toxicity-related drug discontinuation. Children at Rahima Moosa had lower average CD4 counts and a higher proportion of severe immune suppression than those at Khayelitsha, which might have increased their risk for drug toxicity. In addition, clinicians at Rahima Moosa, a tertiary hospital, were probably more likely to have immediate access to monitoring blood results and alternative antiretrovirals. They were also more likely to be paediatricians, who were probably more confident in recognising adverse drug reactions and switching children off of antiretrovirals than the primary care doctors and nurses at Khayelitsha clinics. The percentage of missing reasons for drug discontinuations was higher at Khayelitsha than at Rahima Moosa, so it is also possible that the effect of site on toxicity-related drug discontinuations might be overestimated.

Data were collected from routine clinic practice and we relied on the treating clinicians' diagnoses of toxicity with likely discrepancies across sites and between clinicians. Also, our study focuses on treatment discontinuations relatively early in the course of ART as we assessed only the first discontinuation of a drug. Treatment-limiting toxicities could also have been under-estimated due to loss to follow-up, if children were lost to follow-up due to toxicity. Nevertheless, our study is a large paediatric longitudinal study with long follow-up. It spanned the periods before and after a drug protocol change occurred in South Africa, substitution of stavudine with abacavir, which enabled us to describe abacavir durability. The cohorts in this study are representative of clinic and hospital settings in South Africa and the inclusion of both settings provides a better picture of treatment-limiting toxicity than if only one setting were included. However, the generalisability to other African countries will depend on drug regimens used, availability of alternative drugs and whether clinical monitoring is comparable to our setting.

Conclusions

Durability of first-line ART was relatively high in our study. The introduction of abacavir reduced treatment-limiting toxicity in comparison to stavudine, and the incidence of treatment-limiting toxicity for patients on lopinavir/ritonavir or efavirenz was low. Nevertheless, ongoing monitoring of the durability of first-line ART is required to accurately predict need for alternative drug options in children as infants and children start ART earlier, availability of alternative drugs and formulations increases, and children survive on ART into adolescence and adulthood.

Supporting information

S1 Table. Changes in guidelines for antiretroviral therapy initiation.
(DOCX)

S2 Table. Changes in the recommended first-line antiretroviral therapy.
(DOCX)

S3 Table. Reasons for discontinuations by antiretroviral drug.
(DOCX)

Author Contributions

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